



REVIEW

Regulation of adult neurogenesis by stress, sleep disruption, exercise and inflammation: Implications for depression and antidepressant action[☆]

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Abstract

Adult hippocampal neurogenesis, a once unorthodox concept, has changed into one of the most rapidly growing fields in neuroscience. The present report results from the ECNP targeted expert meeting in 2007 during which cellular plasticity changes were addressed in the adult brain, focusing on neurogenesis and apoptosis in hippocampus and frontal cortex. We discuss recent studies investigating factors that regulate neurogenesis with special emphasis on effects of stress, sleep disruption, exercise and inflammation, a group of seemingly unrelated factors that share at least two unifying properties, namely that they all regulate adult hippocampal neurogenesis and have all been implicated in the pathophysiology of mood disorders.

We conclude that although neurogenesis has been implicated in cognitive function and is stimulated by antidepressant drugs, its functional impact and contribution to the etiology of depression remains unclear. A lasting reduction in neurogenesis following severe or chronic stress exposure, either in adult or early life, may represent impaired hippocampal plasticity and can contribute to the cognitive symptoms of depression, but is, by itself, unlikely to produce the full

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mood disorder. Normalization of reductions in neurogenesis appears at least partly, implicated in antidepressant action.

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1. Introduction: the role of stress and hippocampal formation in mood disorders

The stress system represents an essential alarm system that is activated whenever a discrepancy occurs between the expectation of an organism and the reality it encounters. Lack of information, loss of control, unpredictability or psychosocial demands can all produce stress responses. The same holds for perturbations of a more biological nature, like blood loss, metabolic crises or inflammation. Various sensory and cognitive signals then converge to activate a stress response that triggers several adaptive processes in the body and brain aimed at restoring homeostasis. If stressful situations become chronic and uncontrollable, then an imbalance may occur that can exert deleterious effects on virtually all organs (de Kloet et al., 2005).

Exposure to a single severe, or repetitive, uncontrollable stressor may trigger or facilitate the development of psychopathologies. Major depressive disorder is one among these illnesses known to result from an interaction between environmental stressors and genetic/developmental predispositions (Kessler, 1997; Kendler et al., 1999). Although depressive disorders are traditionally considered to have a neurochemical basis, recent studies suggest that impairments of structural plasticity contribute to their pathophysiology as well (Castrén, 2005; Berton and Nestler, 2006). Many brain structures, ranging from the monoaminergic pathways to limbic–cortical areas, mediate the different symptoms of depression. *In vivo* imaging studies on patients with emotional disorders have repeatedly indicated that a dysregulated status of various structures is apparent such as the prefrontal cortex and subgenual cingulate cortex, as well as the hippocampus and amygdala (Ressler and Mayberg, 2007). In this review, we will largely focus on the hippocampal formation, because of the occurrence of adult neurogenesis in this structure. Hippocampal neurogenesis is regulated by various factors including stress, disturbed sleep, exercise and inflammation. Interestingly, these factors have all been implicated in brain vulnerability and have been suggested to play a role in the pathophysiology of mood disorders, like depression. As such, they may share overlapping mechanisms of action that could e.g. involve glucocorticoids, cytokines and neurotrophic factors, as will be further discussed in detail.

In depressed patients, both the morphology and function of the hippocampus are altered. High resolution *in vivo* magnetic resonance imaging studies consistently document reductions in hippocampal volume (Campbell et al., 2004; Videbech and Ravnkilde, 2004), but the significance and etiology of this volume loss is unclear. It has been hypothesized that hippocampal volume reduction might be the consequence of repeated periods of major depressive disorder (Sheline, 2000; Bremner, 2002; MacQueen et al., 2003). This volume loss translates into disrupted function as indicated by the cognitive impairments, which are one of the

symptoms of major depression. Indeed, depressed patients often exhibit deficits in declarative learning and memory and diminished cognitive flexibility (e.g. Austin et al., 2001). Altered hippocampal function is furthermore likely to influence the activity of other brain structures, in particular the prefrontal cortex and the amygdala; key areas in emotional regulation. Since the hippocampus provides a negative feedback control of the hypothalamic–pituitary–adrenocortical (HPA) axis (Ulrich-Lai and Herman, 2009), a distorted function of the hippocampus may further contribute to HPA axis dysregulation, which is common in almost 50% of depressed patients (Swaab et al., 2005).

2. Stress affects hippocampal function and structure

After it was discovered that glucocorticoid receptors are abundantly expressed in the hippocampal formation, this brain area has come into the focus of preclinical stress research (de Kloet et al., 1975). Since then, a large body of evidence has been gathered, demonstrating that stress, via elevated levels of glucocorticoids, affects both hippocampal structure and function (McEwen, 2006a, Joëls et al., 2007). Functionally, chronic stress is generally associated with reductions in hippocampal excitability, long-term potentiation and hippocampal memory, but positive effects of stress on these parameters have also been described, depending on the timing and type of stressor (Kim and Diamond, 2002; Joëls et al., 2007). Morphological consequences of chronic stress include volume reductions as well as a number of cellular changes, most notably dendritic retraction and a suppressed rate of adult neurogenesis (McEwen, 2006a, Joëls et al., 2007).

Hippocampal volume loss is well documented in stress-related disorders as well as in patients treated with synthetic glucocorticoids, or suffering from Cushing's syndrome (Starkman et al., 1992; Sapolsky, 2000; Sheline, 2000; Bremner, 2002; Gianaros et al., 2007). The traditional explanation for this stress-induced hippocampal volume decrease was that elevated glucocorticoids have neurotoxic effects on the hippocampus (Sapolsky, 2000). Particularly neuronal death in the CA3 and CA1 subregions has been emphasized (Sapolsky et al., 1990). However, recent studies which employed more sophisticated cell counting methods failed to find massive neuronal loss after chronic stress or chronic corticosteroid application in animals, or in the hippocampus of depressed individuals (Vollmann-Honsdorf et al., 1997; Sousa et al., 1998; Leverenz et al., 1999; Lucassen et al., 2001, 2004; Müller et al., 2001; Stockmeier et al., 2004). The concept that major neuronal loss cannot explain the hippocampal volume changes observed after stress is consistent with observations that many of the stress-induced structural changes are transient and often spontaneously disappear when animals are subjected to a recovery period (Heine et al., 2004a,b) or when elevated corticosteroid levels are normalized again (Starkman et al.,

1992). Therefore, volume changes must be derived from other factors than cell death. Candidate cellular mechanisms are (atrophy of) the somatodendritic components, adult neurogenesis, glial changes, but factors like shifts in fluid balance cannot be excluded either (for detailed discussion see [Czéh and Lucassen, 2007](#)).

The most thoroughly documented stress-induced structural change is the dendritic reorganization that occurs parallel to the loss of spines and synapses and together with alterations in postsynaptic densities. Chronic stress or experimentally increased corticosterone concentrations induce shrinkage of the apical dendrites of the CA3 and to a lesser extent of CA1 pyramidal cells and dentate granule cells ([McEwen, 2006a](#); [Fuchs et al., 2006](#); [Sousa et al., 2008](#)). The most often proposed explanation for dendritic remodeling is that the neurons need to protect themselves from the excitotoxic effect of glutamate by reducing their input surface area. These changes of neuronal morphology are likely to contribute to various cognitive deficits that have been described as a result of chronic stress exposure ([Conrad, 2006](#); [Sousa et al., 2008](#)). Another possible functional outcome of dendritic retraction may be a disturbance of HPA axis regulation, leading to unregulated glucocorticoid release ([Conrad, 2006](#)).

3. Adult neurogenesis

Adult neurogenesis (AN) refers to the production of new neurons in an adult brain. AN is a prominent example of adult neuroplasticity, that occurs in most vertebrate species including humans ([Eriksson et al., 1998](#), but see [Amrein et al., 2007](#)). In young adult rodents thousands of new granule neurons are generated everyday ([Cameron and McKay, 2001](#)) though significant differences exist even within different mouse strains ([Kempermann and Gage, 2002](#)). The process of AN is dynamically regulated by various environmental factors and rapidly declines with age (in rodents: [Kuhn et al., 1997](#); [Heine et al., 2004a](#); in tree shrews: [Simon et al., 2005](#); in humans: [Manganas et al., 2007](#)). Neurogenesis also occurs in the subventricular zone (SVZ) of the ventricle wall in many mammals, and has been reported in human brain as well ([Curtis et al., 2007](#), [Sanai et al., 2007](#)). Several independent groups have observed low levels of neurogenesis also in other brain structures like the amygdala, striatum and neocortex, but negative results exist as well ([Gould et al., 1999](#), [Bernier et al., 2002](#), [Kornack and Rakic, 2001](#); [Cameron and Dayer, 2008](#); [Rakic, 2002](#)). Part of the difficulty in studying AN in regions such as the neocortex could reside in the fact that new cortical neurons probably belong to small subclasses of interneurons dispersed over large neocortical volumes ([Cameron and Dayer, 2008](#)).

In contrast to its abundance during embryonic development, hippocampal neurogenesis in the adult is much less frequent. Yet, AN follows a similar complex multi-step process that starts with the proliferation of progenitor cells, followed by their morphological and physiological maturation. The latter is often referred to as the "survival" process, that ends with a fully functional neuron that is integrated into the pre-existing hippocampal network ([Fig. 1](#)) (for detailed overview see e.g. [Kempermann, 2006](#); [Balu and Lucki, 2009](#)). The existence and numbers of true multipotent neural stem cells residing in the adult dentate gyrus (DG) is

still a disputed issue. Experimental data report that a heterogeneous population of precursor cells is located and proliferates in the subgranular zone, a narrow layer located between the dentate granule cell layer and hilus. These precursor cells show a characteristic phenotype of radial astrocytes ([Seri et al., 2001](#)) and can generate new cells. Daughter cells of these progenitors proliferate at high frequency and are often observed as bromodeoxyuridine (BrdU)-positive cell clusters; they have been named amplifying neural progenitors ([Encinas et al., 2006](#)). The maturing newborn neurons subsequently extend their axons and dendrites, a process followed by the formation of spines and functional synapses (See [Fig. 1](#) for a diagram illustrating the main aspects of the maturation process).

New neurons display characteristic functional properties such as a lower threshold for induction of long-term potentiation (LTP) and robust LTP ([Schmidt-Hieber et al., 2004](#)). Recent data indicate that the subsequent survival of the newly generated neurons is regulated by their input-dependent activity ([Tashiro et al., 2006](#)). There is a significant overproduction of newborn cells and neurons that do not become integrated into the pre-existing network are rapidly eliminated by apoptotic cell death ([Dayer et al., 2003](#)). This process provides a significant turnover of granule cells in the dentate gyrus of young rodents. In monkeys this turnover rate is significantly lower while no quantitative data are yet available for humans ([Cameron and McKay, 2001](#); [Kornack and Rakic, 1999](#)).

Adult neurogenesis in the dentate gyrus is potently stimulated by exercise and enriched environmental housing ([Kempermann et al., 1997](#); [Brown et al., 2003](#)). It has been suggested that data on the incidence of AN originating from laboratory rodents, that generally live in impoverished conditions, represents an underestimation of the true occurrence of AN in animals living in natural (complex) environments. A recent finding, however, appears to challenge this concept, as cell proliferation and the number of immature neurons in the hippocampus of adult wild living rats were found to be within the normal range of captive-bred rats ([Epp et al., 2009](#)).

The exact functional role of the newborn granular neurons remains to be determined. Based on the fact that the hippocampus plays a central role in the acquisition and consolidation of episodic-declarative memories, and in view of the selective occurrence of AN in this structure, it is tempting to argue that newborn neurons have a key role in spatial learning and pattern separation. Indeed there have been numerous attempts to link these two processes to each other (see e.g. [Bruehl-Jungerman et al., 2007](#); [Imayoshi et al., 2008](#); [Dupret et al., 2007, 2008](#); [Garthe et al., 2009](#); [Oomen et al., 2009](#)). Primates are thought to have the highest cognitive capacities among mammals. In case the newly generated neurons are truly essential for learning, an unresolved issue is why rats and mice seem to have higher rates of neurogenesis than primates.

4. Stress and exercise regulate adult hippocampal neurogenesis

Stress is one of the most potent environmental parameters known to suppress adult neurogenesis, as shown in several

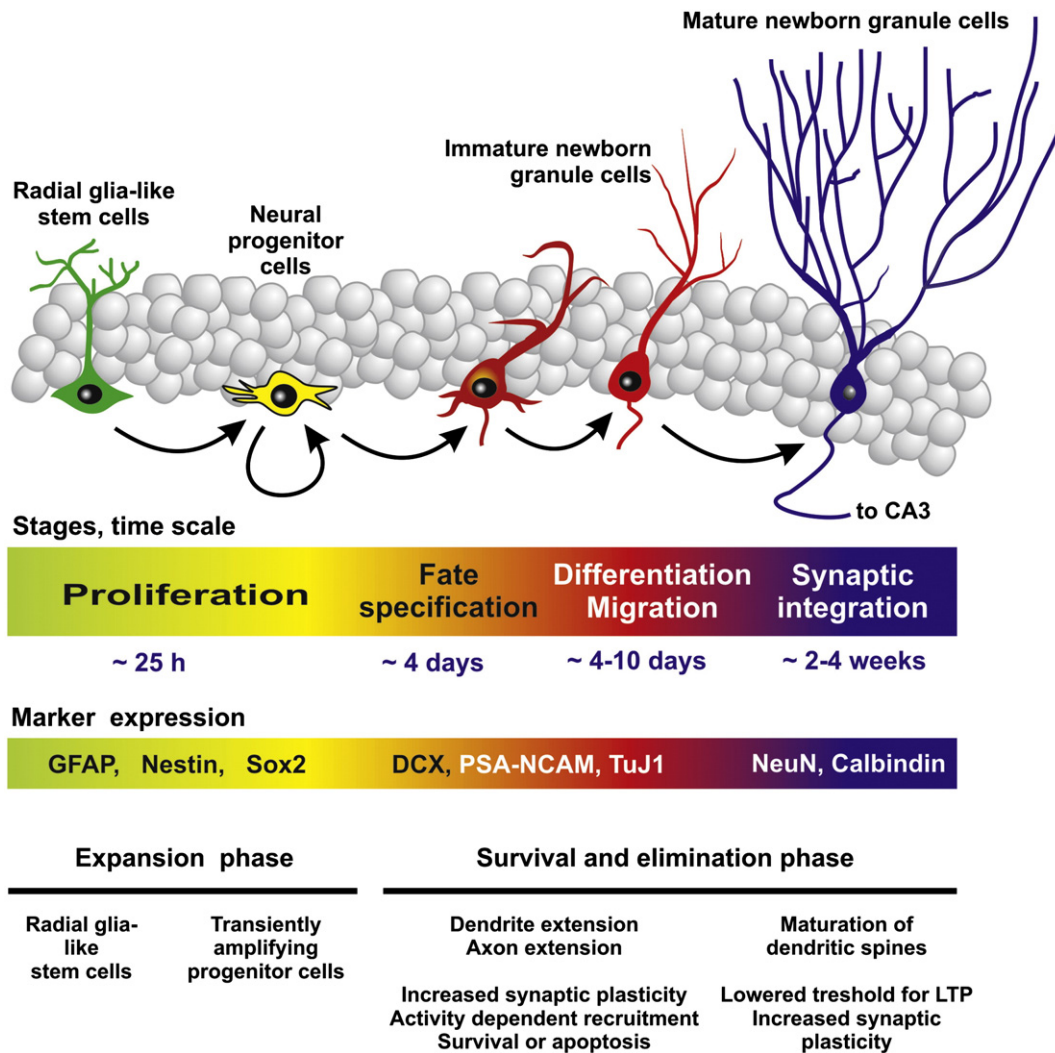


Figure 1 Schematic diagram illustrating the neuronal differentiation cascade of newborn cells located in the adult hippocampal dentate gyrus (modified from [Enikolopov and Overstreet-Wadiche, 2008](#)). Abbreviations used: GFAP: glial fibrillary acidic protein; Sox2: sex determining region Y (SRY)-box 2; DCX: doublecortin; PSA-NCAM: polysialylated form of the neural cell adhesion molecule; TuJ1: β -tubulin III; NeuN: neuronal nuclear antigen.

different species, using various stress paradigms ([Mirescu and Gould, 2006](#); [Lucassen et al., 2009c](#)). Both psychosocial ([Gould et al., 1997](#); [Czéh et al., 2002](#)) and physical stressors ([Malberg and Duman, 2003](#); [Pham et al., 2003](#); [Vollmayr et al., 2003](#)) all inhibit one or more phases of the neurogenesis process ([Oomen et al., 2007](#)). Both acute and chronic stress exposures have a potent suppressive effect on proliferation, thus the duration of the stress does not seem to be a relevant factor ([Gould et al., 1997](#); [Heine et al., 2004c](#); [Czéh et al., 2002](#)). Furthermore, stress appears to interfere with all stages of neuronal renewal, and inhibits both proliferation and survival ([Fig. 2](#)) ([Czéh et al., 2001, 2002](#); [Mirescu and Gould, 2006](#); [Oomen et al., 2007](#); [Wong and Herbert, 2004](#)).

Stress-induced reductions in proliferation could result from apoptosis of progenitor cells, or from cell cycle arrest. After acute stress, a reduction in proliferation was paralleled by increased numbers of apoptotic cells, yet no distinction was made between apoptosis of newborn or mature cells.

Following chronic stress, both proliferation and apoptosis were reduced, parallel to increases in the cell cycle inhibitor p27Kip1, indicating that more cells had entered cell cycle arrest and that the granule cell turnover had thus slowed down ([Heine et al., 2004b,c](#)).

The exact underlying cellular mechanisms mediating the inhibitory effect of stress are largely unknown. The adrenal glucocorticoid hormones (GCs; corticosterone in rodents; cortisol in man) have been pointed out as key players in this process ([Wong and Herbert, 2004; 2005](#)) and both MR and GR, as well as NMDA receptors have been identified on progenitor cells. At the same time, several examples exist of a persistent and lasting inhibition of AN after an initial stressor, and despite a later normalization of GC levels (e.g. [Czéh et al., 2002](#); [Mirescu and Gould, 2006](#)). These findings suggest that while glucocorticoids may be involved in the initial suppression of cell proliferation, particularly in early life when neurogenesis is abundant, they are not always necessary for the maintenance of this effect. A large number of other factors may also

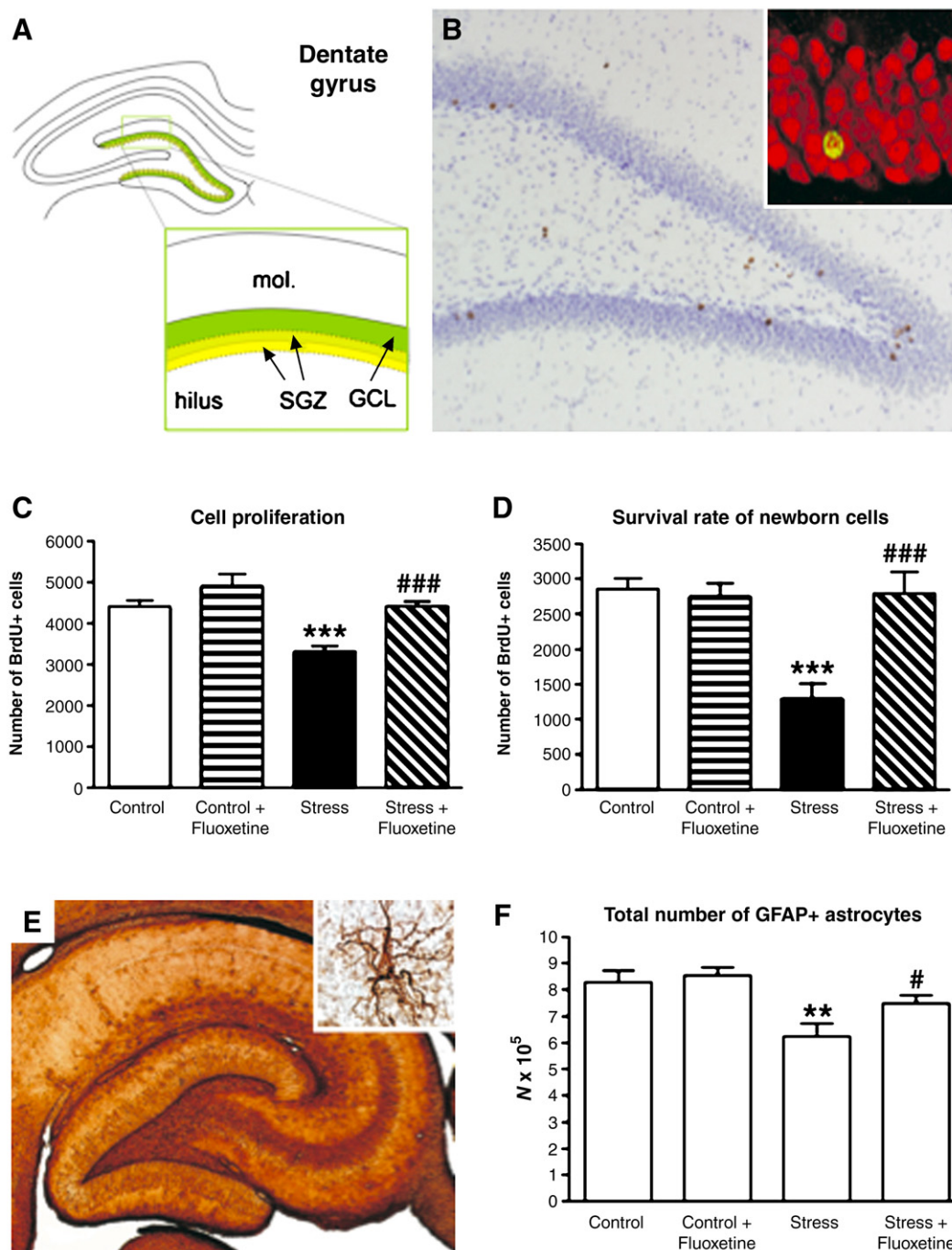


Figure 2 A: Adult hippocampal neurogenesis occurs in the subgranular zone (SGZ) of the dentate gyrus (DG) adjacent to the granule cell layer (GCL). B: Newborn granule cells (brown) in the rat DG. Insert in B shows a confocal microscopy image of a double labelled cell: red reflects mature neurons (NeuN), green–yellow is the proliferation marker bromodeoxyuridine (BrdU) labelling of a newly generated neuron. C–D: Chronic social stress inhibits both the cell proliferation rate and survival rate of the newly generated cells, whereas concomitant fluoxetine treatment can counteract this effect of stress. E: A representative image of GFAP-staining in the dentate gyrus. GFAP (glial fibrillary acidic protein) labels astroglia, insert shows an individual GFAP-positive astrocyte. F: Chronic stress results in reduced numbers of astroglia in the hippocampus, whereas fluoxetine blocked this effect of stress. $P < 0.05$ compared to control; # $P < 0.05$ compared to stress. For details see Czéh et al. (2006, 2007). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

mediate the stress-induced inhibition of AN. The stress-induced increase in glutamate release via NMDA receptor activation is another leading candidate in this process (Gould et al., 1997; Nacher and McEwen, 2006).

Stress is also known to affect the levels of various neurotransmitters that have all been implicated in the regulation of AN: GABA (Ge et al., 2007), serotonin (Djavadian, 2004), noradrenalin (Joca et al., 2007) and

dopamine (Domínguez-Escriba et al., 2006), to name a few examples. Other neurotransmitter systems, such as the cannabinoids, opioids, nitric oxide and various neuropeptides may contribute as well (see e.g. Balu and Lucki, 2009). Importantly, stress also reduces the expression of several growth and neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), nerve growth factor (NGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF), that all can influence neurogenesis (see e.g. Schmidt and Duman, 2007). The role of gonadal steroids should not be neglected either (Galea, 2008). The proximity of the precursors to blood vessels further suggests a strong interaction with the vasculature and it is this population that is particularly sensitive to stress (Heine et al., 2005). Also, astrocytes are important in this respect as they support the survival of developing neurons, possess glucocorticoid receptors and are significantly affected by some but not all types of stress (Fig. 2) (Czeh et al., 2006; Banasr et al., in press; Oomen et al., 2009).

When studying the effects of stress on adult neurogenesis in laboratory conditions it is important to realize that many variables influence the outcome of such studies, as inter-individual and gender differences in stress coping, handling, time of day at sacrifice and previous exposure to stressful learning tasks can all be of influence (e.g. Holmes et al., 2004; Ehninger and Kempermann, 2003). An interesting

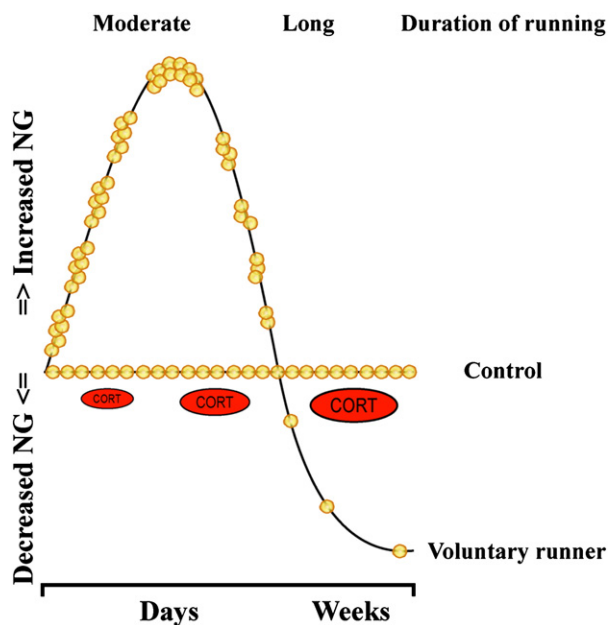


Figure 3 Schematic representation of the differential effects of voluntary running on adult hippocampal neurogenesis. Whereas short term running for 9 days potentially increases neurogenesis levels (>400%), prolonged running for 24 days induces a strong reduction in neurogenesis to approximately 50% of control levels. These changes are paralleled by the development of an activated HPA axis and a gradual rise in corticosterone levels, as represented by the size of the red ovals (see Naylor et al., 2005; Droste et al., 2003). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

contradiction also exists regarding the generally positive effect of exercise on AN (Van Praag et al., 1999). Exercise is generally associated with beneficial changes, also in its effects on mood (Ernst et al., 2006; Brene et al., 2007). In rats, short term voluntary running for 9 days potentially stimulated neurogenesis whereas long-term running for 24 days induced a strong down-regulation of progenitor proliferation rate to approximately 50% of non-running controls (Fig. 3). These latter findings were paralleled by a gradual activation of the HPA axis and the opioid system (Droste et al., 2003; Naylor et al., 2005; Lou et al., 2008). Furthermore, by decreasing or modulating the daily running distance of long-term running animals, the HPA axis activation was prevented and a return to normal proliferation levels was found (Naylor et al., 2005; Lou et al., 2008). Hence, prolonged running can develop into a stressor, overruling the positive effects of exercise on AN, and may even induce dependency-like behavior (Droste et al., 2003). This suggests that positive stimuli for AN can only be effective when HPA axis activation is minimal.

5. The long lasting effects of perinatal stress exposure

The set point of HPA axis activity is programmed by genotype, but can be changed by early development. In humans, early life stressors are among the strongest predisposing factors for major depression in later life. Aversive experiences, both *in utero* or neonatally, like early maternal separation or abuse, can result in sustained HPA axis activation and lasting alterations in the stress response that may predispose individuals to adult onset depression, anxiety disorder, or both (Heim et al., 2008).

In experimental conditions, exposure of pregnant animals to stress affects critical periods of fetal brain development that can persistently alter structural, emotional and neuroendocrine parameters in the offspring which results in altered anxiety-like behavior, increased HPA axis reactivity and memory deficits in adult life (Welberg and Seckl, 2001; Kofman, 2002; Weinstock, 2008). Subjecting pregnant rats or non-human primates to stress induces long lasting reductions in adult neurogenesis in the offspring (Lemaire et al., 2000; Coe et al., 2003; Lucassen et al., 2009a,b, but see Tauber et al., 2008).

For rat (and non-human primate) newborns, the most important environmental factor during early development is the mother. Rat pups that receive more maternal care during this period are generally less anxious later in life and show enhanced survival of newborn cells in the dentate gyrus (Bredy et al., 2003). Variations in maternal care determine HPA axis properties through epigenetic modulation (Liu et al., 2000) while the amount of maternal care received by the offspring differs between the sexes (Oomen et al., 2009). Of interest, maternal deprivation, or low levels of maternal care, reduces hippocampal neurogenesis in some (Mirescu et al., 2004; Bredy et al., 2003), but not all studies (Greisen et al., 2005). Apparently, the experimental outcome critically depends on the timing of deprivation and subsequent analysis.

Parallel to the changes in adult neurogenesis following early maternal separation, an altered incidence of cell death

occurs as well (Mirescu et al., 2004; Zhang et al., 2002). Notably, changes in neurogenesis after maternal deprivation occur in a sex-dependent manner (Oomen et al., 2009) and some could be normalized by fluoxetine treatment (Lee et al., 2001). Gonadal steroids are likely factors that determine such sex-dependent changes. Estrogens are thought to exert a protective role here. They can exert non-genomic effects directly and indirectly on the newly generated cells in neonatal and adult rat dentate gyrus while specific estrogen receptors have been found on immature doublecortin-positive neurons (Herrick et al., 2006). Evidence suggests that acute estradiol initially enhances and subsequently suppresses cell proliferation in the dentate gyrus of adult female rodents but may have limited effects in male rodents (Galea, 2008). Testosterone on the other hand, promotes differentiation and survival of the newborn neurons, but not cell proliferation, in adult male rodents (Galea, 2008). Hence, gonadal steroids contribute to the development of sex differences in neurogenesis and may modulate differential effects after perinatal stress exposure.

6. Sleep disruption as a stressor

Sleep is a very general feature of all mammals and plays an important role e.g. in homeostatic functions (Tononi and Cirelli, 2006). Chronic sleep disruption can be regarded as a physiological stressor, as it impairs brain functions, increases the sympathetic tone, blood pressure and evening cortisol levels, raises the levels of pro-inflammatory cytokines, and also elevates insulin and blood glucose (McEwen, 2006b; Meerlo et al., 2008). Disturbed sleep is not only a common symptom of mood disorders, but may also sensitize individuals to the development of depression. Consistent with this, primary insomnia often precedes and predicts depressive episodes (Riemann and Voderholzer, 2003). Experimental studies in rats have now shown that chronic sleep curtailment gradually leads to neurobiological and neuroendocrine changes similar to those found in depression (Roman et al., 2005a; Novati et al., 2008). Preclinical studies demonstrate that chronically disrupted and restricted sleep can interfere

with adult neurogenesis (Roman et al., 2005b; Mirescu et al., 2006; Guzman-Marin et al., 2007; Mueller et al., 2008). On the basis of these findings, it has been hypothesized that chronically disrupted sleep, by inhibiting neurogenesis, may contribute to the etiology of depression (Meerlo et al., 2009).

Sleep disruption for a period shorter than one day has little effect on the basal rate of cell proliferation and survival (Roman et al., 2005b; Guzman-Marin et al., 2007), yet, one study showed that even a mild restriction of sleep may prevent the increase in AN that occurs after hippocampal-dependent learning (Hairston et al., 2005). Since sleep deprivation also disturbs hippocampal-dependent memory formation (Stickgold and Walker, 2005), it could thus be that sleep loss may also interfere with cognition by affecting stages of dentate neurogenesis.

The mechanisms by which sleep disruption affects hippocampal neurogenesis are not fully understood. It has been proposed that this inhibitory effect of prolonged sleep deprivation on AN might be an indirect result of stress (Mirescu et al., 2006). Indeed, sleep loss can be considered stressful and is sometimes associated with mildly elevated GC levels (Meerlo et al., 2008). Also, prolonged sleep disruption gradually causes alterations in HPA axis regulation similar to those seen in depression (Meerlo et al., 2002; Novati et al., 2008). One study has suggested that lowering circulating GC concentrations may prevent the sleep deprivation-induced suppression of hippocampal neurogenesis (Mirescu et al., 2006). On the other hand, a number of studies with adrenalectomized rats have clearly shown that prolonged sleep loss can inhibit neurogenesis by ways that are independent of adrenal glucocorticoid hormones (Fig. 4) (Guzman-Marin et al., 2007; Mueller et al., 2008).

Besides glucocorticoids, many other factors are affected by sleep deprivation or sleep disruption, and some of these may provide a link between insufficient sleep and reductions in adult neurogenesis. For example, serotonin promotes neurogenesis, in part via the serotonin-1A receptor (Banar et al., 2004). Interesting in this respect is that chronic sleep restriction reduced the sensitivity of the serotonin-1A receptor system (Roman et al., 2005a). This reduction

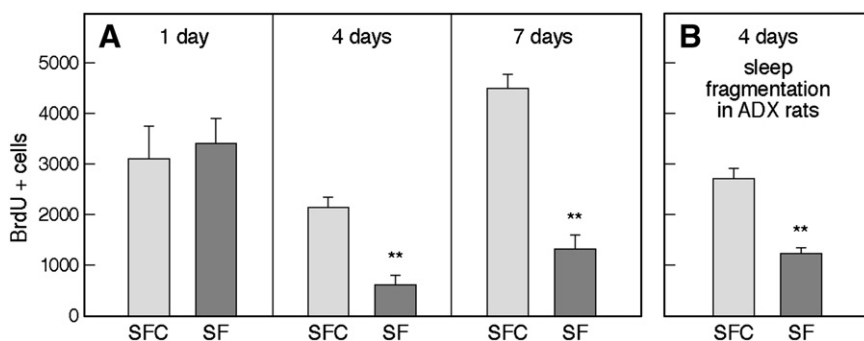


Figure 4 A: Hippocampal cell proliferation in rats subjected to sleep fragmentation (SF) by forced treadmill walking and in control animals that were subjected to forced walking but had sufficient time to sleep (SFC). Whereas 1 day of SF had no effect on cell proliferation, the numbers of BrdU-positive cells in the dorsal DG were significantly reduced after 4 or 7 days of SF. B: Effects of 4 days SF on cell proliferation in adrenalectomized (ADX) rats that received basal corticosterone in their drinking water. Independent of changes in corticosterone, a 55% reduction in the number of BrdU-positive cells was found after SF compared with ADX SFC controls. $P < 0.01$ compared to controls. After Guzman-Marin et al. (2007), with permission.

develops during the course of prolonged sleep restriction, consistent with the finding that also the suppression of adult neurogenesis generally occurs only after a prolonged period of sleep disturbance. Reductions in AN following sleep deprivation might also be related to increased levels of pro-inflammatory cytokines (see next chapter). Both interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) are increased after sleep restriction (Irwin et al., 2006; Haack et al., 2007). Plasma IL-6 levels are also increased in patients with primary insomnia (Burgos et al., 2006). Exposure to both IL-6 and TNF- α decreases neurogenesis *in vitro* suggesting that these cytokines may mediate at least some of the detrimental effects of neuroinflammation on hippocampal neurogenesis *in vivo* (Monje et al., 2003). In summary, the mechanisms by which prolonged sleep disturbance affects adult neurogenesis include several complex factors that are also relevant for the etiology of mood disorders (Meerlo et al., 2009; Lucassen et al., 2009b).

7. Inflammation as a stressor and the role of microglia

As already noted above, the effect of stress and sleep disruption on hippocampal neurogenesis may in part be mediated by pro-inflammatory cytokines. The HPA axis is activated not only by stress, but also during disease processes, and by pro-inflammatory cytokines such as IL-6 or exogenous interferon alpha (Cassidy and O'Keane, 2000). During inflammation, cells of the immune system produce pro-inflammatory cytokines such as interleukin-1 (IL-1) and IL-6, which elicit various (patho)physiological reactions, that together coordinate the "nonspecific symptoms of sickness" and activate the HPA axis (Berkenbosch et al., 1987); elevated GC levels are generally immunosuppressive and then prevent the immune system from overshooting (Dunn, 2006). Thus, a clear bi-directional communication exists between the immune and neuroendocrine systems (Rhen and Cidlowski, 2005).

Interleukins are also produced within the brain during ischemia, dementia, multiple sclerosis and epilepsy (Skaper, 2007; Ravizza et al., 2008). In most of these conditions, microglial cells produce interleukins that are generally considered detrimental for neuronal viability, although interleukins have also been implicated in processes such as brain plasticity (Johansson et al., 2008; Spulber et al., 2008). Hence, neuroinflammation, defined by microglial activation and the presence of pro-inflammatory mediators, represents a stressor that may affect AN. More recent evidence, however, suggests that microglia can have a dual role and, depending on their state of activation, they can either inhibit or stimulate AN both in the intact and injured brain (Ekdahl et al., 2009). It is also conceivable that various functionally divergent subpopulations of microglia exist, some having pro-, others antineurogenic effects (Ekdahl et al., 2009).

Inflammation and cytokine expression largely inhibit AN directly (Vallieres et al., 2002; Monje et al., 2003) while immune modulators like transforming growth factor (TGF)- β (Wachs et al., 2006) have a concentration-dependent pro-neurogenic potential in the adult brain (Battista et al., 2006). Other pro-inflammatory cytokines such as TNF- α (Iosif et al., 2006) or interferon- α decrease AN through modulation

of IL-1 (Kaneko et al., 2006). In addition, impairment of IL-1 β action prevents the attenuated rate of AN in response to stress, supporting the idea that pro-inflammatory mediators and local cues in the brain play a role in restricting AN (Koo and Duman, 2008).

Conversely, factors capable of affecting cell genesis can also influence microglial activation. As part of the neuroinflammatory response, activated microglia modulates the neurogenic niche and, dependent on whether they are activated by IL-4 or by IFN- γ , microglia cells can differentially induce oligodendrogenesis and neurogenesis, respectively (Butovsky et al., 2006). Reducing neuroinflammation by specific drugs was further shown to restore or increase AN in different pathological models (Ekdahl et al., 2009; Monje et al., 2003) while T-cells even seem to influence hippocampal plasticity through effects on progenitor cells (Ziv et al., 2006).

Finally, it should be noted that psychological stress stimulates pro-inflammatory cytokine production in patients experiencing stress and anxiety. Also in depressed patients, increases in macrophage activity and in the production of pro-inflammatory cytokines have been consistently reported (Dantzer et al., 2008).

8. Stress affects cyto genesis not only in the hippocampus but also in the prefrontal cortex

The hippocampal formation is in the focus of this review, but it is clear that the hippocampus is not the only limbic structure where neuroplasticity is affected by stress or antidepressant treatment (Sairanen et al., 2007; Maya Vetencourt et al., 2008). Functional impairments of the hippocampus are obviously not solely responsible for the symptoms observed in depression. Amongst others, the prefrontal cortex and amygdala are important structures in this respect (Ressler and Mayberg, 2007).

The prefrontal cortex (PFC) is implicated in a number of higher cognitive functions as well as in processing emotions and regulation of the stress response (Cerqueira et al., 2008; Holmes and Wellman, 2009). In the medial prefrontal cortex (mPFC) of experimental animals, stress-induced morphological changes have been revealed that are comparable to what is seen in the hippocampus with some significant differences (Czéh et al., 2008). In the mPFC, stress leads to the regression of apical dendrites of pyramidal neurons (Cook and Wellman, 2004; Radley et al., 2004; Cerqueira et al., 2008) and inhibits adult cell proliferation (Czéh et al., 2007; Banasr et al., 2007). However, phenotypic analysis of the newborn cells in the mPFC reveals that most of them develop into glia and only a minority into neurons (Cameron and Dayer, 2008). Accordingly, for the mPFC the inhibitory effect of stress essentially involves adult gliogenesis. Human studies reporting on volume reduction and glial cell loss in prefrontal areas of patients with mood disorders (Drevets, 2001; Rajkowska and Miguel-Hidalgo, 2007) are of particular interest in this respect.

Ongoing, low-frequent neurogenesis has been reported also in the cortex of adult rats and non-human primates (Dayer et al., 2005; Gould et al., 1999), but these findings raised substantial skepticism (Kornack and Rakic, 2001), and the question of whether AN actually occurs to a considerable

extent in the cortex is still debated (Gould, 2007; Cameron and Dayer, 2008; Imayoshi et al., 2008). It is worth to note here, that in humans, neocortical neurogenesis has been shown to be restricted to prenatal developmental stages (Bhardwaj et al., 2006), and cytogenesis has not yet been documented in the adult human neocortex (Manganas et al., 2007). Interestingly, the expression of doublecortin, an endogenous marker for immature neurons (Couillard-Despres et al., 2005) has also been observed in a subpopulation of mature glia cells in the human cortex (Verwer et al., 2007) and in considerable numbers in the adult primate amygdala and piriform cortex (Bernier et al., 2002). So far, there is no evidence that stress or antidepressant treatment could affect adult cortical neurogenesis, but this possibility should be investigated.

The studies demonstrating opposing effects of stress and antidepressant treatments on cytogenesis in the mPFC reveal that the majority of the newly generated cells express the chondroitin sulfate proteoglycan NG2 (Neuron-glia 2) (Fig. 5) (Czeh et al., 2007; Banasr et al., 2007). NG2 identifies a glial cell population that is widely and uniformly distributed throughout gray and white matter of the mature CNS, representing 5–8% of the total glial cell population (Butt et al., 2005). The exact functional role of this glia type is still largely unknown, especially because NG2-positive cells most probably represent functionally heterogeneous populations. Interestingly, there is some evidence that NG2-positive cells have the ability to differentiate into neurons, both under *in vitro* and *in vivo* conditions, i.e. they may have stem-cell-like properties (Lin and Bergles, 2004). Since stress affects the proliferation of these cells, and because a fraction of these NG2-expressing progenitors may eventually differentiate into new GABAergic neurons (Cameron and Dayer, 2008), this process might also be affected by stress. The hypothesis that glial cell loss, either by cell death or by inhibition of adult gliogenesis, contributes to the core symptoms of depression is supported by a recent study, in which pharmacologic ablation of glial cells in the mPFC resulted in comparable depressive-like behavior as exposing animals to chronic unpredictable stress (Banasr and Duman, 2008).

Hemispheric specialization of the prefrontal cortex in emotional processing is well documented in humans (Davidson, 1998). There is evidence that a similar lateralized regulation of the stress response is also present in other mammals including rodents (Gratton and Sullivan, 2005). A number of studies on rats have now shown that whereas the right mPFC integrates emotional and physiological responses to long-term stressful situations, the left mPFC is more involved in the regulation of immediate stress responses (Sullivan and Gratton, 2002; Cerqueira et al., 2008). Interestingly, a recent study found an intrinsic hemispheric asymmetry in the incidence of cytogenesis in the adult mPFC, i.e. in the left mPFC, both the proliferation rate and survival of the newborn cells were always higher (Fig. 5). Furthermore, chronic stress had a greater suppressive effect on cytogenesis in the left PFC, resulting in a reversed asymmetry (Fig. 5) (Czeh et al., 2007).

Lateralized gliogenesis in the mPFC might reflect functional asymmetry. The higher occurrence of gliogenesis in the left PFC may indicate the left "dominance" of this region in normal, unchallenged animals. The stress-induced reversal of this lateralization resulted in higher incidence of cytogenesis in the right mPFC, which may reflect hyperactivation of this

area during chronic stress. It is tempting to relate these preclinical findings to the neuropsychological models of emotional processing which hypothesize that positive (or approach-related) emotions are lateralized towards the left hemisphere, whereas negative (or withdrawal-related) emotions are lateralized towards the right hemisphere (Rotenberg, 2004). In humans, electroencephalographic (EEG) studies relate decreased left hemisphere activation to depressive conditions, and associate hyperfunction in the right hemisphere with anxiety disorders (Sullivan and Gratton, 2002; Shenal et al., 2003). Depressed mood has further been associated with hypometabolism and volumetric reduction also of the left PFC (Drevets et al., 1997; Drevets, 2000). The significance of hemispheric lateralization in the regulation of emotional reactivity and stress responses is not yet understood, but it is clear that this lateralization phenomenon transcends species and is not restricted to the PFC.

9. Stress-induced changes in adult neurogenesis; relevant for depression?

Recently, the 'neurogenic theory' of depression has been put forward linking a suppressed rate of adult hippocampal neurogenesis to (the vulnerability for) depression. This idea postulates that a reduced production of new neurons in the hippocampus contributes to the pathogenesis of depression and that successful antidepressant treatment requires an enhancement in hippocampal neurogenesis (Duman, 2004; Sahay and Hen, 2007). The most important building blocks of this theory were the following findings: 1) stress inhibits adult hippocampal neurogenesis (in animals) and is a risk factor for depression in predisposed humans; 2) depressed patients often have cognitive deficits and smaller hippocampal volumes which might be the result of suppressed neurogenesis or altered cellular turnover rates; 3) antidepressant treatment stimulates neurogenesis and reverses the inhibitory effect of stress; 4) most antidepressant drugs do not exert their therapeutic effects until after 3–4 weeks of administration, which parallels the time course of the maturation of the newly generated neurons; 5) ablation of hippocampal neurogenesis blocks the behavioral effects of antidepressant treatment (in mice) (Malberg et al., 2000; Czeh et al., 2001; Oomen et al., 2007; Santarelli et al., 2003; Warner-Schmidt and Duman, 2006; Sahay and Hen, 2007).

There are, however, several findings which do not fit into this concept: 1) depletion of neurogenesis by means other than stress, e.g. by cranial irradiation, fails to produce a "depressive-like" state in animals (Airan et al., 2007); 2) reductions in hippocampal volume and in adult neurogenesis are not specific for depression and have also been implicated in various other psychiatric disorders (e.g. schizophrenia, dementia, addiction and anxiety) (Kempermann et al., 2008; Thompson et al., 2008; Revest et al., 2009). Also, both neurogenesis-dependent and -independent mechanisms of antidepressant action have been demonstrated (Sahay and Hen, 2007; David et al., 2009) that may involve growth factors and/or inflammatory mediators (Greene et al., 2009; Koo and Duman, 2008). In fact, we still lack a functional theory that explains how exactly newborn neurons in the adult hippocampus could contribute to the regulation of mood, or to a specific symptom of depression. Instead, it has been proposed that the suppressed rate of AN may contribute to

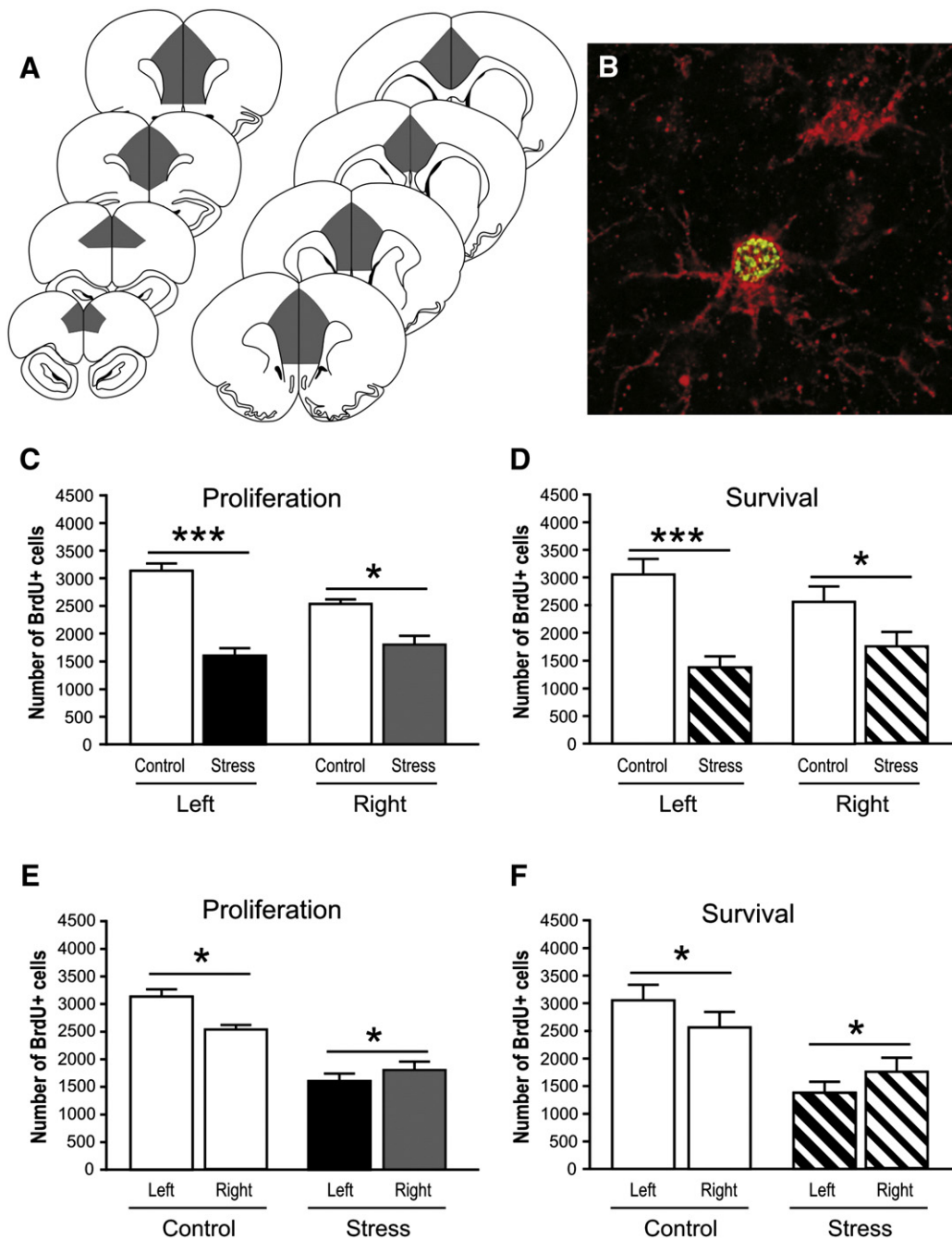


Figure 5 A: The medial prefrontal cortical areas are displayed on a series of plates, modified from a rat brain atlas. The effect of chronic social defeat stress on adult cyto-genesis has been investigated in this cortical region. B: Majority of the newborn cells in the rat prefrontal cortex differentiate into NG2-positive glia. A confocal microscopy image of a double labelled newly generated glial cell: red reflects the glial marker NG2, green–yellow is the proliferation marker BrdU labelling a newly generated cell. C–D: Chronic social stress inhibits both the cell proliferation rate and survival rate of the newly generated cells. Statistics: one-way ANOVA followed by Student–Newman–Keuls post hoc analysis. E–F: The same data set rearranged in a way that facilitates the hemispheric comparison. Cyto-genesis in the medial prefrontal cortex showed intrinsic hemispheric asymmetry. In control animals, both the cell proliferative activity (E) and survival rate of newborn cells (F) were always higher in the left hemisphere, whereas chronic stress (stress) reversed this asymmetry. Statistics: paired *t*-test. For details see Czéh et al. (2007). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the cognitive impairments common in the above listed psychiatric disorders (Kempermann et al., 2008).

Given the technical limitations to visualize neurogenesis in the live brain of humans, convincing evidence for the

central role of reduced neurogenesis in depression would have to come from a direct examination of this process in hippocampal tissue of depressed patients. To date, there are only two studies that addressed this question. One has been

published by Reif et al. (2006), in which the authors compared the level of neural stem-cell proliferation in *post mortem* brain samples from patients with major depression, bipolar affective disorder, schizophrenia, and control subjects. They could not find any evidence of reduced neurogenesis in the hippocampi of depressed patients. Furthermore, antidepressant treatment did not increase neural stem-cell proliferation. Unexpectedly, significantly reduced numbers of newly formed cells were found only in schizophrenic patients. However, this study was based on a relatively small sample size and further studies are warranted.

The other more recent *post mortem* study is by Boldrini et al. (2009). This compared the number of progenitor and dividing cells in 7 controls, 5 untreated patients with major depressive disorder and 7 depressed patients under antidepressant medication (four of them were treated with selective serotonin reuptake inhibitors (SSRIs) and three of them with tricyclic antidepressants (TCAs)). They found that in untreated depressed subjects the number of nestin-positive progenitors was significantly decreased, while the number of Ki-67-reactive dividing cells was 50% less than in controls, but this difference was statistically not significant. Furthermore, both the SSRI and TCA treatment increased the number of nestin-positive progenitors and TCAs had a robust stimulatory effect on the number of Ki-67-reactive dividing cells. But the SSRIs had no effect on the number of dividing cells. However, one has to keep in mind that the studies by Reif et al. (2006) and

Boldrini et al. (2009) are based on a relatively small sample size and further studies with larger samples are warranted. In this regard one approach which might address this issue more precisely could be the visualization of neurogenesis in live subjects using advanced *in vivo* imaging techniques.

In summary, to date there is no clear convincing clinical evidence that an altered rate of adult dentate neurogenesis is critical to the etiology of major depression. Although adult neurogenesis may not be essential for the development of depression, it may be required for clinically effective antidepressant treatment (Sahay & Hen, 2007; Surget et al., 2008). Hence, stimulation of neurogenesis has been regarded as a promising strategy for identifying new antidepressant targets. Accordingly, when tested in chronic stress paradigms, several candidate antidepressant compounds, like corticotrophin-releasing factor (CRF1), vasopressin (V1b) or glucocorticoid receptor antagonist (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 inhibitory effects of stress on proliferation or neurogenesis (Figs. 2 and 6). Other, non-pharmacological approaches, like vagus nerve and deep brain stimulation have been tested as well (Revesz et al., 2008; Toda et al., 2008).

Future studies will have to reveal whether screening compounds for their neurogenic potential is a meaningful approach in drug discovery. Today we know that AN can be stimulated by almost all currently available antidepressant

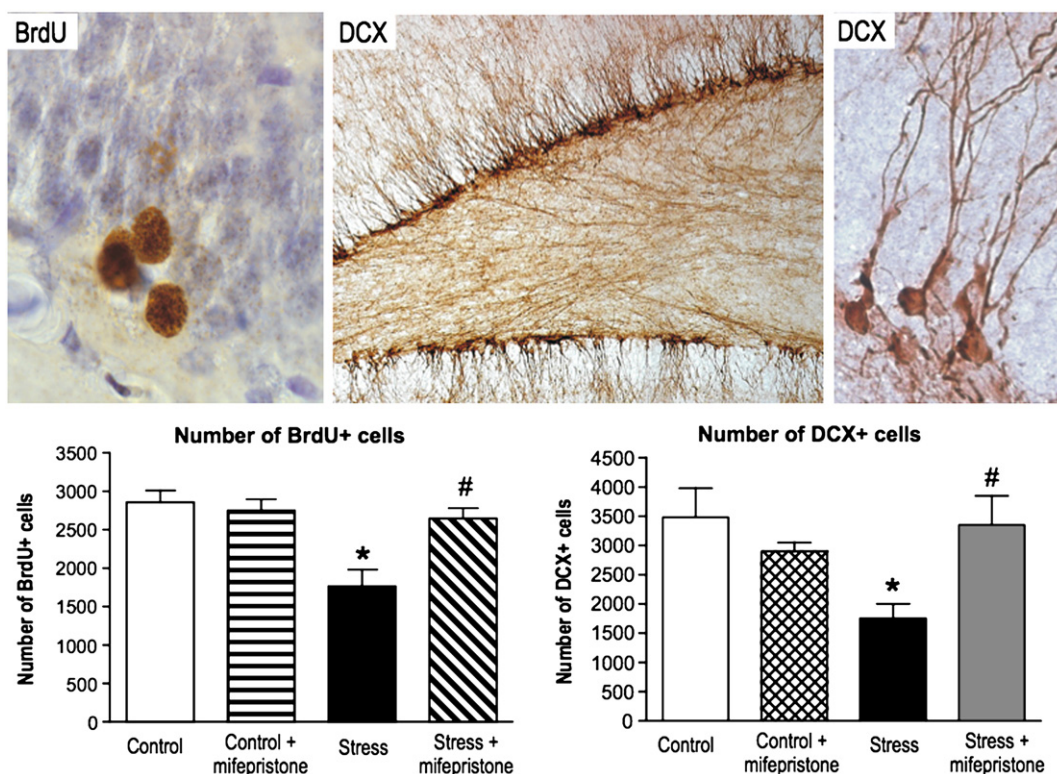


Figure 6 Top panels show examples of BrdU+ and doublecortin (DCX)+ immunostained cells in the DG. DCX-positive somata are located in the SGZ with extensions passing through the GCL. Lower panels display BrdU- and DCX-positive cell numbers in rats subjected to 21 days of chronic unpredictable stress. 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 for details).

treatments including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), electroconvulsive therapy (ECT), atypical antipsychotics and behavioral therapy (Sahay and Hen, 2007; Warner-Schmidt and Duman 2006; Pollak et al., 2008).

10. Concluding remarks

Stress, glucocorticoids, inflammation and sleep deprivation all interfere with one or more of the phases of the neurogenetic process. However, this inhibitory effect can normalize after a recovery period, voluntary exercise or antidepressant treatment. While adult neurogenesis has been implicated in cognitive functions, as well as in the regulation of mood and anxiety, and in the therapeutic effects of antidepressant drugs, its functional impact and contribution to the etiology of depression remains unclear. Admittedly, we still lack a functional theory that explains how exactly newborn neurons in the dentate gyrus of the adult hippocampus can contribute to the regulation of mood, or to specific symptoms of depression, besides the cognitive deficits, which are not specific to mood disorders. In view of the currently available evidence, a reduced rate of neurogenesis may be indicative of impaired hippocampal plasticity, but by itself alone, reduced AN is unlikely to produce depression. Lasting reductions in turnover rate of DG granule cells, however, alter the average age and overall composition of the DG cell population and will thereby influence the properties and functioning of the hippocampal circuit. Whether stress-induced reductions in adult neurogenesis occur in humans, awaits further investigations.

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Conflict of interest

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