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CHAPTER

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Adult Neurogenesis, Chronic Stress and Depression

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INTRODUCTION

Stress occurs whenever an endogenous or exogenous challenge is perceived as unpleasant, aversive, or threatening for the homeostasis or survival of an individual. Following exposure to stress, various sensory and cognitive signals that trigger specific processes in the body and brain converge, helping the individual to suppress several ongoing processes and refocus attention to cope with the stressor. Even though stress is often considered a "modern disease," the stress response itself occurs in many organisms and has been conserved throughout evolution. It enables individuals to adapt to challenges in their environment and regain homeostasis.

Stress is a very broad term and no single entity. Stress can be psychological in nature and, e.g., be triggered by interpersonal or financial

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problems or result from a loss of control or unpredictability considering the outcome of a given situation (Ursin & Eriksen, 2004). Also, more biological challenges such as blood loss, dehydration or inflammation, elicit stress responses. Stress can further be acute (e.g., when facing a predator) or chronic (living in poverty or in a broken family). Important elements that determine the nature and impact of a stressor are its (un)predictability, (un)controllability, intensity, and the context in which stress occurs. The perception and interpretation of a stressor, as well as the magnitude and duration of an individual's response to a given stressor, depend largely on his/her genetic background, sex, personality, and early life history (Joels, Karst, Krugers, & Lucassen, 2007; Joels, Sarabdjitsingh, Karst, 2012; Kim et al., 2013; Koolhaas et al., 2011; Lucassen, Fitzsimons, et al., 2013; Lucassen, Naninck, et al., 2013).

The physiological responses to stress can be divided into a fast and a more delayed response. In the classic neuroendocrine stress circuit, several limbic and hypothalamic brain regions integrate a variety of inputs, and together determine the magnitude and specificity of the behavioral, neural, and hormonal responses of the individual to a particular stressor (Joels & Baram, 2009; Joels et al., 2012).

The first phase of the stress response involves a rapid activation of the autonomic nervous system that causes epinephrine and norepinephrine release from the adrenal medulla. These hormones quickly elevate basal metabolic rate, blood pressure, and respiration in seconds to minutes and increase blood flow to the organs essential for the "fight-or-flight" response, such as heart, lungs, and muscles.

The second, slower response to stress involves activation of the hypothalamic–pituitary–adrenal (HPA) axis that controls the release of glucocorticoid (GC) hormones (corticosterone in rodents and cortisol in humans) from the adrenal cortex. As transcriptional regulators, GCs generally act in a slow, genomic manner, but faster GC actions have also been described (Joels et al., 2012). Furthermore, other signaling pathways, such as the gonadal axis and the metabolic and immune system, act in concert with the HPA axis and together they help to redirect energy resources such that attention can be focused on the most urgent and important elements, whereas "maintenance" functions like food digestion or reproduction are temporarily suppressed.

Activation of the HPA axis is triggered by corticotropin-releasing hormone (CRH) in the paraventricular nucleus (PVN) that in turn induces adrenocorticotropic hormone (ACTH) release from the pituitary, which causes the release of GCs from the adrenal. Regulation occurs through negative feedback of GCs that bind to the high-affinity mineralocorticoid receptor (MR) and lower affinity glucocorticoid receptors (GR) (de Kloet, Joëls, & Holsboer, 2005). The GR helps to maintain GC levels within physiological limits (Erdmann, Berger, & Schütz, 2008; de Kloet et al., 2005; Kretz, Reichardt, Schütz, & Bock, 1999) and aberrant GR expression has, e.g., been

implicated in hypercortisolism, stress resistance, anxiety, and depression (de Kloet et al., 2005; Ridder et al., 2005; Wei et al., 2007). Furthermore, GC plasma levels are under strict circadian and ultradian control (Liston et al., 2013; Qian, Droste, Lightman, Reul, & Linthorst, 2012) and together with GR and MR function determine an individual's sensitivity and responsivity to stress (Harris, Holmes, de Kloet, Chapman, & Seckl, 2013; Medina et al., 2013; Pruessner et al., 2010; Sousa, Cerqueira, & Almeida, 2008).

On their release in the periphery, GCs affect numerous important functions such as energy, inflammation, and lipid metabolism, among others. Thus, an imbalance in stress hormone regulation can have deleterious consequences, particularly for the brain, where GCs modulate memory, fear, and attention (de Kloet et al., 2005). Whereas acute stress is generally adaptive, chronic stress may alter the MR/GR balance (Harris et al., 2013; de Kloet et al., 2005; Qi et al., 2013) or HPA feedback and result in (prolonged) overexposure of the brain and body to stress hormones, and thus to changes in many of the functions, processes, and behaviors affected by GCs as noted above.

The abundant presence of GRs, particularly in the hippocampus, makes this brain structure very sensitive to stress (de Kloet et al., 2005; Lucassen et al., 2014; Swaab, Bao, & Lucassen, 2005; Wang et al., 2013). GRs have considerable genetic diversity in humans and changes in MR and GR (variants) have been implicated in stress disorders such as major depression disorder (MDD), in stress responsivity and in the associated reductions in hippocampal volume (Alt et al., 2010; Czéh & Lucassen, 2007; Klok, Alt, et al., 2011; Klok, Giltay, et al., 2011; Medina et al., 2013; Qi et al., 2013; Ridder et al., 2005; Sapolsky, 2000; Sinclair, Tsai, Woon, & Weickert, 2011; Spijker et al., 2011; Vinkers et al., 2014; Wang, Joëls, Swaab, & Lucassen, 2012). In functional terms, chronic stress has been associated with reductions in hippocampal excitability, long-term potentiation, and hippocampal memory, but positive effects that depend on the timing, type, and controllability of a stressor have also been described (Joels et al., 2007, 2012). Morphological consequences of chronic stress commonly include hippocampal volume reductions, dendritic atrophy, and reductions in neurogenesis (for a review, see Lucassen et al., 2014, and references therein).

STRESS-RELATED CHANGES IN MAJOR DEPRESSION

Stress is one of the most common risk factors for the development of mood disorders such as MDD, which is thought to result from interactions between genetic predispositions and environmental interactions (Karg, Burmeister, Shedden, & Sen, 2011; Risch et al., 2009). Especially stressful life events experienced during early childhood or adolescence can program plasticity and increase the risk for MDD (Bilbo & Schwarz, 2009;

Bland et al., 2010; Boku et al., 2014; Brunson et al., 2005; Co et al., 2003; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Koehl, van der Veen, Gonzales, Piazza, & Abrous, 2012; Korosi et al., 2012; Leuner, 2010; Lucassen, Naninck, et al., 2013; Mirescu, Peters, & Gould, 2004; Risch et al., 2009). Indeed, in a large proportion of depressed patients, the HPA axis activation and GC feedback resistance are common, as reflected by the high percentage of dexamethasone nonsuppressors in this population, hypertrophy of the adrenals and pituitary, increased plasma levels of cortisol, and increases in CRH and AVP expression in the PVN (Lucassen et al., 2014; Raadsheer et al., 1995; Swaab et al., 2005). Notably, depressed subjects show a remarkable heterogeneity in neuroendocrine function and the proportion of depressed individuals demonstrating overt HPA axis abnormalities may range from 35% to 65%.

Maladaptive responses to stress and the associated GC hypersecretion can induce hyperemotional states, mood dysfunction, and cognitive impairments in depressed patients. This is often paralleled by volume changes in various brain regions, including the hippocampus. In the literature, variations in hippocampal volume have been reported in depression, which can relate to differences in disease duration, anatomical delineation, lateralization, early life conditions, and genotype. In general, amygdalar, prefrontal, and hippocampal changes in MDD are well-replicated findings in psychiatry (Cobb et al., 2013; Czéh, Fuchs, Wiborg, & Simon, 2015; Drevets, Price, & Furey, 2008; Kempton et al., 2011; Lorenzetti, Allen, Fornito, & Yücel, 2009). Whether hippocampal volume loss reflects a cause or a consequence of MDD remains unclear but lower hippocampal volumes in patients can be predicted by a more extensive depressive episode duration and recurrence, the size of their integrated cortisol responses, and a history of early life stress. Also, a smaller hippocampal volume could predispose for the development of psychopathology (Czéh & Lucassen, 2007; Lucassen et al., 2014; Sapolsky, 2000).

Preclinical and postmortem studies indicate that chronic stress and depression affect different hippocampal subfields, and different structural substrates, to a different extent. In addition to sex-specific changes in GR expression (Medina et al., 2013; Wang et al., 2012), differences across its transversal and longitudinal axis and connectivity changes were found. Detailed high-field MRI measurements (Huang et al., 2013) revealed that the mean volumes of the DG and CA1–3 subregions were smaller in non-medicated or recently unmedicated depressed patients than in healthy controls. Along the longitudinal axis, a smaller volume was mainly found posteriorly, i.e., in the hippocampal body and tail, rather than anteriorly. Of interest, both the subfield and the posterior hippocampal volume reductions seen in unmedicated depression were absent after antidepressant treatment. The posterior hippocampus may differ from the anterior part when studying volume changes or treatment outcome (Kheirbek & Hen, 2011; MacQueen, Yucel, Taylor, Macdonald, & Joffe, 2008).

In a postmortem study, total hippocampal volume in depression was decreased with increasing duration of depressive illness. There was no significant difference between depressed and control cases in the total number or density of neurons or glia in the CA1, CA2/3, hilus, or DG subregion (Cobb et al., 2013). However, both granule cell and glial cell numbers increased with age in depressed patients on medication, which may reflect proliferative effects of antidepressants (see below) and suggest that GC-induced volume reductions parallel to increased cellular densities are best explained by assuming cell shrinkage and changes in neuropil rather than cell loss (Lucassen et al., 2014; Stockmeier et al., 2004; Swaab et al., 2005). The finding that the loss of brain volume in Cushing's syndrome is reversible after correction of hypercortisolism is consistent with this concept (Bordeau et al., 2002; Starkman et al., 1999). Another option is that volume changes may relate to (lasting) changes in structural plasticity and/or neurogenesis (Czéh & Lucassen, 2007; Jacobs, van Praag, & Gage, 2000; Kempermann, Krebs, & Fabel, 2008; Sapolsky, 2000), as will be discussed below.

STRUCTURAL PLASTICITY AND ADULT NEUROGENESIS

Traditionally, MDD and stress-related disturbances were explained by neurochemical (mainly monoaminergic) imbalances, thought to take place mainly at the synaptic level. More recent studies have now indicated that impairments in structural plasticity also contribute to, e.g., the volumetric changes and pathophysiology of these disorders. Various candidate cellular substrates, such as dendritic retraction, spine alterations, neuronal loss, or glial changes, that are stress sensitive, have been proposed. However, it remains elusive whether changes in these substrates can be considered truly "pathological" or whether they reflect more dynamic adaptations to stress, that can, at least to some extent, be transient and/or reversible, as discussed before (Czéh & Lucassen, 2007; Heine, Maslam, Zareno, Joels, & Lucassen, 2004; Lucassen et al., 2014; Sapolsky, 2000).

One highly plastic and dynamic cellular substrate is adult neurogenesis (AN). AN refers to neural stem cells that continue to produce new neurons in the adult brain (see Fig. 8.1 for a schematic representation). New neuron formation in the adult hippocampus received considerable attention during recent years as it has been implicated, e.g., in (aspects of) mood, epilepsy, cognition, and pattern separation (Abrous & Wojtowicz, 2015; Aimone, Deng, Gage, 2011; Bielefeld et al., 2014; Cho et al., 2015; Clelland et al., 2009; Déry, Goldstein, & Becker, 2015; Jessberger et al., 2009; Jessberger & Gage, 2014; Oomen, Bekinschtein, Kent, Saksida, & Bussey, 2014; Oomen et al., 2013; Richetin et al., 2015; Sahay et al., 2011; Sierra et al., 2015; Tronel et al., 2015). Also, the adult-generated cells are regulated

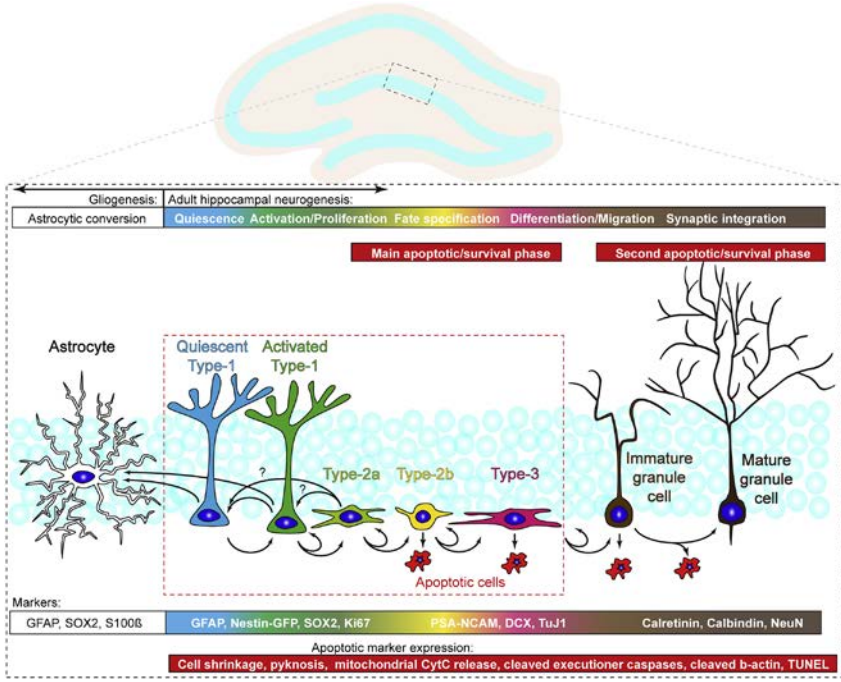


FIGURE 8.1 Schematic representation of neurogenesis in the adult hippocampus, showing the different stages of the neurogenic cascade, the different cell types, and the expression of some of the cell type-specific markers typically used to characterize them. *Arrows* indicate possible transitions between cell types originating from a type 1 neuronal stem cell (NSC) with self-renewal potential. The scheme is based on Encinas et al. (2006) and Sierra et al. (2010).

by (early) stress and various molecular factors. They express GRs (see Fig. 8.1 and Anacker et al., 2013; Gould, McEwen, Tanapat, Galea, & Fuchs, 1997; Heine, Maslam, Joëls, & Lucassen, 2004; Heine, Maslam, Zareno, et al., 2004; Lehmann, Brachman, Martinowich, Schloesser, & Herkenham, 2013; Lemaire, Koehl, Le Moal, & Abrous, 2000; Lucassen, Meerlo, et al., 2010; Lucassen, Fitzsimons, et al., 2013; Lucassen, Naninck, et al., 2013; Montaron et al., 2003; Pham, Nacher, Hof, & McEwen, 2003; Schoenfeld & Gould, 2013; Schouten, Buijink, Lucassen, & Fitzsimons, 2012; Schouten et al., 2015; Song et al., 2012; Wong & Herbert, 2004, 2005) and have been implicated in cognition, anxiety, pattern separation, behavioral flexibility, and the pathophysiology of depression (Clelland et al., 2009; Déry et al., 2015; Duman, 2004; Eisch & Petrik, 2012; Fitzsimons et al., 2013; Jacobs et al., 2000; Kempermann, 2008; Kempermann et al., 2008; Kempermann & Kronenberg, 2003; Lucassen, Meerlo, et al., 2010; Lucassen et al., 2014; Lucassen, Stumpel, Wang, Aronica, 2010; Opendak & Gould, 2015; Petrik, Lagace, & Eisch, 2012; Revest et al., 2009).

The neurogenic hypothesis of depression was postulated based on three observations. First, stress is a risk factor for the development of depression and associated with reductions in hippocampal volume. Stress also reduces neurogenesis in the hippocampus. Second, most antidepressants generally require a period of several weeks to exert their beneficial action, similar to the time frame that newborn neuronal precursors need to integrate and contribute as functional neurons to the adult DG circuitry. Third, antidepressant treatment and the resulting increases in serotonin levels, e.g., promote cell proliferation and generation of new neurons in the hippocampus (Boldrini et al., 2012; Malberg & Duman, 2003; Sahay & Hen, 2007; Wu et al., 2014) that has further been implicated in stress response regulation (Anacker & Pariante, 2012; Lucassen, Fitzsimons, et al., 2013; Opendak & Gould, 2011; Snyder, Soumier, Brewer, Pickel, & Cameron, 2011; Surget et al., 2011).

It is important to note that exceptions exist too, where neurogenesis or newborn cell survival is not stimulated by antidepressants, an effect that appears to depend on animal species and mouse strain, sex, age, and early life history, and on the pharmacology of the antidepressant, or may become apparent only under disease-specific conditions, or only in more anxious mouse strains (Couillard-Despres et al., 2009; Cowen, Takase, Fornal, Jacobs, 2008; David et al., 2009; Hodes, Hill-Smith, Suckow, Cooper, Lucki, 2009; Hodes, Yang, Van Kooy, Santollo, & Shors, 2009; Holick, Lee, Hen, & Dulawa, 2008; Huang, Bannerman, Flint, 2008; Klomp, Václavů, Meerhoff, Reneman, & Lucassen, 2014; Marlatt, Lucassen, & van Praag, 2010; Mendez-David et al., 2014; Navailles, Hof, & Schmauss, 2008; Santarelli et al., 2003; Snyder et al., 2009). Also, anatomical differences within the hippocampus are involved (Kheirbek & Hen, 2011) while indirect effects of serotonin, e.g., on other forms of plasticity, or in interaction with other drugs, may also influence antidepressant effects on neurogenesis and brain plasticity (Maya Vetencourt et al., 2008; Wu & Castrén, 2009). Moreover, a reduction in neurogenesis per se, i.e., other than induced by stress, does not cause a "depressed" phenotype (Henn & Vollmayr, 2004; Lucassen, Fitzsimons, et al., 2013; Snyder et al., 2011; Vollmayr, Simonis, Weber, Gass, & Henn, 2003). Later studies have suggested that neurogenesis is implicated in antidepressant drug actions in rodents and primates and that blocking the proneurogenic effects of antidepressants prevented the behavioral effects of these drugs measured in some animal models (see also Figs. 8.1 and 8.2, and Santarelli et al., 2003; Sahay & Hen, 2007; Surget et al., 2008; Perera et al., 2011).

So far, however, a coherent functional theory is still lacking as to how a limited number of new hippocampal neurons in only a subregion of the DG can contribute to brain features and functions that are as general as mood or depressive symptoms. This is besides the cognitive deficits, which are related to, but not specific for, mood disorders. Although a reduced rate

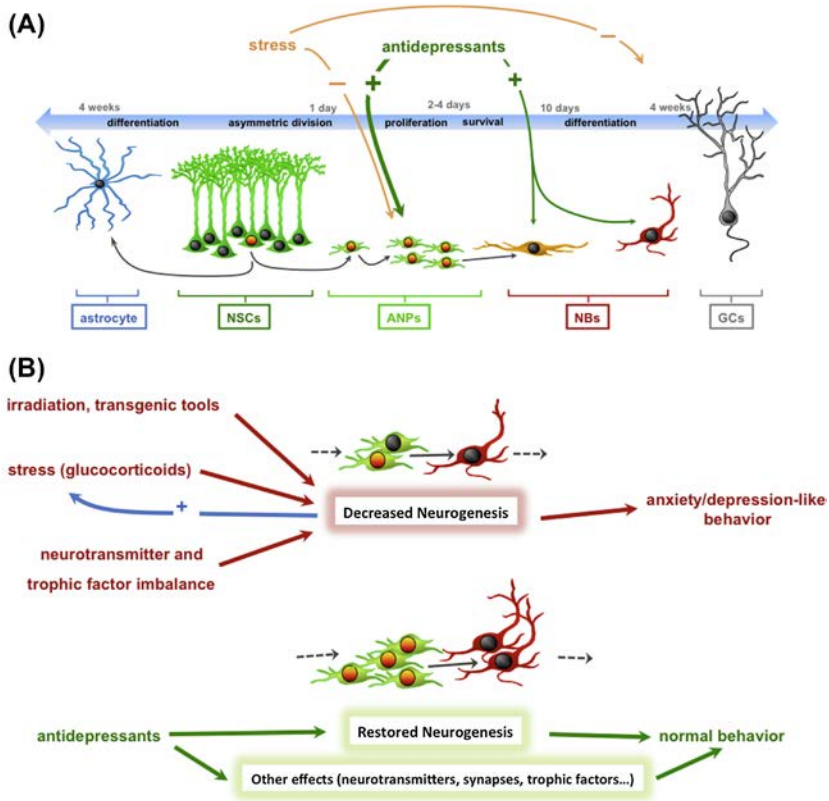


FIGURE 8.2 Schematic representation of the different stages of neurogenesis and their relationship/sensitivity to stress and depression. (A) Model of adult hippocampal neurogenesis. Neural stem cells (NSCs) are activated and enter the cell cycle to produce amplifying neuronal precursors (ANPs). These can proliferate and die, or differentiate into neuroblasts (NBs) and eventually into granule cells (GCs). Stress can reduce newborn cell proliferation and also their survival and differentiation (see also Heine, Maslam, Joëls, et al., 2004; Heine, Maslam, Zareno, et al., 2004 and Wong and Herbert, 2004). Many antidepressants, including treatment with antiglucocorticoids, exert the opposite effect. (B) An acute decrease in neurogenesis per se is not sufficient to provoke depression or depression-like behavior, but when neurogenesis is decreased by an imbalance of neurotransmitters or trophic factors, or induced with transgenic tools or, e.g., irradiation, it can increase the response to stress, which by itself can further diminish neurogenesis (blue +). As a result, depression-like behavior can emerge in experimental animals. Most antidepressants increase neurogenesis, a response that has been shown to be required for their (functional) antidepressant action, most likely in combination with other effects at the neurotransmitter, trophic factor, and/or synaptic levels. Chronic exposure to stress, or to stress early in life, can lastingly reduce AN, resulting in a diminished neurogenic reserve and a reduced cognitive potential and flexibility, associated with depression (Kheirbek, Klemenhagen, Sahay, & Hen, 2012).

of neurogenesis may reflect impaired hippocampal plasticity, reductions in adult neurogenesis alone are unlikely to produce depression. Lasting reductions in the turnover rate of DG granule cells, however, will, over time, clearly alter the average age and overall composition of the DG cell population and thereby influence properties of the hippocampal circuit.

Neural stem cells present in the hippocampus and their progeny go through different stages of proliferation (apoptotic), cell selection, fate specification, migration, and neuronal differentiation before they are eventually integrated as new functional neurons into the preexisting adult hippocampal network (Fig. 8.1) (Abrous et al., 2005; Jessberger & Gage, 2014; Kempermann, 2012; Opendak & Gould, 2015; Zhao, Deng, & Gage, 2008). Neurogenesis and related structural plasticity have also been reported in other brain structures, such as the amygdala, striatum, hypothalamus, and neocortex, but to a more limited extent, with differences between species and often occurring in response to specific challenges or injury. Whether the cellular/structural plasticity in these other brain regions is also regulated by similar environmental factors, such as stress, is less well studied (Amrein, Isler, & Lipp, 2011; Cavegn et al., 2013; Gould, 2007).

AN is dynamically regulated by various hormonal and environmental factors and drugs and declines with age. Neurogenesis in the hippocampal DG is potently stimulated by exercise and environmental enrichment, notably parallel to changes in hippocampal function (Holmes, Galea, Mistlberger, & Kempermann, 2004; Kannangara et al., 2011; Kempermann, 2012; Kempermann et al., 2010; Kobilo et al., 2011; Vivar, Potter, & van Praag, 2013; Voss et al., 2013). Exercise also exerts effects on the stress axis itself (Droste et al., 2003) and on growth factor levels (Marlatt, Potter, Lucassen, & van Praag, 2012; Vivar et al., 2013). Whereas rewarding experiences can also stimulate neurogenesis, aversive experiences like stress generally decrease proliferation and neurogenesis in the hippocampus (Balu & Lucki, 2009; Lucassen, Meerlo, et al., 2010; Lucassen et al., 2014).

STRESS REGULATION OF NEUROGENESIS

Stress is one of the best known environmental inhibitors of AN. Both psychosocial (Czéh et al., 2002; Gould et al., 1997) and physical stressors (Malberg & Duman, 2003; Pham et al., 2003; Vollmayr et al., 2003) can suppress one or more phases of the neurogenesis process (see Figs. 8.2 and 8.3 and Czéh et al., 2001, 2006, 2002; Lucassen, Meerlo, et al., 2010; Lucassen et al., 2014; Mirescu & Gould, 2006). In classical studies, predator stress produced significant reductions in hippocampal proliferation (Czéh et al., 2001; Gould et al., 1997; see Lucassen et al., 2014, and Czéh et al., 2015, for recent reviews) and both acute and chronic unpredictable stress can suppress proliferation while also other stressors, including physical restraint,

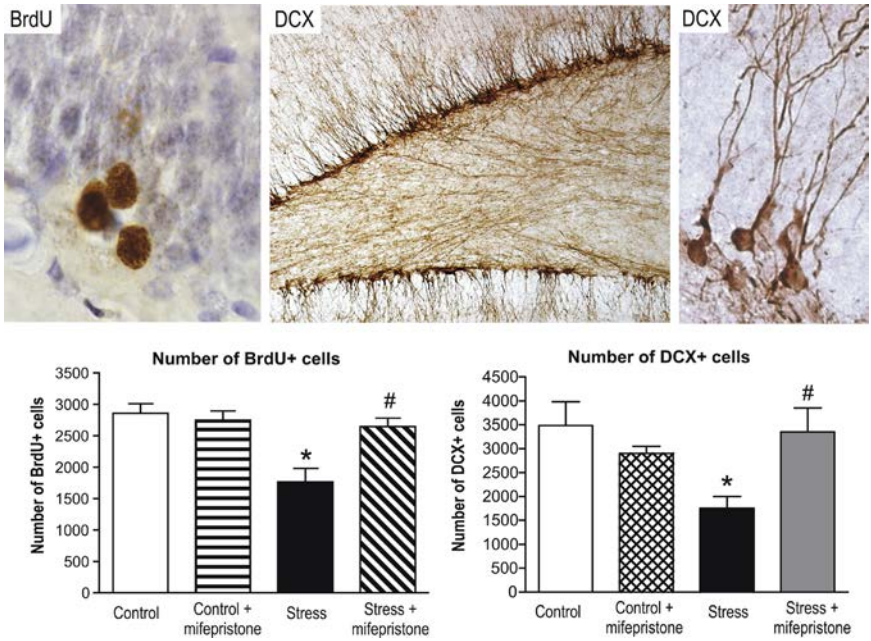


FIGURE 8.3 Effects of prolonged stress or glucocorticoid treatment on neurogenesis and the rescue effect of GR blockade. Top panels show examples of BrdU+ and Doublecortin (DCX)+ immunostained cells in the rat hippocampal dentate gyrus (DG). DCX-positive somata are located in the SGZ with their extensions (arrowheads) passing through the GCL. Lower panels display BrdU- (left graph) and DCX-positive cell numbers (right graph) in a 1 in 10 series of hippocampal sections of rats subjected to 21 days of chronic unpredictable stress (Oomen et al., 2007) similar results have been found after chronic corticosterone treatment (Mayer et al., 2006). The significant reduction in both BrdU- (21-day-old cells) and DCX-positive cell numbers after chronic stress or corticosterone treatment is normalized by 4 days of high dose treatment with the GR antagonist mifepristone, whereas the drug alone has no effect (see Mayer et al., 2006, and Oomen et al., 2007; Zalachoras et al., 2013, for details). * indicates $p < 0.001$ relative to the control group in the left graph and $p < 0.05$ in the right graph. Similar recovery is found when mifepristone is applied for only 1 day (Hu et al., 2012).

social defeat, inescapable foot shock, sleep deprivation, and inflammation can decrease the numbers of new neurons in the dentate gyrus (Czéh et al., 2002; Dagyte et al., 2009; Gould et al., 1997; Heine, Maslam, Joëls, et al., 2004; Heine, Maslam, Zareno, et al., 2004; Hulshof, Novati, Luiten, den Boer, & Meerlo, 2012; Lucassen, Meerlo, et al., 2010; Lucassen, Stumpel, et al., 2010; Pham et al., 2003; Schoenfeld & Gould, 2013; Wu et al., 2014). Interestingly, also an absence of an effect or even increases in neurogenesis have been reported after stress in some instances, but here, differences in temporal design may have been involved, or repeated stressors could have become predictable or were relatively mild and may actually have enriched an otherwise "boring" environment and could thus have been perceived as rewarding experiences (Parihar, Hattiangady, Kuruba, Shuai, & Shetty, 2011).

Also the duration of the stress period and the anatomical location may be of influence as acute stress could, e.g., induce proliferation in the dorsal hippocampus under specific conditions (Kirby et al., 2013; Kheirbek & Hen, 2011).

When no other transmitter systems are altered, the stressor is unpredictable and its nature severe, then reductions in neurogenesis are commonly seen. In fact, multiple stages of the neurogenic process are then affected, including proliferation of the neural stem cells and amplifying progenitor cells, as well as subsequent neuronal differentiation phase and dendritic expansion. Stress not only reduces proliferation and neurogenesis in many different species, it may also shift neural stem cells away from neuronal differentiation and instead "redirect" them toward the generation of oligodendrocytes (Chetty et al., 2014). Although not studied in great detail yet, such stress-induced fate shifts may have important functional consequences, e.g., for the myelination of axons and/or mossy fibers, and hence network connectivity.

Thus, while different types of stress can trigger different behavioral and functional responses, GCs are considered instrumental in mediating the effects of stress, e.g., on new neuron production. Chronic exogenous administration of GCs to animals affects cell proliferation, neuronal differentiation, and cell survival, as well as the production of oligodendrocytes and (micro-)glia responses and behavior (Bland et al., 2010; Butovsky et al., 2006; Chetty et al., 2014; Ekdahl, Kokaia, & Lindvall, 2009; Hu et al., 2012; Lehmann et al., 2013; Mayer et al., 2006). Moreover, the reductions in neurogenesis after stress, and many of the related molecular alterations as well (Datson et al., 2012), can be prevented by, e.g., blocking GCs from the adrenal or HPA mediators, using, e.g., CRH or GR antagonists (Alonso et al., 2004). Also, a short treatment for 1 or 3 days with a GR antagonist already normalized stress or GC-induced reductions in hippocampal neurogenesis (Hu et al., 2012; Mayer et al., 2006; Oomen, Mayer, de Kloet, Joels, & Lucassen, 2007; Zalachoras et al., 2013) (see also Fig. 8.3).

Although more information has become available on molecular control and timing of stem cell regulation (Anacker et al., 2013;Fitzsimons et al., 2014, 2013; Miller et al., 2013; Schouten et al., 2012, 2015), the precise mechanisms by which GCs decrease neurogenesis remains unknown. NMDA receptors, GRs, and MRs are present on the new cells, albeit in different ratios over time, that likely act in concert to mediate effects of stress on neurogenesis (Montaron et al., 2003; Wong & Herbert, 2004, 2005). Notably, GR knockdown, selectively in cells of the hippocampal neurogenic niche, accelerates their neuronal differentiation and migration, induces ectopic positioning, alters their dendritic complexity, and increases their dendritic spines and basal excitability but impairs contextual freezing during fear conditioning (Fitzsimons et al., 2013). Hence, GR expression in, and thus stress sensitivity of, the newborn hippocampal cells is important for their structural and functional integration in the hippocampal circuit.

The precursors are further located closely to blood vessels, which is of relevance as it is indeed this population that is particularly sensitive to stress (Heine, Zareno, Maslam, Joels, & Lucassen, 2005). Astrocytes are also important as this cell type supports the survival of developing neurons, possesses GR, and are affected by some types of stress (Banasr & Duman, 2008; Czéh, Simon, Schmelting, Hiemke, & Fuchs, 2006; Oomen et al., 2009) and changes in this cell population can contribute to depressive-like behavior (Banasr & Duman, 2008).

Stress further slows down neuronal differentiation, as evidenced by the upregulation of markers indicating cell cycle arrest (Heine, Maslam, Joëls, et al., 2004) and related changes in granule cell dendritic trees. Stress and GCs also reduce the survival of neurons produced prior to the stressful experience. While the underlying mechanism is largely unknown, this is thought to be mediated by inhibitory effects on neurotrophins such as brain-derived neurotrophic factor (BDNF) (Schmidt & Duman, 2007). The reduction in newborn cell survival likely also involves microglia, which are known to phagocytose newborn neuronal precursors (Ekdahl et al., 2009; Guadagno et al., 2013; Hinwood, Morandini, Day, & Walker, 2012; Morris, Clark, Zinn, & Vissel, 2013; Sierra et al., 2010). Indeed, stress influences microglia and their responsivity, which may modulate their efficiency in cleaning up debris. Although under normal conditions, "resting" or unchallenged microglia do not trigger apoptosis of those cells that they efficiently phagocytose in the hippocampal neurogenic niche (Sierra et al., 2010), microglia could help reduce new neuron survival under acute and chronic stress (Jakubs et al., 2008), by becoming activated and releasing cytokines and chemokines with neurotoxic effects (Johansson, Price, & Modo, 2008; Koo & Duman, 2008; Spulber, Oprica, Bartfai, Winblad, & Schultzberg, 2008). Also, they could undergo changes in intrinsic properties such as motility and morphology (Walker, Nilsson, & Jones, 2013). Whether they have the capacity to switch to a model in which they can actually induce apoptosis of neuronal precursors in the hippocampal neurogenic niche, as has been shown in vitro via TNFa (Guadagno et al., 2013), remains to be determined.

Although a role for (nor)adrenaline has not been studied in detail with respect to stress-induced changes in neurogenesis, an important difference between several studies is whether or not GC levels remain elevated after the exposure to the stressor has ended. In some psychosocial stress models, the GC "milieu" is altered in a lasting manner and GC levels remain elevated for prolonged periods of time, which has stronger inhibitory effects on AN than apparently severe, but predictable, physical stressors, such as restraint (Wong & Herbert, 2004). Several examples of a persistent and lasting inhibition of AN after an initial stressor exist, despite a later normalization of GC levels (e.g., Czéh et al., 2002; Mirescu & Gould, 2006; Schoenfeld & Gould, 2013). Also, GC levels can remain elevated after the onset of the first, often psychosocial, stressor that suppresses neurogenesis

for prolonged periods. In other, milder models, stress hormone levels generally normalize, yet neurogenesis remains reduced (Schoenfeld & Gould, 2013; Van Bokhoven et al., 2011). This suggests that while GCs are involved in the initial suppression of proliferation, they are not always necessary for the maintenance of this effect.

When studying the effects of stress on adult neurogenesis under laboratory conditions, it is important to realize that many variables influence the outcome of such studies, as interindividual and gender differences in stress coping, handling, time of day at sacrifice, and previous exposure to stressful learning tasks can influence stress responses and neurogenesis (e.g., Ehninger & Kempermann, 2006; Holmes et al., 2004). In addition to stress hormones like GCs, also other mediators of the stress system that interact with neurogenesis are changed. Models employing repeated injections with exogenous GCs to imitate the hypercortisolism found, e.g., in depression, exert negative feedback at the level of the pituitary and inhibit the endogenous production of GCs by the adrenals. As a result, ACTH and CRH levels are very low in GC-treated rodents, a condition which is in contrast to the endogenous HPA axis activation seen in chronically stressed animals and patients where CRH, ACTH, and GCs are elevated. A large number of other factors may also contribute to the stress-induced inhibition of AN, such as the stress-induced increase in glutamate release via NMDA receptor activation (Gould et al., 1997; Nacher & McEwen, 2006; Schoenfeld & Gould, 2013).

Stress further affects various neurotransmitters implicated in the regulation of neurogenesis: GABA (Ge, Yang, Hsu, Ming, & Song, 2007), serotonin (Djavadian, 2004), noradrenaline (Joca et al., 2007), acetylcholine (Bruel-Jungerman, Lucassen, & Francis, 2011), and dopamine, e.g., (Domínguez-Escribà et al., 2006; Takamura et al., 2014). GABA deserves special mention as it has been recently reported to be a key regulator for the recruitment and activation of hippocampal neural stem cells. The balance of activation and quiescence would be controlled by tonic release of GABA by neighboring interneurons. Higher levels would promote quiescence while lower levels would promote activation of neural stem cells, via GABAA receptors expressed by them (Song et al., 2012). Also other neurotransmitter systems such as the cannabinoids, opioids, nitric oxide, various neuropeptides, and also gonadal steroids may contribute (see, e.g., Balu & Lucki, 2009; Galea, 2008). Importantly, stress reduces the expression of several growth and neurotrophic factors, such as BDNF, insulin-like growth factor-1, nerve growth factor, epidermal growth factor, and vascular endothelial growth factor, that can influence neurogenesis (see, e.g., Schmidt & Duman, 2007; Wilson, 2014).

Chronic stress can also affect proliferation of glial cells as, e.g., seen in the medial prefrontal cortex of rats after social defeat, after chronic unpredictable stress, or after chronic GC administration. Similarly, prolonged

and elevated GC treatment inhibited NG2-positive cell proliferation, reflecting changes in oligodendrocyte precursors. Chronic stress also promotes structural remodeling of microglia and can enhance the release of proinflammatory cytokines from microglia, and can even mediate aspects of depressive-like behavior (Kreisel et al., 2014).

Astrocytes are also key components of the "neurogenic niche" that provides the necessary local microenvironment for neurogenesis. For instance, astrocytes participate physically in the establishment of synapses between newborn and preexistent neurons, and the inhibition of glutamate reuptake by astrocytes significantly impairs postsynaptic currents and facilitates paired-pulse facilitation in adult-born neurons (Krzisch et al., 2015). Furthermore, astrocytes promote neuronal differentiation by secreting ephrin-B2 acting on ephrin-B4 receptors present in neural stem cells and modulating β-catenin in a Wnt-independent manner (Ashton et al., 2012). Since astrocytes also contain GRs and can be regulated by stress, this implies that stress can also modulate neural progenitors through interactions with astrocytes (Vallieres et al., 2002; Wang et al., 2013).

Stress-induced suppression of adult neurogenesis has been associated with impaired performance on various cognitive tasks that require the hippocampus, such as spatial navigation learning and object memory (Braun & Jessberger, 2014; Oomen et al., 2014). It should be noted that these effects are typically observed within a shorter time frame than what would be expected for the involvement and integration of newborn neurons, which should be taken into account in the experimental design. In addition, additional younger, immature, and excitable neurons, as well as the older populations of DG cells, exist that are sensitive too, and could contribute to hippocampal performance. As a more specific test for the new neurons in the DG per se, pattern separation has received a lot of attention recently (see above).

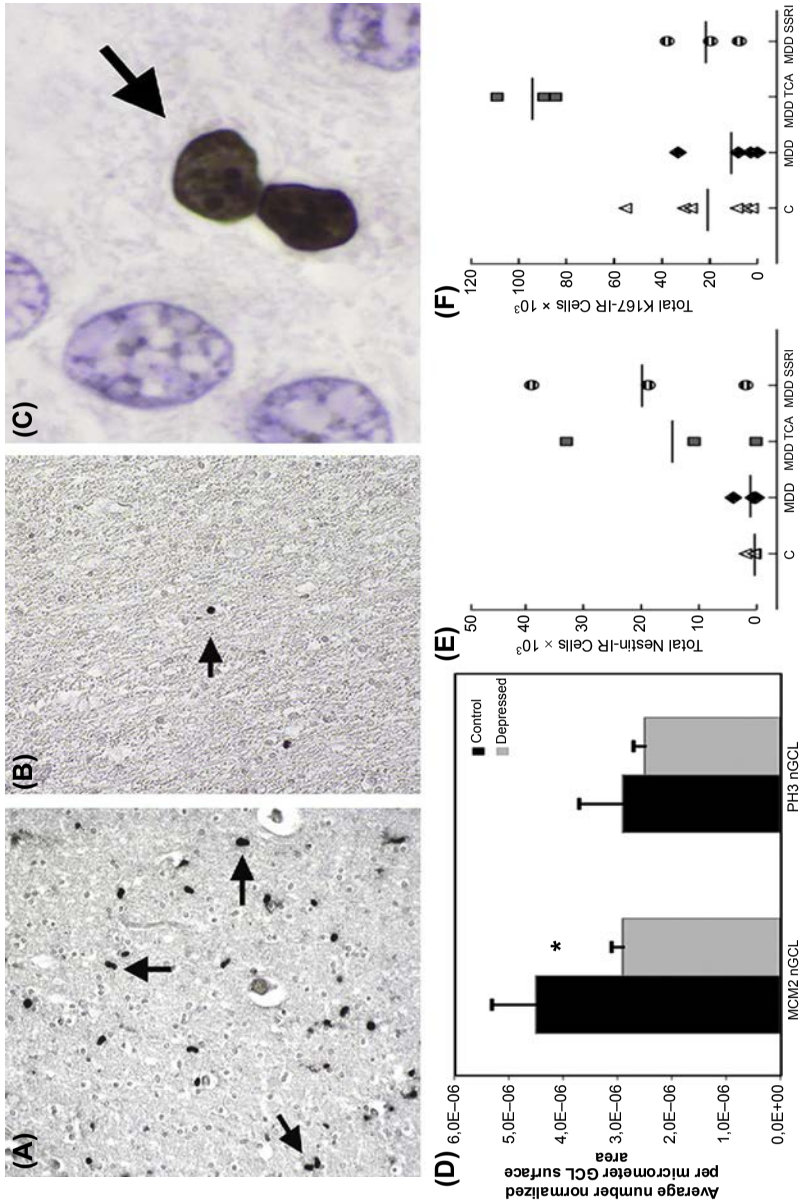
An extensive literature further indicates that AN is sensitive to stress exposure during the early life period. As this is beyond the scope of this chapter, early life stress will only be discussed briefly. The set point of HPA axis activity, and possibly also of neurogenesis regulation, is, on the one hand, programmed by genotype, but can be further modified by early development, and, e.g., by epigenetic changes (Lucassen, Naninck, et al., 2013). In humans, early life stressors (ELS) are among the strongest predisposing factors for developing psychopathology and cognitive decline later in life (Baram et al., 2012; Heim et al., 2008; Loman, Gunnar, & Early Experience Stress and Neurobehavioral Development Center, 2010; Maselko, Kubzansky, Lipsitt, & Buka, 2011; Risch et al., 2009; Teicher, Anderson, & Polcari, 2012) and in experimental conditions where emotional and cognitive functions are altered after ELS (Aisa, Tordera, Lasheras, Del Río, & Ramírez, 2007; Baram et al., 2012; Brunson et al., 2005; Ivy et al., 2010; Oomen et al., 2010). Also neurogenesis is sensitive to stress during the perinatal period, the effects of which often depend on sex and

on the developmental stage during which the organism experienced stress (Coe et al., 2003; Galea, 2008; Kim et al., 2013; Korosi et al., 2012; Lemaire et al., 2000; Loi, Koricka, Lucassen, & Joëls, 2014; Lucassen et al., 2009; Lucassen, Naninck, et al., 2013; Mirescu et al., 2004; Naninck et al., 2015), although exceptions exist as well (Tauber et al., 2008).

NEUROGENESIS AND MAJOR DEPRESSION

Given the clear association among stress, hippocampal volume reductions, and major depression, it came as no surprise that antidepressants could affect hippocampal neurogenesis in several animal models (for a recent overview, see Czéh et al., 2015). Given the technical limitations to visualize neurogenesis in vivo, only few studies have so far addressed this issue in human brain tissue. Reif, Fritzen, Finger, Strobel, and Lauer (2006) failed to find differences in neural stem cell proliferation in postmortem brain samples between patients suffering from MDD, bipolar disorder, or schizophrenia and control subjects. Antidepressants did not alter these numbers but changes were found in schizophrenia. More recent studies (Boldrini et al., 2012, 2009; Lucassen et al., 2014; Lucassen, Stumpel, et al., 2010) (see Fig. 8.4) compared progenitor and dividing cells with different immunocytochemical markers and found that in hippocampal tissues of untreated depressed subjects, the numbers of progenitor cells were significantly decreased. Both treatments with selective serotonin-reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) increased the number of nestin-positive progenitors and TCAs had a robust stimulatory effect on the number of Ki-67-reactive dividing cells. These changes were reported in middle aged (Boldrini et al., 2012, 2009) but not in older depressed patients (Lucassen, Meerlo, et al., 2010; Lucassen, Stumpel, et al., 2010), possibly because of limited power or due to age-related differences in plasticity in these patients (see also Felice et al., 2015).

In a postmortem study on MDD patients, the volume of the histologically defined DG was determined and found to be in fact 68% larger in SSRI-treated depressed subjects, while SSRI treatment substantially increased neural progenitor cells in the dentate gyrus. A recent study by Huang et al. (2013) found smaller DG volumes using MRI in unmedicated depressed patients, which was confirmed at postmortem analysis, which is consistent with the neurogenic hypothesis of depression. Interestingly, both subfield and posterior hippocampal volume reductions were only seen in unmedicated depression but were absent in patients treated with antidepressants. Although it is so far not simple to detect ongoing neurogenesis in vivo (Manganas et al., 2007), these data are consistent with preclinical studies demonstrating subregional specific and opposite effects of stress or depression and antidepressant treatment.


(A)
(B)
(C)
(D)
Average number normalized per micrometer GCL surface area
6,0E–06
5,0E–06
4,0E–06
3,0E–06
2,0E–06
1,0E–06
0,0E+00
Control
Depressed
*
MCM2 nGCL
PH3 nGCL
(E)
Total Nestin-IR Cells × 10³
50
40
30
20
10
0
C
MDD
MDD TCA
MDD SSRI
(F)
Total K167-IR Cells × 10³
120
100
80
60
40
20
0
C
MDD
MDD TCA
MDD SSRI

Although AN may thus not be essential for the development of depression, it may be required for clinically effective antidepressant treatment (Perera et al., 2011; Santarelli et al., 2003; Surget et al., 2008, 2011). Hence, stimulation of neurogenesis has been regarded as a promising strategy for identifying new antidepressant targets (see also Figs. 8.1 and 8.2). Accordingly, when tested in chronic stress paradigms, several candidate antidepressant compounds, such as corticotrophin-releasing factor (CRF1), vasopressin (V1b), or glucocorticoid receptor antagonists (Alonso et al., 2004; Oomen et al., 2007; Surget et al., 2008), tianeptine (Czéh et al., 2001) or selective neurokinin-1 (NK1) receptor antagonists (Czéh et al., 2005) could indeed normalize the inhibitory effects of stress on proliferation or neurogenesis.

Hippocampal volume loss is well documented in various psychopathologies and also in patients with Cushing's disease and in subjects treated with synthetic GCs (Bourdeau et al., 2002; for a review, see Lucassen et al., 2014, and references therein). In addition to neurochemical changes, structural connectivity and plasticity changes, including neurogenesis, may contribute to its etiology as well. However, it remains elusive how exactly a subpopulation of newborn neurons can contribute to general features such as stress regulation, mood, and depression (Anacker & Pariante, 2012; Lehmann et al., 2013; Lucassen, Fitzsimons, et al., 2013; Lucassen et al., 2014; Opendak & Gould, 2011; Snyder et al., 2011).

Although a reduced rate of neurogenesis may reflect impaired hippocampal plasticity, reductions in adult neurogenesis per se, i.e., induced by irradiation, but without the concomitant presence of stress, are unlikely to

FIGURE 8.4 Changes in cell proliferation in postmortem human brain tissue of depressed and antidepressant-treated patients. (A) Cells immunopositive for the cell cycle marker minichromosome maintenance protein 2 (MCM2) that is involved in the control of DNA replication. Many MCM2-immunopositive cells and doublets (arrows) are observed in cortical tissue of a 2-year-old subject that served as positive control for the immunocytochemical procedure. (B) As expected, MCM2-ir cell numbers are strongly reduced to very low numbers (arrow) in a 69-year-old control subject. (C) Detail of an MCM2-ir doublet of two cells that appear to have recently separated in the hippocampus of a depressed patient (arrow), cresyl violet counterstain. (D) Graphs depicting numbers of MCM2 and phosphorylated histone H3 (PH3)-immunopositive cells (the latter marker reflecting the late G2 and M phases of cell division). PH3-immunoreactive cells in the subgranular zone and granular cell layer of the dentate gyrus, normalized to the surface area of the GCL. A significant reduction was found for MCM2, but not PH3, in elderly (average age of 68 years) depressed patients compared to controls. (E) Neural progenitor and (F) dividing cells (nestin and Ki-67-positive, respectively) are increased in the dentate gyrus of younger (average ages of 40 and 54 years) patients with major depressive disorder (MDD) who were treated with antidepressants compared to untreated MDDs and control subjects. Progenitor numbers (E, nestin-positive) were higher in MDD patients treated with tricyclics (TCA) or with selective serotonin reuptake inhibitors (SSRI), compared to untreated MDD and control cases, whereas the numbers of dividing cells (F, Ki-67-ir) were higher only in the TCA but not the SSRI-treated group. *Reproduced from Lucassen P.J., Pruessner J., Sousa N., Almeida O.F., Van Dam A.M., Rajkowska G., et al. (2014). Neuropathology of stress.* Acta Neuropathologica, 127, *109–135.*

produce depression (Henn & Vollmayr, 2004). Lasting and stress-related reductions in DG neurogenesis will, however, alter turnover rate, average cellular age, and overall composition of the DG, and in the long term modify DG volume, and thereby influence the properties and vulnerability of the hippocampal circuit (Teicher et al., 2012). Indeed, hippocampal volume changes often coincide with stressful episodes in depressed patients, correlating with cognitive impairments.

The hippocampus is further thought to provide negative feedback control of the HPA axis, in which neurogenesis is at least partly implicated. Initial disturbances in hippocampal neurogenesis or output may thus disturb feedback and hence amplify HPA axis dysregulation that is common in approximately 50% of the depressed patients. Since massive cell loss could not be demonstrated in the hippocampus, the observed hippocampal volume changes could be due to (atrophy of) the somatodendritic or synaptic components, but also glia or changes in fluid balance may be involved (Czéh et al., 2006; Lucassen et al., 2014). Interestingly, AN might form a link between depression and stress. When neurogenesis is ablated, either by X-irradiation or by selective killing of mitotically active GFAP-expressing cells (neural stem cells) in mice, stressors induce a significantly stronger effect, measured both by blood levels of cortisone and by behavioral outcome in tests such as novelty-suppressed feeding, forced swimming, and the sucrose preference test (Snyder et al., 2011). Thus AN has been postulated to act as a buffer to both stress responses and depressive behavior.

CONCLUSIONS

Different types of stress and glucocorticoid and antidepressant treatment often interfere with one or more phases of the neurogenetic process. While inhibitory effects of acute stress can normalize after a recovery period, e.g., reductions in neurogenesis that are caused by chronic, severe, and/or unpredictable stress may last longer and have functional consequences. While neurogenesis has been implicated in cognition, mood, and anxiety regulation as well as in the therapeutic effects of antidepressant drugs, its exact role, i.e., cause or consequence, in relation to depression remains poorly understood. A reduced rate of neurogenesis may reflect impaired hippocampal plasticity, but reductions in AN alone are unlikely to produce depression and may require additional stress exposure, e.g., during critical developmental periods. Lasting reductions in turnover rate of DG granule cells, e.g., influenced by genotype or programmed by early life events, may alter the overall composition of the DG cell population. This, in turn, could modify stress responsivity and thereby influence functioning of the adult hippocampal circuit as well as the vulnerability for developing brain disorders.

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References

Abrous, D. N., Koehl, M., & Le Moal, M. (2005). Adult neurogenesis: from precursors to network and physiology. *Physiological Reviews*, *85*, 523–569.

Abrous, D. N., & Wojtowicz, J. M. (June 1, 2015). Interaction between neurogenesis and hippocampal memory system: new vistas. *Cold Spring Harbor Perspectives in Biology*, *7*(6). pii:a018952.

Aimone, J. B., Deng, W., & Gage, F. H. (May 26, 2011). Resolving new memories: a critical look at the dentate gyrus, adult neurogenesis, and pattern separation. *Neuron*, *70*(4), 589–596.

Aisa, B., Tordera, R., Lasheras, B., Del Río, J., & Ramírez, M. J. (2007). Cognitive impairment associated to HPA axis hyperactivity after maternal separation in rats. *Psychoneuroendocrinology*, *32*, 256–266.

Alonso, R., Griebel, G., Pavone, G., Stemmelin, J., Le Fur, G., & Soubrié, P. (2004). Blockade of CRF(1) or V(1b) receptors reverses stress-induced suppression of neurogenesis in a mouse model of depression. *Molecular Psychiatry*, *9*(3), 278–286, 224.

Alt, S. R., Turner, J. D., Klok, M. D., Meijer, O. C., Lakke, E. A., Derijk, R. H., et al. (2010). Differential expression of glucocorticoid receptor transcripts in major depressive disorder is not epigenetically programmed. *Psychoneuroendocrinology*, *35*(4), 544–556.

Amrein, I., Isler, K., & Lipp, H. P. (September 2011). Comparing adult hippocampal neurogenesis in mammalian species and orders: influence of chronological age and life history stage. *European Journal of Neuroscience*, *34*(6), 978–987.

Anacker, C., Cattaneo, A., Luoni, A., Musaelyan, K., Zunszain, P. A., Milanesi, E., et al. (2013). Glucocorticoid-related molecular signaling pathways regulating hippocampal neurogenesis. *Neuropsychopharmacology*, *38*, 872–883.

Anacker, C., & Pariante, C. M. (2012). Can adult neurogenesis buffer stress responses and depressive behaviour? *Molecular Psychiatry*, *17*, 9–10.

Ashton, R. S., Conway, A., Pangarkar, C., Bergen, J., Lim, K. I., Shah, P., et al. (2012). Astrocytes regulate adult hippocampal neurogenesis through ephrin-B signaling. *Nature Neuroscience*, *15*(10), 1399–1406.

Balu, D. T., & Lucki, I. (2009). Adult hippocampal neurogenesis: regulation, functional implications, and contribution to disease pathology. *Neuroscience and Biobehavioral Reviews*, *33*, 232–252.

Banasr, M., & Duman, R. S. (2008). Glial loss in the prefrontal cortex is sufficient to induce depressive-like behaviors. *Biological Psychiatry*, *64*, 863–870.

Baram, T. Z., Davis, E. P., Obenaus, A., Sandman, C. A., Small, S. L., Solodkin, A., et al. (2012). Fragmentation and unpredictability of early-life experience in mental disorders. *American Journal of Psychiatry*, *169*, 907–915.

Bielefeld, P., van Vliet, E. A., Gorter, J. A., Lucassen, P. J., & Fitzsimons, C. P. (January 2014). Different subsets of newborn granule cells: a possible role in epileptogenesis? *European Journal of Neuroscience*, *39*(1), 1–11.

Bilbo, S. D., & Schwarz, J. M. (2009). Early-life programming of later-life brain and behavior: a critical role for the immune system. *Frontiers in Behavioral Neuroscience*, *3*, 1–14.

Bland, S. T., Beckley, J. T., Young, S., Tsang, V., Watkins, L. R., Maier, S. F., et al. (2010). Enduring consequences of early-life infection on glial and neural cell genesis within cognitive regions of the brain. *Brain Behavior and Immunity*, *24*, 329–338.

Boku, S., Toda, H., Nakagawa, S., Kato, A., Inoue, T., Koyama, T., et al. (2014). Neonatal maternal separation alters the capacity of adult neural precursor cells to differentiate into neurons via methylation of retinoic acid receptor gene promoter. *Biological Psychiatry*, *77*(4), 335–344.

Boldrini, M., Hen, R., Underwood, M. D., Rosoklija, G. B., Dwork, A. J., Mann, J. J., et al. (2012). Hippocampal angiogenesis and progenitor cell proliferation are increased with antidepressant use in major depression. *Biological Psychiatry*, *72*, 562–571.

Boldrini, M., Underwood, M. D., Hen, R., Rosoklija, G. B., Dwork, A. J., John Mann, J., et al. (2009). Antidepressants increase neural progenitor cells in the human hippocampus. *Neuropsychopharmacology*, *34*, 2376–2389.

Bourdeau, I., Bard, C., Noël, B., Leclerc, I., Cordeau, M.-P., Bélair, M., et al. (2002). Loss of brain volume in endogenous Cushing's syndrome and its reversibility after correction of hypercortisolism. *Journal of Clinical Endocrinology and Metabolism*, *87*, 1949–1954.

Braun, S. M., & Jessberger, S. (May 2014). Adult neurogenesis: mechanisms and functional significance. *Development*, *141*(10), 1983–1986.

Bruel-Jungerman, E., Lucassen, P. J., & Francis, F. (2011). Cholinergic influences on cortical development and adult neurogenesis. *Behavioural Brain Research*, *221*, 379–388.

Brunson, K. L., Kramár, E., Lin, B., Chen, Y., Colgin, L. L., Yanagihara, T. K., et al. (2005). Mechanisms of late-onset cognitive decline after early-life stress. *Journal of Neuroscience*, *25*, 9328–9338.

Butovsky, O., Ziv, Y., Schwartz, A., Landa, G., Talpalar, A. E., Pluchino, S., et al. (2006). Microglia activated by IL-4 or IFN-gamma differentially induce neurogenesis and oligodendrogenesis from adult stem/progenitor cells. *Molecular and Cellular Neuroscience*, *31*, 149–160.

Cavegn, N., van Dijk, R. M., Menges, D., Brettschneider, H., Phalanndwa, M., Chimimba, C. T., et al. (2013). Habitat-specific shaping of proliferation and neuronal differentiation in adult hippocampal neurogenesis of wild rodents. *Frontiers in Neuroscience*, *7*, 59.

Chetty, S., Friedman, A. R., Taravosh-Lahn, K., Kirby, E. D., Mirescu, C., Guo, F., et al. (2014). Stress and glucocorticoids promote oligodendrogenesis in the adult hippocampus. *Molecular Psychiatry*, *19*(12), 1275–1283.

Cho, K. O., Lybrand, Z. R., Ito, N., Brulet, R., Tafacory, F., Zhang, L., et al. (2015). Aberrant hippocampal neurogenesis contributes to epilepsy and associated cognitive decline. *Nature Communications*, *6*, 6606.

Clelland, C. D., Choi, M., Romberg, C., Clemenson, G. D., Jr., Fragniere, A., Tyers, P., et al. (2009). A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science*, *325*(5937), 210–213.

Cobb, J. A., Simpson, J., Mahajan, G. J., Overholser, J. C., Jurjus, G. J., Dieter, L., et al. (2013). Hippocampal volume and total cell numbers in major depressive disorder. *Journal of Psychiatric Research*, *47*, 299–306.

Coe, C. L., Kramer, M., Czéh, B., Gould, E., Reeves, A. J., Kirschbaum, C., et al. (2003). Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile rhesus monkeys. *Biological Psychiatry*, *54*, 1025–1034.

Couillard-Despres, S., Wuertinger, C., Kandasamy, M., Caioni, M., Stadler, K., Aigner, R., et al. (2009). Ageing abolishes the effects of fluoxetine on neurogenesis. *Molecular Psychiatry*, *14*, 856–864.

Cowen, D. S., Takase, L. F., Fornal, C. A., & Jacobs, B. L. (2008). Age-dependent decline in hippocampal neurogenesis is not altered by chronic treatment with fluoxetine. *Brain Research*, *1228*, 14–19.

Czéh, B., Fuchs, E., Wiborg, O., & Simon, M. (April 17, 2015). Animal models of major depression and their clinical implications. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *64*, 293–310.

Czéh, B., & Lucassen, P. J. (2007). What causes the hippocampal volume decrease in depression? Are neurogenesis, glial changes and apoptosis implicated? *European Archives of Psychiatry and Clinical Neuroscience*, *257*(5), 250–260.

Czéh, B., Michaelis, T., Watanabe, T., Frahm, J., de Biurrun, G., van Kampen, M., et al. (2001). Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. *Proceedings of the National Academy of Sciences of the United States of America*, *98*, 12796–12801.

Czéh, B., Pudovkina, O., van der Hart, M. G. C., Simon, M., Heilbronner, U., Michaelis, T., et al. (2005). Examining SLV-323, a novel NK1 receptor antagonist, in a chronic psychosocial stress model for depression. *Psychopharmacology (Berlin)*, *180*, 548–557.

Czéh, B., Simon, M., Schmelting, B., Hiemke, C., & Fuchs, E. (2006). Astroglial plasticity in the hippocampus is affected by chronic psychosocial stress and concomitant fluoxetine treatment. *Neuropsychopharmacology*, *31*, 1616–1626.

Czéh, B., Welt, T., Fischer, A. K., Erhardt, A., Schmitt, W., Müller, M. B., et al. (2002). Chronic psychosocial stress and concomitant repetitive transcranial magnetic stimulation: effects on stress hormone levels and adult hippocampal neurogenesis. *Biological Psychiatry*, *52*, 1057–1065.

Dagyte, G., Van der Zee, E. A., Postema, F., Luiten, P. G., Den Boer, J. A., Trentani, A., et al. (2009). Chronic but not acute foot-shock stress leads to temporary suppression of cell proliferation in rat hippocampus. *Neuroscience*, *162*(4), 904–913.

Datson, N. A., Speksnijder, N., Mayer, J. L., Steenbergen, P. J., Korobko, O., Goeman, J., et al. (2012). The transcriptional response to chronic stress and glucocorticoid receptor blockade in the hippocampal dentate gyrus. *Hippocampus*, *22*, 359–371.

David, D. J., Samuels, B. A., Rainer, Q., Wang, J. W., Marsteller, D., Mendez, I., et al. (2009). Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression. *Neuron*, *62*(4), 479–493.

Déry, N., Goldstein, A., & Becker, S. (June 15, 2015). A role for adult hippocampal neurogenesis at multiple time scales: a study of recent and remote memory in humans. *Behavioral Neuroscience*, *129*, 435–449.

Djavadian, R. L. (2004). Serotonin and neurogenesis in the hippocampal dentate gyrus of adult mammals. *Acta Neurobiologiae Experimentalis (Warsaw)*, *64*, 189–200.

Domínguez-Escribà, L., Hernández-Rabaza, V., Soriano-Navarro, M., Barcia, J. A., Romero, F. J., García-Verdugo, J. M., et al. (2006). Chronic cocaine exposure impairs progenitor proliferation but spares survival and maturation of neural precursors in adult rat dentate gyrus. *European Journal of Neuroscience*, *24*(2), 586–594.

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Structure and Function*, *213*, 93–118.

Droste, S. K., Gesing, A., Ulbricht, S., Müller, M. B., Linthorst, A. C. E., & Reul, J. M. H.M. (2003). Effects of long-term voluntary exercise on the mouse hypothalamic-pituitary-adrenocortical axis. *Endocrinology*, *144*, 3012–3023.

Duman, R. S. (2004). Depression: a case of neuronal life and death? *Biological Psychiatry*, *56*, 140–145.

Ehninger, D., & Kempermann, G. (2006). 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 and Behavior*, *5*, 29–39.

Eisch, A. J., & Petrik, D. (2012). Depression and hippocampal neurogenesis: a road to remission? *Science*, *338*(6103), 72–75.

Ekdahl, C. T., Kokaia, Z., & Lindvall, O. (2009). Brain inflammation and adult neurogenesis: the dual role of microglia. *Neuroscience*, *158*, 1021–1029.

Encinas, J. M., Vaahtokari, A., & Enikolopov, G. (May 23, 2006). Fluoxetine targets early progenitor cells in the adult brain. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(21), 8233–8238.

Erdmann, G., Berger, S., & Schütz, G. (2008). Genetic dissection of glucocorticoid receptor function in the mouse brain. *Journal of Neuroendocrinology*, *20*, 655–659.

Felice, D., O'Leary, O. F., Cryan, J. F., Dinan, T. G., Gardier, A. M., Sánchez, C., et al. (2015). When ageing meets the blues: Are current antidepressants effective in depressed aged patients? *Neuroscience and Biobehavioral Reviews*, *55*, 478–497.

Fitzsimons, C. P., van Bodegraven, E., Schouten, M., Lardenoije, R., Kompotis, K., Kenis, G., et al. (2014). Epigenetic regulation of adult neural stem cells: implications for Alzheimer's disease. *Molecular Neurodegeneration*, *9*, 25.

Fitzsimons, C. P., van Hooijdonk, L. W. A., Schouten, M., Zalachoras, I., Brinks, V., Zheng, T., et al. (2013). Knockdown of the glucocorticoid receptor alters functional integration of newborn neurons in the adult hippocampus and impairs fear-motivated behavior. *Molecular Psychiatry*, *18*, 993–1005.

Galea, L. A. (2008). Gonadal hormone modulation of neurogenesis in the dentate gyrus of adult male and female rodents. *Brain Research Reviews*, *57*, 332–341.

Ge, S., Yang, C.-H., Hsu, K.-S., Ming, G.-L., & Song, H. (2007). A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. *Neuron*, *54*, 559–566.

Gould, E. (2007). How widespread is adult neurogenesis in mammals? *Nature Reviews Neuroscience*, *8*(6), 481–488.

Gould, E., McEwen, B. S., Tanapat, P., Galea, L. A., & Fuchs, E. (1997). Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. *Journal of Neuroscience*, *17*, 2492–2498.

Guadagno, J., Xu, X., Karajgikar, M., Brown, A., & Cregan, S. P. (March 14, 2013). Microglia-derived TNFα induces apoptosis in neural precursor cells via transcriptional activation of the Bcl-2 family member Puma. *Cell Death and Disease*, *4*, e538.

Harris, A. P., Holmes, M. C., de Kloet, E. R., Chapman, K. E., & Seckl, J. R. (2013). Mineralocorticoid and glucocorticoid receptor balance in control of HPA axis and behaviour. *Psychoneuroendocrinology*, *38*, 648–658.

Heim, C., Newport, D., Mletzko, T., Miller, A., & Nemeroff, C. (2008). The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology*, *33*, 693–710.

Heine, V. M., Maslam, S., Joëls, M., & Lucassen, P. J. (2004). Increased P27KIP1 protein expression in the dentate gyrus of chronically stressed rats indicates G1 arrest involvement. *Neuroscience*, *129*, 593–601.

Heine, V. M., Maslam, S., Zareno, J., Joels, M., & Lucassen, P. J. (2004). Suppressed proliferation and apoptotic changes in the rat dentate gyrus after acute and chronic stress are reversible. *European Journal of Neuroscience*, *19*, 131–144.

Heine, V. M., Zareno, J., Maslam, S., Joels, M., & Lucassen, P. J. (2005). Chronic stress in the adult dentate gyrus reduces cell proliferation near the vasculature and VEGF and Flk-1 protein expression. *European Journal of Neuroscience*, *21*, 1304–1314.

Henn, F. A., & Vollmayr, B. (2004). Neurogenesis and depression: etiology or epiphenomenon? *Biological Psychiatry*, *56*(3), 146–150.

Hinwood, M., Morandini, J., Day, T. A., & Walker, F. R. (2012). Evidence that microglia mediate the neurobiological effects of chronic psychological stress on the medial prefrontal cortex. *Cerebral Cortex*, *22*, 1442–1454.

Hodes, G. E., Hill-Smith, T. E., Suckow, R. F., Cooper, T. B., & Lucki, I. (2009). Sex specific effects of chronic fluoxetine treatment on neuroplasticity and pharmacokinetics in mice. *Journal of Pharmacology and Experimental Therapeutics*, *332*(1), 266–273.

Hodes, G. E., Yang, L., Van Kooy, J., Santollo, J., & Shors, T. J. (2009). Prozac during puberty: distinctive effects on neurogenesis as a function of age and sex. *Neuroscience*, *163*(2), 609–617.

Holick, K. A., Lee, D. C., Hen, R., & Dulawa, S. C. (2008). Behavioral effects of chronic fluoxetine in Balb/cJ mice do not require adult hippocampal neurogenesis or the serotonin 1A receptor. *Neuropsychopharmacology*, *33*, 406–417.

Holmes, M. M., Galea, L. A. M., Mistlberger, R. E., & Kempermann, G. (2004). Adult hippocampal neurogenesis and voluntary running activity: circadian and dose-dependent effects. *Journal of Neuroscience Research*, *76*, 216–222.

Hu, P., Oomen, C., van Dam, A. M., Wester, J., Zhou, J. N., Joëls, M., et al. (2012). A single-day treatment with mifepristone is sufficient to normalize chronic glucocorticoid induced suppression of hippocampal cell proliferation. *PLoS One*, *7*, e46224.

Huang, Y., Coupland, N. J., Lebel, R. M., Carter, R., Seres, P., Wilman, A. H., et al. (2013). Structural changes in hippocampal subfields in major depressive disorder: a high-field magnetic resonance imaging study. *Biological Psychiatry*, *74*, 62–68.

Huang, G. J., Bannerman, D., & Flint, J. (2008). Chronic fluoxetine treatment alters behavior, but not adult hippocampal neurogenesis, in BALB/cJ mice. *Molecular Psychiatry*, *13*, 119–121.

Hulshof, H. J., Novati, A., Luiten, P. G., den Boer, J. A., & Meerlo, P. (2012). Despite higher glucocorticoid levels and stress responses in female rats, both sexes exhibit similar stress-induced changes in hippocampal neurogenesis. *Behavioural Brain Research*, *234*(2), 357–364.

Ivy, A. S., Rex, C. S., Chen, Y., Dubé, C., Maras, P. M., Grigoriadis, D. E., et al. (2010). Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve excessive activation of CRH receptors. *Journal of Neuroscience*, *30*, 13005–13015.

Jacobs, B. L., van Praag, H., & Gage, F. H. (2000). Adult brain neurogenesis and psychiatry: a novel theory of depression. *MolecularPsychiatry*, *5*(3), 262–269.

Jakubs, K., Bonde, S., Iosif, R. E., Ekdahl, C. T., Kokaia, Z., Kokaia, M., et al. (2008). Inflammation regulates functional integration of neurons born in adult brain. *Journal of Neuroscience*, *28*, 12477–12488.

Jessberger, S., Clark, R. E., Broadbent, N. J., Clemenson, G. D., Jr., Consiglio, A., Lie, D. C., et al. (January 29, 2009). Dentate gyrus-specific knockdown of adult neurogenesis impairs spatial and object recognition memory in adult rats. *Learning and Memory*, *16*(2), 147–154.

Jessberger, S., & Gage, F. H. (2014). Adult neurogenesis: bridging the gap between mice and humans. *Trends in Cell Biology*, *24*(10), 558–563.

Joels, M., & Baram, T. Z. (2009). The neuro-symphony of stress. *Nature Reviews Neuroscience*, *10*, 459–466.

Joels, M., Karst, H., Krugers, H. J., & Lucassen, P. J. (2007). Chronic stress: implications for neuronal morphology, function and neurogenesis. *Frontiers in Neuroendocrinology*, *28*, 72–96.

Joels, M., Sarabdjitsingh, R. A., & Karst, H. (2012). Unraveling the time domains of corticosteroid hormone influences on brain activity: rapid, slow, and chronic modes. *Pharmacological Reviews*, *64*, 901–938.

Johansson, S., Price, J., & Modo, M. (2008). Effect of inflammatory cytokines on major histocompatibility complex expression and differentiation of human neural stem/progenitor cells. *Stem Cells*, *26*, 2444–2454.

Kannangara, T. S., Lucero, M. J., Gil-Mohapel, J., Drapala, R. J., Simpson, J. M., Christie, B. R., et al. (2011). Running reduces stress and enhances cell genesis in aged mice. *Neurobiology of Aging*, *32*(12), 2279–2286.

Karg, K., Burmeister, M., Shedden, K., & Sen, S. (May 2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. *Archives of General Psychiatry*, *68*(5), 444–454.

Kempermann, G. (2008). The neurogenic reserve hypothesis: what is adult hippocampal neurogenesis good for? *Trends in Neurosciences*, *31*(4), 163–169.

Kempermann, G. (2012). New neurons for 'survival of the fittest'. *Nature Reviews Neuroscience*, *13*, 727–736.

Kempermann, G., Fabel, K., Ehninger, D., Babu, H., Leal-Galicia, P., Garthe, A., et al. (2010). Why and how physical activity promotes experience-induced brain plasticity. *Frontiers in Neuroscience*, *4*, 189.

Kempermann, G., Krebs, J., & Fabel, K. (2008). The contribution of failing adult hippocampal neurogenesis to psychiatric disorders. *Current Opinion in Psychiatry*, *21*, 290–295.

Kempermann, G., & Kronenberg, G. (2003). Depressed new neurons–adult hippocampal neurogenesis and a cellular plasticity hypothesis of major depression. *Biological Psychiatry*, *54*(5), 499–503.

Kempton, M. J., Salvador, Z., Munafò, M. R., Geddes, J. R., Simmons, A., Frangou, S., et al. (2011). Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. *Archives of General Psychiatry*, *68*, 675–690.

Kheirbek, M. A., & Hen, R. (January 2011). Dorsal vs ventral hippocampal neurogenesis: implications for cognition and mood. *Neuropsychopharmacology*, *36*(1), 373–374.

Kheirbek, M. A., Klemenhagen, K. C., Sahay, A., & Hen, R. (December 2012). Neurogenesis and generalization: a new approach to stratify and treat anxiety disorders. *Nature Neuroscience*, *15*(12), 1613–1620.

Kim, J. I., Lee, J. W., Lee, Y. A., Lee, D. H., Han, N. S., Choi, Y. K., et al. (2013). Sexual activity counteracts the suppressive effects of chronic stress on adult hippocampal neurogenesis and recognition memory. *Brain Research*, *1538*, 26–40.

Kirby, E. D., Muroy, S. E., Sun, W. G., Covarrubias, D., Leong, M. J., Barchas, L. A., et al. (April 16, 2013). Acute stress enhances adult rat hippocampal neurogenesis and activation of newborn neurons via secreted astrocytic FGF2. *Elife*, *2*, e00362.

de Kloet, E. R., Joëls, M., & Holsboer, F. (2005). Stress and the brain: from adaptation to disease. *Nature Reviews Neuroscience*, *6*, 463–475.

Klok, M. D., Alt, S. R., Irurzun Lafitte, A. J., Turner, J. D., Lakke, E. A., Huitinga, I., et al. (July 2011). Decreased expression of mineralocorticoid receptor mRNA and its splice variants in postmortem brain regions of patients with major depressive disorder. *Journal of Psychiatric Research*, *45*(7), 871–878.

Klok, M. D., Giltay, E. J., Van der Does, A. J., Geleijnse, J. M., Antypa, N., Penninx, B. W., et al. (2011). A common and functional mineralocorticoid receptor haplotype enhances optimism and protects against depression in females. *Translational Psychiatry*, *1*, e62.

Klomp, A., Václavů, L., Meerhoff, G. F., Reneman, L., & Lucassen, P. J. (2014). Effects of chronic fluoxetine treatment on neurogenesis and tryptophan hydroxylase expression in adolescent and adult rats. *PLoS One*, *9*(5) e97603.

Kobilo, T., Liu, Q. R., Gandhi, K., Mughal, M., Shaham, Y., & van Praag, H. (2011). Running is the neurogenic and neurotrophic stimulus in environmental enrichment. *Learning and Memory*, *18*(9), 605–609.

Koehl, M., van der Veen, R., Gonzales, D., Piazza, P. V., & Abrous, D. N. (2012). Interplay of maternal care and genetic influences in programming adult hippocampal neurogenesis. *Biological Psychiatry*, *72*(4), 282–289.

Koo, J. W., & Duman, R. S. (2008). IL-1beta is an essential mediator of the antineurogenic and anhedonic effects of stress. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 751–756.

Koolhaas, J. M., Bartolomucci, A., Buwalda, B., de Boer, S. F., Flügge, G., Korte, S. M., et al. (2011). Stress revisited: a critical evaluation of the stress concept. *Neuroscience and Biobehavioral Reviews*, *35*, 1291–1301.

Korosi, A., Naninck, E. F. G., Oomen, C. A., Schouten, M., Krugers, H., Fitzsimons, C., et al. (2012). Early-life stress mediated modulation of adult neurogenesis and behavior. *Behavioural Brain Research*, *227*, 400–409.

Kreisel, T., Frank, M. G., Licht, T., Reshef, R., Ben-Menachem-Zidon, O., Baratta, M. V., et al. (2014). Dynamic microglial alterations underlie stress-induced depressive-like behavior and suppressed neurogenesis. *Molecular Psychiatry*, *19*, 699–709.

Kretz, O., Reichardt, H. M., Schütz, G., & Bock, R. (1999). Corticotropin-releasing hormone expression is the major target for glucocorticoid feedback-control at the hypothalamic level. *Brain Research*, *818*, 488–491.

Krzisch, M., Temprana, S. G., Mongiat, L. A., Armida, J., Schmutz, V., Virtanen, M. A., et al. (July 2015). Pre-existing astrocytes form functional perisynaptic processes on neurons generated in the adult hippocampus. *Brain Structure and Function*, *220*(4), 2027–2042.

Lehmann, M. L., Brachman, R. A., Martinowich, K., Schloesser, R. J., & Herkenham, M. (2013). Glucocorticoids orchestrate divergent effects on mood through adult neurogenesis. *Journal of Neuroscience*, *33*, 2961–2972.

Lemaire, V., Koehl, M., Le Moal, M., & Abrous, D. N. (2000). Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, *97*, 11032–11037.

Leuner, B. (2010). Parenting and plasticity. *Trends in Neurosciences*, *33*, 465–473.
Liston, C., Cichon, J. M., Jeanneteau, F., Jia, Z., Chao, M. V., & Gan, W.-B. (2013). Circadian glucocorticoid oscillations promote learning-dependent synapse formation and maintenance. *Nature Publishing Group*, *16*, 698–705.
Loi, M., Koricka, S., Lucassen, P. J., & Joëls, M. (2014). Age- and sex-dependent effects of early life stress on hippocampal neurogenesis. *Frontiers in Endocrinology (Lausanne)*, *5*, 13.
Loman, M. M., Gunnar, M. R., & Early Experience, Stress, and Neurobehavioral Development Center (2010). Early experience and the development of stress reactivity and regulation in children. *Neuroscience and Biobehavioral Reviews*, *34*, 867–876.
Lorenzetti, V., Allen, N. B., Fornito, A., & Yücel, A. (2009). Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. *Journal of Affective Disorders*, *117*, 1–17.
Lucassen, P. J., Bosch, O. J., Jousma, E., Krömer, S. A., Andrew, R., Seckl, J. R., et al. (2009). Prenatal stress reduces postnatal neurogenesis in rats selectively bred for high, but not low, anxiety: possible key role of placental 11β-hydroxysteroid dehydrogenase type 2. *European Journal of Neuroscience*, *29*, 97–103.
Lucassen, P. J., Fitzsimons, C. P., Korosi, A., Joëls, M., Belzung, C., & Abrous, D. N. (2013). Stressing new neurons into depression? *Molecular Psychiatry*, *18*, 396–397.
Lucassen, P. J., Meerlo, P., Naylor, A. S., van Dam, A. M., Dayer, A. G., Fuchs, E., et al. (2010). Regulation of adult neurogenesis by stress, sleep disruption, exercise and inflammation: Implications for depression and antidepressant action. *European Neuropsychopharmacology*, *20*, 1–17.
Lucassen, P. J., Naninck, E. F., van Goudoever, J. B., Fitzsimons, C., Joels, M., & Korosi, A. (2013). Perinatal programming of adult hippocampal structure and function; emerging roles of stress, nutrition and epigenetics. *Trends in Neurosciences*, *36*, 621–631.
Lucassen, P. J., Pruessner, J., Sousa, N., Almeida, O. F., Van Dam, A. M., Rajkowska, G., et al. (2014). Neuropathology of stress. *Acta Neuropathologica*, *127*, 109–135.
Lucassen, P. J., Stumpel, M. W., Wang, Q., & Aronica, E. (2010). Decreased numbers of progenitor cells but no response to antidepressant drugs in the hippocampus of elderly depressed patients. *Neuropharmacology*, *58*, 940–949.
MacQueen, G. M., Yucel, K., Taylor, V. H., Macdonald, K., & Joffe, R. (2008). Posterior hippocampal volumes are associated with remission rates in patients with major depressive disorder. *Biological Psychiatry*, *64*, 880–883.
Malberg, J. E., & Duman, R. S. (2003). Cell proliferation in adult hippocampus is decreased by inescapable stress: reversal by fluoxetine treatment. *Neuropsychopharmacology*, *28*, 1562–1571.
Manganas, L. N., Zhang, X., Li, Y., Hazel, R. D., Smith, S. D., Wagshul, M. E., et al. (2007). Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain. *Science*, *318*, 980–985.
Marlatt, M. W., Lucassen, P. J., & van Praag, H. (2010). Comparison of neurogenic effects of fluoxetine, duloxetine and running in mice. *Brain Research*, *1341*, 93–99.
Marlatt, M. W., Potter, M. C., Lucassen, P. J., & van Praag, H. (2012). Running throughout middle-age improves memory function, hippocampal neurogenesis, and BDNF levels in female C57BL/6J mice. *Developmental Neurobiology*, *72*(6), 943–952.
Maselko, J., Kubzansky, L., Lipsitt, L., & Buka, S. L. (2011). Mother's affection at 8 months predicts emotional distress in adulthood. *Journal of Epidemiology and Community Health*, *65*, 621–625.
Maya Vetencourt, J. F., Sale, A., Viegi, A., Baroncelli, L., De Pasquale, R., O'Leary, O. F., et al. (2008). The antidepressant fluoxetine restores plasticity in the adult visual cortex. *Science*, *320*(5874), 385–388. http://dx.doi.org/10.1126/science.1150516.
Mayer, J. L., Klumpers, L., Maslam, S., de Kloet, E. R., Joëls, M., & Lucassen, P. J. (2006). Brief treatment with the glucocorticoid receptor antagonist mifepristone normalises the corticosterone-induced reduction of adult hippocampal neurogenesis. *Journal of Neuroendocrinology*, *18*, 629–631.

Medina, A., Seasholtz, A. F., Sharma, V., Burke, S., Bunney, W., Myers, R. M., et al. (2013). Glucocorticoid and mineralocorticoid receptor expression in the human hippocampus in major depressive disorder. *Journal of Psychiatric Research*, *47*, 307–314.

Mendez-David, I., David, D. J., Darcet, F., Wu, M. V., Kerdine-Römer, S., Gardier, A. M., et al. (2014). Rapid anxiolytic effects of a 5-HT_4 receptor agonist are mediated by a neurogenesis-independent mechanism. *Neuropsychopharmacology*, *39*(6), 1366–1378.

Miller, J. A., Nathanson, J., Franjic, D., Shim, S., Dalley, R. A., Shapouri, S., et al. (2013). Conserved molecular signatures of neurogenesis in the hippocampal subgranular zone of rodents and primates. *Development*, *140*, 4633–4644.

Mirescu, C., & Gould, E. (2006). Stress and adult neurogenesis. *Hippocampus*, *16*, 233–238.

Mirescu, C., Peters, J. D., & Gould, E. (2004). Early life experience alters response of adult neurogenesis to stress. *Nature Neuroscience*, *7*, 841–846.

Montaron, M. F., Piazza, P. V., Aurousseau, C., Urani, A., Le Moal, M., & Abrous, D. N. (2003). Implication of corticosteroid receptors in the regulation of hippocampal structural plasticity. *European Journal of Neuroscience*, *18*, 3105–3111.

Morris, G. P., Clark, I. A., Zinn, R., & Vissel, B. (2013). Microglia: a new frontier for synaptic plasticity, learning and memory, and neurodegenerative disease research. *Neurobiology of Learning and Memory*, *105*, 40–53.

Nacher, J., & McEwen, B. S. (2006). The role of N-methyl-D-asparate receptors in neurogenesis. *Hippocampus*, *16*, 267–270.

Naninck, E. F. G., Hoeijmakers, L., Kakava-Georgiadou, N., Meesters, A., Lazic, S. E., Lucassen, P. J., et al. (2015). Chronic early-life stress alters developmental and adult neurogenesis and impairs cognitive function in mice. *Hippocampus*, *25*(3), 309–328.

Navailles, S., Hof, P. R., & Schmauss, C. (2008). Antidepressant drug-induced stimulation of mouse hippocampal neurogenesis is age-dependent and altered by early life stress. *Journal of Comparative Neurology*, *509*(4), 372–381.

Oomen, C. A., Bekinschtein, P., Kent, B. A., Saksida, L. M., & Bussey, T. J. (2014). Adult hippocampal neurogenesis and its role in cognition. *WIREs Cognitive Science*, *5*, 573–587. http://dx.doi.org/10.1002/wcs.1304.

Oomen, C. A., Girardi, C. E. N., Cahyadi, R., Verbeek, E. C., Krugers, H., Joels, M., et al. (2009). Opposite effects of early maternal deprivation on neurogenesis in male versus female rats. *PLoS One*, *4*, e3675.

Oomen, C. A., Hvoslef-Eide, M., Heath, C. J., Mar, A. C., Horner, A. E., Bussey, T. J., et al. (2013). The touchscreen operant platform for testing working memory and pattern separation in rats and mice. *Nature Protocols*, *8*, 2006–2021.

Oomen, C. A., Mayer, J. L., de Kloet, E. R., Joels, M., & Lucassen, P. J. (2007). Brief treatment with the glucocorticoid receptor antagonist mifepristone normalizes the reduction in neurogenesis after chronic stress. *European Journal of Neuroscience*, *26*, 3395–3401.

Oomen, C. A., Soeters, H., Audureau, N., Vermunt, L., van Hasselt, F. N., Manders, E. M. M., et al. (2010). Severe early life stress hampers spatial learning and neurogenesis, but improves hippocampal synaptic plasticity and emotional learning under high-stress conditions in adulthood. *Journal of Neuroscience*, *30*, 6635–6645.

Opendak, M., & Gould, E. (October 4, 2011). New neurons maintain efficient stress recovery. *Cell Stem Cell*, *9*(4), 287–288.

Opendak, M., & Gould, E. (2015). Adult neurogenesis: a substrate for experience-dependent change. *Trends in Cognitive Sciences*, *19*(3), 151–161.

Parihar, V. K., Hattiangady, B., Kuruba, R., Shuai, B., & Shetty, A. K. (2011). Predictable chronic mild stress improves mood, hippocampal neurogenesis and memory. *Molecular Psychiatry*, *16*, 171–183.

Perera, T. D., Dwork, A. J., Keegan, K. A., Thirumangalakudi, L., Lipira, C. M., Joyce, N., et al. (2011). Necessity of hippocampal neurogenesis for the therapeutic action of antidepressants in adult nonhuman primates. *PLoS One*, *6*, e17600.

Petrik, D., Lagace, D. C., & Eisch, A. J. (January 2012). The neurogenesis hypothesis of affective and anxiety disorders: are we mistaking the scaffolding for the building? *Neuropharmacology*, *62*(1), 21–34.

Pham, K., Nacher, J., Hof, P. R., & McEwen, B. S. (2003). Repeated restraint stress suppresses neurogenesis and induces biphasic PSA-NCAM expression in the adult rat dentate gyrus. *European Journal of Neuroscience*, *17*, 879–886.

Pruessner, J. C., Dedovic, K., Pruessner, M., Lord, C., Buss, C., Collins, L., et al. (2010). Stress regulation in the central nervous system: evidence from structural and functional neuroimaging studies in human populations – 2008 Curt Richter Award Winner. *Psychoneuroendocrinology*, *35*, 179–191.

Qi, X.-R., Kamphuis, W., Wang, S., Wang, Q., Lucassen, P. J., Zhou, J.-N., et al. (2013). Aberrant stress hormone receptor balance in the human prefrontal cortex and hypothalamic paraventricular nucleus of depressed patients. *Psychoneuroendocrinology*, *38*, 863–870.

Qian, X., Droste, S. K., Lightman, S. L., Reul, J. M., & Linthorst, A. C. E. (2012). Circadian and ultradian rhythms of free glucocorticoid hormone are highly synchronized between the blood, the subcutaneous tissue, and the brain. *Endocrinology*, *153*, 4346–4353.

Raadsheer, F. C., van Heerikhuize, J. J., Lucassen, P. J., Hoogendijk, W. J., Tilders, F. J., & Swaab, D. F. (September 1995). Corticotropin-releasing hormone mRNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. *American Journal of Psychiatry*, *152*(9), 1372–1376.

Reif, A., Fritzen, S., Finger, M., Strobel, A., & Lauer, M. (2006). Neural stem cell proliferation is decreased in schizophrenia, but not in depression. *Molecular Psychiatry*, *11*, 514–522.

Revest, J. M., Dupret, D., Koehl, M., Funk-Reiter, C., Grosjean, N., Piazza, P. V., et al. (2009). Adult hippocampal neurogenesis is involved in anxiety related behaviors. *Molecular Psychiatry*, *14*, 959–967.

Richetin, K., Leclerc, C., Toni, N., Gallopin, T., Pech, S., Roybon, L., et al. (2015). Genetic manipulation of adult-born hippocampal neurons rescues memory in a mouse model of Alzheimer's disease. *Brain*, *138*(Pt 2), 440–455.

Ridder, S., Chourbaji, S., Hellweg, R., Urani, A., Zacher, C., Schmid, W., et al. (2005). Mice with genetically altered glucocorticoid receptor expression show altered sensitivity for stress-induced depressive reactions. *Journal of Neuroscience*, *25*, 6243–6250.

Risch, N., Herrell, R., Lehner, T., Liang, K. Y., Eaves, L., Hoh, J., et al. (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *Journal of the American Medical Association*, *301*(23), 2462–2471.

Sahay, A., & Hen, R. (2007). Adult hippocampal neurogenesis in depression. *Nature Neuroscience*, *10*, 1110–1115.

Sahay, A., Scobie, K. N., Hill, A. S., O'Carroll, C. M., Kheirbek, M. A., Burghardt, N. S., et al. (2011). Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature*, *472*(7344), 466–470.

Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., et al. (2003). Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science*, *301*, 805–809.

Sapolsky, R. M. (October 2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of General Psychiatry*, *57*(10), 925–935.

Schmidt, H. D., & Duman, R. S. (2007). The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. *Behavioural Pharmacology*, *18*, 391–418.

Schoenfeld, T. J., & Gould, E. (2013). Differential effects of stress and glucocorticoids on adult neurogenesis. *Current Topics in Behavioral Neurosciences*, *15*, 139–164.

Schouten, M., Buijink, M. R., Lucassen, P. J., & Fitzsimons, C. P. (2012). New neurons in aging brains: molecular control by small non-coding RNAs. *Frontiers in Neuroscience*, *6*, 25. http://dx.doi.org/10.3389/fnins.2012.00025.

Schouten, M., Fratantoni, S. A., Hubens, C. J., Piersma, S. R., Pham, T. V., Bielefeld, P., et al. (2015). MicroRNA-124 and -137 cooperativity controls caspase-3 activity through BCL2L13 in hippocampal neural stem cells. *Scientific Reports*, *5*, 12448. http://dx.doi.org/10.1038/srep12448.

Sierra, A., Encinas, J. M., Deudero, J. J. P., Chancey, J. H., Enikolopov, G., Overstreet-Wadiche, L. S., et al. (2010). Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. *Cell Stem Cell*, *7*, 483–495.

Sierra, A., Martín-Suárez, S., Valcárcel-Martín, R., Pascual-Brazo, J., Aelvoet, S. A., Abiega, O., et al. (2015). Neuronal hyperactivity accelerates depletion of neural stem cells and impairs hippocampal neurogenesis. *Cell Stem Cell*, *16*(5), 488–503.

Sinclair, D., Tsai, S. Y., Woon, H. G., & Weickert, C. S. (2011). Abnormal glucocorticoid receptor mRNA and protein isoform expression in the prefrontal cortex in psychiatric illness. *Neuropsychopharmacology*, *36*(13), 2698–2709.

Snyder, J. S., Choe, J. S., Clifford, M. A., Jeurling, S. I., Hurley, P., Brown, A., et al. (2009). Adult-born hippocampal neurons are more numerous, faster maturing, and more involved in behavior in rats than in mice. *Journal of Neuroscience.*, *29*(46), 14484–14495.

Snyder, J. S., Soumier, A., Brewer, M., Pickel, J., & Cameron, H. A. (2011). Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature*, *476*, 458–461.

Song, J., Zhong, C., Bonaguidi, M. A., Sun, G. J., Hsu, D., Gu, Y., et al. (September 6, 2012). Neuronal circuitry mechanism regulating adult quiescent neural stem-cell fate decision. *Nature*, *489*(7414), 150–154.

Sousa, N., Cerqueira, J. J., & Almeida, O. (2008). Corticosteroid receptors and neuroplasticity. *Brain Research Reviews*, *57*, 561–570.

Spijker, A. T., Giltay, E. J., van Rossum, E. F., Manenschijn, L., DeRijk, R. H., Haffmans, J., et al. (2011). Glucocorticoid and mineralocorticoid receptor polymorphisms and clinical characteristics in bipolar disorder patients. *Psychoneuroendocrinology*, *36*(10), 1460–1469.

Spulber, S., Oprica, M., Bartfai, T., Winblad, B., & Schultzberg, M. (2008). Blunted neurogenesis and gliosis due to transgenic overexpression of human soluble IL-1ra in the mouse. *European Journal of Neuroscience*, *27*, 549–558.

Starkman, M. N., Giordani, B., Gebarski, S. S., Berent, S., Schork, M. A., & Schteingart, D. E. (1999). Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. *Biological Psychiatry*, *46*(12), 1595–1602.

Stockmeier, C. A., Mahajan, G. J., Konick, L. C., Overholser, J. C., Jurjus, G. J., Meltzer, H. Y., et al. (2004). Cellular changes in the postmortem hippocampus in major depression. *Biological Psychiatry*, *56*, 640–650.

Surget, A., Saxe, M., Leman, S., Ibarguen-Vargas, Y., Chalon, S., Griebel, G., et al. (2008). Drug-dependent requirement of hippocampal neurogenesis in a model of depression and of antidepressant reversal. *Biological Psychiatry*, *64*, 293–301.

Surget, A., Tanti, A., Leonardo, E. D., Laugeray, A., Rainer, Q., Touma, C., et al. (2011). Antidepressants recruit new neurons to improve stress response regulation. *Molecular Psychiatry*, *16*, 1177–1188.

Swaab, D., Bao, A., & Lucassen, P. (2005). The stress system in the human brain in depression and neurodegeneration. *Ageing Research Reviews*, *4*, 141–194.

Takamura, N., Nakagawa, S., Masuda, T., Boku, S., Kato, A., Song, N., et al. (2014). The effect of dopamine on adult hippocampal neurogenesis. *Progress in Neuropsychopharmacology and Biological Psychiatry*, *50*, 116–124. http://dx.doi.org/10.1016/j.pnpbp.2013.12.011. Epub 2013 Dec 26.

Tauber, S. C., Bunkowski, S., Schlumbohm, C., Rühlmann, M., Fuchs, E., Nau, R., et al. (2008). No long-term effect two years after intrauterine exposure to dexamethasone on dentate gyrus volume, neuronal proliferation and differentiation in common marmoset monkeys. *Brain Pathology*, *18*(4), 497–503.

Teicher, M. H., Anderson, C. M., & Polcari, A. (2012). Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. *Proceedings of the National Academy of Sciences of the United States of America*, *109*, 563–572.

Tronel, S., Charrier, V., Sage, C., Maitre, M., Leste-Lasserre, T., & Abrous, D. N. (April 25, 2015). Adult-born dentate neurons are recruited in both spatial memory encoding and retrieval. *Hippocampus*. http://dx.doi.org/10.1002/hipo.22468.

Ursin, H., & Eriksen, H. R. (2004). The cognitive activation theory of stress. *Psychoneuroendocrinology*, *29*, 567–592.

Vallières, L., Campbell, I. L., Gage, F. H., & Sawchenko, P. E. (2002). Reduced hippocampal neurogenesis in adult transgenic mice with chronic astrocytic production of interleukin-6. *Journal of Neuroscience*, *22*, 486–492.

Van Bokhoven, P., Oomen, C. A., Hoogendijk, W. J., Smit, A. B., Lucassen, P. J., & Spijker, S. (2011). Reduction in hippocampal neurogenesis after social defeat is long-lasting and responsive to late antidepressant treatment. *European Journal of Neuroscience*, *33*, 1833–1840.

Vinkers, C. H., Joëls, M., Milaneschi, Y., Kahn, R. S., Penninx, B. W., & Boks, M. P. (2014). Stress exposure across the life span cumulatively increases depression risk and is moderated by neuroticism. *Depression and Anxiety*, *31*(9), 737–745.

Vivar, C., Potter, M. C., & van Praag, H. (2013). All about running: synaptic plasticity, growth factors and adult hippocampal neurogenesis. *Current Topics in Behavioral Neurosciences*, *15*, 189–210.

Vollmayr, B., Simonis, C., Weber, S., Gass, P., & Henn, F. (2003). Reduced cell proliferation in the dentate gyrus is not correlated with the development of learned helplessness. *Biological Psychiatry*, *54*, 1035–1040.

Voss, M. W., Vivar, C., Kramer, A. F., & van Praag, H. (October 2013). Bridging animal and human models of exercise-induced brain plasticity. *Trends in Cognitive Sciences*, *17*(10), 525–544.

Walker, F. R., Nilsson, M., & Jones, K. (October 2013). Acute and chronic stress-induced disturbances of microglial plasticity, phenotype and function. *Current Drug Targets*, *14*(11), 1262–1276.

Wang, Q., Joëls, M., Swaab, D. F., & Lucassen, P. J. (2012). Hippocampal GR expression is increased in elderly depressed females. *Neuropharmacology*, *62*, 527–533.

Wang, Q., Van Heerikhuize, J., Aronica, E., Kawata, M., Seress, L., Joels, M., et al. (2013). Glucocorticoid receptor protein expression in human hippocampus; stability with age. *Neurobiology of Aging*, *34*, 1662–1673.

Wei, Q., Hebda-Bauer, E. K., Pletsch, A., Luo, J., Hoversten, M. T., Osetek, A. J., et al. (2007). Overexpressing the glucocorticoid receptor in forebrain causes an aging-like neuroendocrine phenotype and mild cognitive dysfunction. *Journal of Neuroscience*, *27*, 8836–8844.

Wilson, C. B. (2014). Predator exposure/psychosocial stress animal model of post-traumatic stress disorder modulates neurotransmitters in the rat hippocampus and prefrontal cortex. *PLoS One*, *9*, e89104.

Wong, E. Y. H., & Herbert, J. (2004). The corticoid environment: a determining factor for neural progenitors' survival in the adult hippocampus. *European Journal of Neuroscience*, *20*, 2491–2498.

Wong, E. Y. H., & Herbert, J. (2005). Roles of mineralocorticoid and glucocorticoid receptors in the regulation of progenitor proliferation in the adult hippocampus. *European Journal of Neuroscience*, *22*, 785–792.

Wu, X., & Castrén, E. (2009). Co-treatment with diazepam prevents the effects of fluoxetine on the proliferation and survival of hippocampal dentate granule cells. *Biological Psychiatry*, *66*, 5–8.

Wu, M. V., Shamy, J. L., Bedi, G., Choi, C. W., Wall, M. M., Arango, V., et al. (2014). Impact of social status and antidepressant treatment on neurogenesis in the baboon hippocampus. *Neuropsychopharmacology*, *39*, 1861–1871.

Zalachoras, I., Houtman, R., Atucha, E., Devos, R., Tijssen, A. M., Hu, P., et al. (May 7, 2013). Differential targeting of brain stress circuits with a selective glucocorticoid receptor modulator. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(19), 7910–7915.

Zhao, C., Deng, W., & Gage, F. H. (2008). Mechanisms and functional implications of adult neurogenesis. *Cell*, *132*(4), 645–660.

Further Reading

Battista, D., Ferrari, C. C., Gage, F. H., & Pitossi, F. J. (2006). Neurogenic niche modulation by activated microglia: transforming growth factor beta increases neurogenesis in the adult dentate gyrus. *European Journal of Neuroscience*, *23*, 83–93.

Brené, S., Bjørnebekk, A., Åberg, E., Mathé, A. A., Olson, L., & Werme, M. (2007). Running is rewarding and antidepressive. *Physiology and Behavior*, *92*, 136–140.

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews Neuroscience*, *9*, 46–56.

Kronenberg, G., Bick-Sander, A., Bunk, E., Wolf, C., Ehninger, D., & Kempermann, G. (2006). Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. *Neurobiology of Aging*, *27*(10), 1505–1513.

Monje, M. L., Toda, H., & Palmer, T. D. (2003). Inflammatory blockade restores adult hippocampal neurogenesis. *Science*, *302*, 1760–1765.

Morrens, J., Van Den Broeck, W., & Kempermann, G. (2012). Glial cells in adult neurogenesis. *Glia*, *60*, 159–174.

Naylor, A. S., Bull, C., Nilsson, M. K. L., Zhu, C., Bjork-Eriksson, T., Eriksson, P. S., et al. (2008). Voluntary running rescues adult hippocampal neurogenesis after irradiation of the young mouse brain. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 14632–14637.

Naylor, A. S., Persson, A. I., Eriksson, P. S., Jonsdottir, I. H., & Thorlin, T. (2005). Extended voluntary running inhibits exercise-induced adult hippocampal progenitor proliferation in the spontaneously hypertensive rat. *Journal of Neurophysiology*, *93*, 2406–2414.

Suri, D., Veenit, V., Sarkar, A., Thiagarajan, D., Kumar, A., Nestler, E. J., et al. (2013). Early stress evokes age-dependent biphasic changes in hippocampal neurogenesis, BDNF expression, and cognition. *Biological Psychiatry*, *73*, 658–666.

Wachs, F.-P., Winner, B., Couillard-Despres, S., Schiller, T., Aigner, R., Winkler, J., et al. (2006). Transforming growth factor-beta1 is a negative modulator of adult neurogenesis. *Journal of Neuropathology and Experimental Neurology*, *65*, 358–370.

Weaver, I. C. G., Grant, R. J., & Meaney, M. J. (2002). Maternal behavior regulates long-term hippocampal expression of BAX and apoptosis in the offspring. *Journal of Neurochemistry*, *82*, 998–1002.

Zhu, C., Gao, J., Karlsson, N., Li, Q., & Zhang, Y. (2010). Isoflurane anesthesia induced persistent, progressive memory impairment, caused a loss of neural stem cells, and reduced neurogenesis in young, but not adult rodents. *Journal of Cerebral Blood Flow and Metabolism*, *30*, 1017–1030.

Ziv, Y., Avidan, H., Pluchino, S., Martino, G., & Schwartz, M. (2006). Synergy between immune cells and adult neural stem/progenitor cells promotes functional recovery from spinal cord injury. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 13174–13179.

Zunszain, P. A., Anacker, C., Cattaneo, A., Choudhury, S., Musaelyan, K., Myint, A. M., et al. (2012). Interleukin-1β: a new regulator of the kynurenine pathway affecting human hippocampal neurogenesis. *Neuropsychopharmacology*, *37*, 939–949.