



Contents lists available at SciVerse ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Review

Adverse childhood experiences, allostasis, allostatic load, and age-related disease

Andrea Danese^{a,*}, Bruce S. McEwen^b^a MRC Social, Genetic and Developmental Psychiatry (SGDP) Centre, and Department of Child & Adolescent Psychiatry, Institute of Psychiatry, King's College London, London, UK^b Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY 10065, USA

ARTICLE INFO

Article history:

Received 18 July 2011

Received in revised form 16 August 2011

Accepted 17 August 2011

Available online xxxxx

Keywords:

Adverse childhood experiences

Childhood maltreatment

Stress

Allostasis

Allostatic load

ABSTRACT

How do adverse childhood experiences get 'under the skin' and influence health outcomes through the life-course? Research reviewed here suggests that adverse childhood experiences are associated with changes in biological systems responsible for maintaining physiological stability through environmental changes, or allostasis. Children exposed to maltreatment showed smaller volume of the prefrontal cortex, greater activation of the HPA axis, and elevation in inflammation levels compared to non-maltreated children. Adults with a history of childhood maltreatment showed smaller volume of the prefrontal cortex and hippocampus, greater activation of the HPA axis, and elevation in inflammation levels compared to non-maltreated individuals. Despite the clear limitations in making longitudinal claims from cross-sectional studies, work so far suggests that adverse childhood experiences are associated with enduring changes in the nervous, endocrine, and immune systems. These changes are already observable in childhood years and remain apparent in adult life. Adverse childhood experiences induce significant biological changes in children (biological embedding), modifying the maturation and the operating balance of allostatic systems. Their chronic activation can lead to progressive wear and tear, or allostatic load and overload, and, thus, can exert long-term effects on biological aging and health.

© 2011 Published by Elsevier Inc.

In the past two decades, the concepts of allostasis and allostatic load [1] have provided researchers with a powerful framework to study both the protective effects of stress mediators during acute stress exposure and the damaging effects of stress mediators during chronic or repeated stress exposure. These concepts have been applied to the study of aging and of socioeconomic inequalities in health [2–4]. In this review, we will argue that these concepts could also be broadened to promote the understanding of the short-term and the long-term consequences of adverse childhood experiences. The application of these concepts to the study of stress in childhood includes attention to the biological changes associated with adverse psychosocial experiences in children as well as to the progressive and cumulative wear and tear that is the essence of allostatic load and of its more extreme form, namely allostatic overload [5]. Before addressing early life adversity, we shall provide an overview of the allostatic load/overload concept that represents the cost of the continual adjustment of the internal milieu required by the organism to adapt to environmental, social and personal challenges, often referred to as stressors.

1. Allostasis

Life is made possible by the relative stability of key physiological variables, such as body temperature, energy balance, and blood

composition (*homeostasis*) [6]. This is testified by the narrow variations in these variables that are compatible with life. However, because animals are open biological systems constantly interacting with the environment, the stability of these key physiological variables is threatened by changing environmental conditions.

In order to maximize survival, biological processes have likely been shaped by evolution to maintain stability through changes (*allostasis*) [7]. Allostasis relies upon the ability to detect environmental (external) and physiological (internal) changes, and to activate specialized adaptive responses. Three highly-integrated systems, namely the nervous, the endocrine, and the immune systems, have this ability and, thus, mediate allostatic processes.

Because the nervous, the endocrine, and the immune systems are highly integrated, stimulation of one allostatic system commonly triggers pleiotropic responses in all allostatic systems. For example, pathogen infection is a key stimulus for the activation of the immune system, which prevents the spread of infection and promotes tissue repair [8]. Because of the activation of the immune system, pathogen infection may also trigger metabolic responses, such as the induction of insulin resistance, in order to divert energy from anabolic to catabolic pathways [9]. Indeed, the energy demand of the activated immune response has been causally related to the metabolic syndrome [10]. Furthermore, because of the activation of the immune system, pathogen infection may also trigger behavioral responses, such as hypersomnia, reduced motor activity, and reduced social interaction (i.e., sickness behavior), in order to prevent heat dispersion [11] and to conserve energy for the immune defense [10].

* Corresponding author at: SGDP Centre, P080, Institute of Psychiatry, 16 DeCrespigny Park, London SE5 8AF, UK. Fax: +44 2078480866.

E-mail address: andrea.danese@kcl.ac.uk (A. Danese).

The close integration among allostatic systems is also manifested during the response to psychosocial stress [12]. Psychosocial stressors are detected through a neurobiological network including the thalamus, the sensory cortex, and the amygdala, which has evolved to identify environmental threats for survival [13]. The firing of the amygdala is moderated by two key inhibitory influences. The hippocampus exerts inhibitory control over amygdala activity based on learning processes and memory of previous experiences. The prefrontal cortex exerts inhibitory control over amygdala activity based on executive functions, such as attention and meta-cognition. Therefore, the amygdala, the hippocampus, and the prefrontal cortex form a network of brain areas involved in detecting environmental threats [14]. In response to psychosocial stressors, the amygdala triggers firing in the locus coeruleus, which increases alertness and attention to the environment, and induces a bodily response through the activation of the sympathetic nervous system (the “fight or flight response”). Because of the activation of the sympathetic nervous system, psychosocial stress also triggers inflammation [15], an immune response that could prevent pathogen infection should tissue damage occur. Furthermore, in response to psychosocial stressors the amygdala triggers firing in the paraventricular nucleus of the hypothalamus [16] inducing the neuroendocrine response to stress. The stimulation of the hypothalamic–pituitary–adrenal (HPA) axis under stress [17,18] first supports the increased metabolic demands by mobilizing stored energy and then concurs with the parasympathetic nervous system in terminating the physiological arousal. Each of the mediators of allostasis interacts with other mediators in a complex non-linear fashion showing biphasic effects depending on the level and duration of activation [19].

These findings suggest that highly-integrated allostatic systems, namely the nervous, the endocrine, and the immune systems, promote short-term adaptation in the face of environmental challenges. However, the enduring activation of the allostatic systems may have detrimental consequences.

2. Allostatic load

Chronic or repeated exposure to psychosocial stressors has been linked to prolonged activation of the allostatic systems, with detrimental physiological consequences – *allostatic load*, and its more severe form, *allostatic overload* [5,12].

In the nervous system, the chronic exposure to psychosocial stressors leads to structural and functional abnormalities in stress-sensitive regions, such as the prefrontal cortex, the amygdala and the hippocampus [2,14]. In the prefrontal cortex, chronic stress exposure causes shortening of dendrites and behavioral manifestations, such as impairment in attention, in extinction of fear-conditioned tasks, and in top-down cognitive emotion regulation. In the amygdala, chronic stress exposure causes dendritic growth and behavioral manifestations, such as enhanced response to unlearned fear and fear conditioning. In the hippocampal circuitry, chronic stress exposure causes a plastic remodeling with volumetric reduction of the hippocampus and behavioral manifestations, such as deficits in declarative, contextual, and spatial memory. In addition to excitatory amino acids, monoamines, endogenous opioids, and BDNF, the endocrine and immune systems also contribute to stress-related brain plasticity [2,20–22]. In turn, stress-related brain plasticity could potentiate the response of the endocrine and immune systems to subsequent stressors in a feed-forward cycle.

In the endocrine system [23], chronic exposure to psychosocial stressors is associated with increased corticotropin-releasing factor (CRH) levels, consistent with chronic activation of the HPA axis. Chronic stress is also associated with lower morning cortisol levels and elevated afternoon cortisol levels, resulting in flatter circadian variation and greater daily output of cortisol. Furthermore, chronic stress is associated with smaller cortisol response to the dexamethasone suppression test,

suggesting the development of glucocorticoid resistance [24,25]. HPA axis hyperactivity may be due to stimulatory influences of the amygdala on the paraventricular nucleus of the hypothalamus [14] but also to elevated inflammation levels [26]. If chronic stress persists over extended periods, HPA axis hyperactivity may recede or even to fall below normal levels [23].

In the immune system, chronic exposure to psychosocial stressors leads to enduring elevation in inflammation levels [27]. The elevation in inflammation levels is presumably due to the chronic or repeated stimulation of the sympathetic nervous system [15], as well as to the progressive down-regulation of key anti-inflammatory pathways, such as the HPA axis [24,28] and the parasympathetic nervous system [29,30]. In addition to elevated inflammation levels, chronic stress exposure has been associated with impaired cell-mediated acquired immunity [31,32].

By inducing physiological abnormalities across allostatic systems, chronic or repeated stress exposure could lead to age-related disorders.

3. Age-related disease

Allostatic load or overload [5], the ‘wear and tear’ of the allostatic systems, is likely to mediate the effect of chronic stress on medical and psychiatric disorders related to aging.

First, individuals exposed to chronic stressors are at heightened risk of cardiovascular disease [33–35]. Stress-related amygdala hyper-reactivity, elevation in inflammation levels, and metabolic abnormalities may contribute to atherosclerosis progression promoting the development of cardiovascular disease [36,37].

Second, individuals exposed to chronic stressors are at heightened risk of age-related metabolic disorders [38]. Stress-related elevation in inflammation levels and in cortisol secretion may decrease cell sensitivity to insulin promoting the development of metabolic disorders, such as type 2 diabetes and metabolic syndrome [9,39].

Third, individuals exposed to chronic stressors show accelerated cognitive decline [40]. Stress-related elevation in inflammation levels and in cortisol secretion may contribute to neurodegeneration [4,41–44] promoting cognitive decline and dementia.

Finally, individuals exposed to chronic stressors show accelerated cellular aging [45]. Stress-related elevation in inflammation levels and metabolic abnormalities may contribute to telomere erosion [46,47].

4. Child development

In addition to chronic or repeated stressors during life as a mature individual, stressors experienced in sensitive developmental windows may also have enduring influences on allostasis and allostatic load and overload. Adverse childhood experiences could induce significant biological changes in children (biological embedding), modify the maturation and responsiveness of allostatic systems and, thus, exert long-term effects on health.

The nervous, endocrine, and immune systems are not fully matured at birth and show profound changes during childhood. For example, the human brain shows significant age-related changes at least until young adulthood [48]. Longitudinal studies on normally developing children showed that white matter volume generally increases throughout childhood and adolescence. The increase in myelination underlying the changes in white matter volume is thought to increase the speed of neuronal signals and, thus, to improve connections between different brain areas. In contrast, gray matter volume follows an inverted-U trajectory during the first two decades of life. This pattern is thought to result from synaptic pruning, namely the elimination of unstimulated neuronal structures, as well as from the relative increase in myelination (with reduction of the gray-to-white matter ratio after childhood). These maturational processes unfold in different brain regions at different times, matching cognitive

milestones [49]. The maturation of cortical areas has been studied in the greatest detail [50]. The sensorimotor cortex undergoes maturation in the first 2–3 years of life, aiding the acquisition of sensory and motor skills. The parietal and temporal cortical association regions mature within the first decade of life, subserving the acquisition of basic language and spatial attention. Finally, the prefrontal cortex continues maturing well after puberty, supporting the acquisition of executive functions.

Similarly, the immune system undergoes age-dependent maturation after birth. Newborns are protected against infection by maternal antibodies transferred through the placenta and through milk. In addition to this passive immunity, newborns' adaptation in the face of infection relies upon the activity of their *innate* immune system [51]. Innate immune receptors are encoded through the germ line. They have evolved by natural selection to recognize conserved microorganisms' antigens and to enable rapid response against them without any prior contact [52]. However, innate immune receptors can only recognize a limited number of antigens and, thus, trigger limited responses in newborns. During early development, the colonization and infection of the skin, the gastrointestinal tract, and the lungs enable the interaction of microorganisms with T- and B-cells of the *acquired* immune system [53]. Through these interactions, T- and B-cells acquire an extremely varied repertoire of receptors and fine-tune the immune response.

These examples emphasize that child development is shaped by the interplay between genetic and environmental influences. On the one hand, since birth, newborns are thought to have genetically-mediated abilities to process information that is ubiquitous in the environment and shared by all individuals, such as basic perceptual stimuli or antigens from common pathogens (*experience-expectant* information) [54]. Through development, children then acquire the ability to process information that is idiosyncratic or unique to the individual, such as culture-specific vocabulary or antigens from pathogens that are specific to one's environment (*experience-dependent* information) [54]. Despite the risks of immaturity in newborns, evolution may have selected prolonged post-natal development to facilitate adaptation based on childhood experience-dependent information [55].

Consistent with its key adaptive function, experience-dependent information can profoundly modify the maturation of allostatic systems. For example, the extent to which children are exposed to social stimulation influences their predisposition to social communication difficulties at older ages [56]. Similarly, the extent to which children are exposed to infections influences their predisposition to allergic and autoimmune reactions in adult life (i.e., the hygiene hypothesis) [57]. Just like other experience-dependent information, adverse psychosocial experiences in childhood could modify the maturation of allostatic systems to promote adaptation. Like psychosocial adversities in adult life, adverse childhood experiences are likely to signal high levels of environmental threat and to trigger adaptive responses in the nervous, endocrine, and immune systems in children (i.e., allostasis). Unlike psychosocial adversities in adult life, adverse childhood experiences may result in physiological responses that endure long after the initial threat has ceased, thus becoming detrimental (i.e., allostatic load and overload). Allostatic load could therefore mediate the long-term effect of adverse childhood experiences on psychiatric disorders, such as depression and PTSD [58], and on age-related disease [59].

Although adverse childhood experiences may have significant effects on the development of allostatic systems, the extent of these effects is likely to vary across studies and individuals because of at least three reasons. First, the nature of adverse childhood experiences can be very different depending, for example, on the number, the duration, the timing, the type, and the method of assessment of adversities. Second, the response to even very similar adversities can be very different depending on individual characteristics of resilience and vulnerability including genetic background and previous experiences. Finally, although adverse childhood experiences could impact on the development of

multiple allostatic systems (multifinality), other factors can have similar effects (equifinality) thus buffering or potentiating the association between childhood adversities and allostasis or allostatic load.

In the next sections, we will review the brain, endocrine, and immune correlates of a prototypical adverse childhood experience, namely childhood maltreatment, in children and adults.

5. Biological embedding of adverse psychosocial experiences in children: the role of allostasis

5.1. Nervous system

We will consider here neurobiological and behavioral correlates of maltreatment in children [60], focusing on three key brain regions known to be highly sensitive to psychosocial stress; the prefrontal cortex, the amygdala, and the hippocampus [14].

Convergent findings suggest abnormalities in *prefrontal cortex* functioning in maltreated children. In a recent study, a non-clinical sample of substantiated cases of physical maltreatment, maltreated children showed smaller orbitofrontal cortex volume compared to non-maltreated children [61]. Several other studies examined clinical samples of children with maltreatment-related post-traumatic stress disorder (PTSD). Structural brain-imaging studies reported both smaller [62] and larger [63] prefrontal cortex volume, in children with maltreatment-related PTSD compared to non-maltreated children without PTSD. Children with maltreatment-related PTSD showed lower N-acetylaspartate/creatine ratios in the anterior cingulate compared with controls matched for age, race, socioeconomic status, and IQ level, suggesting possible neuronal damage or loss [64]. Children with maltreatment-related PTSD showed neuropsychological profile suggestive of impaired prefrontal cortex functioning including poor performance in card sorting and word list generation tasks, deficit in sustained attention, and impulsivity [65,66]. Children with maltreatment-related PTSD also showed attenuation of frontal EEG asymmetry compared to control children, which was interpreted to suggest abnormal brain development in this area [67]. Studies of institutionalized children reported consistent findings. Compared to community controls, Romanian adoptees showed poorer concentration and higher activity levels [68], which may be partly mediated by EEG abnormalities [69]. Abnormalities in prefrontal cortex functioning were also suggested by the preliminary evidence of lower prefrontal glucose metabolism in Romanian adoptees compared to adult controls [70]. It is unclear whether impairment in prefrontal functioning should be attributed to delayed maturation of the prefrontal cortex, similar to findings in children with attention deficit and hyperactivity disorder [71,72], or to neuronal damage. Notably, deficits in attention regulation and impulse control described in maltreated children could be modified by placements in safe and warm family environments [73].

Studies to date showed some evidence of larger *amygdala* volume among maltreated children. A study of Romanian children adopted by UK families reported that previously institutionalized children had increased amygdala volume compared to non-institutionalized children [74]. A study of Asian and Eastern European children adopted by US families showed increased amygdala volume only in previously institutionalized children who were 15 months or older at the time of adoption compared with non-institutionalized children [75]. Finally, a meta-analysis of four studies did not find evidence of volumetric changes in the amygdala of children with maltreatment-related PTSD compared to controls [76].

There has been no clear evidence of changes in *hippocampus* volume among maltreated children. One study showed that hippocampus volume was negatively correlated with early life adversities (including maltreatment) in adolescents with and without a family history of depression [77]. In contrast, a meta-analysis of four studies suggested that children with maltreatment-related PTSD did not

show volumetric changes in the hippocampus compared to non-maltreated children without PTSD [76]. In addition, post-institutionalized children did not show volumetric changes in hippocampus volume compared to non-institutionalized controls [74,75].

5.2. Endocrine system

Several studies have explored the effects of maltreatment on the HPA axis in children, including basal functioning, response to psychosocial stress tasks, and response to pharmacological stimulation with corticotrophin-releasing hormone (CRH) [78].

Maltreated children tend to have elevated basal cortisol levels suggestive of chronic activation of the HPA axis. Maltreated children with significant emotional problems showed higher morning, afternoon, and average daily cortisol levels across 1 week [79]. Children with maltreatment-related PTSD showed higher 24-hour urinary free cortisol and daily salivary cortisol levels compared to non-maltreated children without PTSD [80,81]. Romanian adoptees, and particularly those who spent longer time in orphanages, exhibited elevated cortisol levels averaged during the day [82]. Some [83] but not all [84] studies showed that post-institutionalized children might have flatter circadian variation in cortisol levels compared to non-institutionalized children.

In addition to chronic HPA axis activation, maltreated children often exhibit blunted neuroendocrine response to laboratory psychosocial stress tasks, and a blunted HPA response is identified as one of the subtypes of response associated with allostatic load [12]. Children with substantiated maltreatment experiences and no prior psychopathology showed a blunted cortisol response to the Trier Social Stress Test, a psychosocial stress task involving public speaking and mental arithmetical calculation [85]. Furthermore, a sample of maltreated and bullied children from the Environmental Risk (E-Risk) Longitudinal Twin Study showed blunted cortisol response to a psychosocial stress task involving mental arithmetical calculation and public speaking/emotion elicitation [86]. Interestingly, cortisol response to psychosocial stressors was negatively correlated with behavioral problems [87] but was not associated with emotional symptoms [85,87] in maltreated children.

It is possible that the blunted cortisol response to psychosocial stressors in the context of a chronic neuroendocrine activation could be due to a compensatory down-regulation of the central negative feedback mechanism regulating the HPA axis. Consistent with this hypothesis, sexually abused children exhibited blunted ACTH response and normal cortisol response to pharmacological challenge with CRH [88], indicating pituitary hyporesponsiveness to CRH and/or increased glucocorticoid receptor sensitivity to cortisol. However, maltreated children with established depression diagnosis did not show this pituitary down-regulation, and instead exhibited heightened ACTH response to pharmacological challenge with CRH [89] and heightened cortisol response to a psychosocial stress task.

Notably, the neuroendocrine changes described in maltreated children could be modified by placements in safe and warm family environments or by improving family interaction. A family-based therapeutic intervention for fostered preschoolers was effective in increasing morning cortisol levels and diurnal variation in cortisol levels [90]. Furthermore, a parenting program targeting at-risk preschoolers (younger siblings of adjudicated youths) was effective in increasing cortisol response to entry into an unfamiliar peer group [91].

5.3. Immune system

The sensitivity of the developing immune system to childhood psychosocial experiences was initially emphasized by the findings that children exposed to even transient stressful experiences, such as the separation from parents at the beginning of kindergarten, showed significant changes in immune functioning [92]. This

evidence was consistent with studies in adult individuals reporting stress-induced potentiation of inflammation [15,27,93] and impairment in acquired immune response [31,32]. Despite this important early insight, only recently psychobiological studies have started exploring immune system changes in children exposed to adverse psychosocial experiences.

Our team has reported initial evidence of *innate* immune system changes in young people exposed to adverse psychosocial experiences [94]. We observed elevated levels of C-Reactive Protein (CRP), a biomarker of inflammation, in 12-year old children exposed to physical abuse and experiencing current depression. Group differences could not be explained by potential confounders, such as family socio-economic circumstances, obesity, or body temperature.

Stress-related elevation in CRP levels in maltreated children could be an adaptive strategy to prepare the body to face possible physical injury [95]. CRP is a component of the humoral *innate* immune system and facilitates recognition of pathogens and their killing through the activation of complement or the recruitment of macrophages and neutrophils (equivalent to an antibody in the *acquired* immune system) [96,97]. This first line of defense may however be insufficient for pathogen clearance [98,99]. Innate immune mediators therefore also orchestrate the activation of a delayed yet more specific response by the *acquired* immune system. The extent and duration of pro-inflammatory cytokines secretion influence the functional orientation and the strength of the acquired immune response, so that elevated or prolonged secretion of pro-inflammatory cytokines potentiates rapid *acquired* immune response (T-effector cells) at the cost of long-term protection (T-memory cells) [100,101]. Despite providing protection in acute conditions, elevated inflammation levels observed in some maltreated children may therefore be associated with limited protection in the face of chronic infections, such as latent herpes simplex virus (HSV) infections [102].

Consistent with this hypothesis, both post-institutionalized children living in adoptive homes and children with substantiated cases of physical abuse still residing within their families showed elevated secretory IgA for HSV compared to controls, indicating impaired acquired immune response [103]. Group differences were not accounted for by age, gender, race, family socio-economic status, child body-mass index, or child chronic medical problems. These findings suggest that children exposed to adverse psychosocial experiences have impaired acquired immune response in the face of chronic/latent infections, possibly as a result of chronically elevated inflammation levels.

5.4. Comments

The most consistent neurobiological and behavioral findings in children exposed to adverse psychosocial experiences seem to be linked to impaired prefrontal cortex functioning. Maltreated children tend to show smaller prefrontal cortex volume, deficits in executive function, and behavioral problems with rapidly shifting attention, impulsiveness, and increased motor activity. It is possible that some maltreated children may have enlarged amygdala volume, although findings have been inconsistent. Notably, work so far did not identify changes in hippocampal volume in maltreated vs non-maltreated children.

Neuroendocrine findings suggested that maltreated children exhibit chronic activation of the HPA axis and blunted response to psychosocial stressors. This may be due to a compensatory pituitary hyporesponsiveness to CRH and/or increased glucocorticoid receptor sensitivity to cortisol observed in some maltreated children.

Immunological findings in maltreated children point to elevated inflammation levels, which may provide immediate protection in the face of acute tissue damage but could be associated with reduced protection in the face of chronic or latent infections.

The above summary is a necessarily simplistic account of heterogeneous findings in the field. Further research will be necessary to understand the role of potential intervening variables, such as comorbid psychiatric disorders, age, and genetic background in explaining the heterogeneity of the research base. For example, several studies reviewed above compared children with maltreatment-related PTSD to non-maltreated children without PTSD, therefore hampering conclusions about the relative contribution of maltreatment and PTSD on allostatic systems. Nevertheless, there are common themes emerging from the examination of the different allostatic systems in maltreated children.

Maltreated children appear to perceive the environment as unpredictable and threatening. Consistent with changes described in adults exposed to psychosocial stressors [23], maltreated children tend to have elevated basal cortisol levels. Despite the elevated cortisol levels, some maltreated children also exhibit elevated inflammation levels, similar to changes described in adults exposed to psychosocial stressors [27,93]. The increase in inflammation levels could be due both to repeated stimulation of the sympathetic nervous system [15] and to progressive impairment in glucocorticoid signaling [23,24]. Furthermore, elevated inflammation levels may be causing HPA axis hyperactivity [26]. Notably, maltreated children who are given the opportunity to experience safe and warm environments show normalized HPA axis functioning [90,91], suggesting that physiological changes linked to maltreatment are reversible in childhood.

Maltreated children adopt coping strategies that may improve adaptation in the context of an unpredictable and threatening environment. Changes in allostatic systems should be understood based on the ecological context in which maltreated children live. The neurobiological and behavioral correlates of maltreatment, such as rapidly shifting attention, impulsiveness, and increased motor activity could be advantageous strategies when threats are frequent and unexpected, and rapid reactions could be vital for survival [104]. Furthermore, chronic elevation in cortisol levels could support the increased metabolic demands by mobilizing stored energy. Finally, elevation in inflammation levels may prepare the body to face physical injuries. Because of the unpredictable and threatening context, the allostatic changes described in maltreated children could promote adaptation to the environment and, thus, be beneficial in the short-term [105].

Maltreated children adopt strategies that could be detrimental in the longer term. The context-dependent shift to short-term strategies could prevent maltreated children to achieve longer-term objectives. Despite the adaptive advantages emphasized above, changes in allostatic systems described in maltreated children may be detrimental for child development. Rapidly shifting attention, impulsiveness, and increased motor activity could impair key learning processes, such as emotion regulation, education, and socialization [106], resulting in negative enduring effects on health, wealth, and criminality [107]. Chronic elevation in cortisol levels could lead to important metabolic imbalances, promoting obesity [108]. Elevated inflammation levels in childhood may influence the functional orientation of immune system development, potentiating rapid and nonspecific immune responses at the cost of poorer long-term protection in the face of chronic infections [94,103].

6. Long-term effects of adverse childhood experiences in adult individuals: the role of allostatic load

6.1. Nervous system

Consistent with the evidence in children, adults with a history of childhood maltreatment also showed smaller *prefrontal cortex* volume. In a non-clinical sample, adults with a history of childhood harsh corporal punishment showed smaller volume in the left dorsolateral and the right medial prefrontal cortex [109]. In a different non-clinical sample, adults who experienced greater levels of childhood stress including

maltreatment showed smaller volume in the anterior cingulate cortex [110]. Furthermore, maltreated adult individuals showed smaller medial prefrontal cortex regardless of symptoms of depression or anxiety [111]. Finally, depressed patients with a history of childhood maltreatment showed smaller volume in the rostral anterior cingulate cortex, with a larger reduction in patients with greater exposure to childhood maltreatment [112].

Studies to date showed some evidence of smaller *amygdala* volume among adults with a history of childhood maltreatment. In a non-clinical sample, early adversities appeared to interact with BDNF genotype in predicting smaller amygdala volume [113]. Patients with borderline personality disorder and a history of childhood maltreatment showed smaller amygdala volume than controls [114,115]. Patients with dissociative disorder and a history of childhood maltreatment showed smaller amygdala volume than a control group [116]. Brain imaging findings may be associated with abnormal function of the amygdala, as suggested by evidence of increased startle reactivity in maltreated vs non-maltreated individuals [117]. However, other studies found no differences in amygdala volume in maltreated vs non-maltreated individuals. In a non-clinical sample, adults who experienced childhood stress including maltreatment did not show changes in amygdala volume compared to controls [110]. Furthermore, adult patients with maltreatment-related PTSD did not show smaller amygdala volume than healthy controls [118].

Several studies reported reduced *hippocampus* volume in adults with a history of childhood maltreatment [119]. Most [113,120,121] but not all [110] studies in non-clinical samples reported smaller hippocampal volume in adults with a history of childhood maltreatment compared to non-maltreated individuals. Few studies investigated hippocampus volume in adult patients with PTSD and a history of childhood maltreatment. Most [118,122] but not all [123] studies reported smaller hippocampus volume in adult patients with maltreatment-related PTSD versus healthy controls, leading to meta-analytic evidence of smaller hippocampus volume in this population [76]. Adult individuals with maltreatment-related PTSD also showed deficits in declarative memory [124]. Depressed patients with a history of childhood maltreatment showed smaller hippocampus than both depressed patients without a history of childhood maltreatment and non-maltreated/non-depressed individuals [125]. Patients with borderline personality disorder showed smaller hippocampus volume than controls, and hippocampus volume negatively correlated with the exposure to childhood maltreatment in this population [114,115]. Finally, patients with dissociative disorder and a history of childhood maltreatment showed smaller hippocampus volume than a control group [116].

6.2. Endocrine system

Consistent with the evidence in children, adults with a history of childhood maltreatment also showed chronic activation of the HPA axis. For example, depressed and non-depressed adults who reported high levels of distress in preschool years including experiences of childhood maltreatment showed high CRH levels in the cerebrospinal fluid [126]. The downstream effects of CRH hyperactivity are heterogeneous and may be moderated by the presence or absence of current psychopathology.

Research has been undertaken in adult individuals with a history of childhood maltreatment but no current psychopathology in order to identify neuroendocrine changes underlying resilience in the face of childhood adversities. 'Resilient' adults showed HPA axis changes comparable to those observed in maltreated children without psychiatric disorders. For example, adults with a history of childhood maltreatment but no current depression or PTSD showed blunted ACTH and cortisol response to the Trier Social Stress Test compared to non-maltreated controls [127]. Furthermore, adults with a history of childhood maltreatment but no current psychiatric diagnosis showed

blunted ACTH and cortisol response to pharmacological challenge with the dexamethasone/CRH test, indicating pituitary hyporesponsiveness to CRH and/or increased glucocorticoid receptor sensitivity [128].

Research on adult individuals with a history of childhood maltreatment and current psychopathology led to opposite findings. Similar to the evidence in maltreated and depressed children [89,129], findings in adults with a history of childhood maltreatment and current psychopathology suggest an impairment in the compensatory mechanisms for CRH hyperactivity. For example, adults with a history of childhood maltreatment and current depression showed greater ACTH and cortisol response to the Trier Social Stress Test compared to non-maltreated and non-depressed controls [130]. In addition, adults with a history of childhood maltreatment and current depression showed greater ACTH and cortisol response to pharmacological challenge with the dexamethasone/CRH test [131]. Heightened responsiveness to the dexamethasone/CRH test was also reported in adults with a history of childhood maltreatment and diagnosis of borderline personality disorder [132]. These findings suggest that adults with a history of childhood maltreatment and current psychopathology show pituitary hyperresponsiveness to CRH and/or reduced glucocorticoid receptor sensitivity.

It is remarkable that adults with current psychopathology but without a history of childhood maltreatment did not appear to show significant HPA axis abnormalities. For example, non-maltreated depressed individuals showed comparable HPA axis response to the Trier Social Stress Test and to the dexamethasone/CRH test to control individuals [130,131]. As such, the HPA axis abnormalities observed in depressed and maltreated individuals are unlikely to simply represent a correlate of depression in maltreated adults. In contrast, elevation in cortisol levels and impaired compensatory mechanisms, such as pituitary hyper-responsiveness to CRH and/or reduced glucocorticoid receptor sensitivity, may contribute to increasing the risk of depression in maltreated individuals [24,25,133].

6.3. Immune system

Consistent with the evidence in children, adults with a history of childhood maltreatment also showed elevated inflammation levels. Our team tested the association between a prospectively-collected measure of childhood maltreatment and circulating inflammation biomarkers at age 32 years among participants to the Dunedin Multidisciplinary Health and Development Study. Children who had been exposed to maternal rejection, harsh parenting, disruptive caregiver changes, physical abuse or sexual abuse were more likely than non-maltreated children to show greater levels of multiple clinically-relevant inflammation biomarkers, such as C-reactive protein, fibrinogen, white blood cell count, in adulthood [134]. Consistent with the HPA axis abnormalities described above, the effect of childhood maltreatment on inflammation biomarkers was accentuated in adult individuals with current depression diagnosis. Furthermore, adult individuals with current depression diagnosis but no maltreatment history only showed a non-significant increase in inflammation biomarkers [135]. These observations were consistent with reports from other epidemiological studies. Among adult participants to the EPIC-Norfolk Study, reports of childhood maltreatment were associated with elevated white blood cell count at two subsequent waves of assessment [136]. Among black, but not white, adult participants to the MIDUS survey, reports of early life adversities were associated with elevated levels of interleukin-6, fibrinogen, endothelial leukocyte adhesion molecule-1, and soluble intercellular adhesion molecule-1 [137]. Furthermore, among an old-age group of caregivers, reports of childhood maltreatment were associated with elevated levels of interleukin-6 and tumor necrosis factor- α regardless of the major chronic stressor of dementia family care-giving [138].

Adult individuals with a history of childhood maltreatment showed not only elevated baseline inflammation levels but also

greater inflammatory response to psychosocial stress. Compared to non-depressed individuals, patients with major depression and increased early life stress showed greater interleukin-6 secretion and NF- κ B DNA-binding in response to the Trier Social Stress Test [139]. Moreover, 'resilient' adult individuals with a history of childhood maltreatment but no current psychopathology showed greater interleukin-6 secretion and maximum interleukin-6 concentration in response to the Trier Social Stress Test [140].

Chronic elevation in inflammation levels may disrupt acquired immune system functioning by potentiating rapid acquired immune response (effector cells) at the cost of long-term protection (memory cells) [100,101]. Consistent with this hypothesis, adults with a history of childhood maltreatment and current PTSD diagnosis showed higher percentage of effector cells and lower percentage of memory cells compared to controls [141]. Furthermore, adults with a history of childhood maltreatment and current PTSD diagnosis showed greater delayed-type hypersensitivity than control individuals [142], a phenomenon mediated by antigen-specific effector T cells in the skin [143].

6.4. Comments

Adults with a history of childhood maltreatment showed smaller prefrontal cortex volume, which may be related to deficit in executive function [144]. Some but not all studies suggested that maltreated individuals might exhibit smaller amygdala volume and increased startle response than non-maltreated individuals. Perhaps the most consistent neurobiological finding in adults with a history of childhood maltreatment was the reduction in hippocampal volume with associated deficit in declarative memory.

Neuroendocrine findings in maltreated adults appeared to vary according to the presence or absence of concurrent psychiatric disorders. On the one hand, maltreated individuals with no current psychiatric disorder exhibited chronic activation of the HPA axis and blunted response to psychosocial stressors, presumably due to compensatory pituitary hyporesponsiveness to CRH and/or increased glucocorticoid receptor sensitivity to cortisol. On the other hand, maltreated individuals with current psychiatric disorders exhibited chronic activation of the HPA axis and heightened response to psychosocial stressors, presumably due to impairment in the above compensatory mechanisms.

Immunological studies suggested that adults with a history of childhood maltreatment showed elevated basal levels of inflammation biomarkers, which were greatest in those with concurrent psychopathology. In addition to chronic baseline elevation in inflammation levels, maltreated adults also showed greater inflammatory response in the face of laboratory psychosocial stressors. Heightened inflammation levels appeared to be accompanied by a switch in the adaptive immune system, favoring rapid acquired immune response at the cost of impaired long-term protection, as manifested by an increased effector/memory cell ratio and greater delayed-type hypersensitivity in maltreated individuals.

There are some important differences between findings in allostatic systems of children and adults who experienced maltreatment. Although amygdala volume seemed to be increased in maltreated children, amygdala volume was normal or decreased in adults with a history of maltreatment. The apparent transient nature of amygdala abnormalities might be due to earlier maturation of the amygdala compared to cortical areas (e.g., prefrontal cortex) [145] and, thus, to the limited ability of childhood psychosocial experiences to influence its maturation and long-term changes. Furthermore, although hippocampus volume seemed to be unaffected in maltreated children, hippocampus volume was decreased in adults with a history of childhood maltreatment. The apparent progressive nature of hippocampus abnormalities in maltreated individuals might be due to cumulative damage owing to enduring exposure to glucocorticoids

Table 1

Summary of the brain, endocrine and immune correlates of childhood maltreatment in children and adult individuals.

	Children	Adults
Brain	Prefrontal cortex. Smaller volume. Poorer executive functions Amygdala. Possibly larger volume. Hippocampus. No changes Behavior. Poorer attention, greater activity levels, impaired emotion regulation and self-regulatory behaviors	Prefrontal cortex. Smaller volume. Amygdala. Possibly smaller volume. Greater startle response Hippocampus. Smaller volume. Deficit in declarative memory. Behavior. Depression, PTSD, substance abuse
HPA axis	Basal levels. Higher cortisol levels. Flatter cortisol profile TSST. Blunted cortisol response Pharmacological stimulation. Blunted ACTH response and normal cortisol response to CRH test (heightened ACTH response in depressed + maltreated)	Basal levels. Higher CRH levels TSST. Blunted (no mental illness) or heightened (with mental illness) cortisol response Pharmacological stimulation. Blunted (no mental illness) or heightened (with mental illness) ACTH and cortisol responses to DEX/CRH test
Immune system	Innate immunity. Elevated inflammation levels (in depressed + maltreated) Acquired immunity. Poorer response to latent HSV infection	Innate immunity. Elevated inflammation levels Acquired immunity. High T-cytotoxic/T-helper ratio. Greater type-IV hypersensitivity response

or inflammation mediators [20,22]. In turn, the progressive hippocampus damage could contribute to increasing risk of depression and PTSD in adult individuals with a history of childhood maltreatment [146].

Strikingly, there are several similarities between findings in allostatic systems of children and adults who experienced maltreatment. Both maltreated children and maltreated adults showed structural and functional abnormalities in the prefrontal cortex. These abnormalities may be linked to behavioral disorders described in this population, such as deficits in attention, impulsivity, hyperactivity, substance abuse, conduct problems, and antisocial behavior [147]. These neurobiological abnormalities may also be linked to impairment in top-down emotional regulation leading to depression and post-traumatic stress disorder [58]. Furthermore, both maltreated children and maltreated adults showed high basal levels of HPA axis mediators presumably indicative of high levels of perceived threat. The ability of the HPA axis to adapt to this overload may depend upon the presence or absence of psychopathology, such as depression or PTSD. Finally, both maltreated children and adults appeared to show elevated levels of inflammation and switch to more immediate adaptive immune response. Despite the clear limitations in making longitudinal claims from cross-sectional studies [148], work so far suggests that adverse childhood experiences are associated with enduring changes in allostatic systems that are already observable in childhood years and remain apparent in adult life.

The similarities between findings in allostatic systems of children and adults who experienced maltreatment are striking because they seem to persist regardless of the changes in their environment. Years after maltreatment had ceased, adults with a history of childhood maltreatment still showed significant changes in allostatic systems. These changes appeared to be independent of objective and subjective measures of adult stress exposure [134], suggesting that they were not simply due to continuities in risky environments between childhood and adult life. When activated chronically and out of context, allostasis ceases to be adaptive, may lead to allostatic load, and, thus, may promote disease as maltreated individuals age.

7. Adverse childhood experiences and age-related disease

Adverse childhood experiences predict adult neurobiological, metabolic, and immune changes related to the development of age-related disease. For example, findings from the Dunedin study showed that childhood maltreatment, childhood socio-economic disadvantage, and childhood social isolation predicted elevated risk of depression, clustering of metabolic risk factors, and elevated inflammation levels in adult life [59]. The effects of adverse psychosocial experiences in childhood were independent of several other established risk factors for age-related disease. Because of their independent and

cumulative effects on multiple allostatic systems, adverse childhood experiences could lead to age-related disease.

Consistent with this prediction, several studies have reported associations between adverse childhood experiences and chronic/age-related conditions. A series of classic papers from the Adverse Childhood Experiences (ACE) Study started a prolific area of investigation by uncovering the link between retrospective reports of childhood adversities and risk for age-related disease including cardiovascular disease and type-2 diabetes in individuals from a health maintenance organization [149]. These findings have been consistently replicated in several independent samples [150] and have been supported by longitudinal observations [151,152].

The association between adverse childhood experiences and age-related disease is also supported by the initial evidence of accelerated biological aging in maltreated individuals. Adults with a history of childhood maltreatment showed reduced telomere length compared to non-maltreated individuals in most [153–156], but not all studies [157].

8. Conclusion and future directions

Adverse childhood experiences appeared to be associated with changes in the nervous, endocrine, and immune systems in children and adults (see Table 1). Previous research showed that experiences during child development (experience-dependent information) could influence maturational processes and, thus, exert long-term effects. For example, childhood social experiences influence adult social functioning [56], and childhood infection influence adult immune functioning [57]. Cross-effects between allostatic systems are also likely to occur. For example, experimental work in animal models showed that childhood infection influences adult behavior, HPA axis activity, and immune system functioning [158,159]. Here we reviewed research suggesting that stressful experiences in childhood may induce significant biological changes (biological embedding) and, thus, influence the physiological response to stress in adult life.

In the same way as changes in allostatic systems maintain stability of key bodily functions in the face of stressful experiences in adulthood [14], these changes could also contribute to the adaptation to adverse childhood experiences. This may be true up to a point as long as there are support systems for a child that help buffer early life adversity and keep the stress “tolerable” as opposed to “toxic”. Indeed, toxic stress, which includes the most severe forms of childhood adversity as well as lack of adequate buffering, results in profound functional impairment associated with harmful consequences on health and wealth throughout the life-course.

When are physiological responses to adverse childhood experiences protective and when do they become damaging? A tentative answer involves consideration of context, priorities, and timing. The

context in which the physiological response to stress has evolved was rich in physical threats to survival, which have significantly decreased over the past few centuries [160]. The priorities that have shaped the physiological responses to stress throughout evolution are survival and reproduction, and not academic achievement or healthy aging [161]. Therefore, to the extent that adverse childhood experiences involve frequent and unpredictable threats to survival, changes in allostatic systems in children may represent adaptive strategies reflecting those ancient priorities. However, as the context becomes less noxious and priorities shift from immediate to long-term goals, changes in allostatic systems may become detrimental. Finally, context and priorities vary over time [162–164]. Changes in allostatic system that may promote adaptation to psychosocial adversities in childhood are likely to be unnecessary and potentially detrimental if they persist years after the original threat has ceased.

In order to better characterize the effects of adverse childhood experiences on allostasis, allostatic load, and age-related disease, future research may consider the following recommendations. First, to improve the generalizability of research findings, biological correlates of adverse childhood experiences should be explored in large population-representative samples. As such, it will be important to develop and validate new techniques that enable researchers to collect biological samples in the community [165,166]. Second, because of the limitations of longitudinal claims based on cross-sectional studies [148], it will be important to promote efforts involving repeated collection of biological data in longitudinal studies. Third, because adverse childhood experiences are not randomly distributed in the population and often accompany exposure to other risk factors, future research should strive to conceptualize and test relevant alternative hypotheses [167]. Fourth, because of the fragmentation in the data so far, future studies should aim to directly test mediation hypotheses by measuring childhood adversities, biomarkers, and clinical outcomes in the same individuals. Fifth, to characterize the heterogeneity of current research findings, it will be important to explore resilience and vulnerability factors, such as genes and psychopathology [59,135,168,169]. Sixth, because the nervous, endocrine, and immune systems are highly integrated, changes in allostatic systems should be assessed simultaneously in the same samples. Seventh, to clarify the molecular mechanisms converting psychosocial stress exposure in childhood in biological risk for disease, future research should broaden the emerging evidence relating adverse childhood experiences to changes in epigenetic states and gene expression [170,171]. Finally, in order to minimize the detrimental, long-term effects of adverse childhood experiences on health, it will be important to test if interventions targeting the behavioral sequelae of childhood maltreatment could also reduce related abnormalities in the endocrine and the immune systems. A better understanding of the effects of adverse childhood experiences on allostasis, allostatic load, and age-related disease will inform the development of innovative preventive and therapeutic strategies [172].

Acknowledgments

Dr. Andrea Danese is supported by a Brain & Behavior Research Foundation/NARSAD Young Investigator Award. Dr. Bruce McEwen acknowledges the National Scientific Council on the Developing Child.

References

- McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. *Arch Intern Med* 1993;153(18):2093–101.
- McEwen BS, Gianaros PJ. Stress- and allostasis-induced brain plasticity. *Annu Rev Med* 2010;62:431–45.
- McEwen BS, Gianaros PJ. Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. *Ann N Y Acad Sci* 2010;1186:190–222.
- Seeman T, Epel E, Gruenewald T, Karlamangla A, McEwen BS. Socio-economic differentials in peripheral biology: cumulative allostatic load. *Ann N Y Acad Sci* 2010;1186:223–39.
- McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. *Horm Behav* 2003;43(1):2–15.
- Guyton A. *Textbook of medical physiology*. In: Hall JE, editor. 12 ed. Saunders; 2010. p. 1120.
- Sterling PE. Allostasis: a new paradigm to explain arousal pathology. In: Fisher SRJ, editor. *Handbook of life stress, cognition and health*. New York: John Wiley; 1988. p. 629–49.
- Medzhitov R. Origin and physiological roles of inflammation. *Nature* 2008;454(7203):428–35.
- Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006;444(7121):860–7.
- Straub RH. Concepts of evolutionary medicine and energy regulation contribute to the etiology of systemic chronic inflammatory diseases. *Brain Behav Immun* 2011;25(1):1–5.
- Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 2008;9(1):46–56.
- McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998;338(3):171–9.
- LeDoux JE. Emotion circuits in the brain. *Annu Rev Neurosci* 2000;23:155–84.
- McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev* 2007;87(3):873–904.
- Bierhaus A, Wolf J, Andrassy M, Rohleder N, Humpert PM, Petrov D. A mechanism converting psychosocial stress into mononuclear cell activation. *Proc Natl Acad Sci* 2003;100(4):1920–5.
- Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci* 2009;10(6):397–409.
- Kirschbaum C, Pirke KM, Hellhammer DH. The 'trier social stress test'—a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology* 1993;28(1–2):76–81.
- Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol Bull* 2004;130(3):355–91.
- McEwen BS. Protective and damaging effects of stress mediators: central role of the brain. *Dialogues Clin Neurosci* 2006;8(4):367–81.
- Sapolsky RM, Krey LC, McEwen A, Bruce S. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocr Rev* 1986;7(3):284–301.
- Marsland AL, Gianaros PJ, Abramowitch SM, Manuck SB, Hariri AR. Interleukin-6 covaries inversely with hippocampal grey matter volume in middle-aged adults. *Biol Psychiatry* 2008;64(6):484–90.
- Koo JW, Duman RS. IL-1 is an essential mediator of the antineurogenic and anhedonic effects of stress. *Proc Natl Acad Sci* 2008;105(2):751–6.
- Miller GE, Chen E, Zhou ES. If it goes up, must it come down? Chronic stress and the hypothalamic–pituitary–adrenocortical axis in humans. *Psychol Bull* 2007;133(1):25–45.
- Raison CL, Miller AH. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am J Psychiatry* 2003;160(9):1554–65.
- Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology* 2008;33(6):693–710.
- Besedovsky H, del Rey A, Sorkin E, Dinarello C. Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science* 1986;233(4764):652–4.
- Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine il-6. *Proc Natl Acad Sci U S A* 2003;100(15):9090–5.
- Chrousos GP. The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. *N Engl J Med* 1995;332(20):1351–63.
- Tracey KJ. The inflammatory reflex. *Nature* 2002;420(6917):853–9.
- Thayer JF, Sternberg EM. Neural aspects of immunomodulation: focus on the vagus nerve. *Brain Behav Immun* 2010;24(8):1223–8.
- Cohen S, Tyrrell DA, Smith AP. Psychological stress and susceptibility to the common cold. *N Engl J Med* 1991;325(9):606–12.
- Glaser R, Rabin B, Chesney M, Cohen S, Natelson B. Stress-induced immunomodulation: implications for infectious diseases? *JAMA* 1999;281(24):2268–70.
- Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999;99(16):2192–217.
- Jones DJ, Bromberger JT, Sutton-Tyrrell K, Matthews KA. Lifetime history of depression and carotid atherosclerosis in middle-aged women. *Arch Gen Psychiatry* 2003;60(2):153–60.
- Kendler KS, Gardner CO, Fiske A, Gatz M. Major depression and coronary artery disease in the Swedish twin registry: phenotypic, genetic, and environmental sources of comorbidity. *Arch Gen Psychiatry* 2009;66(8):857–63.
- Libby P. Inflammation in atherosclerosis. *Nature* 2002;420(6917):868–74.
- Gianaros PJ, Hariri AR, Sheu LK, Muldoon MF, Sutton-Tyrrell K, Manuck SB. Preclinical atherosclerosis covaries with individual differences in reactivity and functional connectivity of the amygdala. *Biol Psychiatry* 2009;65(11):943–50.
- Chandola T, Brunner E, Marmot M. Chronic stress at work and the metabolic syndrome: prospective study. *BMJ* 2006;332(7540):521–5.
- Rosmond R. Role of stress in the pathogenesis of the metabolic syndrome. *Psychoneuroendocrinology* 2005;30(1):1–10.

- [40] Peavy GM, Salmon DP, Jacobson MW, Hervey A, Gamst AC, Wolfson T, et al. Effects of chronic stress on memory decline in cognitively normal and mildly impaired older adults. *Am J Psychiatry* 2009;166(12):1384–91.
- [41] Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, Kerr S, et al. Systemic inflammation and disease progression in Alzheimer disease. *Neurology* 2009;73(10):768–74.
- [42] Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, et al. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat Neurosci* 1998;1(1):69–73.
- [43] Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. *Nature* 2010;464(7288):529–35.
- [44] Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. *Cell* 2010;140(6):918–34.
- [45] Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, et al. Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci U S A* 2004;101(49):17312–5.
- [46] Epel E. 'Psychobiomarkers' of aging: insights from the telomere/telomerase maintenance system. *Psychophysics* 2006;43:S4–5.
- [47] Wolkowitz OM, Mellon SH, Epel ES, Lin J, Dhabhar FS, Su YL, et al. Leukocyte telomere length in major depression: correlations with chronicity, inflammation and oxidative stress – preliminary findings. *PLoS One* 2011;6(3).
- [48] Giedd JN, Rapoport JL. Structural MRI of pediatric brain development: What have we learned and where are we going? *Neuron* 2010;67(5):728–34.
- [49] Casey BJ, Galvan A, Hare TA. Changes in cerebral functional organization during cognitive development. *Curr Opin Neurobiol* 2005;15(2):239–44.
- [50] Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A* 2004;101(21):8174–9.
- [51] Levy O. Innate immunity of the newborn: basic mechanisms and clinical correlates. *Nat Rev Immunol* 2007;7(5):379–90.
- [52] Medzhitov R, Janeway Jr C. Innate immunity. *N Engl J Med* 2000;343(5):338–44.
- [53] Adkins B, Leclerc C, Marshall-Clarke S. Neonatal adaptive immunity comes of age. *Nat Rev Immunol* 2004;4(7):553–64.
- [54] Greenough WT, Black JE, Wallace CS. Experience and brain development. *Child Dev* 1987;58(3):539–59.
- [55] Bateson P, Barker D, Clutton-Brock T, Deb D, D'Udine B, Foley RA, et al. Developmental plasticity and human health. *Nature* 2004;430(6998):419–21.
- [56] Rutter M, Kreppner J, Croft C, Murin M, Colvert E, Beckett C, et al. Early adolescent outcomes of institutionally deprived and non-deprived adoptees. III. Quasi-autism. *J Child Psychol Psychiatry* 2007;48(12):1200–7.
- [57] J-Fo Bach. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002;347(12):911–20.
- [58] Nanni V, Uher, R, Danese, A. Childhood maltreatment predicts unfavourable course of illness and treatment outcome in depression: A meta-analysis. *Am J Psychiatry* 2011, doi:10.1176/appi.ajp.2011.11020335.
- [59] Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, Pariante CM, et al. Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. *Arch Pediatr Adolesc Med* 2009;163(12):1135–43.
- [60] McCrory E, De Brito SA, Viding E. Research review: The neurobiology and genetics of maltreatment and adversity. *J Child Psychol Psychiatry* 2010;51(10):1079–95.
- [61] Hanson JL, Chung MK, Avants BB, Shirtcliff EA, Gee JC, Davidson RJ, et al. Early stress is associated with alterations in the orbitofrontal cortex: a tensor-based morphometry investigation of brain structure and behavioral risk. *J Neurosci* 2010;30(22):7466–72.
- [62] De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Beers SR, Hall J, et al. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. *Biol Psychiatry* 2002;52(11):1066–78.
- [63] Carrion VG, Weems CF, Watson C, Eliez S, Menon V, Reiss AL. Converging evidence for abnormalities of the prefrontal cortex and evaluation of midsagittal structures in pediatric posttraumatic stress disorder: an MRI study. *Psychiatry Res* 2009;172(3):226–34.
- [64] De Bellis MD, Keshavan MS, Spencer S, Hall J. N-Acetylaspartate concentration in the anterior cingulate of maltreated children and adolescents with PTSD. *Am J Psychiatry* 2000;157(7):1175–7.
- [65] Beers SR, De Bellis MD. Neuropsychological function in children with maltreatment-related posttraumatic stress disorder. *Am J Psychiatry* 2002;159(3):483–6.
- [66] Pine DS, Mogg K, Bradley BP, Montgomery L, Monk CS, McClure E, et al. Attention bias to threat in maltreated children: implications for vulnerability to stress-related psychopathology. *Am J Psychiatry* 2005;162(2):291–6.
- [67] Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD, et al. Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. *Biol Psychiatry* 2001;50(12):943–51.
- [68] Rutter M, O'Connor TG. Are there biological programming effects for psychological development? Findings from a study of Romanian adoptees. *Dev Psychol* 2004;40(1):81–94.
- [69] McLaughlin KA, Fox NA, Zeanah CH, Sheridan MA, Marshall P, Nelson CA. Delayed maturation in brain electrical activity partially explains the association between early environmental deprivation and symptoms of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2010;68(4):329–36.
- [70] Chugani HT, Behen ME, Muzik O, Juhász C, Nagy F, Chugani DC. Local brain functional activity following early deprivation: a study of postinstitutionalized Romanian orphans. *Neuroimage* 2001;14(6):1290–301.
- [71] Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci U S A* 2007;104(49):19649–54.
- [72] Rubia K. Neuro-anatomic evidence for the maturational delay hypothesis of ADHD. *Proc Natl Acad Sci U S A* 2007;104(50):19663–4.
- [73] Linares LO, Li M, Shrout PE, Ramirez-Gaité M, Hope S, Albert A, et al. The course of inattention and hyperactivity/impulsivity symptoms after foster placement. *Pediatrics* 2010;125(3):e489–98.
- [74] Mehta MA, Golemb NI, Nosarti C, Colvert E, Mota A, Williams SC, et al. Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian adoptees study pilot. *J Child Psychol Psychiatry* 2009;50(8):943–51.
- [75] Tottenham N, Hare TA, Quinn BT, McCarty TW, Nurse M, Gilhooly T, et al. Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Dev Sci* 2010;13(1):46–61.
- [76] Woon FL, Hedges DW. Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. *Hippocampus* 2008;18(8):729–36.
- [77] Rao U, Chen LA, Bidesi AS, Shad MU, Thomas MA, Hammen CL. Hippocampal changes associated with early-life adversity and vulnerability to depression. *Biol Psychiatry* 2010;67(4):357–64.
- [78] Tarullo AR, Gunnar MR. Child maltreatment and the developing HPA axis. *Horm Behav* 2006;50(4):632–9.
- [79] Cicchetti D, Rogosch FA. The impact of child maltreatment and psychopathology on neuroendocrine functioning. *Dev Psychopathol* 2001;13(4):783–804.
- [80] De Bellis MD, Baum AS, Birmaher B, Keshavan MS, Eccard CH, Boring AM, et al. Developmental traumatology part i: biological stress systems. *Biol Psychiatry* 1999;45(10):1259–70.
- [81] Carrion VG, Weems CF, Ray RD, Glaser B, Hessl D, Reiss AL. Diurnal salivary cortisol in pediatric posttraumatic stress disorder. *Biol Psychiatry* 2002;51(7):575–82.
- [82] Gunnar MR, Morison SJ, Chisholm K, Schuder M. Salivary cortisol levels in children adopted from Romanian orphanages. *Dev Psychopathol* 2001;13(3):611–28.
- [83] Carlson M, Earls F. Psychological and neuroendocrinological sequelae of early social deprivation in institutionalized children in Romania. *Ann N Y Acad Sci* 1997;807:419–28.
- [84] Kertes DA, Gunnar MR, Madsen NJ, Long JD. Early deprivation and home basal cortisol levels: a study of internationally adopted children. *Dev Psychopathol* 2008;20(2):473–91.
- [85] MacMillan HL, Georgiades K, Duku EK, Shea A, Steiner M, Niec A, et al. Cortisol response to stress in female youths exposed to childhood maltreatment: results of the youth mood project. *Biol Psychiatry* 2009;66(1):62–8.
- [86] Ouellet-Morin I, Danese A, Bowes L, Shakoor S, Ambler A, Pariante CM, et al. A discordant monozygotic twin design shows blunted cortisol reactivity among bullied children. *J Am Acad Child Adolesc Psychiatry* 2011;50(6):574–82.
- [87] Ouellet-Morin I, Odgers CL, Danese A, Bowes L, Shakoor S, Papadopoulos AS, Caspi A, Moffitt TE, Arseneault L. Blunted Cortisol Responses to Stress Signal Social and Behavioral Problems Among Maltreated/Bullied 12-Year-Old Children. *Biol Psychiatry* 2011, doi:10.1016/j.biopsych.2011.06.017.
- [88] De Bellis MD, Chrousos GP, Dorn LD, Burke L, Helmers K, Kling MA, et al. Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. *J Clin Endocrinol Metab* 1994;78(2):249–55.
- [89] Kaufman J, Birmaher B, Perel J, Dahl RE, Moreci P, Nelson B, et al. The corticotropin-releasing hormone challenge in depressed abused, depressed non-abused, and normal control children. *Biol Psychiatry* 1997;42(8):669–79.
- [90] Fisher PA, Stoolmiller M, Gunnar MR, Burraston BO. Effects of a therapeutic intervention for foster preschoolers on diurnal cortisol activity. *Psychoneuroendocrinology* 2007;32(8–10):892–905.
- [91] Brotman LM, Gouley KK, Huang KY, Kamboukos D, Fratto C, Pine DS. Effects of a psychosocial family-based preventive intervention on cortisol response to a social challenge in preschoolers at high risk for antisocial behavior. *Arch Gen Psychiatry* 2007;64(10):1172–9.
- [92] Boyce WT, Adams S, Tschann JM, Cohen F, Wara D, Gunnar MR. Adrenocortical and behavioral predictors of immune responses to starting school. *Pediatr Res* 1995;38(6):1009–17.
- [93] Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain Behav Immun* 2007;21(7):901–12.
- [94] Danese A, Caspi A, Williams B, Ambler A, Sugden K, Mika J, et al. Biological embedding of stress through inflammation processes in childhood. *Mol Psychiatry* 2011;16(3):244–6.
- [95] Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull* 2004;130(4):601–30.
- [96] Bottazzi B, Garlanda C, Salvaroli G, Jeannin P, Manfredi A, Mantovani A. Pentraxins as a key component of innate immunity. *Curr Opin Immunol* 2006;18(1):10–5.
- [97] Bottazzi B, Doni A, Garlanda C, Mantovani A. An integrated view of humoral innate immunity: pentraxins as a paradigm. *Annu Rev Immunol* 2010;28:157–83.
- [98] Medzhitov R. Recognition of microorganisms and activation of the immune response. *Nature* 2007;449(7164):819–26.
- [99] Iwasaki A, Medzhitov R. Regulation of adaptive immunity by the innate immune system. *Science* 2010;327(5963):291–5.
- [100] Harty JT, Badovinac VP. Shaping and reshaping cd8(+) t-cell memory. *Nat Rev Immunol* 2008;8(2):107–19.
- [101] Jameson SC, Masopust D. Diversity in T cell memory: an embarrassment of riches. *Immunity* 2009;31(6):859–71.
- [102] Khanna KM, Lepisto AJ, Decman V, Hendricks RL. Immune control of herpes simplex virus during latency. *Curr Opin Immunol* 2004;16(4):463–9.

- [103] Shirtcliff EA, Coe CL, Pollak SD. Early childhood stress is associated with elevated antibody levels to herpes simplex virus type 1. *Proc Natl Acad Sci U S A* 2009;106(8):2963–7.
- [104] Jensen PS, Mrazek D, Knapp PK, Steinberg L, Pfeffer C, Schowalter J, et al. Evolution and revolution in child psychiatry: ADHD as a disorder of adaptation. *J Am Acad Child Adolesc Psychiatry* 1997;36(12):1672–81.
- [105] Boyce WT, Ellis BJ. Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Dev Psychopathol* 2005;17(2):271–301.
- [106] Shonkoff JP. Building the brain's "air traffic control" system: how early experiences shape the development of executive function. Contract No.: 11. Harvard: Harvard University; 2011.
- [107] Moffitt TE, Arseneault L, Belsky D, Dickson N, Hancox RJ, Harrington H, et al. A gradient of childhood self-control predicts health, wealth, and public safety. *Proc Natl Acad Sci U S A* 2011;108(7):2693–8.
- [108] Bentley T, Widom CS. A 30-year follow-up of the effects of child abuse and neglect on obesity in adulthood. *Obesity (Silver Spring)* 2009;17(10):1900–5.
- [109] Tomoda A, Suzuki H, Rabi K, Sheu YS, Polcari A, Teicher MH. Reduced prefrontal cortical gray matter volume in young adults exposed to harsh corporal punishment. *Neuroimage* 2009;47(Suppl 2):T66–71.
- [110] Cohen RA, Grieve S, Hoth KF, Paul RH, Sweet L, Tate D, et al. Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. *Biol Psychiatry* 2006;59(10):975–82.
- [111] van Harmelen A-L, van Tol M-J, van der Wee NJA, Veltman DJ, Aleman A, Spinhoven P, et al. Reduced medial prefrontal cortex volume in adults reporting childhood emotional maltreatment. *Biol Psychiatry* 2010;68(9):832–8.
- [112] Treadway MT, Grant MM, Ding Z, Hollon SD, Gore JC, Shelton RC. Early adverse events, HPA activity and rostral anterior cingulate volume in MDD. *PLoS One* 2009;4(3):e4887.
- [113] Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, Schofield PR, et al. Interactions between BDNF val66met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. *Mol Psychiatry* 2009;14(7):681–95.
- [114] Driessen M, Herrmann J, Stahl K, Zwaan M, Meier S, Hill A, et al. Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Arch Gen Psychiatry* 2000;57(12):1115–22.
- [115] Sala M, Caverzasi E, Lazzaretti M, Morandotti N, De Vidovich G, Marraffini E, et al. Dorsolateral prefrontal cortex and hippocampus sustain impulsivity and aggressiveness in borderline personality disorder. *J Affect Disord* 2011;131(1–3):417–21.
- [116] Vermetten E, Schmahl C, Lindner S, Loewenstein RJ, Bremner JD. Hippocampal and amygdalar volumes in dissociative identity disorder. *Am J Psychiatry* 2006;163(4):630–6.
- [117] Jovanovic T, Blanding NQ, Norrholm SD, Duncan E, Bradley B, Ressler KJ. Childhood abuse is associated with increased startle reactivity in adulthood. *Depress Anxiety* 2009;26(11):1018–26.
- [118] Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, et al. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. *Biol Psychiatry* 1997;41(1):23–32.
- [119] Geuze E, Vermetten E, Bremner JD. MR-based in vivo hippocampal volumetrics: 2. Findings in neuropsychiatric disorders. *Mol Psychiatry* 2005;10(2):160–84.
- [120] Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B. Hippocampal volume in women victimized by childhood sexual abuse. *Psychol Med* 1997;27(4):951–9.
- [121] Frodi T, Reinhold E, Koutsouleris N, Donohoe G, Bondy B, Reiser M, et al. Childhood stress, serotonin transporter gene and brain structures in major depression. *Neuropsychopharmacology* 2010;35(6):1383–90.
- [122] Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, et al. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *Am J Psychiatry* 2003;160(5):924–32.
- [123] Pederson CL, Maurer SH, Kaminski PL, Zander KA, Peters CM, Stokes-Crowe LA, et al. Hippocampal volume and memory performance in a community-based sample of women with posttraumatic stress disorder secondary to child abuse. *J Trauma Stress* 2004;17(1):37–40.
- [124] Bremner JD, Vermetten E, Afzal N, Vythilingam M. Deficits in verbal declarative memory function in women with childhood sexual abuse-related posttraumatic stress disorder. *J Nerv Ment Dis* 2004;192(10):643–9.
- [125] Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, et al. Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry* 2002;159(12):2072–80.
- [126] Carpenter LL, Tyrka AR, McDougle CJ, Malison RT, Owens MJ, Nemeroff CB, et al. Cerebrospinal fluid corticotropin-releasing factor and perceived early-life stress in depressed patients and healthy control subjects. *Neuropsychopharmacology* 2004;29(4):777–84.
- [127] Carpenter LL, Carvalho JP, Tyrka AR, Wier LM, Mello AF, Mello MF, et al. Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. *Biol Psychiatry* 2007;62(10):1080–7.
- [128] Carpenter LL, Tyrka AR, Ross NS, Khoury L, Anderson GM, Price LH. Effect of childhood emotional abuse and age on cortisol responsivity in adulthood. *Biol Psychiatry* 2009;66(1):69–75.
- [129] Rao U, Hammen C, Ortiz LR, Chen LA, Poland RE. Effects of early and recent adverse experiences on adrenal response to psychosocial stress in depressed adolescents. *Biol Psychiatry* 2008;64(6):521–6.
- [130] Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA* 2000;284(5):592–7.
- [131] Heim C, Mletzko T, Purselle D, Musselman DL, Nemeroff CB. The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. *Biol Psychiatry* 2008;63(4):398–405.
- [132] Rinne T, de Kloet ER, Wouters L, Goekoop JG, DeRijk RH, van den Brink W. Hyperresponsiveness of hypothalamic-pituitary-adrenal axis to combined dexamethasone/corticotropin-releasing hormone challenge in female borderline personality disorder subjects with a history of sustained childhood abuse. *Biol Psychiatry* 2002;52(11):1102–12.
- [133] Pariante CM, Miller AH. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biol Psychiatry* 2001;49(5):391–404.
- [134] Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. *Proc Natl Acad Sci U S A* 2007;104(4):1319–24.
- [135] Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Arch Gen Psychiatry* 2008;65(4):409–15.
- [136] Surtees P, Wainwright N, Day N, Brayne C, Luben R, Khaw KT. Adverse experience in childhood as a developmental risk factor for altered immune status in adulthood. *Int J Behav Med* 2003;10(3):251–68.
- [137] Slopen N, Lewis TT, Gruenewald TL, Mujahid MS, Ryff CD, Albert MA, et al. Early life adversity and inflammation in African Americans and whites in the midlife in the United States survey. *Psychosom Med* 2010;72(7):694–701.
- [138] Kiecolt-Glaser JK, Gouin JP, Weng NP, Malarkey WB, Beversdorf DQ, Glaser R. Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. *Psychosom Med* 2011;73(1):16–22.
- [139] Pace TW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, et al. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am J Psychiatry* 2006;163(9):1630–3.
- [140] Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. *Neuropsychopharmacology* 2010;35(13):2617–23.
- [141] Lemieux A, Coe CL, Carnes M. Symptom severity predicts degree of T cell activation in adult women following childhood maltreatment. *Brain Behav Immun* 2008;22(6):994–1003.
- [142] Altemus M, Cloitre M, Dhabhar FS. Enhanced cellular immune response in women with PTSD related to childhood abuse. *Am J Psychiatry* 2003;160(9):1705–7.
- [143] CJ Janeway PT, Walport M, Shlomchik MJ. Immunobiology: the immune system in health and disease. 5 ed. New York: Garland Science; 2001.
- [144] Smith EE, Jonides J. Storage and executive processes in the frontal lobes. *Science* 1999;283(5408):1657–61.
- [145] Monk CS. The development of emotion-related neural circuitry in health and psychopathology. *Dev Psychopathol* 2008;20(4):1231–50.
- [146] Brown ES, Rush AJ, McEwen BS. Hippocampal remodeling and damage by corticosteroids: implications for mood disorders. *Neuropsychopharmacology* 1999;21(4):474–84.
- [147] Moffitt TE, Arseneault L, Jaffee SR, Kim-Cohen J, Koenen KC, Odgers CL, et al. Research review: DSM-V conduct disorder: research needs for an evidence base. *J Child Psychol Psychiatry* 2008;49(1):3–33.
- [148] Kraemer HC, Yesavage JA, Taylor JL, Kupfer D. How can we learn about developmental processes from cross-sectional studies, or can we? *Am J Psychiatry* 2000;157(2):163–71.
- [149] Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the adverse childhood experiences (ace) study. *Am J Prev Med* 1998;14(4):245–58.
- [150] Wegman HL, Stetler C. A meta-analytic review of the effects of childhood abuse on medical outcomes in adulthood. *Psychosom Med* 2009;71(8):805–12.
- [151] Thomas C, Hypponen E, Power C. Obesity and type 2 diabetes risk in midadult life: the role of childhood adversity. *Pediatrics* 2008;121(5):e1240–9.
- [152] Alastalo H, Raikonen K, Pesonen AK, Osmond C, Barker DJ, Kajantie E, et al. Cardiovascular health of Finnish war evacuees 60 years later. *Ann Med* 2009;41(1):66–72.
- [153] Tyrka AR, Price LH, Kao HT, Porton B, Marsella SA, Carpenter LL. Childhood maltreatment and telomere shortening: preliminary support for an effect of early stress on cellular aging. *Biol Psychiatry* 2010;67(6):531–4.
- [154] Kananen L, Surakka I, Pirkola S, Suvisaari J, Lonnqvist J, Peltonen L, et al. Childhood adversities are associated with shorter telomere length at adult age both in individuals with an anxiety disorder and controls. *PLoS One* 2010;5(5):e10826.
- [155] O'Donovan A, Epel E, Lin J, Wolkowitz O, Cohen B, Maguen S, et al. Childhood trauma associated with short leukocyte telomere length in posttraumatic stress disorder. *Biol Psychiatry* 2011;70(5):465–71.
- [156] Drury SS, Theall K, Gleason MM, Smyke AT, De Vivo I, Wong JY, et al. Telomere length and early severe social deprivation: linking early adversity and cellular aging. *Mol Psychiatry* 2011. doi:10.1038/mp.2011.53.
- [157] Glass D, Parts L, Knowles D, Aviv A, Spector TD. No correlation between childhood maltreatment and telomere length. *Biol Psychiatry* 2010;68(6):e21–2 author reply e3–4.
- [158] Shanks N, Windle RJ, Perks PA, Harbuz MS, Jessop DS, Ingram CD, et al. Early-life exposure to endotoxin alters hypothalamic-pituitary-adrenal function and predisposes to inflammation. *Proc Natl Acad Sci U S A* 2000;97(10):5645–50.
- [159] Bilbo SD, Schwarz JM. Early-life programming of later-life brain and behavior: a critical role for the immune system. *Front Behav Neurosci* 2009;3:14.
- [160] Sapolsky RM. Why zebras don't get ulcers. W.H Freeman & Co Ltd.; 1998. 434 pp.

- [161] Dawkins R. *The selfish gene*. Oxford: Oxford Paperbacks; 1998.
- [162] Kuzawa CW, Quinn EA. Developmental origins of adult function and health: evolutionary hypotheses. *Ann Rev Anthropol* 2009;38:131–47.
- [163] Gluckman PD, Hanson MA, Bateson P, Beedle AS, Law CM, Bhutta ZA, et al. Towards a new developmental synthesis: adaptive developmental plasticity and human disease. *Lancet* 2009;373(9675):1654–7.
- [164] Worthman CM, Kuzara J. Life history and the early origins of health differentials. *Am J Hum Biol* 2005;17(1):95–112.
- [165] Ouellet-Morin I, Danese A, Williams B, Arseneault L. Validation of a high-sensitivity assay for c-reactive protein in human saliva. *Brain Behav Immun* 2011;25(4):640–6.
- [166] McDade TW, Williams S, Snodgrass JJ. What a drop can do: dried blood spots as a minimally invasive method for integrating biomarkers into population-based research. *Demography* 2007;44(4):899–925.
- [167] Rutter M, Pickles A, Murray R, Eaves L. Testing hypotheses on specific environmental causal effects on behavior. *Psychol Bull* 2001;127(3):291–324.
- [168] Polanczyk G, Caspi A, Williams B, Price TS, Danese A, Sugden K, et al. Protective effect of CRHR1 gene variants on the development of adult depression following childhood maltreatment: replication and extension. *Arch Gen Psychiatry* 2009;66(9):978–85.
- [169] Danese A. Genetic opportunities for psychiatric epidemiology: on life stress and depression. *Epidemiol Psychiatr Soc* 2008;17(3):201–10.
- [170] Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, et al. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. *Proc Natl Acad Sci U S A* 2009;106(34):14716–21.
- [171] McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 2009;12(3):342–8.
- [172] Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. *JAMA* 2009;301(21):2252–9.