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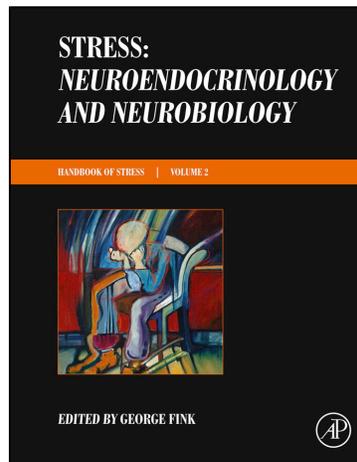
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Early Life Stress- and Sex-Dependent Effects on Hippocampal Neurogenesis

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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.

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 cytotogenesis and neurogenesis has also been reported in other brain structures, like the

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 behavior¹⁶¹ 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

behavior¹³² 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 molecular²⁸ and physiological⁸⁵ 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

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 hormones⁵⁷ 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 arrest⁵⁴ 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 decline.^{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

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 hypo-responsive 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 exposure¹⁷³ 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

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 P9¹²⁹ 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 cellular²¹³ 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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References

1. Abrous DN, Koehl M, Le Moal M. Adult neurogenesis: from precursors to network and physiology. *Physiol Rev*. 2005;85(2):523–569.
2. Aimone JB, Deng W, Gage FH. Adult neurogenesis: integrating theories and separating functions. *Trends Cogn Sci*. 2010;14(7):325–337. doi:S1364-6613(10)00088-4. pii:10.1016/j.tics.2010.04.003.
3. Aisa B, Elizalde N, Tordera R, Lasheras B, Del Rio J, Ramirez MJ. Effects of neonatal stress on markers of synaptic plasticity in the hippocampus: implications for spatial memory. *Hippocampus*. 2009;19(12):1222–1231.
4. Aisa B, Tordera R, Lasheras B, Del Rio J, Ramirez MJ. Cognitive impairment associated to HPA axis hyperactivity after maternal separation in rats. *Psychoneuroendocrinology*. 2007;32(3):256–266.
5. Alonso R, Griebel G, Pavone G, Stemmelin J, Le Fur G, Soubrie P. Blockade of CRF(1) or V(1b) receptors reverses stress-induced suppression of neurogenesis in a mouse model of depression. *Mol Psychiatry*. 2004;9(3):278–286.
6. Anacker C, Cattaneo A, Luoni A, et al. Glucocorticoid-related molecular signaling pathways regulating hippocampal neurogenesis. *Neuropsychopharmacology*. 2013;38(5):872–883. <http://dx.doi.org/10.1038/npp.2012.253>.
7. Bagot RC, van Hasselt FN, Champagne DL, Meaney MJ, Krugers HJ, Joels M. Maternal care determines rapid effects of stress mediators on synaptic plasticity in adult rat hippocampal dentate gyrus. *Neurobiol Learn Mem*. 2009;92(3):292–300.
8. Bale TL, Baram TZ, Brown AS, et al. Early life programming and neurodevelopmental disorders. *Biol Psychiatry*. 2010;68(4):314–319. <http://dx.doi.org/10.1016/j.biopsych.2010.05.028>.

9. Balu DT, Lucki I. Adult hippocampal neurogenesis: regulation, functional implications, and contribution to disease pathology. *Neurosci Biobehav Rev.* 2009;33(3):232–252. <http://dx.doi.org/10.1016/j.neubiorev.2008.08.007>.
10. Banasr M, Duman RS. Regulation of neurogenesis and gliogenesis by stress and antidepressant treatment. *CNS Neurol Disord Drug Targets.* 2007;6(5):311–320.
11. Baram TZ, Davis EP, Obenaus A, et al. Fragmentation and unpredictability of early-life experience in mental disorders. *Am J Psychiatry.* 2012;169(9):907–915. <http://dx.doi.org/10.1176/appi.ajp.2012.11091347>.
12. Bekinschtein P, Oomen CA, Saksida LM, Bussey TJ. Effects of environmental enrichment and voluntary exercise on neurogenesis, learning and memory, and pattern separation: BDNF as a critical variable? *Semin Cell Dev Biol.* 2011;22(5):536–542. <http://dx.doi.org/10.1016/j.semcdb.2011.07.002>.
13. Belnoue L, Grosjean N, Ladeveze E, Abrous DN, Koehl M. Prenatal stress inhibits hippocampal neurogenesis but spares olfactory bulb neurogenesis. *PLoS One.* 2013;8(8):e72972. <http://dx.doi.org/10.1371/journal.pone.0072972>.
14. Binder EB, Bradley RG, Liu W, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA.* 2008;299(11):1291–1305. <http://dx.doi.org/10.1001/jama.299.11.1291>.
- 14a. Bland ST, Beckley JT, Young S, et al. Enduring consequences of early-life infection on glial and neural cell genesis within cognitive regions of the brain. *Brain Behav Immun.* 2010;24:329–338.
15. Boku S, Toda H, Nakagawa S, et al. Neonatal maternal separation alters the capacity of adult neural precursor cells to differentiate into neurons via methylation of retinoic acid receptor gene promoter. *Biol Psychiatry.* 2015;77(4):335–344. <http://dx.doi.org/10.1016/j.biopsych.2014.07.008>.
16. Bruel-Jungerman E, Lucassen PJ, Francis F. Cholinergic influences on cortical development and adult neurogenesis. *Behav Brain Res.* 2011;221(2):379–388. <http://dx.doi.org/10.1016/j.bbr.2011.01.021>.
17. Brunson KL, Kramar E, Lin B, et al. Mechanisms of late-onset cognitive decline after early-life stress. *J Neurosci.* 2005;25(41):9328–9338.
18. Champagne DL, Bagot RC, van Hasselt F, et al. Maternal care and hippocampal plasticity: evidence for experience-dependent structural plasticity, altered synaptic functioning, and differential responsiveness to glucocorticoids and stress. *J Neurosci.* 2008;28(23):6037–6045.
19. Chen Y, Baram TZ. Toward understanding how early-life stress reprograms cognitive and emotional brain networks. *Neuropsychopharmacology.* 2016;41(1):197–206. <http://dx.doi.org/10.1038/npp.2015.181>.
20. Chetty S, Friedman AR, Taravosh-Lahn K, et al. Stress and glucocorticoids promote oligodendrogenesis in the adult hippocampus. *Mol Psychiatry.* 2014;19(12):1275–1283. <http://dx.doi.org/10.1038/mp.2013.190>.
21. Chu DA, Williams LM, Harris AW, Bryant RA, Gatt JM. Early life trauma predicts self-reported levels of depressive and anxiety symptoms in nonclinical community adults: relative contributions of early life stressor types and adult trauma exposure. *J Psychiatr Res.* 2013;47(1):23–32. <http://dx.doi.org/10.1016/j.jpsychires.2012.08.006>.
22. Clelland CD, Choi M, Romberg C, et al. A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science.* 2009;325(5937):210–213.
23. Cottrell EC, Seckl JR. Prenatal stress, glucocorticoids and the programming of adult disease. *Front Behav Neurosci.* 2009;3:19. <http://dx.doi.org/10.3389/neuro.08.019.2009>.
24. Czeh B, Lucassen PJ. What causes the hippocampal volume decrease in depression? Are neurogenesis, glial changes and apoptosis implicated? *Eur Arch Psychiatry Clin Neurosci.* 2007;257(5):250–260.
25. Czeh B, Simon M, Schmelting B, Hiemke C, Fuchs E. Astroglial plasticity in the hippocampus is affected by chronic psychosocial stress and concomitant fluoxetine treatment. *Neuropsychopharmacology.* 2006;31(8):1616–1626.
26. Czeh B, Welt T, Fischer AK, et al. Chronic psychosocial stress and concomitant repetitive transcranial magnetic stimulation: effects on stress hormone levels and adult hippocampal neurogenesis. *Biol Psychiatry.* 2002;52(11):1057–1065.
27. Dagyte G, Van der Zee EA, Postema F, et al. Chronic but not acute foot-shock stress leads to temporary suppression of cell proliferation in rat hippocampus. *Neuroscience.* 2009;162(4):904–913.
28. Datson NA, Speksnijder N, Mayer JL, et al. The transcriptional response to chronic stress and glucocorticoid receptor blockade in the hippocampal dentate gyrus. *Hippocampus.* 2012;22(2):359–371. <http://dx.doi.org/10.1002/hipo.20905>.
29. de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. *Nat Rev Neurosci.* 2005;6(6):463–475.
30. de Rooij SR, Veenendaal MV, Raikkonen K, Roseboom TJ. Personality and stress appraisal in adults prenatally exposed to the Dutch famine. *Early Hum Dev.* 2012;88(5):321–325. <http://dx.doi.org/10.1016/j.earlhumdev.2011.09.002>.
31. De Wolff MS, van Ijzendoorn MH. Sensitivity and attachment: a meta-analysis on parental antecedents of infant attachment. *Child Dev.* 1997;68(4):571–591.
32. Djavadian RL. Serotonin and neurogenesis in the hippocampal dentate gyrus of adult mammals. *Acta Neurobiol Exp (Wars).* 2004;64(2):189–200.
33. Dominguez-Escriba L, Hernandez-Rabaza V, Soriano-Navarro M, et al. Chronic cocaine exposure impairs progenitor proliferation but spares survival and maturation of neural precursors in adult rat dentate gyrus. *Eur J Neurosci.* 2006;24(2):586–594. <http://dx.doi.org/10.1111/j.1460-9568.2006.04924.x>.
34. Dranovsky A, Hen R. Hippocampal neurogenesis: regulation by stress and antidepressants. *Biol Psychiatry.* 2006;59(12):1136–1143.
35. Droste SK, Gesing A, Ulbricht S, Muller MB, Linthorst AC, Reul JM. Effects of long-term voluntary exercise on the mouse hypothalamic-pituitary-adrenocortical axis. *Endocrinology.* 2003;144(7):3012–3023.
36. Ehninger D, Kempermann G. Paradoxical effects of learning the Morris water maze on adult hippocampal neurogenesis in mice may be explained by a combination of stress and physical activity. *Genes Brain Behav.* 2006;5(1):29–39.
37. Encinas JM, Sierra A. Neural stem cell deforestation as the main force driving the age-related decline in adult hippocampal neurogenesis. *Behav Brain Res.* 2012;227(2):433–439. <http://dx.doi.org/10.1016/j.bbr.2011.10.010>.
38. Erdmann G, Berger S, Schutz G. Genetic dissection of glucocorticoid receptor function in the mouse brain. *J Neuroendocrinol.* 2008;20(6):655–659. <http://dx.doi.org/10.1111/j.1365-2826.2008.01717.x>.
39. Fitzsimons C, Herbert J, Schouten M, Meijer OC, Lucassen PJ, Lightman SL. Circadian and ultradian gluc effects of glucocorticoids on neural stem cells and adult hippocampal neurogenesis. *Front Neuroendocrinol.* 2016;41:44–58. <http://dx.doi.org/10.1016/j.yfrne.2016.05.001>.
40. Fitzsimons CP, van Hooijdonk LW, Schouten M, et al. Knockdown of the glucocorticoid receptor alters functional integration of newborn neurons in the adult hippocampus and impairs fear-motivated behavior. *Mol Psychiatry.* 2013;18(9):993–1005. <http://dx.doi.org/10.1038/mp.2012.123>.
41. Fukuda A, Fukuda H, Swanpalmer J, et al. Age-dependent sensitivity of the developing brain to irradiation is correlated with the number and vulnerability of progenitor cells. *J Neurochem.* 2005;92(3):569–584. <http://dx.doi.org/10.1111/j.1471-4159.2004.02894.x>.
42. Galea LA. Gonadal hormone modulation of neurogenesis in the dentate gyrus of adult male and female rodents. *Brain Res Rev.* 2008;57(2):332–341.

I. NEUROENDOCRINE CONTROL OF THE STRESS RESPONSE

43. Garcia A, Steiner B, Kronenberg G, Bick-Sander A, Kempermann G. Age-dependent expression of glucocorticoid- and mineralocorticoid receptors on neural precursor cell populations in the adult murine hippocampus. *Aging Cell*. 2004;3(6):363–371.
44. Ge S, Yang CH, Hsu KS, Ming GL, Song H. A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. *Neuron*. 2007;54(4):559–566. doi:S0896-6273(07)00334-0 pii:10.1016/j.neuron.2007.05.002.
45. Gould E. How widespread is adult neurogenesis in mammals? *Nat Rev Neurosci*. 2007;8(6):481–488. <http://dx.doi.org/10.1038/nrn2147>.
46. Gould E, McEwen BS, Tanapat P, Galea LA, Fuchs E. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. *J Neurosci*. 1997;17(7):2492–2498.
47. Greisen MH, Altar CA, Bolwig TG, Whitehead R, Wortwein G. Increased adult hippocampal brain-derived neurotrophic factor and normal levels of neurogenesis in maternal separation rats. *J Neurosci Res*. 2005;79(6):772–778.
48. Guadagno J, Swan P, Shaikh R, Cregan SP. Microglia-derived IL-1 β triggers p53-mediated cell cycle arrest and apoptosis in neural precursor cells. *Cell Death Dis*. 2015;6:e1779. <http://dx.doi.org/10.1038/cddis.2015.151>.
49. Gupta A, Labus J, Kilpatrick LA, et al. Interactions of early adversity with stress-related gene polymorphisms impact regional brain structure in females. *Brain Struct Funct*. 2016;221(3):1667–1679. <http://dx.doi.org/10.1007/s00429-015-0996-9>.
50. Hanson ND, Owens MJ, Boss-Williams KA, Weiss JM, Nemeroff CB. Several stressors fail to reduce adult hippocampal neurogenesis. *Psychoneuroendocrinology*. 2011;36(10):1520–1529. <http://dx.doi.org/10.1016/j.psyneuen.2011.04.006>.
51. Hanson ND, Owens MJ, Nemeroff CB. Depression, antidepressants, and neurogenesis: a critical reappraisal. *Neuropsychopharmacology*. 2011;36(13):2589–2602. <http://dx.doi.org/10.1038/npp.2011.220>.
52. Harris AP, Holmes MC, de Kloet ER, Chapman KE, Seckl JR. Mineralocorticoid and glucocorticoid receptor balance in control of HPA axis and behaviour. *Psychoneuroendocrinology*. 2013;38(5):648–658. <http://dx.doi.org/10.1016/j.psyneuen.2012.08.007>.
53. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology*. 2008;33(6):693–710.
54. Heine VM, Maslam S, Joels M, Lucassen PJ. Increased P27KIP1 protein expression in the dentate gyrus of chronically stressed rats indicates G1 arrest involvement. *Neuroscience*. 2004;129(3):593–601.
55. Heine VM, Maslam S, Joels M, Lucassen PJ. Prominent decline of newborn cell proliferation, differentiation, and apoptosis in the aging dentate gyrus, in absence of an age-related hypothalamus-pituitary-adrenal axis activation. *Neurobiol Aging*. 2004;25(3):361–375.
56. Heine VM, Maslam S, Zareno J, Joels M, Lucassen PJ. Suppressed proliferation and apoptotic changes in the rat dentate gyrus after acute and chronic stress are reversible. *Eur J Neurosci*. 2004;19(1):131–144.
57. Heine VM, Zareno J, Maslam S, Joels M, Lucassen PJ. Chronic stress in the adult dentate gyrus reduces cell proliferation near the vasculature and VEGF and Flk-1 protein expression. *Eur J Neurosci*. 2005;21(5):1304–1314.
58. Hill AS, Sahay A, Hen R. Increasing adult hippocampal neurogenesis is sufficient to reduce anxiety and depression-like behaviors. *Neuropsychopharmacology*. 2015;40(10):2368–2378. <http://dx.doi.org/10.1038/npp.2015.85>.
59. Hinwood M, Morandini J, Day TA, Walker FR. Evidence that microglia mediate the neurobiological effects of chronic psychological stress on the medial prefrontal cortex. *Cereb Cortex*. 2012;22(6):1442–1454. <http://dx.doi.org/10.1093/cercor/bhr229>.
60. Holmes MM, Galea LA, Mistlberger RE, Kempermann G. Adult hippocampal neurogenesis and voluntary running activity: circadian and dose-dependent effects. *J Neurosci Res*. 2004;76(2):216–222.
61. Hu P, Liu J, Wang J, et al. Chronic retinoic acid treatment suppresses adult hippocampal neurogenesis, in close correlation with depressive-like behavior. *Hippocampus*. 2016;26(7):911–923. <http://dx.doi.org/10.1002/hipo.22574>.
62. Hu P, Oomen C, van Dam AM, et al. A single-day treatment with mifepristone is sufficient to normalize chronic glucocorticoid induced suppression of hippocampal cell proliferation. *PLoS One*. 2012;7(9):e46224. <http://dx.doi.org/10.1371/journal.pone.0046224>.
63. Ivy AS, Brunson KL, Sandman C, Baram TZ. Dysfunctional nurturing behavior in rat dams with limited access to nesting material: a clinically relevant model for early-life stress. *Neuroscience*. 2008;154(3):1132–1142.
64. Jakubs K, Bonde S, Iosif RE, et al. Inflammation regulates functional integration of neurons born in adult brain. *J Neurosci*. 2008;28(47):12477–12488. <http://dx.doi.org/10.1523/JNEUROSCI.3240-08.2008>.
65. Jayatissa MN, Bisgaard C, Tingstrom A, Papp M, Wiborg O. Hippocampal cytogenesis correlates to escitalopram-mediated recovery in a chronic mild stress rat model of depression. *Neuropsychopharmacology*. 2006;31(11):2395–2404.
66. Jayatissa MN, Henningsen K, West MJ, Wiborg O. Decreased cell proliferation in the dentate gyrus does not associate with development of anhedonic-like symptoms in rats. *Brain Res*. 2009;1290:133–141. <http://dx.doi.org/10.1016/j.brainres.2009.07.001>.
67. Jessberger S, Gage FH. Adult neurogenesis: bridging the gap between mice and humans. *Trends Cell Biol*. 2014;24(10):558–563. <http://dx.doi.org/10.1016/j.tcb.2014.07.003>.
68. Joca SR, Ferreira FR, Guimaraes FS. Modulation of stress consequences by hippocampal monoaminergic, glutamatergic and nitrenergic neurotransmitter systems. *Stress*. 2007;10(3):227–249. <http://dx.doi.org/10.1080/10253890701223130>.
69. Joels M, Baram TZ. The neuro-symphony of stress. *Nat Rev Neurosci*. 2009;10(6):459–466.
70. Joels M, Karst H, Krugers HJ, Lucassen PJ. Chronic stress; implications for neuron morphology, function and neurogenesis. *Front Neuroendocrinol*. 2007;28(2–3):72–96.
71. Joels M, Pu Z, Wiegert O, Oitzl MS, Krugers HJ. Learning under stress: how does it work? *Trends Cogn Sci*. 2006;10(4):152–158.
72. Joels M, Sarabdjitsingh RA, Karst H. Unraveling the time domains of corticosteroid hormone influences on brain activity: rapid, slow, and chronic modes. *Pharmacol Rev*. 2012;64(4):901–938. <http://dx.doi.org/10.1124/pr.112.005892>.
73. Kanatsou S, Fearey BC, Kuil LE, et al. Overexpression of mineralocorticoid receptors partially prevents chronic stress-induced reductions in hippocampal memory and structural plasticity. *PLoS One*. 2015;10(11):e0142012. <http://dx.doi.org/10.1371/journal.pone.0142012>.
74. Kanatsou S, Ter Horst JP, Harris AP, Seckl J, Krugers HJ, Joels M. Effects of mineralocorticoid receptor overexpression on anxiety and memory after early life stress in female mice. *Front Behav Neurosci*. 2016;9.
75. Kannagara TS, Lucero MJ, Gil-Mohapel J, et al. Running reduces stress and enhances cell genesis in aged mice. *Neurobiol Aging*. 2011;32(12):2279–2286. <http://dx.doi.org/10.1016/j.neurobiolaging.2009.12.025>.
76. Karst H, Berger S, Erdmann G, Schutz G, Joels M. Metaplasticity of amygdalar responses to the stress hormone corticosterone. *Proc Natl Acad Sci USA*. 2010;107(32):14449–14454. <http://dx.doi.org/10.1073/pnas.0914381107>.
77. Kempermann G. New neurons for 'survival of the fittest'. *Nat Rev Neurosci*. 2012;13(10):727–736. <http://dx.doi.org/10.1038/nrn3319>.

I. NEUROENDOCRINE CONTROL OF THE STRESS RESPONSE

78. Kempermann G, Fabel K, Ehninger D, et al. Why and how physical activity promotes experience-induced brain plasticity. *Front Neurosci.* 2010;4:189. <http://dx.doi.org/10.3389/fnins.2010.00189>.
79. Koehl M, van der Veen R, Gonzales D, Piazza PV, Abrous DN. Interplay of maternal care and genetic influences in programming adult hippocampal neurogenesis. *Biol Psychiatry.* 2012;72(4):282–289. <http://dx.doi.org/10.1016/j.biopsych.2012.03.001>.
80. Koolhaas JM, Bartolomucci A, Buwalda B, et al. Stress revisited: a critical evaluation of the stress concept. *Neurosci Biobehav Rev.* 2011;35(5):1291–1301. <http://dx.doi.org/10.1016/j.neubiorev.2011.02.003>.
81. Korevaar DA, Hooff L, ter Riet G. Systematic reviews and meta-analyses of preclinical studies: publication bias in laboratory animal experiments. *Lab Anim.* 2011;45(4):225–230. <http://dx.doi.org/10.1258/la.2011.010121>.
82. Korosi A, Naninck EF, Oomen CA, et al. Early-life stress mediated modulation of adult neurogenesis and behavior. *Behav Brain Res.* 2012;227(2):400–409. <http://dx.doi.org/10.1016/j.bbr.2011.07.037>.
83. Kreisel T, Frank MG, Licht T, et al. Dynamic microglial alterations underlie stress-induced depressive-like behavior and suppressed neurogenesis. *Mol Psychiatry.* 2014;19(6):699–709. <http://dx.doi.org/10.1038/mp.2013.155>.
84. Kretz O, Reichardt HM, Schutz G, Bock R. Corticotropin-releasing hormone expression is the major target for glucocorticoid feedback-control at the hypothalamic level. *Brain Res.* 1999;818(2):488–491.
85. Krugers HJ, Goltstein PM, van der Linden S, Joels M. Blockade of glucocorticoid receptors rapidly restores hippocampal CA1 synaptic plasticity after exposure to chronic stress. *Eur J Neurosci.* 2006;23(11):3051–3055.
86. Krugers HJ, Joels M. Long-lasting consequences of early life stress on brain structure, emotion and cognition. *Curr Top Behav Neurosci.* 2014;18:81–92. http://dx.doi.org/10.1007/7854_2014_289.
87. Kuhn HG, Dickinson-Anson H, Gage FH. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. *J Neurosci.* 1996;16(6):2027–2033.
88. Kundakovic M, Champagne FA. Early-life experience, epigenetics, and the developing brain. *Neuropsychopharmacology.* 2015;40(1):141–153. <http://dx.doi.org/10.1038/npp.2014.140>.
89. Lajud N, Torner L. Early life stress and hippocampal neurogenesis in the neonate: sexual dimorphism, long term consequences and possible mediators. *Front Mol Neurosci.* 2015;8:3. <http://dx.doi.org/10.3389/fnmol.2015.00003>.
90. Lehmann ML, Brachman RA, Martinowich K, Schloesser RJ, Herkenham M. Glucocorticoids orchestrate divergent effects on mood through adult neurogenesis. *J Neurosci.* 2013;33(7):2961–2972. <http://dx.doi.org/10.1523/JNEUROSCI.3878-12.2013>.
91. Lemaire V, Koehl M, Le Moal M, Abrous DN. Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proc Natl Acad Sci USA.* 2000;97(20):11032–11037.
92. Leslie AT, Akers KG, Krakowski AD, et al. Impact of early adverse experience on complexity of adult-generated neurons. *Transl Psychiatry.* 2011;1:e35. <http://dx.doi.org/10.1038/tp.2011.38>.
93. Levine S. Developmental determinants of sensitivity and resistance to stress. *Psychoneuroendocrinology.* 2005;30(10):939–946.
94. Levone BR, Cryan JF, O'Leary OF. Role of adult hippocampal neurogenesis in stress resilience. *Neurobiol Stress.* 2015;1(1):147–155.
95. Lin YL, Wang S. Prenatal lipopolysaccharide exposure increases depression-like behaviors and reduces hippocampal neurogenesis in adult rats. *Behav Brain Res.* 2014;259:24–34. <http://dx.doi.org/10.1016/j.bbr.2013.10.034>.
96. Liston C, Cichon JM, Jeanneteau F, Jia Z, Chao MV, Gan WB. Circadian glucocorticoid oscillations promote learning-dependent synapse formation and maintenance. *Nat Neurosci.* 2013;16(6):698–705. <http://dx.doi.org/10.1038/nn.3387>.
97. Llorens-Martin M, Jurado-Arjona J, Bolos M, Pallas-Bazarra N, Avila J. Forced swimming sabotages the morphological and synaptic maturation of newborn granule neurons and triggers a unique pro-inflammatory milieu in the hippocampus. *Brain Behav Immun.* 2016;53:242–254. <http://dx.doi.org/10.1016/j.bbi.2015.12.019>.
98. Loi M, Koricka S, Lucassen PJ, Joels M. Age- and sex-dependent effects of early life stress on hippocampal neurogenesis. *Front Endocrinol (Lausanne).* 2014;5:13. <http://dx.doi.org/10.3389/fendo.2014.00013>.
99. Loman MM, Gunnar MR, Early Experience S, & Neurobehavioral Development C. Early experience and the development of stress reactivity and regulation in children. *Neurosci Biobehav Rev.* 2010;34(6):867–876. <http://dx.doi.org/10.1016/j.neubiorev.2009.05.007>.
100. Lucassen PJ, Bosch OJ, Jousma E, et al. Prenatal stress reduces postnatal neurogenesis in rats selectively bred for high, but not low, anxiety: possible key role of placental 11beta-hydroxysteroid dehydrogenase type 2. *Eur J Neurosci.* 2009;29(1):97–103. <http://dx.doi.org/10.1111/j.1460-9568.2008.06543.x>.
101. Lucassen PJ, Fitzsimons CP, Korosi A, Joels M, Belzung C, Abrous DN. Stressing new neurons into depression? *Mol Psychiatry.* 2013;18(4):396–397. <http://dx.doi.org/10.1038/mp.2012.39>.
102. Lucassen PJ, Meerlo P, Naylor AS, et al. Regulation of adult neurogenesis by stress, sleep disruption, exercise and inflammation: implications for depression and antidepressant action. *Eur Neuropsychopharmacol.* 2010;20(1):1–17.
103. Lucassen PJ, Naninck EF, van Goudoever JB, Fitzsimons C, Joels M, Korosi A. Perinatal programming of adult hippocampal structure and function; emerging roles of stress, nutrition and epigenetics. *Trends Neurosci.* 2013;36(11):621–631. <http://dx.doi.org/10.1016/j.tins.2013.08.002>.
104. Lucassen PJ, Pruessner J, Sousa N, et al. Neuropathology of stress. *Acta Neuropathol.* 2014;127(1):109–135. <http://dx.doi.org/10.1007/s00401-013-1223-5>.
105. Lucassen PJ, Stumpel MW, Wang Q, Aronica E. Decreased numbers of progenitor cells but no response to antidepressant drugs in the hippocampus of elderly depressed patients. *Neuropharmacology.* 2010;58:940–949.
106. Lyons DM, Buckmaster PS, Lee AG, et al. Stress coping stimulates hippocampal neurogenesis in adult monkeys. *Proc Natl Acad Sci USA.* 2010;107(33):14823–14827. <http://dx.doi.org/10.1073/pnas.0914568107>.
107. Mahmoud R, Wainwright SR, Galea LA. Sex hormones and adult hippocampal neurogenesis: regulation, implications, and potential mechanisms. *Front Neuroendocrinol.* April 2016;41:129–152. <http://dx.doi.org/10.1016/j.yfrne.2016.03.002>.
108. Malberg JE, Duman RS. Cell proliferation in adult hippocampus is decreased by inescapable stress: reversal by fluoxetine treatment. *Neuropsychopharmacology.* 2003;28(9):1562–1571.
109. Mandyam CD, Crawford EF, Eisch AJ, Rivier CL, Richardson HN. Stress experienced in utero reduces sexual dichotomies in neurogenesis, microenvironment, and cell death in the adult rat hippocampus. *Dev Neurobiol.* 2008;68(5):575–589.
110. Marco EM, Llorente R, Lopez-Gallardo M, et al. The maternal deprivation animal model revisited. *Neurosci Biobehav Rev.* 2015;51:151–163. <http://dx.doi.org/10.1016/j.neubiorev.2015.01.015>.
111. Marlatt MW, Potter MC, Lucassen PJ, van Praag H. Running throughout middle-age improves memory function, hippocampal neurogenesis, and BDNF levels in female C57BL/6J mice. *Dev Neurobiol.* 2012;72(6):943–952. <http://dx.doi.org/10.1002/dneu.22009>.
112. Marlatt MW, Philippens I, Manders E, et al. Distinct structural plasticity in the hippocampus and amygdala of the middle-aged common marmoset (*Callithrix jacchus*). *Exp Neurol.* 2011;230:91–301.

I. NEUROENDOCRINE CONTROL OF THE STRESS RESPONSE

113. Maselko J, Kubzansky L, Lipsitt L, Buka SL. Mother's affection at 8 months predicts emotional distress in adulthood. *J Epidemiol Community Health*. 2011;65(7):621–625. <http://dx.doi.org/10.1136/jech.2009.097873>.
114. Matos RJ, Orozco-Solis R, Lopes de Souza S, Manhaes-de-Castro R, Bolanos-Jimenez F. Nutrient restriction during early life reduces cell proliferation in the hippocampus at adulthood but does not impair the neuronal differentiation process of the new generated cells. *Neuroscience*. 2011;196:16–24. <http://dx.doi.org/10.1016/j.neuroscience.2011.08.071>.
115. Mayer JL, Klumpers L, Maslam S, de Kloet ER, Joels M, Lucassen PJ. Brief treatment with the glucocorticoid receptor antagonist mifepristone normalises the corticosterone-induced reduction of adult hippocampal neurogenesis. *J Neuroendocrinol*. 2006;18(8):629–631.
116. McGowan PO, Szyf M. The epigenetics of social adversity in early life: implications for mental health outcomes. *Neurobiol Dis*. 2010;39(1):66–72. <http://dx.doi.org/10.1016/j.nbd.2009.12.026>.
117. Meaney MJ, Szyf M, Seckl JR. Epigenetic mechanisms of perinatal programming of hypothalamic-pituitary-adrenal function and health. *Trends Mol Med*. 2007;13(7):269–277. <http://dx.doi.org/10.1016/j.molmed.2007.05.003>.
118. Medina A, Seasholtz AF, Sharma V, et al. Glucocorticoid and mineralocorticoid receptor expression in the human hippocampus in major depressive disorder. *J Psychiatr Res*. 2013;47(3):307–314. <http://dx.doi.org/10.1016/j.jpsychires.2012.11.002>.
119. Miller JA, Nathanson J, Franjic D, et al. Conserved molecular signatures of neurogenesis in the hippocampal subgranular zone of rodents and primates. *Development*. 2013;140(22):4633–4644. <http://dx.doi.org/10.1242/dev.097212>.
120. Mirescu C, Gould E. Stress and adult neurogenesis. *Hippocampus*. 2006;16(3):233–238.
121. Mirescu C, Peters JD, Gould E. Early life experience alters response of adult neurogenesis to stress. *Nat Neurosci*. 2004;7(8):841–846.
122. Mitra R, Sundlass K, Parker KJ, Schatzberg AF, Lyons DM. Social stress-related behavior affects hippocampal cell proliferation in mice. *Physiol Behav*. 2006;89(2):123–127.
123. Montaron MF, Drapeau E, Dupret D, et al. Lifelong corticosterone level determines age-related decline in neurogenesis and memory. *Neurobiol Aging*. 2006;27(4):645–654.
124. Montaron MF, Koehl M, Lemaire V, Drapeau E, Abrous DN, Le Moal M. Environmentally induced long-term structural changes: cues for functional orientation and vulnerabilities. *Neurotox Res*. 2004;6(7–8):571–580.
125. Montaron MF, Piazza PV, Aourousseau C, Urani A, Le Moal M, Abrous DN. Implication of corticosteroid receptors in the regulation of hippocampal structural plasticity. *Eur J Neurosci*. 2003;18(11):3105–3111.
126. Morris GP, Clark IA, Zinn R, Vissel B. Microglia: a new frontier for synaptic plasticity, learning and memory, and neurodegenerative disease research. *Neurobiol Learn Mem*. 2013;105:40–53. <http://dx.doi.org/10.1016/j.nlm.2013.07.002>.
127. Musaelyan K, Egeland M, Fernandes C, Pariante CM, Zunszain PA, Thuret S. Modulation of adult hippocampal neurogenesis by early-life environmental challenges triggering immune activation. *Neural Plast*. 2014;2014:194396. <http://dx.doi.org/10.1155/2014/194396>.
128. Nacher J, McEwen BS. The role of N-methyl-D-aspartate receptors in neurogenesis. *Hippocampus*. 2006;16(3):267–270.
129. Naninck EF, Hoeijmakers L, Kakava-Georgiadou N, et al. Chronic early life stress alters developmental and adult neurogenesis and impairs cognitive function in mice. *Hippocampus*. 2015;25(3):309–328. <http://dx.doi.org/10.1002/hipo.22374>.
130. Naylor AS, Bull C, Nilsson MK, et al. Voluntary running rescues adult hippocampal neurogenesis after irradiation of the young mouse brain. *Proc Natl Acad Sci USA*. 2008;105(38):14632–14637. <http://dx.doi.org/10.1073/pnas.071128105>.
131. Nemeroff CB. Paradise lost: the neurobiological and clinical consequences of child abuse and neglect. *Neuron*. 2016;89(5):892–909. <http://dx.doi.org/10.1016/j.neuron.2016.01.019>.
132. Nishijima T, Llorens-Martin M, Tejada GS, et al. Cessation of voluntary wheel running increases anxiety-like behavior and impairs adult hippocampal neurogenesis in mice. *Behav Brain Res*. 2013;245:34–41. <http://dx.doi.org/10.1016/j.bbr.2013.02.009>.
133. O'Leary OF, Cryan JF. A ventral view on antidepressant action: roles for adult hippocampal neurogenesis along the dorsoventral axis. *Trends Pharmacol Sci*. 2014;35(12):675–687. <http://dx.doi.org/10.1016/j.tips.2014.09.011>.
134. O'Leary OF, O'Connor RM, Cryan JF. Lithium-induced effects on adult hippocampal neurogenesis are topographically segregated along the dorso-ventral axis of stressed mice. *Neuropharmacology*. 2012;62(1):247–255. <http://dx.doi.org/10.1016/j.neuropharm.2011.07.015>.
135. Oomen CA, Bekinschtein P, Kent BA, Saksida LM, Bussey TJ. Adult hippocampal neurogenesis and its role in cognition. *Wiley Interdiscip Rev Cogn Sci*. 2014;5(5):573–587. <http://dx.doi.org/10.1002/wcs.1304>.
136. Oomen CA, Girardi CE, Cahyadi R, et al. Opposite effects of early maternal deprivation on neurogenesis in male versus female rats. *PLoS One*. 2009;4(1):e3675.
137. Oomen CA, Mayer JL, de Kloet ER, Joels M, Lucassen PJ. Brief treatment with the glucocorticoid receptor antagonist mifepristone normalizes the reduction in neurogenesis after chronic stress. *Eur J Neurosci*. 2007;26(12):3395–3401.
138. Oomen CA, Soeters H, Audureau N, et al. Early maternal deprivation affects dentate gyrus structure and emotional learning in adult female rats. *Psychopharmacology Berl*. 2011;214(1):249–260. <http://dx.doi.org/10.1007/s00213-010-1922-8>.
139. Oomen CA, Soeters H, Audureau N, et al. Severe early life stress hampers spatial learning and neurogenesis, but improves hippocampal synaptic plasticity and emotional learning under high-stress conditions in adulthood. *J Neurosci*. 2010;30(19):6635–6645. <http://dx.doi.org/10.1523/JNEUROSCI.0247-10.2010>.
140. Palmer TD, Willhoite AR, Gage FH. Vascular niche for adult hippocampal neurogenesis. *J Comp Neurol*. 2000;425(4):479–494.
141. Parihar VK, Hattiangady B, Kuruba R, Shuai B, Shetty AK. Predictable chronic mild stress improves mood, hippocampal neurogenesis and memory. *Mol Psychiatry*. 2011;16(2):171–183. <http://dx.doi.org/10.1038/mp.2009.130>.
142. Perera TD, Dwork AJ, Keegan KA, et al. Necessity of hippocampal neurogenesis for the therapeutic action of antidepressants in adult nonhuman primates. *PLoS One*. 2011;6(4):e17600. <http://dx.doi.org/10.1371/journal.pone.0017600>.
143. Pham K, McEwen BS, Ledoux JE, Nader K. Fear learning transiently impairs hippocampal cell proliferation. *Neuroscience*. 2005;130(1):17–24.
144. Pham K, Nacher J, Hof PR, McEwen BS. Repeated restraint stress suppresses neurogenesis and induces biphasic PSA-NCAM expression in the adult rat dentate gyrus. *Eur J Neurosci*. 2003;17(4):879–886.
145. Pryce CR, Feldon J. Long-term neurobehavioural impact of the postnatal environment in rats: manipulations, effects and mediating mechanisms. *Neurosci Biobehav Rev*. 2003;27(1–2):57–71.
146. Qi XR, Kamphuis W, Wang S, et al. Aberrant stress hormone receptor balance in the human prefrontal cortex and hypothalamic paraventricular nucleus of depressed patients. *Psychoneuroendocrinology*. 2013;38(6):863–870. <http://dx.doi.org/10.1016/j.psyneuen.2012.09.014>.
147. Qian X, Droste SK, Lightman SL, Reul JM, Linthorst AC. Circadian and ultradian rhythms of free glucocorticoid hormone are highly synchronized between the blood, the subcutaneous tissue, and the brain. *Endocrinology*. 2012;153(9):4346–4353. <http://dx.doi.org/10.1210/en.2012-1484>.

I. NEUROENDOCRINE CONTROL OF THE STRESS RESPONSE

148. Revest JM, Dupret D, Koehl M, et al. Adult hippocampal neurogenesis is involved in anxiety-related behaviors. *Mol Psychiatry*. 2009;14(10):959–967. <http://dx.doi.org/10.1038/mp.2009.15>.
149. Ridder S, Chourbaji S, Hellweg R, et al. Mice with genetically altered glucocorticoid receptor expression show altered sensitivity for stress-induced depressive reactions. *J Neurosci*. 2005;25(26):6243–6250. <http://dx.doi.org/10.1523/JNEUROSCI.0736-05.2005>.
150. Sah A, Schmuckermair C, Sartori SB, et al. Anxiety- rather than depression-like behavior is associated with adult neurogenesis in a female mouse model of higher trait anxiety- and comorbid depression-like behavior. *Transl Psychiatry*. 2012;2:e171. <http://dx.doi.org/10.1038/tp.2012.94>.
151. Sahay A, Hen R. Adult hippocampal neurogenesis in depression. *Nat Neurosci*. 2007;10(9):1110–1115.
152. Sahay A, Scobie KN, Hill AS, et al. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature*. 2011;472(7344):466–470. <http://dx.doi.org/10.1038/nature09817>.
153. Sahay A, Wilson DA, Hen R. Pattern separation: a common function for new neurons in hippocampus and olfactory bulb. *Neuron*. 2011;70(4):582–588. <http://dx.doi.org/10.1016/j.neuron.2011.05.012>.
154. Sampedro-Piquero P, Begega A, Arias JL. Increase of glucocorticoid receptor expression after environmental enrichment: relations to spatial memory, exploration and anxiety-related behaviors. *Physiol Behav*. 2014;129:118–129. <http://dx.doi.org/10.1016/j.physbeh.2014.02.048>.
155. Santarelli L, Saxe M, Gross C, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science*. 2003;301(5634):805–809.
156. Sapolsky RM, Uno H, Rebert CS, Finch CE. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J Neurosci*. 1990;10(9):2897–2902.
157. Sarabdjitsingh RA, Conway-Campbell BL, Leggett JD, et al. Stress responsiveness varies over the ultradian glucocorticoid cycle in a brain-region-specific manner. *Endocrinology*. 2010;151(11):5369–5379. <http://dx.doi.org/10.1210/en.2010-0832>.
158. Sarabdjitsingh RA, Jezequel J, Pasricha N, et al. Ultradian corticosterone pulses balance glutamatergic transmission and synaptic plasticity. *Proc Natl Acad Sci USA*. 2014;111(39):14265–14270. <http://dx.doi.org/10.1073/pnas.1411216111>.
159. Sarabdjitsingh RA, Joels M, de Kloet ER. Glucocorticoid pulsatility and rapid corticosteroid actions in the central stress response. *Physiol Behav*. 2012;106(1):73–80. <http://dx.doi.org/10.1016/j.physbeh.2011.09.017>.
160. Saxe MD, Battaglia F, Wang JW, et al. Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. *Proc Natl Acad Sci USA*. 2006;103(46):17501–17506.
161. Schloesser RJ, Lehmann M, Martinowich K, Manji HK, Herkenham M. Environmental enrichment requires adult neurogenesis to facilitate the recovery from psychosocial stress. *Mol Psychiatry*. 2010;15(12):1152–1163. <http://dx.doi.org/10.1038/mp.2010.34>.
162. Schmidt HD, Duman RS. The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. *Behav Pharmacol*. 2007;18(5–6):391–418. <http://dx.doi.org/10.1097/FBP.0b013e3282ee2aa8>.
163. Schmitz C, Rhodes ME, Bludau M, et al. Depression: reduced number of granule cells in the hippocampus of female, but not male, rats due to prenatal restraint stress. *Mol Psychiatry*. 2002;7(7):810–813.
164. Schoenfeld TJ, Cameron HA. Adult neurogenesis and mental illness. *Neuropsychopharmacology*. 2015;40(1):113–128. <http://dx.doi.org/10.1038/npp.2014.230>.
165. Schoenfeld TJ, Gould E. Differential effects of stress and glucocorticoids on adult neurogenesis. *Curr Top Behav Neurosci*. 2013;15:139–164. http://dx.doi.org/10.1007/7854_2012_233.
166. Schouten M, Buijink MR, Lucassen PJ, Fitzsimons CP. New neurons in aging brains: molecular control by small non-coding RNAs. *Front Neurosci*. 2012;6:25. <http://dx.doi.org/10.3389/fnins.2012.00025>.
167. Schwabe L, Joels M, Roozendaal B, Wolf OT, Oitzl MS. Stress effects on memory: an update and integration. *Neurosci Biobehav Rev*. 2012;36(7):1740–1749. <http://dx.doi.org/10.1016/j.neubiorev.2011.07.002>.
168. Seo DO, Carillo MA, Chih-Hsiung Lim S, Tanaka KF, Drew MR. Adult hippocampal neurogenesis modulates fear learning through associative and nonassociative mechanisms. *J Neurosci*. 2015;35(32):11330–11345. <http://dx.doi.org/10.1523/JNEUROSCI.0483-15.2015>.
169. Sierra A, Beccari S, Diaz-Aparicio I, Encinas JM, Comeau S, Tremblay ME. Surveillance, phagocytosis, and inflammation: how never-resting microglia influence adult hippocampal neurogenesis. *Neural Plast*. 2014;610343. <http://dx.doi.org/10.1155/2014/610343>.
170. Sierra A, Encinas JM, Deudero JJ, et al. Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. *Cell Stem Cell*. 2010;7(4):483–495. <http://dx.doi.org/10.1016/j.stem.2010.08.014>.
171. Sierra A, Martin-Suarez S, Valcarcel-Martin R, et al. Neuronal hyperactivity accelerates depletion of neural stem cells and impairs hippocampal neurogenesis. *Cell Stem Cell*. 2015;16(5):488–503. <http://dx.doi.org/10.1016/j.stem.2015.04.003>.
172. Simon M, Czeh B, Fuchs E. Age-dependent susceptibility of adult hippocampal cell proliferation to chronic psychosocial stress. *Brain Res*. 2005;1049(2):244–248.
173. Singh AK, Gupta S, Jiang Y, Younus M, Ramzan M. In vitro neurogenesis from neural progenitor cells isolated from the hippocampus region of the brain of adult rats exposed to ethanol during early development through their alcohol-drinking mothers. *Alcohol Alcohol*. 2009;44(2):185–198. <http://dx.doi.org/10.1093/alcac/agn109>.
174. Singh-Taylor A, Korosi A, Molet J, Gunn BG, Baram TZ. Synaptic rewiring of stress-sensitive neurons by early-life experience: a mechanism for resilience? *Neurobiol Stress*. 2015;1:109–115. <http://dx.doi.org/10.1016/j.ynstr.2014.10.007>.
175. Snyder JS, Soumier A, Brewer M, Pickel J, Cameron HA. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature*. 2011;476(7361):458–461. <http://dx.doi.org/10.1038/nature10287>.
176. Sousa N. The dynamics of the stress neuromatrix. *Mol Psychiatry*. 2016;21:302–312.
177. Spadafora R, Gonzalez FF, Derugin N, Wendland M, Ferriero D, McQuillen P. Altered fate of subventricular zone progenitor cells and reduced neurogenesis following neonatal stroke. *Dev Neurosci*. 2010;32(2):101–113. <http://dx.doi.org/10.1159/000279654>.
178. Sultan S, Li L, Moss J, et al. Synaptic integration of adult-born hippocampal neurons is locally controlled by astrocytes. *Neuron*. 2015;88(5):957–972. <http://dx.doi.org/10.1016/j.neuron.2015.10.037>.
179. Surget A, Tanti A, Leonardo ED, et al. Antidepressants recruit new neurons to improve stress response regulation. *Mol Psychiatry*. 2011;16(12):1177–1188. <http://dx.doi.org/10.1038/mp.2011.48>.
180. Suri D, Veenit V, Sarkar A, et al. Early stress evokes age-dependent biphasic changes in hippocampal neurogenesis, BDNF expression, and cognition. *Biol Psychiatry*. 2013;73(7):658–666. <http://dx.doi.org/10.1016/j.biopsych.2012.10.023>.
181. Swaab DF, Bao AM, Lucassen PJ. The stress system in the human brain in depression and neurodegeneration. *Ageing Res Rev*. 2005;4(2):141–194.
182. Takamura N, Nakagawa S, Masuda T, et al. The effect of dopamine on adult hippocampal neurogenesis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;50:116–124. <http://dx.doi.org/10.1016/j.pnpbp.2013.12.011>.

I. NEUROENDOCRINE CONTROL OF THE STRESS RESPONSE

183. Tamura M, Sajo M, Kakita A, Matsuki N, Koyama R. Prenatal stress inhibits neuronal maturation through downregulation of mineralocorticoid receptors. *J Neurosci.* 2011;31(32):11505–11514. <http://dx.doi.org/10.1523/JNEUROSCI.3447-10.2011>.
184. Tanti A, Belzung C. Neurogenesis along the septo-temporal axis of the hippocampus: are depression and the action of antidepressants region-specific? *Neuroscience.* 2013;252:234–252. <http://dx.doi.org/10.1016/j.neuroscience.2013.08.017>.
185. Tanti A, Rainer Q, Minier F, Surget A, Belzung C. Differential environmental regulation of neurogenesis along the septo-temporal axis of the hippocampus. *Neuropharmacology.* 2012;63(3):374–384. <http://dx.doi.org/10.1016/j.neuropharm.2012.04.022>.
186. Tasker JG. Rapid glucocorticoid actions in the hypothalamus as a mechanism of homeostatic integration. *Obesity (Silver Spring).* 2006;14(suppl 5):259S–265S. <http://dx.doi.org/10.1038/oby.2006.320>.
187. Tauber SC, Bunkowski S, Schlumbohm C, et al. No long-term effect two years after intrauterine exposure to dexamethasone on dentate gyrus volume, neuronal proliferation and differentiation in common marmoset monkeys. *Brain Pathol.* 2008;18(4):497–503.
188. Teicher MH, Anderson CM, Polcari A. Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. *Proc Natl Acad Sci USA.* 2012;109(9):E563–E572. <http://dx.doi.org/10.1073/pnas.1115396109>.
189. Toni N, Laplagne DA, Zhao C, et al. Neurons born in the adult dentate gyrus form functional synapses with target cells. *Nat Neurosci.* 2008;11(8):901–907.
190. Ursin H, Eriksen HR. The cognitive activation theory of stress. *Psychoneuroendocrinology.* 2004;29(5):567–592. [http://dx.doi.org/10.1016/S0306-4530\(03\)00091-X](http://dx.doi.org/10.1016/S0306-4530(03)00091-X).
191. Vallieres L, Campbell IL, Gage FH, Sawchenko PE. Reduced hippocampal neurogenesis in adult transgenic mice with chronic astrocytic production of interleukin-6. *J Neurosci.* 2002;22(2):486–492.
192. Van Bokhoven P, Oomen CA, Hoogendijk WJ, Smit AB, Lucassen PJ, Spijker S. Reduction in hippocampal neurogenesis after social defeat is long-lasting and responsive to late antidepressant treatment. *Eur J Neurosci.* 2011;33(10):1833–1840. <http://dx.doi.org/10.1111/j.1460-9568.2011.07668.x>.
193. Van der Borgh K, Meerlo P, Luiten PG, Eggen BJ, Van der Zee EA. Effects of active shock avoidance learning on hippocampal neurogenesis and plasma levels of corticosterone. *Behav Brain Res.* 2005;157(1):23–30.
194. van der Doelen RH, Kozicz T, Homberg JR. Adaptive fitness; early life adversity improves adult stress coping in heterozygous serotonin transporter knockout rats. *Mol Psychiatry.* 2013;18(12):1244–1245. <http://dx.doi.org/10.1038/mp.2012.186>.
195. van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci.* 1999;2(3):266–270.
196. Veena J, Srikumar BN, Mahati K, Bhagya V, Raju TR, Shankaranarayana Rao BS. Enriched environment restores hippocampal cell proliferation and ameliorates cognitive deficits in chronically stressed rats. *J Neurosci Res.* 2009;87(4):831–843.
197. Vinkers CH, Joels M, Milaneschi Y, Kahn RS, Penninx BW, Boks MP. Stress exposure across the life span cumulatively increases depression risk and is moderated by neuroticism. *Depress Anxiety.* 2014;31(9):737–745. <http://dx.doi.org/10.1002/da.22262>.
198. Vivar C, Potter MC, Choi J, et al. Monosynaptic inputs to new neurons in the dentate gyrus. *Nat Commun.* 2012;3:1107. <http://dx.doi.org/10.1038/ncomms2101>.
199. Vivar C, Potter MC, van Praag H. All about running: synaptic plasticity, growth factors and adult hippocampal neurogenesis. *Curr Top Behav Neurosci.* 2013;15:189–210. http://dx.doi.org/10.1007/7854_2012_220.
200. Vivinetto AL, Suarez MM, Rivarola MA. Neurobiological effects of neonatal maternal separation and post-weaning environmental enrichment. *Behav Brain Res.* 2013;240:110–118. <http://dx.doi.org/10.1016/j.bbr.2012.11.014>.
201. Vollmayr B, Simonis C, Weber S, Gass P, Henn F. Reduced cell proliferation in the dentate gyrus is not correlated with the development of learned helplessness. *Biol Psychiatry.* 2003;54(10):1035–1040.
202. Wang Q, Joels M, Swaab DF, Lucassen PJ. Hippocampal GR expression is increased in elderly depressed females. *Neuropharmacology.* 2012;62(1):527–533. <http://dx.doi.org/10.1016/j.neuropharm.2011.09.014>.
203. Wang Q, Van Heerikhuizen J, Aronica E, et al. Glucocorticoid receptor protein expression in human hippocampus; stability with age. *Neurobiol Aging.* 2013;34(6):1662–1673. <http://dx.doi.org/10.1016/j.neurobiolaging.2012.11.019>.
204. Weaver IC, Szyf M, Meaney MJ. From maternal care to gene expression: DNA methylation and the maternal programming of stress responses. *Endocr Res.* 2002;28(4):699.
205. Wei Q, Hebda-Bauer EK, Pletsch A, et al. Overexpressing the glucocorticoid receptor in forebrain causes an aging-like neuroendocrine phenotype and mild cognitive dysfunction. *J Neurosci.* 2007;27(33):8836–8844. <http://dx.doi.org/10.1523/JNEUROSCI.0910-07.2007>.
206. Weinstock M. Sex-dependent changes induced by prenatal stress in cortical and hippocampal morphology and behaviour in rats: an update. *Stress.* 2011;14(6):604–613. <http://dx.doi.org/10.3109/10253890.2011.588294>.
207. Westenbroek C, Den Boer JA, Veenhuis M, Ter Horst GJ. Chronic stress and social housing differentially affect neurogenesis in male and female rats. *Brain Res Bull.* 2004;64(4):303–308.
208. Wilson CB, Ebenezer PJ, McLaughlin LD, Francis J. Predator exposure/psychosocial stress animal model of post-traumatic stress disorder modulates neurotransmitters in the rat hippocampus and prefrontal cortex. *PLoS One.* 2014;9(2):e89104. <http://dx.doi.org/10.1371/journal.pone.0089104>.
209. Wong EY, Herbert J. The corticoid environment: a determining factor for neural progenitors' survival in the adult hippocampus. *Eur J Neurosci.* 2004;20(10):2491–2498.
210. Wong EY, Herbert J. Roles of mineralocorticoid and glucocorticoid receptors in the regulation of progenitor proliferation in the adult hippocampus. *Eur J Neurosci.* 2005;22(4):785–792.
211. Wong EY, Herbert J. Raised circulating corticosterone inhibits neuronal differentiation of progenitor cells in the adult hippocampus. *Neuroscience.* 2006;137(1):83–92.
212. Wu MV, Shamy JL, Bedi G, et al. Impact of social status and antidepressant treatment on neurogenesis in the baboon hippocampus. *Neuropsychopharmacology.* 2014;39(8):1861–1871. <http://dx.doi.org/10.1038/npp.2014.33>.
213. Yu S, Patchev AV, Wu Y, et al. Depletion of the neural precursor cell pool by glucocorticoids. *Ann Neurol.* 2010;67(1):21–30. <http://dx.doi.org/10.1002/ana.21812>.
214. Yun S, Donovan MH, Ross MN, et al. Stress-induced anxiety- and depressive-like phenotype associated with transient reduction in neurogenesis in adult nestin-CreERT2/diphtheria toxin fragment a transgenic mice. *PLoS One.* 2016;11(1):e0147256. <http://dx.doi.org/10.1371/journal.pone.0147256>.
215. Zhang CL, Zou Y, He W, Gage FH, Evans RM. A role for adult TLX-positive neural stem cells in learning and behaviour. *Nature.* 2008;451(7181):1004–1007. <http://dx.doi.org/10.1038/nature06562>.
216. Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. *Cell.* 2008;132(4):645–660. <http://dx.doi.org/10.1016/j.cell.2008.01.033>.
217. Zhu C, Gao J, Karlsson N, et al. Isoflurane anesthesia induced persistent, progressive memory impairment, caused a loss of neural stem cells, and reduced neurogenesis in young, but not adult, rodents. *J Cereb Blood Flow Metab.* 2010;30(5):1017–1030. <http://dx.doi.org/10.1038/jcbfm.2009.274>.

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