Major Depression: A Role for Hippocampal Neurogenesis?

Margherita M. Lee, Andreas Reif and Angelika G. Schmitt

Abstract Since its discovery in mammals, adult neurogenesis, the process of generating functional neurons from neural progenitor cells in the adult brain, has inspired numerous animal studies. These have revealed that adult neurogenesis is a highly regulated phenomenon. Enriched environment, exercise and learning for instance, are positive regulators while stress and age are major negative regulators. Stressful life events are not only shown to reduce adult neurogenesis levels but are also discussed to be a key element in the development of various neuropsychiatric disorders such as depression. Interestingly, altered monoaminergic brain levels resulting from antidepressant treatment are shown to have a strong reinforcing effect on adult neurogenesis. Additionally, disturbed adult neurogenesis, possibly resulting in a malfunctioning hippocampus, may contribute to the cognitive deficits and reduced hippocampal volumes observed in depressed patients. Hence, the question arises as to whether disturbed adult neurogenesis and the etiopathogenesis of depression are causally linked. In this chapter, we discuss the possible causal interrelation of disturbed adult neurogenesis and the etiopathogenesis of depression as well as the possibility that adult neurogenesis is not exclusively linked to depression but is also linked to other psychiatric disorders including schizophrenia and neurodegenerative diseases like Alzheimer's disease. Additionally, we look at the functional relevance of adult neurogenesis in different species, upon which we base our discussion as to whether adult neurogenesis could be causally linked to

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the development of certain brain disorders in humans, or whether it is only an epiphenomenon.

Keywords Adult neurogenesis · Hippocampus · Subgranular zone · Neural Progenitor Cells · Stress

Contents

1 Introduction

Neurogenesis constitutes the process in which neural stem or progenitor cells give rise to new nerve cells during ontogenesis. Adult neurogenesis, the birth of new neurons in the adult brain, was first discovered in the 1960s by Joseph Altman (Altman 1962; Altman and Das 1965, 1967) and forgotten soon after, until it was rediscovered in the 1980s and 1990s in various species from songbirds to primates including humans (Goldman and Nottebohm 1983; Barnea and Nottebohm 1996; Eriksson et al. 1998; Gould et al. 1999b). Substantial production of new neurons in the adult mammalian brain is mainly restricted to the olfactory system, namely the subventricular zone of the lateral ventricle, and the dentate gyrus (DG) of the hippocampal formation. Not all newly formed cells survive, many of them die within weeks after generation (Dayer et al. 2003). Hippocampal adult neurogenesis is restricted to a relatively limited area, the subgranular zone (SGZ) of the DG (red line in Fig. 1). Currently, adult neurogenesis is thought to consist of several developmental stages (Kempermann et al. 2004; Ming and Song 2005) that are characterized by morphologically distinct cells (inset in Fig. 1). Two different types of adult neural stem cells (NSCs) can be found in the SGZ of the DG (no. 1 and 2 in Fig. 1). Type 1 cells represent radial glia-like cells, and type 2 cells are non-radial neural progenitor cells (NPCs). Both are capable of self-replication but possibly have a reciprocal lineage relationship. They proliferate and their offspring (No. 3 in Fig. 1) differentiate and migrate into the granule cell layer of the DG, and show low proliferative potential. Later, these cells extend their dendrites toward the molecular layer of the DG, and their axons extend into the hilus and the Cornu

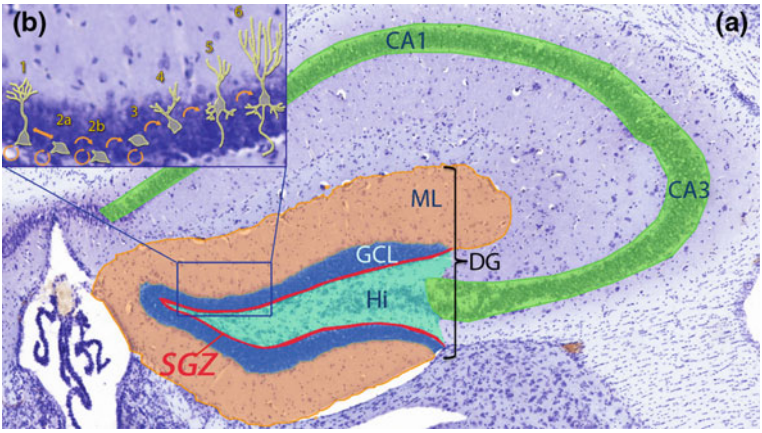


Fig. 1 *The hippocampus, one of the major sites of adult neurogenesis*. **a** Photomicrograph of a Nissl-stained coronal section displaying the mouse hippocampal formation with color accented subregions. The dentate gyrus (DG), which consists of the molecular layer (ML), the granule cell layer (GCL), and the hilus (Hi), as well as the hippocampus proper, which can be subdivided tangentially into the cornu ammonis (CA) sectors CA1, CA2 (not indicated), and CA3 are displayed. The subgranular zone (SGZ), a narrow layer of cells located between the GCL and hilus of the DG, contains adult progenitor cells and is accentuated with red. **b** Schematic representation of cells in different adult neurogenesis stages. The generation of new neurons in the DG can be divided into at least 6 stages. Two different types of adult neural stem cells reside at the SGZ of the DG. Cell No. 1 represents type 1 (radial) neural stem cells, and cells No. 2a/b represent non-radial neural stem cells, which possibly have a reciprocal lineage relationship and are capable of self-replication. Cell No. 3 represents migratory progenitor cells, which show little proliferative action. Cells No. 4–6 represent different stages of postmitotic newborn cells fated to finally become mature granule cells

ammonis area (CA) 3 (No. 4–6 in Fig. 1). Finally, the adult newborn neurons become functionally integrated into the hippocampal network, receiving inputs from the entorhinal cortex and sending outputs to hippocampal area CA3 and the hilus. Although, the physiological and behavioral role of adult neurogenesis is still under debate (Kempermann 2008; Deng et al. 2010; Burghardt et al. 2012; Glasper et al. 2012), nowadays, it is well accepted that it carries on from the late embryonic stage through to old age. The discovery of hippocampal adult neurogenesis has led to an explosion of research in neuroscience over the past two decades.

Typically adult neurogenesis is detected via immunohistochemistry. This can either be performed using 5-bromo-2-deoxyuridine (BrdU) antibodies following intraperitoneal (i.p.) BrdU administration (Gratzner 1982) or using antibodies detecting different endogenous adult neurogenesis markers without the need for stressful i.p. treatment of the respective animals (von Bohlen und Halbach 2011). BrdU can be given either once or a number of times, then incorporating into replicating DNA in place of thymidine (also called deoxythymidine). Neurons that have incorporated the injected BrdU during mitosis and which have subsequently differentiated into neurons, can be identified via double-labeling with antibodies

against neuron markers such as NeuN. The use of various antibodies detecting endogenous adult neurogenesis allows the further division of adult neurogenesis into different developmental stages, and allows the monitoring of neurogenesis at these different stages in the same hippocampus using serial sections. This is possible since the various developmental stages correlate with the expression of different markers (von Bohlen und Halbach 2011). For the detection of cell proliferation at the initial phase of the birth of new neurons (adult neurogenesis) antibodies against the cell cycle marker Ki67 is commonly used (Kee et al. 2002). It should be mentioned, however, that antibodies against Ki67 detect mitotic cells regardless of their identity or fate (Gerdes et al. 1991; Scholzen and Gerdes 2000). Other very popular endogenous adult neurogenesis markers include (i) nestin, an intermediate filament expressed in many, if not all, NPCs, (ii) NeuroD, a basic helix-loop-helix protein and a differentiation factor for neurogenesis in diverse species, (iii) the polysialylated embryonic form of the neural cell adhesion molecule (NCAM), abbreviated to PSA-NCAM which has been found in cells that seem to be NPCs related to neural stem cells, iv) TUC (TOAD [turned on after division]/Ulip [UNC-33- like protein]/CRMP [collapsin response-mediator protein])-4 can be used as a marker for early postmitotic neurons but seems also to be expressed in mitotic cells during neurogenesis, and (v) doublecortin (DCX), a protein that promotes microtubule polymerization, which is present in migrating neuroblasts and young neurons (for review see: von Bohlen und Halbach 2011). As DNA labeling by BrdU is potentially toxic, and therefore a confounding factor in some experiments, the importance of these adult neurogenesis-related antibodies for further investigations of the adult neurogenesis phenomenon is often underemphasized.

In the late 1990s, studies relying on the BrdU integration method, brought about a number of discoveries regarding the regulation of adult neurogenesis. Among the positive regulators are enriched environment, voluntary exercise, as well as learning and memory tasks (Kempermann et al. 1997; Gould et al. 1999a; van Praag et al. 1999, 2005). In 1997, Kempermann and his colleagues discovered that mice exposed to an enriched environment, namely a homecage equipped with a running-wheel, toys and tunnels, displayed significantly more new neurons than mice housed in a conventional cage (Kempermann et al. 1997). In addition, Henriette van Praag and co-workers demonstrated that voluntary running resulted in an increase of BrdU-positive cells, indicating that physical activity can regulate hippocampal neurogenesis (van Praag et al. 1999). Other regulatory factors are neurotransmitters such as serotonin, which can both enhance the proliferation of NPCs and the production of new neurons (Gould 1999), gonadal hormones (Spritzer and Galea 2007; Galea 2008; Spritzer et al. 2011), and trophic factors such as brain-derived neurotrophic factor (BDNF) (Bekinschtein et al. 2011). Moreover, chronic antidepressant treatments markedly stimulate hippocampal neurogenesis (Malberg et al. 2000; Paizanis et al. 2007). Negative regulators of adult neurogenesis include binge alcohol exposure in adolescence (Morris et al. 2010) and oxidative stress (Taupin 2010), to give just a few examples. However, the most prominent negative regulators of adult neurogenesis are age (Seki and

Arai 1995; Kuhn et al. 1996; Kempermann et al. 1998; Amrein et al. 2011) and stress exposure during all ontogenetic phases (Gould et al. 1998; Gould and Tanapat 1999; Mirescu et al. 2004; Lucassen et al. 2010a; Hanson et al. 2011).

In addition to a genetic predisposition, stress can be looked upon as a key vulnerability factor in the development of various neuropsychiatric disorders. The intense regulation by stress (among other factors), strongly implicates adult neurogenesis in a variety of pathophysiological mechanisms. Therefore, one of the topics under intense research is the correlation between adult neurogenesis and the pathophysiology of psychiatric disorders like fear and anxiety (Santarelli et al. 2003; Saxe et al. 2006; Revest et al. 2009), major depression (Boldrini et al. 2009; Boldrini and Arango 2010; Lucassen et al. 2010b; Anacker et al. 2011; Snyder et al. 2011), and schizophrenia (Reif et al. 2007). The possible relevance of hippocampal adult neurogenesis for pathological mechanisms underlying major depression as well as other neuropsychiatric disorders is critically discussed in this review.

2 Adult Neurogenesis, Stress and Hippocampal Volume

Stress can be defined as a condition where an environmental demand exceeds the natural regulatory capacity of an organism, particularly in situations that include unpredictability and uncontrollability (Koolhaas et al. 2011). Moreover, stress can be looked upon as a significant causal agent, in the aetiology of a number of neuropsychiatric disorders such as schizophrenia (Wahlberg et al. 1997; van Os et al. 2010), but predominantly in the development of anxiety disorders and depression (Caspi et al. 2003; van Praag 2004; Pittenger and Duman 2008; Saveanu and Nemeroff 2012). The experience of a stressful situation results in the stimulation of the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis activity is governed by the secretion of corticotropin releasing hormone/factor (CRH/CRF) and vasopressin from the hypothalamus, which in turn activates the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary to stimulate the secretion of the glucocorticoids (cortisol in humans and corticosterone in rodents) from the adrenal cortex. Released glucocorticoids then interact with their receptors in multiple body compartments including the brain (e.g. hippocampus, hypothalamus) where they serve a vital function in feedback inhibition of their own secretion. Additionally, glucocorticoids regulate neuronal survival, neurogenesis and hippocampal volume, as well as the acquisition of new memories and the emotional appraisal of events (Pariante and Lightman 2008).

HPA hyperactivity is regarded as causally linked to depression and to the modes of action of antidepressants (Holsboer 2001). Altered feedback inhibition in depressed patients resulting in HPA hyperactivity was demonstrated by use of the combined dexamethasone (DEX)/CRH test, a refined laboratory test for psychiatric disorders). For this test, patients are administered DEX the night prior to testing and then CRH the following afternoon (Heuser et al. 1994). Measurement of plasma cortisol and ACTH levels before, during, and after CRH administration

revealed, that depressed patients release significantly more cortisol and ACTH after DEX and a CRH challenge in comparison with age-matched controls. This so-called DEX/CRH test phenomenon supports the assumption that psychiatric patients are prone to blunted glucocorticoid feedback regulation during the acute illness episode. Diminished glucocorticoid receptor (GR) expression or function has been postulated as causative factor (Heuser et al. 1994).

Based on these findings, Ridder et al. generated GR-heterozygous mutant mice (GR ±), which have a 50 % reduction of GR protein levels in the brain (Ridder et al. 2005). Similar to depressed patients, these mice display reduced feedback inhibition of the HPA axis and a pathological DEX/CRH test in which higher levels of circulating glucocorticoids could be measured in response to the CRH challenge compared to GR- wildtype littermates. Elevated levels of glucocorticoids, for instance as found in chronically stressed individuals, stimulate hippocampal glutamate release (Moghaddam et al. 1994) which in turn diminish stem cell proliferation in the adult DG (Gould and Tanapat 1999). Thus, it does not come as a surprise that GR +/− mice display significantly less BrdU-positive cells in the DG compared to wildtype mice (Kronenberg et al. 2009). Behaviorally, GR +/− mice show increased learned helplessness, a well-established analog of depression-like behavior in mice (Ridder et al. 2005). In their study published in 2007, Thomas and co-workers were able to show that acute psychosocial stress leads to a reduced number of new neurons in the DG of rats. Interestingly, stem cell proliferation itself remained unaltered, whereas short- and long-term survival of the newborn cells was decreased (Thomas et al. 2007). This implicates that acute social stress has a sustained impact on the integration of newborn cells into the hippocampal neural network by diminishing their chance of survival. On the other hand, a recent study showed that coping with intermittent social stress, which is an essential aspect of living in complex social environments, stimulates adult neurogenesis in adult monkeys (Lyons et al. 2010). On the basis of this finding, one could speculate that stress coping follows similar mechanisms as living in an enriched environment, which is known to prompt adult neurogenesis (Kempermann et al. 1997).

HPA axis dysregulation and the adverse effect of increased glucocorticoid concentrations on adult neurogenesis may be one out of several possible causes of the well-documented phenomenon of a decreased hippocampal volume in patients with mood disorders. Several forms of stress, and especially repeated periods of stress, are suggested to cause a reduction of hippocampal volume. Among these are traumatic life events and early life stress such as childhood maltreatment which are often found to be a key component in the life history of patients with mood disorders such as post-traumatic stress-disorder and major depression (Smith 2005; Pittenger and Duman 2008; Teicher et al. 2012). In these subjects, and especially in patients with a history of several depressive episodes, magnetic resonance imaging (MRI) studies revealed significantly smaller hippocampal volumes (especially on the left side) in comparison to controls but with no differences in total cerebral volumes (Sheline 1996; Bremner et al. 2000). This result was later

confirmed in two meta-analyses of MRI studies of hippocampal volume in depression (Campbell et al. 2004; Videbech and Ravnkilde 2004). Moreover, it was found that significant neuromorphologic abnormalities in the hippocampus, as well as the dorso-lateral prefrontal cortex and anterior cingulum, of patients with depression were associated with a more severe outcome (Frodl et al. 2008a, b). On the other hand, patients treated repeatedly with antidepressants, such as the SSRIs sertraline, citalopram and paroxetine, the tricyclic antidepressants amitriptyline, amitriptylinoxide and doxepin, or other newer antidepressants like venlafaxine, reboxetine, and mirtazapine, showed a significant volume increase in the left hippocampus compared to the baseline volume (Frodl et al. 2008a). However, neuroimaging and *post mortem* studies also report an average hippocampal volume loss of 4–8 % in schizophrenic patients compared to controls (Geuze et al. 2005; Honea et al. 2005). Notably, reduced brain and/or hippocampal volumes could be already detected in patients at the first episode of schizophrenia, which points to biochemical changes inducing a morphological sequelae in the already predisposed brains or at least in brains of patients with a short disease story (Steen et al. 2006; Watson et al. 2012).

Much has been speculated about the possible mechanisms underpinning these structural changes. Sheline and co-workers suggested that the hippocampal atrophy reflects a neuronal loss due to a progressive process associated with glucocorticoid neurotoxicity (Sheline 1996). To understand how the hippocampus responds at the cellular and subcellular level to glucocorticoids, and how such changes are related to volume measures, Tata and co-workers carried out a study of the effects of long-term glucocorticoids on hippocampal CA3 volume, and identified altered dendritic and glial processes as well as altered numbers and sizes of synapses (Tata et al. 2006; Tata and Anderson 2010). These authors suggested that corticosterone caused astrocytes to take up a larger proportion of the tissue, with the result that the tissue volume was made up of a smaller proportion of neuronal processes and a pronounced loss of synapses. On the other hand, Stockmeier et al. reported in their *post mortem* study of hippocampus tissue that in major depression, the packing density of glia, pyramidal neurons, and granule cell neurons was significantly increased in all hippocampal subfields including the DG, and that pyramidal neuron soma size was significantly decreased as well (Stockmeier et al. 2004). These authors suggested that a significant reduction in neuropil in major depression may account for the decreased hippocampal volume detected by neuroimaging. In addition, they speculated that differential shrinkage of frozen sections of the hippocampus may be caused by an altered water content in hippocampus in major depression (Stockmeier et al. 2004). The findings on hippocampal volume loss due to stress and/or depression, combined with the numerous findings of a stress-induced decrease of adult neurogenesis, have inspired the idea that these two phenomena are causally linked (Jacobs 2002). Czeh and Lucassen, however, argued that either a massive neuronal loss or a suppression of adult neurogenesis in the DG can be excluded, as no major cell loss was apparent in human *post mortem* brain tissue of severely depressed patients (Czeh and Lucassen 2007). Moreover, they argued that in humans, adult

neurogenesis adds too few neurons per day for the suppression of this process to provide a significant contribution to the 10–15 % reduction in hippocampal volume in depressed patients determined by the meta-analyses of Campbell et al. (2004) and Videbech and Ravnkilde (2004). However, they also considered that the slowing down of neuronal turnover in the DG by altering both cytogenesis and apoptosis would affect the composition of neurons in the DG, and may have an impact on the connectivity, input, and output properties of the hippocampal circuit, and thus hippocampal function.

3 Antidepressants and Adult Neurogenesis

The stimulatory effect of antidepressant treatment on adult neurogenesis is observed across different species, from rodents (Madsen et al. 2000; Malberg et al. 2000), tree shrews (Czeh et al. 2001), and monkeys (Perera et al. 2007) through to humans (Boldrini et al. 2009). Numerous studies have provided evidence that major classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs) like fluoxetine and selective norepinephrine reuptake inhibitors such as reboxetine (Malberg et al. 2000; Kodama et al. 2004; Namestkova et al. 2005; Encinas et al. 2006), increase adult neurogenesis. However, different studies have obtained different results, depending on certain parameters including the type of antidepressant and length of treatment. For instance, upregulated NPC proliferation rate and immature neuron survival rate was only achieved by chronic (14 or more days) but not acute (<10 days) treatment with SSRIs and the tricyclic antidepressant imipramine (as reviewed by Hanson et al. 2011), which is consistent with the time course for the therapeutic action of antidepressants. Administration of SSRIs results in elevated extracellular levels of 5-HT, which has been shown to have a positive effect on adult neurogenesis (Gould 1999; Brezun and Daszuta 2000; Banasr et al. 2004). Several studies including the work of Santarelli using 5-HT_{1A} receptor knockout mice (Santarelli et al. 2003), suggest this positive effect of 5-HT and SSRIs on neurogenesis is primarily mediated by 5-HT_{1A} receptor activation. These data are in accord with findings that during brain development, 5-HT is a key regulator of cell division and to modulate different processes including neurogenesis, apoptosis, axon branching, and dendritogenesis (Gaspar et al. 2003). Moreover, adverse experiences during early life and adulthood have been shown to alter the brain 5-HT system, and abnormalities in 5-HT are also strongly linked to the damaging effects of stress and, particularly, stress-induced neuropsychiatric disorders (Lowry et al. 2005; Holmes 2008; Lanfumey et al. 2008).

Among non-drug treatments that have behavioral antidepressant effects and also elevate adult neurogenesis are electroconvulsive shock (Madsen et al. 2000; Malberg et al. 2000; Hellsten et al. 2002), sleep deprivation (Grassi Zucconi et al. 2006), environmental enrichment (Veena et al. 2009), and exercise (van Praag et al. 1999; van Praag et al. 2005; Hanson et al. 2011). Conditioned inhibition of

fear (or learned safety) which was shown to reduce depression-like behavior in mice, also promoted the survival of newborn cells in the DG (Pollak et al. 2008). Interestingly, this type of behavioral antidepressant increased the expression of BDNF in the hippocampus and lead to altered expression of genes involved in the dopamine and neuropeptide but not 5-HT system in the basolateral amygdala (Pollak et al. 2008). After several preclinical reports suggested that melatonin, the main product of the pineal gland, itself could be effective as an antidepressant (Overstreet et al. 1998, Papp et al. 2003), Ramirez-Rodriguez and co-workers looked for a possible influence of melatonin on adult neurogenesis. They revealed that NPC proliferation in the DG was not modified by acute or chronic melatonin treatment but the survival of new neurons was promoted by melatonin resulting in a net-increase of the production of new mature neurons (Ramirez-Rodriguez et al. 2009). However, repetitive transcranial magnetic stimulation which has a clinically observed antidepressant effect and attenuates the HPA axis in some studies, did not increase adult neurogenesis (Czeh et al. 2002). So far, the vast majority of substances with antidepressant effects but not all non-drug antidepressant treatments are reported to increase adult neurogenesis (Sahay and Hen 2007; Kempermann 2008; Hanson et al. 2011).

In contrast to antidepressants, studies of antipsychotic drugs, encompassing both acute and chronic treatment regimes, found no change in levels of stem cell proliferation in rodents (Wakade et al. 2002; Halim et al. 2004; Schmitt et al. 2004; Wang et al. 2004), although one such study demonstrated an increase in adult neurogenesis (Dawirs et al. 1998).

Whether adult neurogenesis may be a prerequisite for antidepressant action is not yet clear. The group of Santarelli for instance showed that disrupting antidepressant-induced adult neurogenesis using X-ray irradiation blocks neurogenic and behavioral responses of mice to antidepressants (Santarelli et al. 2003). Also the positive effect of environment enrichment on behavioral traits developed due to chronic social stress was found to be critically dependent on adult neurogenesis (Schloesser et al. 2010). Consequently, Meshi and co-workers investigated the causality of these effects by testing the effect of environmental enrichment on spatial learning and anxiety-like behavior in X-ray irradiated mice. In contrast to the study of Santarelli et al. (2003), Meshi and co-workers found that adult neurogenesis was not required for the behavioral effects of environmental enrichment on spatial learning, habituation to an unfamiliar environment, and conflict-based anxiety (Meshi et al. 2006).

A different explanation for the actions of antidepressant treatment on the hippocampus is given by Kobayashi et al. (2010). Specifically, these authors showed that chronic treatment of adult mice with fluoxetine-induced morphological and electrophysiological features of immature granule cells such as reduced expression of calbindin and reduced synaptic facilitation of dentate-to-CA3 signal transmission (Kobayashi et al. 2010). It was argued that these changes cannot be explained simply by an increase in newly generated immature neurons, but rather identify the phenomenon as “dematuration” of mature granule cells. Thus, it was concluded that 5-HT-targeted antidepressants reversed the established state of neuronal

maturation in the adult hippocampus (Kobayashi et al. 2010). This effect of restoring neurons to a postnatal state by fluoxetine is not completely new. For instance, earlier Maya Vetencourt and colleagues showed that chronic administration of fluoxetine to adult rats restored plasticity in the visual cortex, a property which is usually restricted to a critical period during postnatal development, and is normally absent in the adult brain because of a decline of plasticity due to the maturation of intracortical inhibition (Maya Vetencourt et al. 2008).

4 Possible Function of Adult-Generated New Neurons in the Hippocampus

Although many studies show a clear link between environmental manipulations and changes in adult neurogenesis, it is unclear which aspect of the respective experience causes these changes, and which brain processes causing changes in behavior are modulated by altered adult neurogenesis. It is established that newborn granule cells finally integrate into the hippocampal networks, but there are still open questions concerning the functional integration of these neurons into behaviorally relevant neural networks. Thus, the real functional significance of adult neurogenesis, and specifically newborn neurons in the DG, is still under debate.

The involvement of the hippocampus, one of two brain sites where neurogenesis continues throughout life, in learning processes and memory formation has long been recognized (O'Keefe and Nadel 1978). Acquired memory initially depends on the hippocampus for the process of permanent memory formation. The hippocampus is an essential structure for specific types of memory, such as episodic memory and spatial memory (Squire et al. 1992, 1993). With regard to spatial learning, hippocampal neurons are thought to form a cognitive map of the environment based on multiple cues. Moreover, recent studies in animals and humans point to a role of the hippocampus in pattern separation, that is the disambiguation of related stimuli often during emotional learning (Snyder and Cameron 2012). Through its interactions with brain structures associated with emotion such as the amygdala, the hippocampus is also implicated in emotional behavior. Lesions of the amygdala, for instance, do not impair spatial maze learning but disrupts fear conditioning. Moreover, activation of the amygdala during strong emotional stimuli like those experienced in fear conditioning can enhance hippocampal-dependent learning (Cahill and McGaugh 1998; Bannerman et al. 2002). Thus, it is not surprising that the hippocampus is also an integral part of stress reactions; the region expresses high levels of glucocorticoid receptors and contributes to negative feedback mechanisms of the HPA axis (Jacobson and Sapolsky 1991).

Moser and Moser suggested that the hippocampus is functionally differentiated along its dorsoventral (septotemporal) axis (Moser and Moser 1998). Anatomical

studies performed in the rat indicate that cortical and subcortical connections of the dorsal hippocampus (ventral hippocampus in primate) and ventral hippocampus (dorsal hippocampus in primates) are different (Swanson and Cowan 1977; van Groen and Wyss 1990). In rodents, spatial memory and episodic memory appears to depend on dorsal and not ventral hipocampus (Moser et al. 1995; Davachi and Wagner 2002; Broadbent et al. 2004). On the other hand, the ventral but not dorsal hippocampus is thought to mediate stress responses and therefore be involved in emotional behavior (Henke 1990; Herman et al. 1998; Fanselow and Dong 2010; Segal et al. 2010).

Increasing evidence suggests that the production of new neurons in the adult hippocampus participates in these different learning processes and memory formations. For example, the work of Kitamura and co-workers (2009) suggests that the level of adult neurogenesis in hippocampus plays a role determining the hippocampal-dependent period of memory. Using two different mouse models in which adult neurogenesis was physically (X-ray irradiation) or genetically (transgenic mice overexpressing follistatin in a forebrain-specific manner which depletes neurogenesis in hippocampus) suppressed, it was found that decreased adult neurogenesis was associated with a prolonged hippocampal-dependent period of associative fear memory (Kitamura et al. 2009). Conversely, increased adult neurogenesis resulting from voluntary exercise was found to speed up the decay rate of hippocampal-dependent memory (Kitamura et al. 2009).

Animal studies have shown a correlation between increased neurogenesis and improved performance on hippocampal-dependent learning tasks such as spatial learning (Gould et al. 1999a; Nilsson et al. 1999; van Praag et al. 1999; Drapeau et al. 2003; Ramirez-Amaya et al. 2006; Dupret et al. 2008; Imayoshi et al. 2008; Zhang et al. 2008; Deng et al. 2009) and contextual fear learning (Pham et al. 2005; Saxe et al. 2006). During memory formation the DG has recently been proposed to play a role in the process of transforming similar representations or memories into highly dissimilar, non-overlapping representations, or, in other words—the formation of distinct and orthogonal representations of mnemonic information. Experimental studies revealed that adult mice with increased hippocampal neurogenesis were more efficient at differentiating between overlapping contextual representations, suggestive of enhanced pattern separation (Sahay et al. 2011). On the other hand, mice with ablated hippocampal neurogenesis showed impaired spatial discrimination (Clelland et al. 2009). Thus, newborn neurons may be necessary for normal pattern separation function in the DG of adult mice (Clelland et al. 2009; Sahay et al. 2011). Burghardt and co-workers went one step further and suggested that adult neurogenesis contributes to cognitive flexibility (Burghardt et al. 2012). Specifically, this group used variants of the active place avoidance task in combination with two independent neurogenesis ablation techniques (X-ray irradiation and transgenic mice) to reveal that adult neurogenesis was necessary for changing a learned response to a stimulus-evoked memory (Burghardt et al. 2012).

Recent studies suggest a role for neurogenesis in the adult hippocampus in emotional memory formation. It is suggested that new neurons may influence

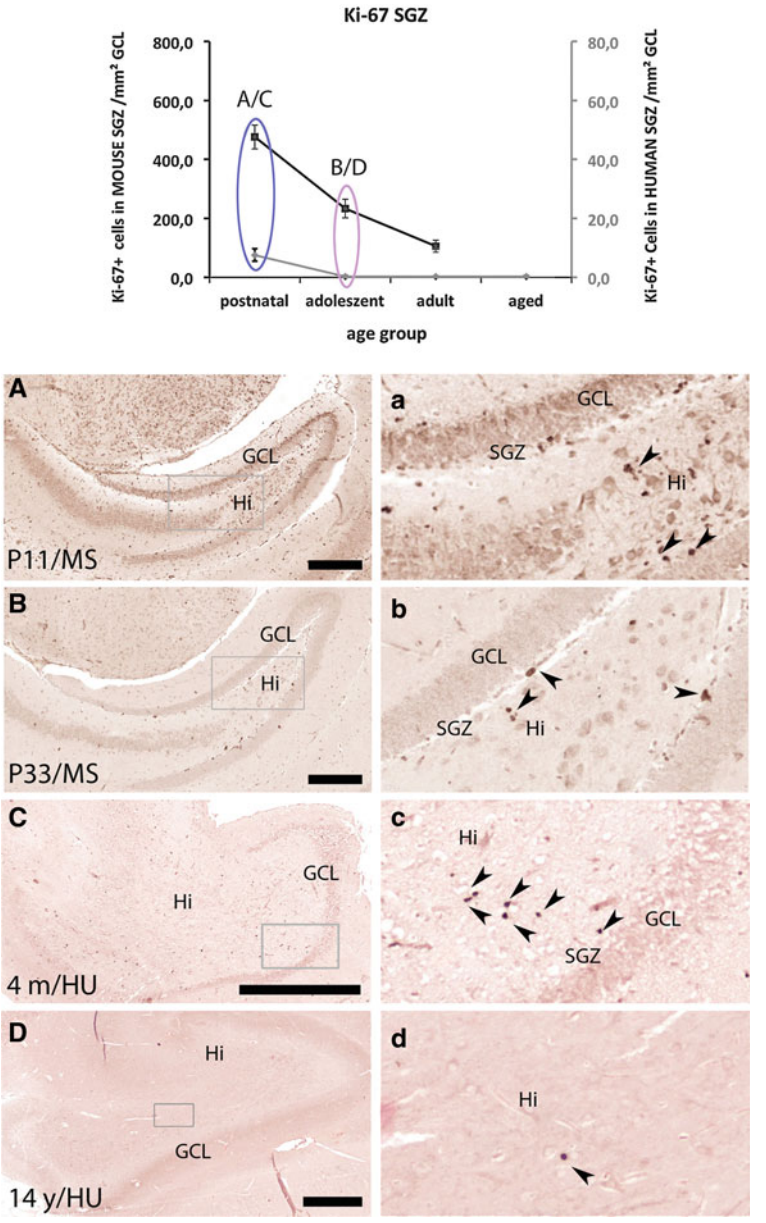
learning and memory primarily in tasks that involve significant emotional arousal, or co-activation of the hippocampus and amygdala (Saxe et al. 2006). This is an important issue as impaired regulation of emotional memory is a feature of several affective disorders such as anxiety, depression and post-traumatic stress disorder. Both the amygdala and hippocampus are key elements in the neural circuitry generating and processing of emotions, and emotional memory. The interdependency of hippocampal adult neurogenesis and the activity of specific amygdala nuclei in emotional memory circuits was clearly shown by Kirby et al. (2012). In particular, lesions of the basolateral amygdala, but not of the central amygdala nucleus, resulted in reduced levels of hippocampal neurogenesis in the adult rat. Lesion of the basolateral amygdala nucleus shown to selectively prevent the activation of NPC proliferation in response to a fear conditioning task (Kirby et al. 2012). Snyder and co-workers suggested that new DG neurons play an important role in the buffering of stress responses, which is especially meaningful (in addition to their direct function in encoding of information) in the context of learning and memory processes under novel or aversive conditions (Snyder et al. 2011).

Although it has been clearly shown that adult neurogenesis is involved in different types of learning and memory processes, the mechanism, role and importance of newborn cells at different differentiation stages, and their regulation has to be further clarified. Moreover, the cascade of events linking the birth of new neurons to learning processes is unclear, as is the way in which new neurons are integrated into and/or removed from behaviorally relevant hippocampal neural networks. First insights into these issues were gained from a study of Dupret and co-workers on the effect of spatial learning in the Morris water maze on cell birth and death in the rodent hippocampus. This work revealed that spatial learning is associated with three different events: learning promoted survival of relatively mature neurons, apoptosis of more immature cells, and finally, proliferation of neural precursors (Dupret et al. 2007). The impact of the maturation stage of adult-born dentate granule cells on cognition is further underscored by the work of Deng et al. (2009). They found that mice with a reduced population of adult-born DG cells during an immature stage of development displayed deficits in both long-term memory retention in the Morris water maze and extinction of spatial preference and context-evoked fear (Deng et al. 2009). In contrast to the positive effect of spatial learning on NPC proliferation, contextual fear learning (at least) transiently suppressed cell proliferation with no change in cell survival, and differentiation in the DG of adult rats (Pham et al. 2005). This inhibition of NPC proliferation during the contextual fear conditioning process appears to be due specifically to the formation of an association between the context and shock during training, which is an amygdala-dependent function.

An important question to be answered in the future is whether adult neurogenesis is essential for appropriate learning processes and memory formation not only in rodents, but also in humans. Our knowledge of adult neurogenesis is largely derived from rodent or non-human primate studies (for review see: Kempermann 2002; Ming and Song 2005, 2011; Snyder and Cameron 2012),

with there being only a handful of relevant studies in humans (Eriksson et al. 1998; Reif et al. 2006; Boldrini et al. 2009; Coras et al. 2010; Knoth et al. 2010; Lucassen et al. 2010b). There are only a few clues as to how far the situation in animal models really reflects that of the adult and aging human hippocampus. The ongoing birth of new neurons in the adult hippocampus is most prominent in rodents, but adult neurogenesis levels vary considerably among species, being lowest or missing in primates and bats, respectively (Amrein et al. 2011). As shown in Fig. 2 our own study revealed that the level of proliferating (Ki-67 positive) cells in DG of humans is reduced by a factor of 50 compared to mice (Lee et al. 2010). So far only a fraction of mammalian species has been investigated, therefore, further comparative studies are needed in order to recognize whether adult neurogenesis has a common function across species, or whether it mediates species-specific hippocampal functions as may be the case for spatial learning in rodents (Dupret et al. 2008; Imayoshi et al. 2008; Zhang et al. 2008; Deng et al. 2009). Across all species investigated so far, adult neurogenesis declines strongly from infancy to midlife (Amrein et al. 2011). As stated by Altman and colleagues in 1973, this infers a role for neurogenesis in transforming juvenile demeanor from an unpredictable to a predictable nature, typically characterizing the behavior of mammals once they have reached their reproductive phase in life. Additionally, any attempts to link differences in adult neurogenesis with hippocampus-dependent actions, encounter the problem that primates, and humans in particular, show comparatively low levels of adult neurogenesis (Eriksson et al. 1998; Gould 1999). Moreover, adult neurogenesis seems to become rudimentary in humans after 30 years of age (Fahrner et al. 2007). The question is how the activity-dependent incorporation of a low number of neurons into the hippocampal network can lead to a functional benefit during the lifespan of an individual. The so-called "neurogenic reserve" hypothesis suggested by Kempermann in 2008 addresses this problem by suggesting that adult neurogenesis in hippocampus might produce an activity- and experience-dependent potential for sustained cellular plasticity with increasing age, thereby providing such greater capacity and efficiency (Kempermann 2008). As shown in animal experiments, but not yet in humans, both physical and cognitive 'activity' reduces the age-dependent decline in NPC proliferation in the DG (Kempermann and Gage 1999; Kempermann et al. 2002; Kronenberg et al. 2006). Future studies are needed to test the "neurogenic reserve" hypothesis also in humans.

In addition to the decline of adult neurogenesis with aging, the distribution pattern of adult neurogenesis-related cell types (e.g. proliferating NPCs, adult-born immature and mature neurons) changes as the individuals grow older. Both, immunohistochemistry against Ki-67 as well as BrdU-labeling in the brains of young (postnatal day 5–19) Wistar rats, revealed that cell proliferation in early postnatal neurogenesis, a transition state between the embryonic and adult neurogenesis, occurred mainly in the hilus and only partly in the SGZ (Namba et al. 2005). In rats older than P19, most proliferating cells were found in the SGZ (Namba et al. 2005). This principle could be replicated for



mice in our own study, however, not for humans (Lee et al. 2010). So far it seems that in humans most of the proliferating cells—detected with Ki-67—can be found in the hilus across all ages, from infants to seniors (Lee et al. 2010) (see Fig. 2).

◀ **Fig. 2** *Hippocampal adult neurogenesis in mice and men during ontogeny. Top* Diagram displaying the density of Ki-67-positive proliferating cells (cells/mm^2 granule cell layer, GCL) in the subgranular zone (SGZ) of humans and mice of the age groups postnatal, adolescent, adult, and aged (only humans). Density of proliferating cells in the dentate gyrus (DG) of mice is up to 50-fold higher compared to humans in corresponding age groups (postnatal; adolescent; adult). *Bottom* Representative images of immunostained hippocampal sections using antibodies detecting Ki-67, a marker for proliferating cells. Ki-67-positive cells in the murine (A,a; B,b) and human (C,c; D,d) DG of roughly corresponding age groups. With regard to brain development postnatal day (P)11 in mice approximately corresponds to 4 months (m) of age in humans (HU) and both together represent the postnatal group. P33/MS roughly corresponds to 14 years (y) of age in Humans (14y/HU), which represent the adolescent group. Note, that the number of Ki-67-immunoreactive cells (*arrowheads* in a,b,c,d) decreases along aging, and that in the DG of the P33 old mouse these proliferating cells primarily are localized in the SGZ (B,b), and not in the Hilus (Hi), as it is shown in stained human sections of both ages (C,c; D,d) as well as in the DG of the P11 old mouse (A,a). GCL = granule cell layer; Scale bars in A/B = 250 μm and equals 100 μm in a/b; Scale bars in C/D = 1000 μm and equals 100 μm in c/d

5 Extended Adult Neurogenesis Hypothesis: Finding Links Between Adult Neurogenesis and Depression, as Well as Various Brain Disorders

So far only three studies have been published that use *post mortem* human brain tissue to investigate the possible link between adult neurogenesis and major depression. In 2006, we set out to reveal whether hippocampal stem cell proliferation was reduced in depressive patients, and also facilitated by antidepressant treatment. We also investigated whether adult neurogenesis is altered in schizophrenia (Reif et al. 2006). To study the proliferation of progenitor cells in the DG, one of the first steps of adult neurogenesis, we measured the proliferation marker Ki-67 on sections of the anterior hippocampus using quantitative immunocytochemistry. The findings suggested that the progenitor cell number was reduced in *post mortem* brains from schizophrenics, but not patients with depression. Moreover, DG progenitor proliferation did not seem to be modified by antidepressant drug treatment (Reif et al. 2006).

Boldrini and colleagues also hypothesized that antidepressant treatment increases NPC number and cell division in the human DG, and that dividing cells are fewer in subjects with depression (Boldrini et al. 2009). In order to test this hypothesis, whole frozen hippocampi from both antidepressant-treated and untreated subjects with major depression as well as control subjects were fixed, sectioned, and immunostained for NPCs and dividing cell markers (nestin and Ki-67, respectively), NeuN (neuronal nuclear antigen; mature neuron marker), and GFAP (glial fibrillary acidic protein; astrocyte marker), under single- or double-labeling conditions. Two findings of the study were gender and age differences. Thus, nestin-positive NPCs decreased with age, and females had a greater number of nestin-positive NPCs than males. These results accord with earlier animal studies which found that estrogen enhanced NPC proliferation during proestrus in

female rats, resulting in more immature neurons in the hippocampal formation of females compared with males (Tanapat et al. 1999; Galea 2008). Also an age-related decrease in NPC proliferation is reported in rodents (Kuhn et al. 1996). The age-related changes were confirmed for humans in another study, which established that certain neurogenesis-associated features originally identified in rodents, also showed qualitative and quantitative age-related changes in the adult human hippocampus (Knoth et al. 2010). The number of Ki-67-positive dividing cells was not altered by either gender or age. An important finding of Boldrini et al. was that depressed subjects treated with an SSRI had a greater number of nestin-positive NPCs than untreated depressed subjects and controls, but the number of NPCs was not different between depressed patients treated with an SSRI or tricylic antidepressant. Dividing cell number was greater in depressed subjects treated with a tricylic antidepressant than untreated or SSRI-treated depressed subjects and controls. The increase of both nestin-positive NPCs and Ki-67-positive dividing cells in antidepressant treated subjects was primarily restricted to the rostral (anterior) DG. The study found no significant difference in NPCs or dividing cell number between untreated depressed subjects and healthy controls, which corresponds to findings of Reif and co-workers (Reif et al. 2006). Nevertheless, the data in the Boldrini study suggests that the number of NPCs in depressed subjects was higher than in controls, although this difference was not statistically significant. Taking into account that the majority of the subjects died by suicide, these results question whether the reported antidepressant-induced increase in adult neurogenesis in humans is a true effect.

To add to the studies of adult neurogenesis in *post mortem* tissue obtained form subjects with depression, Lucassen, and co-workers found decreased numbers of progenitor cells but no effect of antidepressant treatment in the hippocampus of elderly depressed patients compared to non-depressed elderly controls. This effect was found primarily in MCM2 (minichromosome maintenance protein 2)-immunoreactive progenitor cells but not PH3 (phosphorylated histone 3)-positive proliferating cells (Lucassen et al. 2010b). The authors explained the discrepancies between the different human *post mortem* studies (dealing with the same questions) on the basis of anatomical-, medication- and age-differences between the subjects in the various studies as well as the possibility of neurogenesis-independent mechanisms of antidepressant action. As far as the number of MCM2-positive proliferating cells is concerned, neither an effect of gender nor age was found (Lucassen et al. 2010b).

All the above-mentioned studies of neurogenesis in *post mortem* human tissue have their limitations. One is that some of the antigens measured in these studies such as Ki-67 (Reif et al. 2006; Boldrini et al. 2009) and MCM2 (Lucassen et al. 2010b), are not only expressed in proliferating NPC but in any proliferating cell, including astroglia, microglia, or endothelial cells. This makes it impossible to determine how many of the immunoreactive cells actually differentiate into new neurons. The Boldrini study tried to circumvent this problem by counting cells that were immunoreactive for the NPC-marker nestin (Boldrini et al. 2009). However, as it is unlikely that all of these cells survive, even this marker tells us little about

the number of new functional neurons and the lack or increase thereof in either untreated or treated depressed subjects. Nevertheless, the Boldrini study is currently unique in that it is the only stereological human *post mortem* study published on the subject (Boldrini et al. 2009). This is important as random, systematic sampling is generally regarded as essential for obtaining unbiased and quantitative data (West and Gundersen 1990).

Besides the above evidence of a possible link between adult neurogenesis in the human hippocampus and major depression, adult neurogenesis has also been investigated in other psychiatric and neurological disorders, including neurodegenerative disorders. In our above-mentioned study of Reif et al. (2006) data indicated that proliferation of cells in the DG was significantly reduced in schizophrenic patients, and this finding was offered as a possible contributory explanation for the cognitive deficits of this disorder. In addition to this study, hippocampal neurogenesis has been reported to be increased in epilepsy (Crespel et al. 2005) and Alzheimer's disease (Jin et al. 2004; Marlatt and Lucassen 2010). In the latter case, the expression of immature neuronal marker proteins that signal the birth of new neurons was measured in the hippocampus of senile subjects with Alzheimer's disease (Jin et al. 2004). Compared to controls, Alzheimer brains showed increased expression of DCX and the immature neuronal marker TUC-4 in cells of the SGZ of the hippocampal DG. Another study focussing on younger (pre-senile) Alzheimer's patients found increased proliferation in layers CA1-3, possibly reflecting glial and vascular-associated changes, but not adult neurogenesis (Boekhoorn et al. 2006). In contrast to the human *post mortem* tissue results of Jin et al. (2004), adult neurogenesis was found to be decreased in a genetic mouse model of Alzheimer's disease (TgCRND8 mice), which overexpresses human amyloid ß precursor protein (APP) (Chishti et al. 2001; Herring et al. 2009; Lewejohann et al. 2009). The latter transgenic mice can be distinguished from other mouse models of Alzheimer's disease through the early exhibition (3 months) of ß-amyloid plaque load accompanied by astrogliosis/microgliosis and cognitive deficits (Chishti et al. 2001). Interestingly, enriched environment enhanced neuroplasticity in these mice, and also increased the diminished number of newborn hippocampal cells to wildtype levels (Herring et al. 2009).

Bringing together these above studies, it is possible to postulate that the adult neurogenesis hypothesis of depression should be widened to include a role for adult neurogenesis in a range of neuropsychiatric disorders, which includes neurological and neurodegenerative disorders such as Alzheimer's disease. However it needs to be born in mind that altered adult neurogenesis in these conditions could be an epiphenomenon and not causally involved. Potentially there are multiple mediators of changes in adult neurogenesis including altered availability of cytokines and neurotrophic factors, to name just a few. As an example, in rodents BDNF is known to be increased in the DG and hippocampal CA subfields after chronic antidepressant administration (Nibuya et al. 1995; Dias et al. 2003), and BDNF has been shown to promote the differentiation and survival of progenitor cells in the adult rat brain (Zigova et al. 1998). Another mechanism that may

change levels of adult neurogenesis is suggested in an in vitro study using the multipotent, human hippocampal progenitor cell line HPC03A/07 (Anacker et al. 2011). The latter study identifies a critical role for glucocorticoid receptors in the antidepressant effects on neurogenesis. Thus, the study found that treatment of these cells (for 3–10 days) with the SSRI sertraline, increased neuronal differentiation via a GR-dependent mechanism, possibly mediated through altered cAMP/protein kinase A signaling (Anacker et al. 2011).

6 Summary and Conclusion

The data presented in this review highlight the possibility that altered neurogenesis in the adult hippocampus is integrally involved in the pathophysiology of major depression. Primarily based on data from experimental studies with rodents, there is strong evidence that hippocampal adult neurogenesis is downregulated by stressful conditions and upregulated by antidepressant drugs and some other, but not all, antidepressant treatments. Some experiments have even suggested that neurogenesis is necessary for the behavioral effects of antidepressants (Santarelli et al. 2003), but this finding was not replicated using a different experimental approach (Meshi et al. 2006). Clinical evidence supporting this hypothesis includes reports of reduced hippocampal volume in MRI and *post mortem* studies of depressed patients, findings which could also be associated with cognitive deficits observed in these patients. However, reduced hippocampal volume and cognitive deficits could also be shown in schizophrenic patients as well as in patients with neurodegenerative disorders such as Alzheimer‘s disease.

To date, studies of *post mortem* human hippocampal tissue of patients with various types of neuropsychiatric disorders have not been able to find consistent evidence of altered adult neurogenesis in major depression. Three independent studies have set out to test the hypotheses that antidepressant treatment increases NPC number and proliferation rates, and that adult neurogenesis is disturbed in depressed patients compared to controls, but have produced contradictory findings (Reif et al. 2006; Boldrini et al. 2009; Lucassen et al. 2010b). However, decreased NPC proliferation could be linked to schizophrenia (Reif et al. 2006) and increased adult neurogenesis could be shown in patients with Alzheimer‘s disease (Jin et al. 2004).

Animal studies implicate the involvement of adult neurogenesis in hippocampus-dependent learning and memory processes, such as spatial learning, contextual fear learning and extinction, as well as the process of pattern separation. Recent studies suggest an additional role of hippocampal adult neurogenesis in emotional memory formation, which is an important issue as impaired regulation of emotional memory is a feature of several affective disorders. Early studies of the mechanism by which newborn cells become an integral part of learning and memory processes, suggest that the role of newborn cells depends on their differentiation stage. Moreover, the work of Kitamura et al. (2009) suggests that the

level of adult neurogenesis determines the hippocampus-dependent period of memory formation.

As adult neurogenesis is much more prominent in rodents than human and non-human primates, it can be questioned whether hippocampal adult neurogenesis in different species is regulated in the same way, and has the same functional relevance. Considering this, we highlighted the possible differences of adult neurogenesis levels and distribution patterns of progenitor cells in the DG of humans and rodents. Primates, and humans in particular, show low levels of adult neurogenesis compared to rodents (Eriksson et al. 1998; Gould 1999; Lee et al. 2010), but all species show a clear decline of adult neurogenesis with aging (Seki and Arai 1995; Kuhn et al. 1996; Kempermann et al. 1998; Amrein et al. 2011). In addition, in humans adult neurogenesis-related cells are not predominantly localized in the SGZ from a certain postnatal age (Lee et al. 2010) as in the case of rodents (Namba et al. 2005). Rather, in the human hippocampus most of the NPCs seem to be "stuck" in the hilus (Lee et al. 2010).

Despite much that has been learned from the above-mentioned studies as well as others, one of the burning questions in the field that has not yet been satisfactorily answered is whether changes in adult neurogenesis associated with depression (or other neuropsychiatric disorders) and its treatment, are causally connected. Indeed, increasing preclinical and clinical data give researchers reason to doubt the causal nature of changes in adult neurogenesis and the pathophysiology of neuropsychiatric disorders and their treatment. As a consequence one might wonder whether altered adult neurogenesis is merely an epiphenomenon triggered by various external manipulations. Against this background of many findings, links and suggestions, the real functional significance of adult neurogenesis in general, and, especially the functional relevance of adult neurogenesis in different species, needs further detailed investigation.

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