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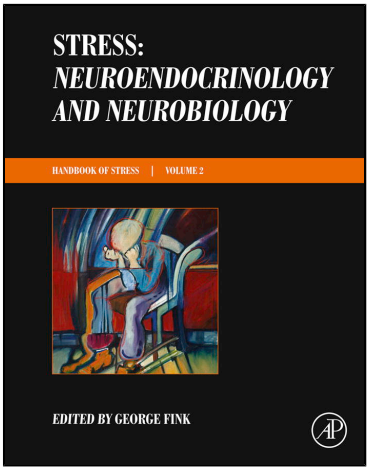

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CHAPTER

13

Early Life Stress- and Sex-Dependent Effects on Hippocampal Neurogenesis

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OUTLINE

Abstract

Neurogenesis refers to the birth of new neurons in an adult brain, a form of structural plasticity that has been implicated in cognition, mood, and anxiety, and is well regulated by environmental and hormonal factors. Exposure to stress (hormones) generally inhibits neurogenesis. Here, we discuss (sex-dependent) effects of stress on adult hippocampal neurogenesis, and focus on stress during the sensitive period of early life. While the effects of acute, mild stress are generally short-lasting and recover quickly, chronic or severe forms of stress can induce longer-lasting reductions in adult neurogenesis, especially when encountered during early life. Some of these inhibitory effects of early stress can normalize after appropriate recovery periods, exercise, drugs targeting the stress system, and some antidepressants. Early life stress may (re-)program hippocampal plasticity, thereby altering the overall composition of the hippocampal circuit. This may modify stress responsivity, hippocampal function, later cognition, and the risk for psychopathology.

STRESS, TIME DOMAINS, AND MEDIATORS OF THE STRESS RESPONSE

In daily life, environmental challenges and exposure to stressful experiences can often not be avoided. Stress could be defined as any environmental demand that exceeds the physiological regulatory capacity of an organism, particularly during unpredictable situations. Stress can be psychological in nature as during financial or work-related problems,[190] or also involve biological changes, such as metabolic crises or inflammation. In many instances, exposure to any (perceived or real) stressor elicits a stress response that enables the individual to respond appropriately and ultimately maintain or regain homeostasis.

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KEY POINTS

- Stem cells are present in the brains of many different species including primates and humans. In a few brain regions, mainly olfactory bulb and hippocampus, these stem cells continue to produce new neurons in the adult brain.
- During this process of "adult neurogenesis," stem cells go through subsequent phases of proliferation, selection, fate specification, migration, and neuronal differentiation before they eventually form fully functional neurons that integrate into the adult neuronal circuit and contribute to brain functions, such as cognition, pattern separation, mood, and anxiety.
- Adult neurogenesis is regulated by many environmental and hormonal factors. Enriched environmental housing and voluntary physical exercise generally stimulate, whereas age and exposure to stress inhibit neurogenesis.
- While effects of acute and mild stress are generally short-lasting and recover quickly, chronic or severe forms of stress can induce lasting reductions in neurogenesis, especially when encountered during early life. Different paradigms and effects are discussed.
- Early life stress may (re-)program hippocampal plasticity, thereby altering the overall composition of the hippocampal circuit, which may modify later stress responsivity, hippocampal function, cognition, and the risk for psychopathology.

The perception and interpretation of different types of stress, and the individual's response to it, depends largely on genetic background, sex, coping strategies, and personality traits. Early life experiences, early nutrition, epigenetics, and gene–environmental interactions are also important in "programming" the adult response to stress, and from there, the risk for psychopathology.[14,70,72,80,101,103,117]

The endocrinological response to stress first involves adrenal epinephrine and norepinephrine release, hormones that elevate blood pressure and respiration, and increase blood flow to essential organs. Later, the hypothalamic–pituitary–adrenal (HPA) axis is activated as well, a classic neuroendocrine circuit that coordinates various emotional, cognitive, neuroendocrine, and autonomic inputs, and determines the specific behavioral, neural, and hormonal repertoire of an individual's response to stress.[69,72] Ultimately, the stress response helps to (re-)direct energy and focus attention on the most urgent elements of a challenge, whereas less urgent, "maintenance" functions (e.g., digestion), are temporarily suppressed.[72]

Activation of the HPA-axis starts with corticotropin-releasing hormone (CRH) production in the paraventricular nucleus (PVN) that eventually releases glucocorticoids (GCs) from the adrenal. Negative feedback of the stress response occurs after binding of GCs to high-affinity mineralocorticoid (MR) and lower-affinity glucocorticoid receptors (GR) in brain.[29] The GR helps to maintain GC levels within physiological limits[38,84] and aberrant GR expression, or GR/MR variants, have for example been implicated in hypercortisolism, hippocampal changes, stress resistance, anxiety, and depression.[29,149,197,202,205] GCs act as transcription factors that bind to glucocorticoid responsive genes where they act in a slow, genomic manner, although also faster, non-genomic actions exist.[76,186] GC plasma levels are under circadian and ultradian control[96,147] that modifies stress sensitivity.[39,52,118,157–159]

Upon their release in the periphery, GCs affect energy, inflammatory responses, and lipid metabolism, among others. Hence, imbalances in GC regulation can have deleterious consequences,[29] which is particularly relevant for the brain, where a high density of GRs exists, especially in the hippocampus, which makes this structure highly responsive to stress.[29,181,203] Indeed, GCs can influence memory, fear, and attention in a negative manner, particularly when exposure to stress is chronic and uncontrollable. This may relate to altered MR/GR levels and/or balance,[29,146] which may alter HPA feedback and increase the risk for psychopathology. Positive effects of stress, such as enhanced memory formation, have been described too, which depend on the timing, type, and controllability of a stressor.[71,167] While functional changes after stress involve reductions in hippocampal excitability, long-term potentiation, and hippocampal memory, morphological consequences of stress include hippocampal volume reductions as well as a number of cellular changes, notably dendritic atrophy and a suppressed rate of adult neurogenesis (see later).[24,104,156]

ADULT NEUROGENESIS

Adult neurogenesis (AN) refers to the production of new neurons in the adult brain. These adult-generated neurons are derived from stem cells that go through stages of proliferation, fate specification and apoptosis, migration, and neuronal differentiation, before they eventually yield new, functional neurons that integrate into the preexisting, adult network of the hippocampus.[1,67,77,189,198,216] AN is dynamically regulated by various environmental factors and declines with age (e.g., Refs. 55,87). Adult cytogenesis and neurogenesis has also been reported in other brain structures, like the

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amygdala, striatum, hypothalamus, and neocortex, with differences between species, and often in response to specific challenges or injury.[45,112]

AN in the dentate gyrus (DG) is potently stimulated by exercise and environmental enrichment, notably parallel to improvements in hippocampal function.[78,199] Whereas rewarding experiences can stimulate AN,[182] aversive experiences like stress generally decrease AN.[9,102,105]

STRESS AND ADULT HIPPOCAMPAL NEUROGENESIS

Exposure to stress during adult life is one of the best known environmental suppressors of AN. Both psychosocial[26,46] and physical stressors[108,144,201] can inhibit one or more phases of the neurogenesis process.[102,105,120] In classical studies, rodents exposed to the odor of a predator generated a strong stress hormone response that was associated with significant parallel reductions in hippocampal proliferation. Both acute and chronic stressors generally suppress proliferation and many different types of stressors, including physical restraint, social defeat, inescapable foot shock, sleep deprivation, and mixed types of multiple, unpredictable or mild stressors, generally all decrease numbers of new neurons in the dentate gyrus.[26,34,46,54,55,65,66,90,122,142,144,165,172,212]

Notably, exceptions exist in stress inhibition of neurogenesis in that negative findings have also been reported.[27,50,51,106,134,141] These might depend on the type of stressor applied, or the species, sex, or strain.[50,51,73,165,207] Interindividual variation in the behavioral susceptibility to stress is also a relevant factor.[94] In some instances, increased AN has been reported after stress, but in these studies, the stressors were often predictable, controllable, and/or mild, may actually have enriched an otherwise boring environment and could have been perceived as rewarding experiences.[141,193,164]

AN in the hippocampus is further required for the beneficial effects of an enriched environment on recovery from stress-induced changes in behavior[161] where it is correlated with increased survival of newborn cells and AN.[161,185] Surprisingly, housing animals in an enriched environment that includes voluntary exercise, increases GCs,[200] suggesting that this rise in GC levels is essential for increased AN in the hippocampus.[154,161] When rats are adrenalectomized, admittedly a highly artificial condition, environmental enrichment-induced increases in AN are no longer apparent,[90] indicating that GCs can facilitate adult hippocampal neurogenesis under specific conditions. Also somewhat counterintuitively, exercise, which is considered a potent stimulus for AN,[195] stimulates GC levels, even though exercise per se reduces stress.[75] Cessation of voluntary exercise subsequently impairs AN and can increase anxietylike behavior[132] consistent with other studies that indicate that changes in AN often correlate with anxiety measures.[58,61,143,148,168,214]

When no other transmitter systems are altered and the stressor is unpredictable or uncontrollable and its nature severe, stress generally reduces AN.[34,56,65,66,90,122,142,144,165,172] In fact, this type of stress can reduce multiple stages of the neurogenic process, including the initial phase of proliferation of the neural stem cells and amplifying progenitor cells, as well as subsequent neuronal differentiation phase and dendritic expansion. Exposure to GCs per se was even shown to deplete the neural precursor pool.[213] Stress not only reduces proliferation and AN in many different species, it may also shift neural stem cells away from neuronal differentiation, and instead "redirect" them towards the generation of oligodendrocytes.[20] Although not studied in great detail yet, such (early) stress-induced fate shifts may have important functional consequences: e.g., for the myelination of axons and/or mossy fibers, and hence network connectivity, particularly when they occur during early development when cell division is massive.

Although different types of stress trigger different behavioral and functional responses, adrenal GCs (GCs; corticosterone in rodents; cortisol in man) are considered instrumental in mediating the suppressing effects of stress on AN.[165] The basis for this assertion is as follows. First, exogenous GC administration to animals has effects similar to those of stress on cell proliferation, neuronal differentiation, and cell survival,[62,115,211,213] as well as on the production of oligodendrocytes and microglia responses. Second, the reductions in AN after stress, and many of the molecular[28] and physiological[85] changes, can be prevented by blocking the GR, for a very short period[62,115,137] or by CRH antagonists.[5] Furthermore, in a transgenic mouse model of AN inhibition, a transient increase in the corticosterone response to stress occurs as well as an attenuated dexamethasone-induced suppression of corticosterone release.[175] This is indicative of a role for the newborn cells in regulating HPA axis activity. On the other hand, ablation of AN by irradiation did not impair basal HPA axis activity.[179,101,103]

Although general blockers of different parameters of the stress system are thus effective, the precise mechanism(s) by which GCs decrease the numbers of new neurons remains poorly understood. More information has become available on its molecular control.[6,119,166] NMDA receptors, GRs and MRs, all present on the new cells, albeit in different ratios over time, likely act in concert to mediate effects of stress on AN.[43,125,209,210] Notably, GR knockdown, selectively in newborn cells, accelerates their neuronal differentiation and migration, alters their dendritic complexity, parallel to impaired contextual freezing during fear conditioning. Hence, GR expression in the newborn hippocampal cells is important

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for structural as well as functional integration into the mature hippocampal circuits involved in fear memory.[40]

Furthermore, most precursors in the brain are located closely to blood vessels.[140] Although often not distinguished in quantitative analysis, this proximity makes this population particularly sensitive to stress hormones[57] and many other peripheral factors. Astrocytes are also of relevance as they closely align the vasculature, express GRs, support the survival of developing neurons, and are involved in their synaptic integration.[178] Notably, astrocytes are affected by some, but not all, types of stress.[10,25,136,191,203]

Stress further slows down neuronal differentiation of the adult-born cells, as evidenced by the upregulation of markers indicating cell cycle arrest[54] that may be induced by specific changes in DNA methylation.[15] Stress also reduces the survival of new neurons that were born already: i.e., prior to the actual stressful experience. A change in "corticoid environment"[211] is thought to be mediated by stress-induced reductions in neurotrophins and survival promoting factors, such as brain-derived neurotrophic factor (BDNF), insulinlike growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) (e.g., Refs. 162,208). Reductions in newborn cell survival may involve microglia, which can phagocytose new neurons. Indeed, stress influences microglia, both number and responsivity, which may modulate their efficiency in clearing debris or dead neurons,[59,126,170] or their capacity to release neurotoxic cytokines.[48,83,97,169]

An important difference between studies on temporal aspects of stress and AN is whether GC levels remain elevated or not after the initial exposure to stress has ended. In some psychosocial stress models, GC levels remain elevated, which has stronger suppressive effects on AN than exposure to severe, but predictable, physical stressors, such as restraint.[209] Several examples exist of a persistent and lasting inhibition of AN after an initial exposure to stress, despite a later lowering of GC levels.[26,120] In contrast, GC levels can remain elevated after a psychosocial stressor, with AN being suppressed long term. In milder models of stress, GC levels generally normalize, yet AN remains reduced.[165,192] This suggests that while GCs are involved in the initial suppression of proliferation, they are not always necessary for maintaining this effect.

When studying effects of stress on AN in laboratory conditions, it is further important to realize that many variables influence the outcome.[12] These variables include interindividual genetic or gender differences in stress coping and resilience,[93] prior handling of the animals, time of day at sacrifice, and previous exposure to stressful learning tasks, e.g., the water maze, or exercise.[35,36,60,111] Anatomical differences exist, such as in projections to specific subregions of the hippocampus or in the larger networks, or neuromatrix.[176] Thus, stress effects on AN might differ between the dorsal or the ventral hippocampus depending upon the stimulus.[133,184]

Many other factors may contribute to the stress-induced inhibition of AN, such as the stress-induced increase in glutamate release and NMDA receptor activation[46,128,165] or through stress effects on various neurotransmitter systems implicated in the regulation of AN, such as GABA,[44] serotonin,[32] noradrenaline,[68] acetylcholine,[16] dopamine,[33,182] cannabinoids, opioids, nitric oxide, and gonadal steroids.[9,42,107] Many antidepressant drugs that interfere with stress-related behavior in animals also modulate AN. The relation between stress, AN, antidepressants, and mental illnesses, such as major depression has been extensively discussed, but is beyond our current scope and we therefore refer to recent literature.[34,104,102,105,108,142,151,155,164,179,184]

In functional terms, AN has been linked to various cognitive measures, with AN being relevant for some, but not all forms of hippocampal dependent learning and memory.[2,22,135,152,153,160,215] Stress-induced suppression of AN is linked to an impaired performance on various hippocampal tasks, such as spatial navigation and object memory, as well as anxiety-like behaviors, as measured with the elevated plus maze, open field and novelty suppressed feeding tasks.[91,123,124,175,196]

LONG-LASTING EFFECTS OF EARLY, PERINATAL STRESS EXPOSURE; SEX DIFFERENCES

The brain is particularly sensitive to stressful experiences during the early postnatal period given the large numbers of dividing cells that form neuronal networks and eventually produce behavior. By interacting with inborn genetic risk factors, environmental factors such as early life stress (ELS) specifically target the development of brain structures and mechanisms involved in emotional and stress regulation.[30,174,194] Thus stress during early life has been implicated in many changes in later brain structure and function, and in an increased risk for psychopathology and age-related cognitive dec line.[19,21,49,53,86,113,116,131,188] Mechanistically, exposure to early stress can induce epigenetic modifications of stress-related genes.[8,23,88,101,103] In addition to changes in the set point of HPA axis activity, e.g., GC feedback sensitivity, regulation of AN also appears to be modified by stress-exposure during the perinatal period.

In experimental conditions, ELS affects hippocampal, emotional and cognitive functions, and stress reactivity later in life.[4,11,17,63,139] AN is very sensitive to ELS and exposure to perinatal stress typically induces reductions in AN in adult offspring[82,91,100,121,129,180] although exceptions also occur.[187] Infection during pregnancy represents a stressor and reduces cell proliferation and AN

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in both juvenile and adult offspring.[95] Undernourished mothers similarly produce offspring with lower rates of cell proliferation and neuronal survival in adulthood.[114] Prenatal stress and maternal separation further decrease the size and complexity of adult born neurons.[92,183] The effects are generally brain region-specific: prenatal stress e.g., impaired AN in the DG but not in the olfactory bulb.[13]

While in utero exposure to stress almost invariably reduces AN in adulthood,[91] postnatal stress exposure yields more variable results, and is modified by maternal and paternal factors, sex, genetic background, and epigenetic changes, although suppression of AN prevails as well.[79,89,98,101,103]

During the early postnatal period, individuals are particularly dependent on parental care, which is important for emotional and cognitive development and for attachment styles.[11,19,31] In rodents, postnatal stress is often induced by disturbing this important mother–child interaction. Many models have been developed, including 24-h maternal deprivation at different days during the stress hyporesponsive period of the first 2 weeks of rodent life. When applied on postnatal day (PND) 3, this can be considered a model for maternal neglect.[110,145] Maternal separation protocols exist as well, where the mother is removed from her pups for shorter periods of time, but this is done repeatedly, e.g., for several days. Interestingly, this generally increases the amount of maternal care and is hence considered less stressful than maternal deprivation. Limiting the amount of nesting and bedding material during the first week of life has further become a popular animal model for ELS. The latter induces lasting effects on AN and cognition, often in a sex-dependent manner. In maternal separation or maternal deprivation paradigms generally reductions are seen in cell proliferation, AN, and the survival of new neurons in adult rodents in the dentate gyrus.[3,92,121,139] These effects often display a clear sex difference and depend on the moment when AN is studied.[89,138,139]

Alternative methods to study effects of stress include selected breeding that can result in animal lines that differ in specific traits, like stress responsivity or resilience, anxiety, or in different displays of maternal care. In such lines, neuronal survival was found to be decreased, and apoptosis increased, in offspring of low-caring mothers versus offspring of high-caring mothers, that differ in their stress response.[204] In addition, repeated maternal separation (MS) leads to lastingly decreased levels of proliferation,[121] without affecting neuronal survival in the DG.[47,121] In a similar model, a biphasic response was also found in hippocampal AN as well as in BDNF expression and cognition, suggesting that ELS may endow animals with a potential adaptive advantage in stressful environments on the short term but with increasing age, is associated with long-term deleterious effects.[180] MS was also shown to alter the capacity of neural precursor cells to differentiate into neurons, which is mediated via methylation of the retinoic acid receptor gene promoter.[15,101,103] Furthermore, in rats selectively bred for inborn levels of anxiety, prenatal stress was reported to decrease the survival of newly-generated cells as well as AN in the hippocampus of high-anxiety breeders only.[100] Interestingly, this lower rate of AN was paralleled by an impaired integration of the newborn neurons when compared to normal rats, specifically in females.[150]

The maternal deprivation paradigm differs from maternal separation in that it is not repeated for several days, and is longer lasting, i.e., 24 h long instead of daily periods of a few hours. Maternal deprivation was found to transiently increase the numbers of immature (DCX-positive) neurons in male rats 3 weeks of age,[136] ultimately leading to reduced proliferation throughout the full rostrocaudal axis of the DG, and reduced differentiation in the caudal part of the DG in adult males.[139] Strikingly different effects of ELS on AN is seen in female rats. Whereas neurogenesis is enhanced at PND21 in male rats, a strong suppression was reported in females after maternal deprivation at PND3.[136] However, as opposed to males, early life adversity does not result in a decreased number of DCX-positive cells, but an overall lower total number of adult dentate gyrus granule cells in adult females.[138] Similarly in mice, chronic ELS affected cognitive function and rates of survival of adult born neurons more robustly in males when compared to females.[74,129]

The effects of prenatal stress on AN are often sex dependent.[107,109,163,206] Male rats show a brief period in adolescence during which neurogenesis, BDNF expression, and spatial learning are actually improved, possibly allowing the individual to temporarily compensate for the effects of early life adversity. Female rats do not show such a period of improved performance but rather show a very strong suppression of neurogenesis during the prepubertal period, which then subsides with age. The consequences of this period of suppressed neurogenesis in females may be long-lasting, and female rats exposed to 24 h of maternal deprivation at PND3 exhibited a lower total number of mature granule cells in adulthood, potentially limiting the number of synaptic contacts that can be established in this region. Finally, it is important to mention that AN can be permanently affected also by other early life stressors that are not necessarily related to the mother–infant interaction alone. For example, early life inflammation,[64,127] radiation therapy,[41,130] anesthesia,[217] stroke,[177] infection,[14a] and ethanol exposure[173] induce long-lasting effects on AN associated with late-onset cognitive impairment.

Despite the large variation in ELS models, species, age of testing, and outcome parameters, the majority of studies reports only mild behavioral changes in

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females after early life adversity, i.e., two-third of the experimental series in female rodents did not show a significant change in behavior after early life adversity. Possibly this number is lower than the actual situation, because the influence of the hormonal cycle, which could have added to variation in the behavioral outcome, is not always taken into account. On the other hand, more likely than not, the prevalence of significant effects, at least in animal studies, is overestimated due to a publication bias towards positive findings.[81] Thus, early life experiences during both pre- and postnatal development can bidirectionally alter hippocampal neuronal plasticity, which supports the possibility that these structural changes might be involved in affected cognition as shown recently by a novel causal statistical method demonstrating that cognitive impairments induced by ELS are largely AN dependent.[129]

When tested in adulthood or middle-age, cell proliferation and AN are usually found to be decreased after stress. Yet, at earlier stages, e.g., at P9[129] or PND 21,[180] AN in males is actually enhanced by ELS, as was BDNF expression and performance in a stressful version of the Morris water maze when studied at 2 months, but impaired at 15 months of age. Apparently, early life adversity can transiently improve the functionality of the dentate gyrus, possibly allowing the organism to survive in the adverse conditions. However, in the long run, this adaptation to early life adversity may deplete specific populations of stem cells and seems to program structural plasticity such that it may become a disadvantage later in life,[82,99,121] most notably under low to moderately stressful conditions. The ELS-induced reduction in neurogenic capacity later in life might be due to increased AN postnatally, that might in fact deplete the neurogenic pool. This phenomenon is consistent with other studies on cellular[213] and in vivo level[37,129,171,180] where effects of early stress or early antidepressant treatment and neuronal hyperactivity were studied.

Interestingly, when tested under stressful conditions, early maternal deprivation improved learning and memory of rats. In fact, contextual learning was enhanced in both contextual and cued fear conditioning task. Long-term potentiation, when measured in the presence of corticosterone, was facilitated in male, not female, MD rats.[138,139] Similar effects on physiology and dendritic structure were observed as a function of maternal care with animals receiving more care having better LTP and more complex dendrites and spines.[7,18] The behavioral phenotype in female rats appeared to be more subtle and confined to amygdala-dependent learning paradigms.[138] Literature on cognitive performance in adult females exposed early in life to these types of ELS is generally less extensive than literature on males, as reviewed recently.[98] These data suggest that early life events, whether adverse or not, might increase the sensitivity of the hippocampus to future environments, and prepare the organism to respond optimally when a similar stress is experienced in adult life as the one encountered shortly after birth.[79,139]

CONCLUDING REMARKS

Stress and GCs interfere with one or more of the phases of the neurogenetic process. Their inhibitory effects can normalize after a recovery period, voluntary exercise, or antidepressant treatment. Adult neurogenesis has been implicated in cognitive functions, in the regulation of mood and anxiety, and in the therapeutic effects of antidepressant drugs. A reduced rate of AN may be indicative of impaired hippocampal plasticity. Lasting reductions in AN or turnover rate of DG granule cells, as programmed by early life events, will alter the overall composition of the DG cell population and can modify stress responsivity and thereby influence functioning of the adult hippocampal circuit and later cognition, as well as the risk for psychopathology.

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