The impact of developmental timing for stress and recovery

Dylan G. Gee *, B.J. Casey

Sackler Institute for Developmental Psychobiology, Weill Cornell Medical College, 1300 York Ave, New York, NY 10065, USA

ARTICLE INFO

Article history:
Received 15 September 2014
Received in revised form
10 February 2015
Accepted 18 February 2015
Available online 19 February 2015

Keywords:
Early-life stress
Development
Resilience
Sensitive period
Neuroplasticity
Amygdala
Prefrontal cortex

ABSTRACT

Stress can have lasting effects on the brain and behavior. Delineating the impact of stress on the developing brain is fundamental for understanding mechanisms through which stress induces persistent effects on behavior that can lead to psychopathology. The growing field of translational developmental neuroscience has revealed a significant role of the timing of stress on risk, resilience, and neuroplasticity. Studies of stress across species have provided essential insight into the mechanisms by which the brain changes and the timing of those changes on outcome. In this article, we review the neurobiological effects of stress and propose a model by which sensitive periods of neural development interact with stressful life events to affect plasticity and the effects of stress on functional outcomes. We then highlight how early-life stress can alter the course of brain development. Finally, we examine mechanisms of buffering against early-life stress that may promote resilience and positive outcomes. The findings are discussed in the context of implications for early identification of risk and resilience factors and development of novel interventions that target the biological state of the developing brain to ultimately ameliorate the adverse consequences of stress during childhood and adolescence.

© 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Stress is a potent environmental risk factor for both mental and physical illness. The effects of stress on the brain depend critically on the timing (age of onset and duration). When stress occurs early in life it can have profound and lasting effects on brain organization and function. Approximately 10% of youth have anxiety and stress-related disorders (Newman et al., 1996; Kim-Cohen et al., 2003; Kessler et al., 2005), and early childhood adversity accounts for over 30% of all mental illnesses (Green et al., 2010). Yet not all children who experience stressful life events develop mental illness. Understanding the mechanisms by which stress alters the developing brain is fundamental for: 1) delineating adaptive and maladaptive changes; 2) identifying resilience and risk factors; and 3) developing interventions for ameliorating risk. This article highlights recent studies that examine the neurobiological effects of the timing and buffering of stressful life events.

2. Brain development and sensitive periods

The brain undergoes dynamic changes throughout the course of development, with important implications for how stress influences the brain and the efficacy of treatments targeting stress-related mental illness at different developmental time points. Nonhuman primate studies show that typical brain development is marked by an initial period of overproduction of synapses, followed by selective stabilization and elimination of a substantial proportion of synapses (Huttenlocher, 1979; Huttenlocher et al., 1982; Bourgeois and Rakic, 1993; LaMantia and Rakic, 1994). Human neuroimaging studies show corresponding patterns, in which gray matter volumes typically peak around 10–12 years of age (Giedd et al., 1999), with significant gray matter loss throughout adolescence and adulthood (Sowell et al., 2001, 2003). Simultaneously, increases in white matter occur through myelination of axons (Brody et al., 1987; Benes et al., 1994). Substantial regional variation exists, with maturation of low-level sensory and motor cortices occurring prior to prefrontal and temporal cortices involved in higher-level cognition and regulation of behavior (Yakovlev and Lecours, 1967; Benes et al., 1994; Sowell et al., 1999, 2001; Gogtay et al., 2004). Such regional changes in brain structure and function across development, as well as changes in the availability of neurochemicals and patterns of cortical cell firing, are posited to lead to transient imbalances that underlie behavioral changes.
during adolescence (Galvan et al., 2006; Casey, Galvan, Getz, 2008). These dynamic changes in brain and behavioral development likely influence how stress at unique developmental time periods alters the brain and how children and adolescents cope with stressors. Exacerbations of acute or chronic stress, may lead to altered stress reactivity and ultimately increase the risk for mental illness.

Understanding neurodevelopmental changes that influence stress reactivity and recovery are critical for enhancing mental health. Sensitive periods refer to times in development when heightened neuroplasticity renders the brain especially amenable to environmental influences (Moroceau and Sullivan, 2006; Callaghan and Richardson, 2011; Yang et al., 2012). The timing of sensitive periods differs by neural circuit and behavioral system, but it may be that sensitive periods occur when brain development is most dynamic, such as infancy and adolescence (Fig. 1). During these periods, environmental input can lead to a series of developmental cascades (Masten and Cicchetti, 2010) that ultimately have significant influences on behavior, of a positive or negative nature. A sensitive period may render the brain more capable of responding to stress in adaptive ways. It could also magnify consequences of stressful life events in maladaptive ways. By contrast, stress that occurs during windows of reduced plasticity (e.g., after the closing of a sensitive period) may yield a brain that is less capable of remodeling itself. Thus, sensitive periods in neurodevelopment may render the developing brain more vulnerable to the effects of later stress, but they could also serve as windows of opportunity, during which there is increased potential for positive adaptation or effective intervention.

Delineating sensitive periods could reveal how the effects of stress differ depending on when in development and what type of stress occurs, as well as when in development certain types of intervention may be most effective for buffering against maladaptive consequences of stress. In this way we may begin to direct the timing and type of interventions at the level of the individual and the nature of the stressor. The extent to which neuroplasticity and brain function change throughout childhood and adolescence suggests that interventions based on the adult brain cannot be simply applied to youth who experience stress-related mental health disorders (Lee et al., 2014). Understanding how sensitive periods shift, constrict, or expand in individuals at different points in development will allow treatments to precisely target the biological state of the developing brain to optimize stress-related interventions.

3. Neurobiology of stress

Studies of mature animals have provided the majority of extant knowledge on the effects of stress at the cellular level and show that stress can significantly remodel brain structure and function (reviewed in McEwen, 2012). Stress results in changes in frontolimbic circuitry that are regional in nature. Chronic stress can lead to hypermetabolism and morphological changes within the amygdala, which is critical for learning about the emotional significance of environmental cues and helping the organism react to the challenge or threat of these cues. In contrast, chronic stress downregulates the hippocampus and prefrontal cortex (PFC), which regulate the stress response. Specifically, studies of rodents show that stress increases dendritic arborization and spine density of the amygdala, with concomitant increases in anxiety-like behaviors (Vyas et al., 2002; Vyas et al., 2003; Mitra et al., 2005). By contrast, stress results in atrophy of the hippocampus and medial PFC (mPFC) (Magarinos et al., 1997; Vyas et al., 2002; Radley et al., 2006). Parallel findings of increased amygdala volume and functional reactivity, smaller hippocampal volume, and altered prefrontal function and connectivity have been observed in humans following stress (Ganzel et al., 2007, 2008; Liston et al., 2006; Liston et al., 2009; Sheridan et al., 2012a,b).

The reversibility of the effects of stress is regional as well. There is a growing body of evidence to suggest that the hippocampus and PFC may have greater capacity for change or plasticity following stress with many of the effects being reversible following the termination of stress (McEwen, 1999; Vyas et al., 2004; Liston et al., 2009). In contrast, stress-induced amygdala morphology and volume changes seem to persist (Vyas et al., 2002; Adamec et al., 2005; Tottenham et al., 2010). Due to its cellular properties, the amygdala

![Sensitive Periods of Brain Development](Image)

**Fig. 1.** Model of sensitive periods of brain development. Periods of rapid and substantial changes in brain development, such as the first three years of life and adolescence (shaded in gray), may provide the most opportunity for adaptive behavioral changes. These sensitive periods of neural development may also render the developing brain most vulnerable to the effects of stress. Figure adapted with permission from Lee et al., 2014 (Copyright 2014 AAAS).
Although all groups showed similar acquisition of cued fear, the adolescent mice and humans, relative to younger and older ages. Consistent with work in rats (McCallum et al., 2010; no longer dangerous (Rothbaum and Davis, 2003). are characterized by an inappropriate fear response to a cue that is such as phobias and posttraumatic stress disorder (PTSD), which cess is critical to the etiology and treatment of anxiety disorders. During fear extinction, cues previously associated with threat. During fear extinction, cues previously associated with threat and stress (Dunn and Whitener, 1986; Feldman et al., 1995; Redgate and Fahringier, 1973), and levels of glucocorticoids are regulated via negative feedback loops at several levels of the axis including the hippocampus and PFC (Diorio et al., 1993; Jacobson and Sapolsky, 1991). Opposing regulatory actions occur in amygdala and fronto-hippocampal regions with upregulation of the former and down-regulation of the latter providing a partial explanation for inverse effects of stress within frontolimbic circuitry. This review focuses on the impact of psychological stressors on neuroplasticity, although glucocorticoids, and their direct manipulation, can modify the brain in anatomically selective ways (Sapolsky, 1986; Liston et al., 2013) and alter the expression of neurotrophic factors essential for neuroplasticity (Smith et al., 1995).

4. Developmental changes in the effects of acute stressors

Adolescence is a unique period in development with many implications for the effects of stress. As adolescents transition from dependence on their caregivers to a more independent state, they face many new challenges to which they must adapt (Romeo, 2010; Spear, 2010; Malter Cohen et al., 2013b). Several studies demonstrate changes in emotional reactivity and frontoamygdaloid circuitry in adolescence with important implications for how stress affects adolescents. For example, we have provided evidence of heightened emotional reactivity during adolescence that leads to anxiety when that reactivity persists long after a potential threat is removed (Hare et al., 2008). These findings parallel findings of increased hormonal stress reactivity during puberty and adolescence (Romeo et al., 2006; Folib et al., 2011).

Potential threats can be stressors depending on how they are perceived. Fear conditioning and extinction paradigms provide a powerful way to examine stress reactivity to and regulation of acute threat. During fear extinction, cues previously associated with threat are presented without the threatening stimulus until the cues are learned to be safe and fear responses decrease. This process is critical to the etiology and treatment of anxiety disorders such as phobias and posttraumatic stress disorder (PTSD), which are characterized by an inappropriate fear response to a cue that is no longer dangerous (Rothbaum and Davis, 2003).

Recently we examined fear learning in infants and humans across development. Consistent with work in rats (McCallum et al., 2010; Kim et al., 2011) we showed differential effects of fear extinction in adolescent mice and humans, relative to younger and older ages. Although all groups showed similar acquisition of cued fear, the adolescents showed attenuated fear extinction learning relative to children and adults (Pattwell et al., 2012). Parallel findings were observed in mice, such that adolescent (postnatal day (P) 29) mice showed diminished fear extinction compared with pre- (P23) and post-adolescent (P70) mice. Examination of frontolimbic circuitry in the mice suggested reduced infralimbic prefrontal activity in adolescence during extinction learning. Taken together, this work suggests that adolescence is marked by prominent changes in neurodevelopment that are likely to interact with the effects of stress to influence behavioral phenotypes later in life.

5. Developmental changes in the effects of chronic stress

The timing of stress and its interactions with dynamic developmental processes are critical to subsequent outcomes (e.g., Lupien et al., 2009; Monk, 2008; Monet et al., 2002; Pechtel and Pizzagalli, 2011; Eiland and Romeo, 2013). Manipulating the timing of stress is challenging in humans. However, a series of studies in developing nonhuman primates has shed new light on the effects of stress as a function of timing. The stress manipulation was a maternal separation paradigm that occurred at either 1 week, 1 month, or 3 months after birth (Cameron, 2001; McCormick et al., 2005). The results showed qualitatively distinct behavioral outcomes depending on the timing of the separation. Monkeys who experienced maternal separation at 1 week exhibited less social-contact behaviors than maternal reared animals. By contrast, monkeys who experienced maternal separation at 1 month showed significantly more social behavior. Examination of gene expression changes in the amygdala at 3 months of age in each group indicated downregulation of mRNA expression throughout the amygdala in the monkeys who were separated from their mothers the earliest (Sabatini et al., 2007). These results suggest that the timing (and duration) of stressors may interact with dynamically changing brain systems to alter behavior in complex and unique ways. Moreover, evidence from rodent models suggests that early-life stress may affect different phenotypes in childhood than adolescence (Raineki et al., 2012; Rincón-Cortés and Sullivan, 2014).

Investigations of naturally occurring stressors in humans provide evidence that the onset and duration of stress matters. In studies of children reared in orphanages abroad and later adopted into stable families, the findings consistently suggest that earlier adoption is better (Rutter, 1998; Gunnar et al., 2000; Tottenham et al., 2010). It remains unclear whether earlier adoption is associated with increased resilience due to a shorter duration of stress or because the stress may interact with sensitive periods for emotional development, or both. It may be that the malleability of the brain decreases over time, such that stress and remediation occurring later in development have differential consequences due to changes in the brain’s ability to adapt or recover.

A study of the impact of the 9/11 terrorist attacks on healthy adults provides further evidence of the importance of timing of stress on its neural and behavioral effects (Ganzel et al., 2007). More than three years after 9/11, individuals who were within 1.5 miles of the disaster had higher amygdala reactivity than those who were over 200 miles away. Notably, the association between proximity and amygdala activation was accounted for by the time since the last worst trauma. These findings show that recovery, even in healthy adults, occurs across many years, while also highlighting the importance of the recency of trauma.

6. Lasting effects of early-life chronic stress

Stress can arise through any number of environments that challenge an individual cognitively, emotionally, or physically, such as uncontrollable or unpredictable settings (e.g., Lupien et al., 2000;
Mature frontoamygdala functional connectivity following maternal deprivation. Left) A group by emotion interaction was observed in the mPFC (p = 0.01, corrected), such that group differences emerged when participants viewed fearful faces. Right) Unlike comparison children who showed immature (positive) amygdala-mPFC connectivity, children with a history of early-life stress (previous institutionalized care) exhibited the mature pattern of inverse amygdala-mPFC functional connectivity (Gee et al., 2013a,b) (Fig. 2). This marked shift in connectivity may reflect early closure of a neural sensitive period that could have long-term consequences for later affective behaviors.

To better understand the functional significance of accelerated neural circuit development we tested whether amygdala-mPFC functional connectivity was related to anxiety. Children with a history of early-life stress had higher levels of anxiety than comparison children, consistent with prior findings. However, youth in the early-life stress group with the mature phenotype of inverse functional connectivity had lower anxiety than those with the immature phenotype of positive functional connectivity. It may be that the earlier emergence of mature connectivity is adaptive in the context of early-life stress. Cortisol levels mediated the relationship between early-life experience and frontoamygdala connectivity, suggesting that stress-related modifications of the LHPA axis may shape the early development of amygdala-mPFC connections. Accelerated frontoamygdala development may serve as an ontogenetic adaptation that reprioritizes development to cope with an early adverse environment. However, the long-term consequences of this accelerated development remain unclear.

7. Translational studies of early-life stress

Naturalistic studies of stress effects in humans have provided critical insight into the neurobiological mechanisms through which stress has lasting effects on emotional behavior. However, the interpretation of these studies is limited by confounds of uncontrolled genetic and environmental factors. To address these concerns we recently conducted a translational study in mice in which we were able to manipulate the type and timing of stress in rodents to mimic the orphanage-rearing environment in humans and

McEwen, 2012; Pollak, 2008; Sheridan et al., 2013; Teicher et al., 2006). However, environments that result in a mismatch between the expected and actual environment may prove particularly stressful (Finlay, 2007; Casey et al., 2010). Environmental stability across a long evolutionary history has led to species-expected experiences, such as caregiving for humans early in life. Consistent with this idea, poor caregiving is one of the most potent stressors for an infant and has long-lasting effects on the brain and behavior (e.g., Sheridan et al., 2012a,b; reviewed in Tottenham, 2012). Maternal separation in rodent pups is associated with greater LHPA axis reactivity (Moriceau et al., 2010), accelerated amygdala development (Moriceau and Sullivan, 2006; Ono et al., 2008), increased anxiety-like behaviors (Romeo et al., 2003), and more social instability in adulthood (Kikusui and Mori, 2009). Human studies of maternal deprivation early in life have shown atypical frontoamygdala development and function with greater amygdala volume, amygdala hyperactivity, and less prefrontal activity to emotional stimuli, as well as long-term impairments in anxiety and social behavior (Mehta et al., 2009; Zeanah et al., 2009; Tottenham et al., 2010, 2011). The enhanced amygdala activity and decreased prefrontal activity in the children with a history of maternal deprivation may suggest that they are less able to suppress irrelevant emotional information leading to dysregulation of emotions. By preschool these children have a rate of mental health disorders that is more than twice that in children who did not experience institutional rearing (Zeanah et al., 2009).

Until recently, less has been known about changes in the long-term course of brain development following early-life stress. Recent studies in our respective laboratories indicate that early-life stress has lasting effects on the organization of frontolimbic circuitry. We specifically examined the effects of orphanage rearing on development of frontoamygdala activity and connectivity. With typical development, task-based frontoamygdala functional connectivity switches from positive coupling in childhood to inverse coupling during the transition to adolescence (Gee et al., 2013a,b) (Fig. 2). This mature pattern of inverse amygdala-mPFC functional connectivity is consistent with the inverse connectivity observed in the literature of emotion regulation in healthy adults (Banks et al., 2007; Hare et al., 2008; Hariri et al., 2003; Kim et al., 2003).

Based on evidence that early-life stress accelerates amygdala development in rodents, we hypothesized that children who experienced maternal deprivation early in life would display altered development of frontoamygdala circuitry. Children who were reared in international orphans as infants and were subsequently adopted into stable families in the U.S. provided a means of examining an isolated period of early-life stress (i.e., institutionalized care) on later brain development and behavior. In contrast to the immature positive functional connectivity displayed in comparison children, the children who experienced early-life stress showed the adult-like pattern of inverse amygdala-mPFC functional connectivity (Gee et al., 2013a,b) (Fig. 2). This marked shift in connectivity may reflect early closure of a neural sensitive period that could have long-term consequences for later affective behaviors.

Fig. 2. Mature frontoamygdala functional connectivity following maternal deprivation. Left) A group by emotion interaction was observed in the mPFC (p < 0.01, corrected), such that group differences emerged when participants viewed fearful faces. Right) Unlike comparison children who showed immature (positive) amygdala-mPFC connectivity, children with a history of early-life stress (previous institutionalized care) exhibited the mature pattern of inverse amygdala-mPFC coupling, such that the stressed children resembled adolescents. The results suggest an early closure of a sensitive period in frontoamygdala development following early-life stress. Error bars = ± 1 SEM; *p < 0.05. Data are reproduced with permission from Gee et al., 2013a (Copyright 2013 Proceedings of the National Academy of Sciences of the United States of America).
examine the long-term effects (Malter Cohen et al., 2013a,b). The early-life stress manipulation involved limiting the nesting material provided to the dams, which disrupted maternal care of the pups (Gilles et al., 1996; Ivy et al., 2008; Rice et al., 2008). This stressor was limited to the pre-weaning period (P2–P21) that paralleled the adoption of most children from orphanages during early childhood.

To capture the heightened emotional reactivity and slowing of response latencies in anticipation of negative emotional information in children reared in the orphanage (Tottenham et al., 2011), we modified a task for the mice to get them to approach potential threat. Specifically we used a paradigm through which mice were trained where to obtain sweetened condensed milk in their home cage. After several days of training we then tested the mice in a brightly lit novel cage. Both juvenile and adult mice that grew up with the stressed dam took longer than the nonstressed mice to approach the milk in the novel cage of potential threat relative to the home cage.

We used measures of c-Fos expression to examine the effects of early-life stress on frontoamygdala circuitry. Mice exposed to early-life stress had persistently elevated levels of c-Fos in the basolateral amygdala relative to the nonstressed mice across development (Fig. 4a). These effects persisted even after the stressor was removed and after maturity of infralimbic (prefrontal) cortical maturation in adulthood (Fig. 4b). These findings in the mice provide converging evidence with that of alterations in amygdala function in humans following early-life stress. Specifically, both mice and humans who experienced early-life stress showed greater amygdala activity and took longer to approach a target in the context of potential threat than nonstressed mice and humans. These results suggest that early-life stress impairs the ability to suppress fear responses in favor of goal-directed behavior, and that these effects persist into adulthood even after the cessation of the stressor and the development of the PFC.

8. Buffering against the effects of stress during development: toward resilience and intervention

Identifying mechanisms to buffer against stressful life events is critical to promoting healthy outcomes following stress, treating stress-related mental health disorders, and ultimately, preventing stress-related forms of mental and physical illness. These efforts must also focus on understanding when specific buffers are most effective in development and how to enhance resilience at unique developmental stages. Resilience involves not only the ability to recover from stress-related damage but also to adapt to changes in the environment (McEwen, 2012). Individuals accustomed to stable, safe environments may vary in the extent to which they can adapt to novel, riskier environments, such as young infants being placed in orphanage care. By contrast, the process of transitioning from a risky environment to a safe, stable environment also requires plasticity and resilience. Children who were reared as infants in orphanage care who are then adopted into stable, loving families face drastic (though typically positive) shifts in their environment.

Caregiving provides a host of regulatory functions in humans, such as buffering against emotion dysregulation and stress reactivity in youth (Campos et al., 1975; Hofer, 1994; McCoy and Masters, 1985; Gunnar and Donzella, 2002). One way in which plasticity may be increased following the closure of sensitive periods is through exercise and environmental enrichment, such as the influence of an exceptionally nurturing, stable family who adopts a child who previously experienced early-life stress. Consistent with this idea, findings from the Bucharest Early Intervention Project show that children who were removed from institutionalized care and placed in foster families had lower rates of internalizing disorders than those who continued in institutional care (Zeanah et al., 2009). Parent-child relationships may thus be central to buffering against stressful life events during certain times in development.

In rodents, a sensitive period for the effects of maternal presence on amygdala development has been identified (Moriceau and Sullivan, 2006; Callaghan and Richardson, 2011). Specifically, maternal presence suppresses corticosterone and amygdala reactivity during an early sensitive period in pre-weaned rodent pups (before P21) that appears to reduce fear and promote attachment.
behaviors. In addition, maternal presence has been shown to reduce cortisol levels in childhood (Hostinar et al., 2014). Though sensitive periods have been more elusive in human development, recent work highlights possible periods during which the environment may have greater influence on the neural circuitry affected by early-life stress in human development.

Frontoamygdala circuitry is particularly sensitive to the effects of the environment in childhood. Based on the identification of a sensitive period for maternal influence in rodents, we tested whether caregiver presence differentially affected frontoamygdala circuitry in children versus adolescents (Gee et al., 2014). We designed an fMRI task that manipulated visual presence of the caregiver with an image of the participant’s mother’s face or a stranger’s face. Participants also completed a laboratory-based behavioral task of affect regulation in the presence of their mother and in the presence of a stranger (order of administration was counterbalanced). Findings revealed that the maternal stimulus phasically induced an adult-like pattern of maternal buffering of maternal influences to buffer against stress reactivity in childhood. Research on nonhuman primates has shown that moderate stress exposure is associated with lower cortisol following stress and decreased anxiety (Parker et al., 2004), as well as increased prefrontal volume and enhanced prefrontal function (Parker et al., 2005; Katz et al., 2009).

Though the concept of stress inoculation remains relatively unexplored in human development, the notion of too much or too little stress yielding suboptimal effects on brain and behavior, but moderate stress yielding benefits in an inverted-U pattern, has been around for some time (Arnsten and Goldman-Rakic, 1990, 1998; McEwen and Sapolsky, 1995). Partial evidence for this notion in humans has been shown with moderate stress early in life being associated with reduced cortisol reactivity to subsequent stressors, compared with mild or severe stress early in life (Gunnar et al., 2009; Hagan et al., 2014). Thus, whether physiological responses to stress are adaptive or maladaptive depends on the nature as well as the timing of the stress.

In addition to environmental interventions, novel studies of brain plasticity are beginning to shed light on ways in which it may be possible to alter plasticity by re-opening sensitive periods (reviewed in Davidson and McEwen, 2012). Evidence from a promising line of studies suggests that shifting the excitatory-inhibitory balance in relevant neural circuits may increase plasticity (Thompson et al., 2008; Bavelier et al., 2010). For example, reductions of inhibitory neural activity in adulthood have increased visual plasticity in rodents (He et al., 2007; Sugiyama et al., 2008; Harauzov et al., 2010) and even restored visual function in amblyopic adult rats (Vetencourt et al., 2008). Interventions to recapitulate sensitive periods have been less explored in humans, but hold promise with future research that will be critical for understanding how behavioral interventions, pharmacological interventions, and environmental manipulations may alter plasticity following the closure of sensitive periods.

![Fig. 4. c-Fos activity by group and age. (A) The density of c-Fos protein in the amygdala following exposure to the threatening context (i.e. novel cage) was elevated in stressed mice across development relative to nonstressed animals. (B) The density of c-Fos protein in the infralimbic PFC increases with age regardless of stress history. Error bars – ± 1 SEM; ‘p < 0.05. Data are reproduced with permission from Malter Cohen et al., 2013a (Copyright 2013 Proceedings of the National Academy of Sciences of the United States of America).](image-url)
9. Neuroplasticity and the effects of stress in adults

Though much remains unknown about the relationship between stress and neuroplasticity during development, recent studies in adult rodents and humans have examined the effects of moderate stress on the plasticity of prefrontal circuitry and function. In these studies, we (Liston et al., 2009) have shown enhanced focus of attention and rewiring of prefrontal circuitry during stress that was reversible when the stressor was of moderate intensity and short-lived (a few weeks). Specifically we tested medical students studying for the boards reporting high levels of stress relative to other students not experiencing examination-related stress. Those individuals reporting high levels of stress showed diminished capacity to shift attention. This enhanced focus of attention was paralleled by diminished functional connectivity within prefrontal circuitry (Fig. 6). Importantly, the attentional and connectivity effects were reversed several weeks later following the board examination (Liston et al., 2009).
These stress-induced alterations of prefrontal circuitry and resulting attentional focus in humans may be best understood in the context of a parallel study in rodents (Liston et al., 2006). Rats were exposed to three weeks of restraint stress. This stress selectively altered prefrontal circuitry and function specific to attention shifting, but not other processes of comparable difficulty (Liston et al., 2006, 2009). The stressed rats showed reduced dendritic arborization and spine density in mPFC (Fig. 6) consistent with prior work showing similar effects following chronic stress (Cook and Wellman, 2004; Radley et al., 2004, 2006), with some evidence that effects on mPFC were reversible (Radley et al., 2005). Stress appears to restrict feedforward projections to PFC, which may focus and maintain attention on the relevant stressor and minimize attentional shifting to irrelevant events that are less important in the face of current stressors. Alterations in prefrontal functional connectivity that bias attention toward one salient category of inputs may be adaptive for dealing with psychosocial stress in the short-term, particularly when these effects reverse following reductions in stress. However, less is known about the reversibility of moderate stress-induced effects during development. Given the reversibility of the effects of stress on hippocampal and prefrontal regions (McEwen, 1999; Vyas et al., 2004; Liston et al., 2009), it may be possible to design interventions that specifically target these regions to reverse negative effects of stress. Moreover, the consideration of sensitive periods will provide important insight into when neuroplasticity may be heightened in these regions such that interventions can be delivered during developmental windows of opportunity.

10. Conclusions

There is an expanding literature on the profound effects of stress on the organization and function of the brain. The timing and nature of stressful events can dictate the adaptiveness or maladaptiveness of the stress response. When stress occurs, how long it lasts, and how its timing interacts with sensitive periods in brain development shape the effects of stress on behavior and risk for psychopathology. Stress-induced remodeling of the brain may help the organism to adapt to short-term needs in a stressful environment; however, changes that were once adaptive may be maladaptive following cessation of the stressor. Stress that occurs early in life has lasting effects that often do not reverse even after cessation of the stressor or after maturity of prefrontal regions implicated in downregulation of stress. Most chronic early-life stressors studied to date involve a mismatch between species-expected experiences and actual experiences, such as sparse and unstable caregiving. Stable parental care plays a significant role in mitigating or buffering the offspring from the effects of early-life stress and facilitates the development of typical emotional regulation. Studies of dynamic models that consider the age and timing of stress and changing environments are critical for moving toward an understanding of how stress promotes and hinders resilience to inform developmentally-tailored interventions that target the biological state of the developing brain for at-risk youth.

Acknowledgements

This work was supported in part by a generous gift from the Mortimer D. Sackler, M.D., family and NIH grant P50 MH079513.

References

Adamec, R.E., Blundell, J., Burton, P., 2005. Neural circuit changes mediating lasting brain and behavioral response to predator stress. Neurosci. Biobehav. Rev. 29 (8), 1225–1241. http://dx.doi.org/10.1016/j.neubiorev.2005.05.007.
Arnsten, A.F., Goldman-Rakic, P.S., 1990. Analysis of alpha-2 adrenergic agonist effects on the delayed non-match-to-sample performance of aged rhesus monkeys. Neurobiol. Aging 11 (6), 583–590.
Arnsten, A.F., Goldman-Rakic, P.S., 1998. Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. Arch. Gen. Psychiat. 55 (4), 362–368.
Lupien, S.J., McEwen, B.S., Gunnar, M.R., Heim, C. 2009. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat. Rev. Neurosci. 10 (6), 434–445. http://dx.doi.org/10.1038/nrn2630.

Lupien, S.J., Parent, S., Evans, A.C., Tremblay, R.E., Zelado, P.D., Corbo, V., Seguin, J.R., 2011. Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. Proc. Natl. Acad. Sci. U. S. A. 108 (34), 14324–14329. http://dx.doi.org/10.1073/pnas.1105371108.

Magarinos, A.M., Verdugo, J.M., McEwen, B.S., 1997. Chronic stress alters synaptic terminal structure in hippocampus. Proc. Natl. Acad. Sci. U. S. A. 94 (25), 14002–14005.

Malter Cohen, M., Jing, D., Yang, R.R., Tottenham, N., Lee, F.S., Casey, B.J., 2013a. Maternal presence serves as a switch between stress and resilience in adolescent rats: effects of D-cycloserine. Neuropsychopharmacol. Off. Publ. Am. Neurosci. Assoc. 38 (12), 2192–2204. http://dx.doi.org/10.1038/npp.2014.62.

Mitra, R., McEwen, B.S., Heim, C. 2005. Stress duration. Proc. Natl. Acad. Sci. U. S. A. 102 (21), 7305–7306. http://dx.doi.org/10.1073/pnas.0403112102.

Mccallum, J., Kim, J.H., Richardson, R., 2010. Impaired extinction retention in mice and humans. Proc. Natl. Acad. Sci. U. S. A. 107 (40), 16323–16328. http://dx.doi.org/10.1073/pnas.1007684107.

Monk, C.S., Pine, D.S., Charney, D.S., 2002. A developmental and neurobiological investigation of stress inoculation in young monkeys. Arch. Gen. Psychiatry 59 (10), 933–940. http://dx.doi.org/10.1001/archpsyc.59.10.933.

Moriceau, S., Sullivan, R.M., 2006. Maternal presence serves as a switch between stress and resilience in adolescent rats: effects of D-cycloserine. Neuropsychopharmacol. Off. Publ. Am. Neurosci. Assoc. 38 (12), 2192–2204. http://dx.doi.org/10.1038/npp.2014.62.
Tottenham, N., 2012. Human amygdala development in the absence of species-expected caregiving. Dev. Psychobiol. 54 (6), 598–611. http://dx.doi.org/10.1002/dev.20531.

Tottenham, N., Sheridan, M., 2009. A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. Front. Hum. Neurosci. 3, 68. http://dx.doi.org/10.3389/neuro.09.068.2009.

Tottenham, N., Hare, T.A., Quinn, B.T., McCary, T.W., Nurse, M., Gilhooly, T., Casey, B.J., 2010. Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. Dev. Sci. 13 (1), 46–61. http://dx.doi.org/10.1111/j.1467-7687.2009.00852.x.

Tottenham, N., Hare, T.A., Millner, A., Gilhooly, T., Zevin, J.D., Casey, B.J., 2011. Elevated amygdala response to faces following early deprivation. Dev. Sci. 14 (2), 190–204. http://dx.doi.org/10.1111/j.1467-7687.2010.00971.x.

Vetencourt, Maya, Sale, J.F., Viegi, A., Baroncelli, A., De Pasquale, L., O'Leary OF, R., Maffei, L., 2008. The antidepressant fluoxetine restores plasticity in the adult visual cortex. Sci. (New York, N.Y.) 320 (5874), 385–388. http://dx.doi.org/10.1126/science.1150516.

Vyas, A., Mitra, R., Shankaranarayana Rao, B.S., Chattarji, S., 2002. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J. Neurosci. Off. J. Soc. Neurosci. 22 (15), 6810–6818 doi: 10.1523/JNEUROSCI.0266-02.2002.

Yang, E.J., Lin, E.W., Hensch, T.K., 2012. Critical period for acoustic preference in mice. Proc. Natl. Acad. Sci. U. S. A. 109 (Suppl. 2), 17213–17220. http://dx.doi.org/10.1073/pnas.1200705109.

Yakovlev, P.I., Lecours, A.R., 1967. The myelogenetic cycles of regional maturation of the brain. In: Minkowski, A. (Ed.), Regional Development of the Brain in Early Life. Blackwell Scientific, Oxford, pp. 3–70.