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Annual Research Review: The neurobiology and physiology of resilience and adaptation across the life course

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Background: Adaptation is key to survival. An organism must adapt to environmental challenges in order to be able to thrive in the environment in which they find themselves. Resilience can be thought of as a measure of the ability of an organism to adapt, and to withstand challenges to its stability. In higher animals, the brain is a key player in this process of adaptation and resilience, and through a process known as "allostasis" can obtain "stability through change"; protecting homeostasis in the face of stressors in the environment. Mediators of allostasis, such as glucocorticoids, can cause changes in the structure and function of neural circuits, clearly impacting behavior. How developmental stage interacts with stress and leads to long-lasting changes is a key question addressed in this review. **Scope and Methods:** We discuss the concept of allostasis, its role in resilience, the neural and physiological systems mediating these responses, the modulatory role of development, and the consequences for adult functioning. We present this in the context of mediators the brain and body engage to protect against threats to homeostasis. The review has been informed by comprehensive searches on PubMed and Scopus through November 2012. **Findings:** Stressors in the environment can have long lasting effects on development, depending upon the stage of life at which they are experienced. As such, adverse childhood experiences can alter resilience of individuals, making it more difficult for them to respond normally to adverse situations in adulthood, but the brain maintains the capacity to re-enter a more plastic state where such effects can be mitigated. **Conclusions:** The brain regulates responses that allow for adaptation to challenges in the environment. The capacity of the brain and body to withstand challenges to stability can be considered as "resilience". While adverse childhood experiences can have long-term negative consequences, under the right circumstances, the brain can re-enter plastic states, and negative outcomes may be mitigated, even later in life. **Keywords:** Allostasis, hormones, neurobiology, aging, brain development.

Introduction

The primary function of any organism is to survive, reproduce, and ensure that its genetic material is successfully transmitted to the next generation. This is as biologically true of single-celled organisms as it is of humans. While the complexity of these survival responses varies dramatically through phylogeny, it is clear that all life has devised mechanisms to achieve this seemingly simplistic goal. In mammals, and all other vertebrates for that matter, maintaining homeostasis is essential for survival. These homeostatic drives span a wide gamut, from the seemingly 'simple' task of regulating body temperature, to more complex whole organism responses such as getting adequate food and sleep. Threats to homeostasis, be they real or perceived, are taken as threats to survival, and an animal's physiology engages a set of responses that are meant to defend homeostasis, usually by attempting to remove the threat. In most cases, these threats are externally generated, by an environmental perturbation that causes a shift in some underlying physiological system. However, and this is particularly clear in humans, *internally* generated threats also play a role, such as ruminating on one's life problems, constant thinking about unachieved goals, or blaming oneself for any number of mishaps that could occur in the course of a single day (Schulkin, McEwen & Gold, 1994). For instance, sleep can be dramatically disrupted in individuals exposed to endotoxin challenges (Raison, Lowry & Rook, 2010; Risold & Swanson, 1996). However, these same sleep and biological timing processes can also be affected by ruminating about why one was passed up for a promotion at work. As such, from the simple to the complex, threats to homeostasis can be considered an index of survival, and the brain is the key organ that mobilizes the body's defenses, for better or worse, to mitigate such threats, and return the organism to homeostatic balance. This review discusses these brain–body interactions in relation to the neurobiology and physiology of adaptation across the life course. In this discussion, we shall note the powerful role of early life experiences in setting the responsiveness of the brain and body through the life course.

The brain is the key organ that determines successful adaptation or damage

The brain is the central organ of adaptation to stressors because it constantly samples the environment, determines what is threatening or potentially

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threatening, and determines behavioral responses such as fighting or fleeing; moreover, the brain also regulates autonomic, neuroendocrine and metabolic systems, and responds to their hormonal and neural feedback, which, in turn, can shape the structure and function of the brain throughout the life course (McEwen, 1998; McEwen & Gianaros, 2011). In this context, it is important to introduce the concept of allostasis, or 'stability through change'. The brain activates mediators of allostasis when threats to homeostasis, most commonly referred to as 'stressors' are detected. These mediators allow the organism to function in the face of altered physiological parameters, in the hopes that such functioning will result in successfully coping with, and the eventual termination of, the stressor. Thus, allostasis allows an organism to adapt to environmental perturbation in the short term. The adaptive process that occurs via allostasis helps maintain homeostasis; however, overuse and dysregulation of this process can lead to 'allostatic load' or 'allostatic overload' involving 'wear and tear' on body and brain and acceleration of pathophysiology leading to many of the diseases that are common in modern life, from depression to cardiovascular disease (Cohen, Janicki-Deverts & Miller, 2007; McEwen & Gianaros, 2011). Allostatic responses are important in the concept of resilience. Resilience is the ability of an organism to withstand environmental challenges to normal function, and as such, successful allostatic responses can directly contribute to resilience by providing stability in a changing environment. Importantly, the concept of resilience can also be conceptualized in a more long-term view. That is, while resilience in the moment is important (e.g., following acute challenges), long-term resilience is also essential. As such, resilience can also be considered on longer time scales, in which a developing individual is able to withstand challenges that may result in changes to normal function in adulthood. Thus, when investigating resilience, one must appreciate both the short-term acute aspects of resilience and the long-term influences and adaptations that environmental or psychological challenges during sensitive periods of development may have.

Hormones: agents of adaptation and change in the brain

As discussed, the brain and body respond to stressors in the environment through numerous mechanisms. One such mechanism that has received ample study is the role that hormones play in sculpting the brain. Hormones play an important role in brain plasticity and represent an important channel of communication between the brain and the body (McEwen, 2007). Besides steroid hormones of the adrenal glands, those of the thyroid gland, gonads, as well as metabolic hormones also have important effects on the central nervous system (McEwen, 2007). The brain response to circulating hormones extends beyond the hypothalamus to encompass most brain regions, including higher cognitive centers, and involves structural plasticity, among other effects (McEwen, 2007). Structural plasticity includes the turnover of synaptic connections and the growth and shrinkage of dendrites in amygdala, prefrontal cortex (PFC) and hippocampus as well as limited amounts of neurogenesis.

We have studied the role of sex and stress hormones in structural remodeling in the hippocampus. Sex hormones regulate the estrous cycle variation in spine synaptic density on CA1 pyramidal neurons in the female hippocampus, as well as PFC and other areas of the brain; androgens also regulate spine density in similar regions of the male brain (McEwen, 2010). The underlying mechanisms involve estrogen and androgen receptors that are both genomic and nongenomic, meaning that some are located in the cytoplasm and in synaptic terminals, dendrites, mitochondria, and glial cell processes while others are expressed in cell nuclei in pyramidal neurons and in subtypes of GABAergic inhibitory interneurons (Dumitriu, Rapp, McEwen & Morrison, 2010; McEwen, 2010; McEwen & Milner, 2007). This receptor distribution is indicative of a host of nongenomic signaling pathways that influence diverse cellular processes such as actin polymerization, neurotransmitter release, mitochondrial calcium retention, and local protein synthesis (Dumitriu et al., 2010; McEwen, 2010; McEwen & Milner, 2007).

The effects of stress on the hippocampal formation involve the stress-induced retraction of apical dendrites in CA3 pyramidal neurons and the suppression of neurogenesis in the dentate gyrus (McEwen, 2010). A key feature of the former process is the synergistic involvement of circulating glucocorticoids and excitatory amino acids to cause cytoskeletal depolymerization and reversible dendritic retraction (McEwen, 2010), seen most dramatically in the hibernating European hamster (Magarinos, McEwen, Saboureau & Pevet, 2006), but also as a result of chronic stress (McEwen, 2010). It should be noted that the dentate gyrus-CA3 region of the hippocampal formation is particularly vulnerable to seizure-induced damage (McEwen, 2010). Thus, one of the key open questions is the extent to which these stress-induced changes represent an adaptive reduction in vulnerability to excitotoxic damage (McEwen, 2010) or increase the vulnerability of this brain regions to subsequent seizure-induced damage (Conrad, 2008). Ongoing studies of epigenetic mechanisms involving repression of genetic information may help shed light on this question in terms of genomic stability vs. instability (Hunter, McCarthy, Milne, Pfaff & McEwen, 2009).

Investigations of the role of adrenal steroids and the mineralocorticoid (MR) and glucocorticoid receptors (GR) that are expressed in the hippocampus and

other brain regions have led to new information that points to a diverse range of actions on many cellular functions. Besides the traditional genomic role (Oitzl, Reichardt, Joels & de Kloet, 2001; Revest et al., 2005), both MR and GR are expressed in nongenomic sites (Johnson, Farb, Morrison, McEwen & LeDoux, 2005; McEwen & Getz, 2012), have nongenomic roles in glutamate release (Karst et al., 2005; Polman et al., 2012) as well as mitochondrial calcium buffering (Du et al., 2009) and rapid (within hours) formation and down-regulation of spine synapses (Liston & Gan, 2011), dendritic growth, and branching (Gould, Woolley & McEwen, 1990). There are also the effects of adrenal steroids to rapidly increase endocannabinoid synthesis (Hill, Karatsoreos, Hillard & McEwen, 2010; Tasker, Di & Malcher-Lopes, 2006) that may or may not involve the classical GR as opposed to an as yet-undefined membrane glucocorticoid receptor (Polman et al., 2012). Finally, there are reported to be rapid, nongenomic, ligand-independent effects of glucocorticoids to activated trkB receptors for neurotrophins (Jeanneteau, Garabedian & Chao, 2008).

Beyond the hippocampus: effects of stress on structural plasticity in other brain regions

Although the hippocampus has been the focus of much of the initial work on stress-induced changes in brain structure and function, work over the past decade has shown that other brain areas are also involved, and two in particular, the PFC and the amygdala, have received special attention. Whereas the hippocampus plays a central role in learning and memory, as well as in mood, the PFC is a key brain region that regulates executive function, inhibitory control, and cognitive flexibility (Figure 1). The amygdala (AMY) is a key brain region that regulates emotionality, aggression, and affect based learning and memory, such as fear conditioning. Interestingly, these brain regions show somewhat divergent responses to stress and stress mediators, in that they do not always respond in the same way as the hippocampus, that is, they do not only show dendritic retraction. Importantly, the behavioral consequences of chronic stress exposure closely match the changes in underlying brain morphology and function.

As mentioned, the PFC is a key brain region that mediates many 'higher cognitive' functions in humans and nonhuman animals. Whereas the human PFC is extremely complex and large compared with other brain regions, in rodents such as rats and mice, it is much simpler. Yet, even in these species, the PFC exerts clear control over inhibition, attention, and cognitive flexibility (McEwen & Gianaros, 2011). Following chronic stress exposure, neurons of the prelimbic medial PFC (PL) show dramatic shrinkage and loss of complexity; however, neurons of the orbitofrontal PFC (OF) show a clear increase in complexity following chronic stress (Liston et al., 2006), which is interesting when one considers that this part of the PFC is centrally important in processing the affective aspect of cognitive behaviors, and given the changes in the AMY (discussed below) provides an anatomical substrate for the changes in emotionality observed following chronic stress. In both the PL and the OF, the changes in dendritic complexity are accompanied by concomitant changes in dendritic spines, which largely decrease in the PL and increase in the OF.

In this sense, not only are there fewer and less complex dendrites in the PL after chronic stress but

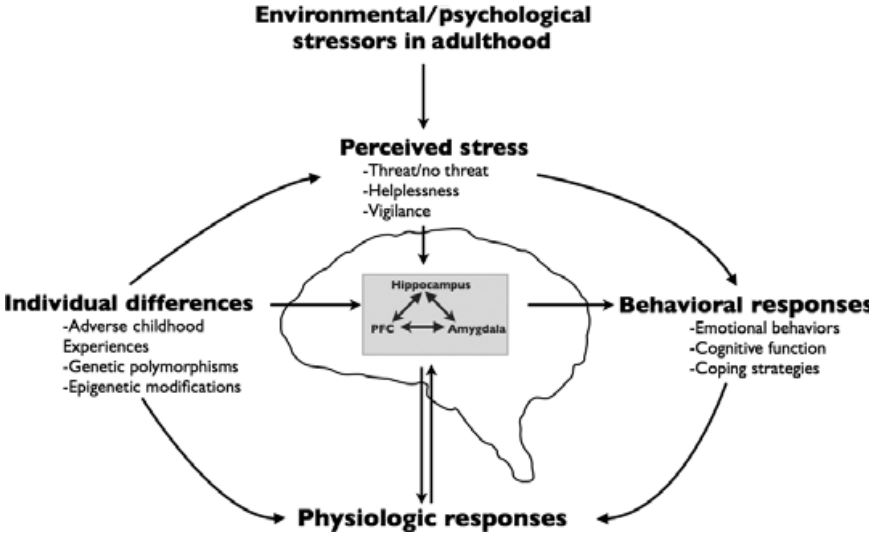

Figure 1 Multiple pathways interact to determine physiological and neurobehavioral responses to stress/trauma in adulthood. The interaction of genetics and early environmental experiences can affect the way an individual responds to stressors or trauma in the environment at the physiological and neurobehavioral levels later in life, thus changing the effects of these negative stimuli on the structure and function of key brain areas involved in emotionality and cognition, particularly the prefrotnal cortex (PFC), amygdala, and the hippocampus. The altered physiological response to perceived stressors can also feedback to modulate these brain areas, thus providing both additional vulnerability, but also potential pathways by which resilience may be bolstered

also those dendrites seem to have fewer dendritic spines, suggesting even less connectivity. In the OF, the effect is the opposite after chronic stress: hypertrophied neurons with an increase in spine density. Along the lines observed in the PFC, in response to chronic stress, the AMY shows hypertrophy of neurons in the basolateral aspect of the nucleus (Vyas, Mitra, Rao & Chattarji, 2002), as well as an increase in the number of dendritic spines in this region, thus greatly increasing the activity of the AMY and responses to emotionally charged stimuli in the environment.

It is important to highlight that these stress-induced changes in each of these brain regions is not occurring in a vacuum. That is, these brain regions are interconnected, and have interacting effects on behavioral output. For instance, the processing of memories with an emotional valence with contextual information in the environment requires intact amygdala–hippocampal connections, whereas on the other hand, the PFC can inhibit AMY activity, and plays a key role in the extinction of fear learning. Thus, when taken as a circuit, one can see how decreased inhibitory outflow from the PFC and increased activity at the AMY can result in a circuit that is fundamentally altered and no longer responds appropriately to stimuli in the environment, particularly emotionally charged stimuli.

Recovery and reversibility: the brain is a resilient organ

The adult as well as developing brain has considerable structural and functional plasticity and capacity for resilience (Karatsoreos & McEwen, 2011) and there are numerous strategies for promoting plasticity involving 'top down' interventions such as physical activity and caloric restriction combined in some cases with pharmaceutical agents as facilitators of plasticity. One of the important questions in current research and practice is how early life events shape the brain and whether adverse early life experiences can be reversed. Evidence from animal models shows the importance not only of the amount of maternal care (Francis, Diorio, Liu & Meaney, 1999) but also the consistency of that care and exposure to novel experiences in cognitive, social development, as well as physical growth (Akers et al., 2008; Tremblay & Chaput, 2012). Prenatal stress (Maccari & Morley-Fletcher, 2007), postnatal separation of pups from their mothers (Eiland & McEwen, 2012), and also stress during puberty (Isgor, Kabbaj, Akil & Watson, 2004) have all been reported to impair hippocampal development and function. Reversible methylation of cytosine residues on DNA is a key feature of the effects of maternal care (Weaver et al., 2004) and such methylation, particularly of the glucocorticoid receptor promoter, has been used as a biomarker of the effects of early life abuse on the human brain (McGowan et al., 2009). Besides these effects that focus largely on the hippocampus, there are reports of the importance of suppression development of the AMY in the ability of young rats to be positively conditioned to odors paired with shock and the role of glucocorticoids in promoting maturation of the AMY to establish the normal role of the AMY in aversive conditioning (Moriceau & Sullivan, 2006). Finally, the food insecurity paradigm in rhesus monkeys involving the variable presentation of food to the mother in amount, time, and location leads to chronic anxiety in the offspring and also potential to develop the metabolic syndrome (Coplan et al., 2001; Kaufman et al., 2005).

Recent experimental findings have begun to challenge our previously held views on the capacity of certain brain circuits to re-enter a plastic state from what was previously considered a more 'crystalized' state that would be resistant to repair or remapping. A noteworthy illustration of this, which also relates to adrenal steroid action, is the reported ability of corticosterone in the drinking water to facilitate the reversal of neonatal monocular deprivation toward establishing binocular vision when adults are also given visual stimulation (Spolidoro et al., 2011). The seminal work of Hubel and Wiesel [reviewed in: (Espinosa & Stryker, 2012)] on the importance of early visual experience in the formation of ocular dominance columns showed how the early environment could shape the wiring of the brain. They showed how changing the visual environment of kittens could change the formation of ocular dominance columns, and if monocular deprivation occurred at a particular time, could impair binocular vision in adulthood. These findings led to changes in the way childhood strabismus and cataracts were treated, and eventually they were awarded a Nobel Prize in Physiology or Medicine for their findings. Although the effects of monocular deprivation remain irrevocable fact, the ability for the brain to recover from this early insult has been re-examined. Specifically, Spolidoro et al. conducted a clever experiment in which rats were monocularly deprived in early life, and the formation of ocular dominance columns in adulthood was explored. As predicted, monocular deprivation early in life altered the formation of these cortical structures. Remarkably, two treatments were able to 'reopen' this previously closed window. If rats were either exposed to corticosterone in their drinking water on alternating days, or underwent short-term food deprivation with food available only every other day, plasticity in this circuit was restored (Spolidoro et al., 2011). Thus, there are mechanisms by which brain circuits previously considered to be permanently established, can be encouraged to become plastic once more. This along with the effects summarized in the previous section of this review, in particular (Liston & Gan, 2011), provides a novel view of the ability of adrenal hormones to promote adaptive plasticity.

Long-term adaptation: when the brain shifts the 'status quo'

The previous section dealt with how hormones that are released from peripheral glands can impact the structure, and function, of the brain. As discussed, in many cases, these effects are reversible, and in most instances, this reversibility is a desired outcome. The brain initially detected an environmental challenge, deployed the appropriate countermeasures to help adjust to these environmental demands, and once the demand ceased, returned back to baseline; a classic example of allostasis. However, there are time points in the course of an organism's development where the environment is able to actively, and lastingly, alter the neural, physiological, and ultimately behavioral systems of the organism to optimize physiology and behavior for the environment and life history stage in which the organism finds itself [e.g., the Adaptive Calibration Model (Mecawi et al., 2011)]. One such key stage of development that has garnered much basic and clinical research is the neonatal period, and the early life experiences of childhood. An excellent example of the strong impact of *in* utero environmental stressors on the long-term function of individuals is the remarkable study of the Dutch 'hunger winter' of 1944 (Kyle & Pichard, 2006). This famine occurred because of German embargo of food and supplies on the Netherlands after the Allied invasion of Normandy, and a particularly harsh winter immediately following the partial lifting of the embargo. In a tour de force study, the Dutch Famine Birth Cohort study explored the sustained effects of this famine on children whose mothers were subjected to this very stressful event. The findings revealed that children of these women were smaller, and more susceptible to obesity, diabetes, cardiovascular disease, and other health problems (Kyle & Pichard, 2006).

Biological embedding, adaptation to a new environment, and cumulative wear and tear

The Dutch Famine Birth Cohort studies, and other studies exploring the effects of more positive environments, have encouraged the development of models and explanations for these long-term effects. Adverse or positive early life experiences lead to 'biological embedding' via gene-environment interplay, and shape the brain and body; in the end, they bias the individual to react in certain ways to stressors generated both externally and internally (Rapp & Gallagher, 1996; Shonkoff, Boyce & McEwen, 2009). In hopes of quantifying how these childhood experiences can contribute to health and long-term well-being, the Adverse Childhood Experiences (ACE) study was launched. The purpose of this study is to devise a metric (the ACE score) that can help to predict how early childhood neglect or abuse will affect an individual's adult health. A guiding notion of this idea is that the early childhood environment can shape both neural and physiological responses to stimuli later in life. An explanation of why such early experiences have long-lasting effects is that all stimuli, good and bad, can result in 'adaptive calibration', in other words, somewhat extreme conditions early in life can alter neural and physiological parameters to function optimally in the expected extreme environment.

Adaptive calibration refers to the notion that these adaptations can serve a useful purpose in a particular environment. For example, an individual that is more vigilant and anxious in a dangerous and chaotic environment is better adapted to that environment as is an individual who is calm, curious, and unafraid from growing up in a stable and safe environment, where long-term planning is possible (Del Giudice et al., 2011). Yet, because the nature of the experiences of these two types of individuals in their respective environments is likely to be quite different, each type of individual is on a different trajectory for health and disease. This is shown by the gradients of diseases of modern life seen across education and income known collectively as socioeconomic status, or SES (Marmot, 2004), as well as a function of gradients of inequality in different societies (Wilkinson & Pickett, 2010). Furthermore, putting those individuals into the opposite kind of environment requires further adaptation and plasticity and can lead to allostatic load and exacerbate pathophysiology and disease when the adaptation causes chronic stress and also an unhealthy lifestyle – for example, lack of exercise, bad food, smoking, substance abuse (McEwen, 2006; McEwen & Lasley, 2002). For example, taking someone from a safe and secure environment into a chaotic and dangerous one may be stressful, but possibly their 'better' neural architecture will allow adaptation; on the other hand, taking someone born into a chaotic environment into a safe one where long-term planning is an adaptive strategy may lead to severe problems (Tough, 2011). In that connection, it is interesting to hypothesize that perhaps the biological embedding that occurred in the Dutch Hunger Winter could have served those children well had the harsh environment that lasted longer. Instead, after the end of the war, and eventual recovery and prosperity of Western Europe, these individuals were faced with a nutritionally rich and more secure environment – conditions that their brains and bodies were perhaps not anticipating based on the environment of early life.

Periods of biological embedding: is it ever too late?

There is no question that there are several periods of development when neurobehavioral function is organized, and become very difficult to change. Over the

life course, there appear to be four slightly overlapping periods that are sensitive to biological embedding. These include the prenatal period (Morley-Fletcher et al., 2011; Mueller & Bale, 2008; Pankevich, Mueller, Brockel & Bale, 2009), the neonatal period (Akers et al., 2008; Francis et al., 1999; Moriceau & Sullivan, 2006), early childhood (Almas et al., 2012; Nelson et al., 2007; Sheridan, Fox, Zeanah, McLaughlin & Nelson, 2012), and adolescence (Casey et al., 2010; Isgor et al., 2004; Pattwell, Bath, Casey, Ninan & Lee, 2011). However, it is important to keep three things in mind. First, the adult brain has the capacity for long-term change (e.g., memories that last a lifetime). Some of these changes may have both neuroanatomical and epigenetic changes. Second, there are different sensitive periods beyond which it is much more difficult to produce change. A more innocuous example of this is the acquisition of language skills, including the ability to acquire a foreign language, or the basic verbal ability and vocabulary as documented by Hart (Hart & Risley, 1995). More serious examples could include the effects on mood and cognition, as described by the orphanage studies discussed above and below. Third, reactivation of plasticity is possible, as the examples from the visual system (Spolidoro et al., 2011; Vetencourt et al., 2008). The key point here is we do not yet know the possibilities and the limits of biological embedding, and when, or how, such early life impacts can be mitigated.

Epigenetics and the impact of early life events and sex differences

As discussed above, early life experiences (particularly ACE) have a lasting impact on brain development and function through epigenetic mechanisms that interact with genotype. On one hand, the multiple genetic factors that contribute to brain development and function are recognized to exist in alleles that confer differential responsiveness to environmental influences [so-called 'reactive alleles' and the orchids vs. dandelion distinction (Boyce & Ellis, 2005; Dobbs, 2009; Suomi, 2006)]. Although this view may help explain how the environment can shape gene expression, there is growing evidence that some early life environments may actually affect subsequent generations, even though those individuals never experienced those aversive situations. For instance, it was demonstrated that the children of the Dutch Hunger Winter were smaller, on average. This suggested some kind of 'epigenetic' ('above the genome') effect. Over the past decade, intensive research has been undertaken to understand how such epigenetic effects are manifested at the behavioral level of subsequent generations, and the specific mechanisms by which such changes occur at the level of genetic information. The work of Liu et al. indicated the type of maternal care experienced by rat pups could alter GR expression in the brain, and alter the response of the hypothalamic pituitary adrenal (HPA) 'stress' axis (Liu et al., 1997). Subsequent work by the laboratory of Michael Meaney elaborated on this, and demonstrated that maternal care could result in the hypermethylation of the GR promoter in the hippocampus, thus altering GR expression, and hence the sensitivity of the hippocampus to glucocorticoids (Weaver et al., 2004). Recently, additional data from the Meaney group have shown that maternal care can change methylation of hippocampal glutamic acid decarboxylase promoter (Zhang et al., 2010), as well as hippocampal metabotropic glutamate receptor 1 promoter activity (Bagot et al., 2012). Thus, we have begun to understand how changes in maternal care and early life experience can alter the properties of neural circuits and their response to stimuli in the environment through epigenetic modifications.

The studies of maternal care by the Meaney group have been supplemented by work by Tang and colleagues on the consistency of maternal care over time and the controlled exposure of pups to novelty, both of which result in enhanced physical, cognitive, and social development (Akers et al., 2008; Tang, Yang, Reeb-Sutherland, Romeo & McEwen, 2012). A key mediator appears to be stress self-regulation by the mother (Tang et al., 2012). Thus, it is not so much the amount of maternal care, but its consistency that provides a stable platform for emotional regulation and cognitive function later in life, and a key factor is the ability of the mother to efficiently turn on her HPA axis stress response (Tang et al., 2012). These observations in the rodent maternal care model are consistent with work on monkey by Parker, Lyons, and colleagues (Parker, Buckmaster, Sundlass, Schatzberg & Lyons, 2006).

The new view of epigenetics now involves many aspects of the regulation of gene expression and abolishes the nature-nurture dichotomy by introducing not only the repression and activation of chromosomes by histones (Allfrey, 1980; Fischle, Wang & Allis, 2003) but also the methylation of cytosine residues on DNA (Maya-Vetencourt et al., 2012; McGowan et al., 2009) and the role of microRNA's and mitochondrial genes (Mehler, 2008). Gradually, we are building a picture of how epigenetic changes, and the mechanisms of gene X environment interaction, can alter resilience of the brain [see review by (Russo, Murrough, Han, Charney & Nestler, 2012)].

There is ample evidence that early life events can impact many facets of the circuitry discussed above, and in some cases, this may be related to changes in the stress axis. For instance, work by Lupien and colleagues has shown that levels of cortisol in children are correlated with their mother's socioeconomic status and depressive symptoms (Lupien, King, Meaney & McEwen, 2000). Interestingly, an increased AMY size has been observed for 10-year-old children that have been exposed to maternal depression from birth (Lupien et al., 2011). In

studies with a similar theme, Pruessner and coworkers have shown that prenatal care can influence adult stress responsivity (Walker, Sapolsky, Meaney, Vale & Rivier, 1986), and that high maternal cortisol early in gestation is correlated with increased AMY size and affective problems in approximately 7-year-old children, particularly in girls. This is particularly interesting as it should also be noted that there are sex differences in how the brain responds to stress both in hippocampus (Galea et al., 1997) and in PFC (Shansky et al., 2004, 2010) that involve both developmentally determined sex differences as well as the actions of estrogens in the mature brain. Much work needs to be done to elucidate when and how these sex differences come about and what they mean for behavior and other brain functions as well as psychopathology and pathophysiology. In addition, numerous studies have demonstrated that cognition is impacted in children from low SES (Farah et al., 2006; Noble, McCandliss & Farah, 2007; Noble, Norman & Farah, 2005; Thompson & Swanson, 2010). Noteworthy new work exploring effects of early life institutionalization has shown correlated changes in neural structure. Work by Sheridan has explored changes in the structure of cortex, through MRI and EEG (Sheridan et al., 2012), of Romanian orphans in the Bucharest Early Intervention Program (BEIP). The BEIP group was made up of randomized individuals who were either institutionalized orphans, maintained in standard care, or previously institutionalized orphans that were placed into high-quality foster care. Numerous studies have explored how changes in the type of care result in altered behavioral outcomes of previously institutionalized children, including indiscriminate social behavior (Drury et al., 2012) and executive function (Bos, Fox, Zeanah & Nelson Iii, 2009; McDermott, Westerlund, Zeanah, Nelson & Fox, 2012). Remarkably, the Sheridan study showed that institutionalized children showed similar decreases in white matter volume when compared with never institutionalized children, regardless of the type of care they received. However, when exploring changes in gray matter, the children who were placed into high-quality foster care showed similar gray matter volume as the never institutionalized children, whereas the standard care as usual orphans showed less gray matter volume (Sheridan et al., 2012). In addition, the question of gene X environment interactions has also been addressed in such early life adversity studies with children in both the BEIP and the English-Romanian Adoption (ERA) study. In the BEIP cohort, Drury et al. showed a relationship between the type of care and if the child was a carrier of either the BDNF val66met allele or the serotonin transporter (5HTT) allele, with respect to indiscriminate social behavior (Drury et al., 2012). In the ERA cohort, Kumsta et al. showed that children carrying the 5HTT allele were at greater risk in developing adolescent emotional difficulties, particularly if they had suffered adverse early life experiences in an institutionalized setting (Kumsta et al., 2010). This study, and that of others, has begun to uncover the links between early life experiences, genetics, neural circuitry, and later affective and neurocognitive problems in children.

Recovering from adverse child experiences: animal models and the human condition

Adverse childhood experiences (ACE, as described above) show lasting effects on physical and mental health (Anda, Butchart, Felitti & Brown, 2010; Danese & McEwen, 2011) and represent the human counterpart of adversity in animal models. Besides prevention (e.g., http://www.nursefamilypartnership.org/; http://developingchild.harvard.edu/index.php/activities/council/), what are the prospects of ameliorating physical and mental health problems once they have emerged as a result of ACE in children and adults? In the animal model domain, treatment of an anxious substrain of rats at birth with the neurotrophic factor, FGF2, reverses the anxiety phenotype in adult life (Turner, Clinton, Thompson, Watson & Akil, 2011). Moreover, a novel antidepressant, agomelatine, shows the ability to reverse some of the affects of prenatal stress on the hippocampus and behavior when give to young adults (Morley-Fletcher et al., 2011). In the human domain, successful cognitive-behavioral therapy has been reported to longitudinally cause reduced AMY volume in anxiety disorders (Holzel et al., 2009) and increased prefrontal cortical gray matter volume in chronic fatigue patients (de Lange et al., 2008). Moreover, regular physical activity in sedentary elderly people increases hippocampal volume (Erickson et al., 2011) and also prefrontal cortical blood flow (Colcombe et al., 2004). Thus, 'top down' behavioral interventions may have the ability to alter the brain and behavior toward more favorable states.

Conclusion

This review has discussed brain–body interactions in relation to the neurobiology and physiology of adaptation to stressors and other challenges across the life course, with particular emphasis on the central role of the brain. We have noted the importance of disturbances of homeostasis, such as disruptions in metabolic systems or sleep, as a predisposing agent to life stressors. We have also emphasized the profound influence of early life experiences (biological embedding) as another predisposing factor for life stressors and the cumulative burden reflected in the terms 'allostatic load and overload'. Thus, from the simple to the complex and from early life to daily experiences, threats to homeostasis can be considered an index of survival, and the brain is the key organ that mobilizes the body's defenses, for better or worse, to remove the

threats, and return the organism to homeostatic balance.

As neurobiologists who are aware of the capacity of the brain to store memories of a lifetime, as well as capacity of the brain for plasticity and vulnerability to stressful experiences, and its ability to influence and respond to systemic physiology and pathophysiology, our overall message is that as a society where lifetime stress is increasing, and where our evolutionary ancient homeostatic systems are facing new perturbations such as high-fat fast food and constantly 'on' society, we cannot afford to ignore these factors even if they are less easy to pinpoint and to prevent or treat. Indeed, although it is a useful adjunct to more targeted 'top down' interventions, pharmacological therapy is not the ultimate solution. We must continue to search for relevant biomarkers (which may involve measuring brain activity or its surrogates with imaging methods) even as society uses strategies of good clinical practice to get relevant personal information and find methods to better prevent or treat by cognitive, behavioral (e.g., mindfulness) and psychotherapy. If we can assemble warning signs during development to determine how to intervene during childhood, or potentially 're-open' aspects of these developmental windows in adulthood, we can combine approaches to help recalibrate a brain that perhaps went down the wrong path. The first step to finding these solutions, particularly in the case of the developing brain, is that we need to be aware of how the environment can sculpt neural circuits through various pathways, and that some of these changes may be long lasting.

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Key points and future directions

- To survive, organisms must adapt and respond to changes in the environment. The process used to achieve stability in the face of environmental perturbations is known as *allostasis*.
- Resilience is the ability of an organism to withstand threats to stability in the environment. In a sense, resilience represents the ability to bend without breaking in the face of environmental or psychological perturbations.
- The mediators of allostasis, such as the glucocorticoids, cytokines, and neurotrophins can thus also be considered as contributing to resilience.
- In both animal models and humans, different stages of the life cycle seem to be more or less malleable. Particularly, early developmental time points seem to be those in which the brain is most plastic and can be affected over the long term by environmental or psychological challenges.
- Adverse childhood experiences (ACE) have been shown to alter the trajectory of neurobehavioral development, and result in long-term effects into adulthood. Moreover, it is clear that these effects are an interaction between environmental exposures and an individual's genotype.
- Epigenetics is an important area for future work to understand how changes in the environment can affect the genome, and how these effects may then show transgenerational transfer.
- It is important to emphasize that we still know little about both the possibilities, and limitations, of reopening windows of plasticity. This knowledge could dramatically alter how interventions are considered during adulthood to address early childhood difficulties.
- Future work should be aimed at exploring the capacity for the adult brain to display plasticity previously only seen during development. In addition, more work is needed to understand the mechanisms by which ACE affects long-term neural function, and if such changes can be reversed.

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