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HIPPOCAMPAL ADULT NEUROGENESIS: ITS REGULATION AND POTENTIAL ROLE IN SPATIAL LEARNING AND MEMORY

Claudia Lieberwirth^{1,*}, Yongliang Pan^{2,3,*}, Yan Liu⁴, Zhibin Zhang³, and Zuoxin Wang⁴

¹ Behavioral Science Department, Utah Valley University, Orem, UT, 84058, USA

² Program in Molecular and Translational Medicine, School of Medicine, Huzhou University, Huzhou 313000, PR China

³ State Key Laboratory of Integrated Management of Pest Insects and Rodents in Agriculture, Institute of Zoology, Chinese Academy of Sciences, Datun Road, Chaoyang District, Beijing 100101, PR China

⁴ Department of Psychology and Program in Neuroscience, Florida State University, Tallahassee, FL 32306-1270, USA

Abstract

Adult neurogenesis, defined here as progenitor cell division generating functionally integrated neurons in the adult brain, occurs within the hippocampus of numerous mammalian species including humans. The present review details various endogenous (e.g., neurotransmitters) and environmental (e.g., physical exercise) factors that have been shown to influence hippocampal adult neurogenesis. In addition, the potential involvement of adult-generated neurons in naturally-occurring spatial learning behavior is discussed by summarizing the literature focusing on traditional animal models (e.g., rats and mice), non-traditional animal models (e.g., tree shrews), as well as natural populations (e.g., chickadees and Siberian chipmunk).

Keywords

adult neurogenesis; hippocampus; spatial learning; memory; Morris water maze; food hoarding

1. Introduction

1.1. Brief history of adult neurogenesis

In the field of neuroscience, it was traditionally believed that neurogenesis, defined here as progenitor cell division generating functionally integrated neurons, only occurs in the developing brain (Ramon y Cajal, 1928). The first evidence of the formation of new neurons in adult rats came from Altman's pioneering studies using thymidine autoradiography (Ming and Song, 2005; Sidman et al., 1959)—a technique labeling dividing cells with [³H]-thymidine, which incorporates into the replicating DNA (Altman and Das, 1965; Altman,

*Corresponding authors, CL: tel: (801) 863-8892; fax: (801) 863-7089; clieberwirth@uvu.edu; YLP: tel.: (86572) 232-1203; fax: (86572) 232-1203; 02402@hutc.zj.cn.

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1966; Altman and Das, 1967). Unfortunately, Altman's findings received little attention at that time. The topic of adult neurogenesis was revisited years later by Kaplan and his colleagues, who provided additional evidence for adult-generated neurons using electron microscopy. In particular, they demonstrated that [³H]-thymidine labeled cells in adult rats display ultra-structural characteristics of neurons (such as dendrites and synapses) (Kaplan and Hinds, 1977; Kaplan and Bell, 1984). However, these findings were also largely ignored. Methodological advancements provided evidence of adult neurogenesis in a variety of mammalian species, which, in turn, led to the acceptance that the adult mammalian brain displays neurogenesis (Gross, 2000; Kempermann and Gage, 1999; Lie et al., 2004). These methodological advancements included the introduction of novel methods to label new cells (e.g., 5-bromo-3'-deoxyuridine, BrdU, labeling) (Gratzner, 1982) and the distinction of neurons from glial cells (e.g., double-labeling of BrdU with neuronal markers such as TuJ1 and NeuN) (e.g., Ming and Song, 2005).

1.2. Common techniques to study adult neurogenesis

The numerous technical developments, which have facilitated the advancement of the field of adult neurogenesis, can be grouped into the following three distinct approaches: (1) using nucleotide analogs, (2) using genetic tools, and (3) using specific markers. First, exogenous nucleotide analogs, such as [³H]-thymidine, BrdU, iododeoxyuridine (IdU), and chlorodeoxyuridine (CldU), are usually administered via intraperitoneal injections and incorporate into the cellular DNA in place of endogenous thymidine during the DNA synthesis phase of the cell cycle (S phase) (Leuner and Gould, 2010; Miller and Nowakowski, 1988). Labeled cells can be identified using autoradiography (for [³H]-thymidine) and immunohistochemistry (for BrdU, IdU, and CldU). [³H]-thymidine and BrdU (but not IdU and CldU) are similar in their efficiency to label dividing cells (Leuner et al., 2009). However, BrdU is more commonly used as it allows phenotypic analysis (see review Lieberwirth and Wang, 2012) and stereological quantification of the newly-generated cells (Scharfman et al., 2005). Varying the pulsing paradigm and the elapsed examination time after pulsing allows the quantitative analysis of distinct stages of adult neurogenesis, namely cell proliferation, neuronal differentiation, and cell survival (Dayer et al., 2003; Paizanis et al., 2007). Furthermore, BrdU immunohistochemistry can be combined with labeling for cell type-specific markers. Fluorescent double- or triple-labeling combined with confocal microscopy can be used to determine whether BrdU-labeled cells express a neuronal or glial phenotype (for reviews see Lieberwirth and Wang, 2012; von Bohlen Und Halbach, 2007). However, BrdU immunostaining has limitations in that it requires tissue fixation and DNA denaturation—making this type of analysis unsuitable for living cells. Secondly, adult neurogenesis can be studied using genetic labeling with viral vectors. Any viral vector, such as the frequently used non-replicative retrovirus, requires invasive stereotaxic surgery to be injected into a specific brain region. These markers are dependent on nuclear membrane breakdown during mitosis, thus their expression is a good indicator of cell division (Christie and Cameron, 2006; Lewis and Emerman, 1994; Ming and Song, 2005). An advantage of viral vectors includes that they usually carry a reporter gene, such as green fluorescent protein, which allows easy identification of cells expressing the retrovirus even in living cells (Ming & Song 2005). As the green fluorescent protein fills the entire structure of the neuron (including the soma and processes), viral vectors allow

electrophysiological and morphological examination of these neurons. However, the use of viral vectors is limited by low infection rates and infection variability between animals (Christie and Cameron, 2006). Lastly, adult neurogenesis can also be studied using endogenous cell cycle markers. These markers include nuclear antigens (such as Ki67, proliferating cell nuclear antigen [PCNA], and minichromosome marker-2 [MCM-2]), which are only expressed in actively dividing cells (Galand and Degraef, 1989; Kee et al., 2002; Scholzen and Gerdes, 2000; Stoeber et al., 2001). The major limitation of these endogenous markers is that they can only be used to analyze cell proliferation, but not the other stages of adult neurogenesis (such as survival or neuronal differentiation) (Lieberwirth and Wang, 2012).

1.3. Evidence of adult neurogenesis in various brain regions

Using these common techniques to study adult-generated neurons, numerous studies have shown that adult neurogenesis continuously occurs in the subventricular zone (SVZ) of the rostral lateral ventricles as well as the subgranular zone of the dentate gyrus (DG) of the hippocampus. Newly-generated cells migrate from the SVZ along the rostral migratory stream to the main olfactory bulb (MOB). Most SVZ-generated cells differentiate into neurons and integrate into the existing olfactory circuitry—where they likely play a role in short-term olfactory memory, olfactory fear-conditioning, and long-term associative olfactory memory (Lledo and Saghatelian, 2005; Ming and Song, 2005; Ming and Song, 2011). Similarly, most cells born in the subgranular zone migrate within the DG, differentiate into neurons (Figure 1), and integrate into the existing DG circuitry (Christie and Cameron, 2006; Lledo and Saghatelian, 2005; Ming and Song, 2005). Various studies suggest that these adult-generated DG neurons may play a role in spatial learning, long-term spatial memory retention, trace conditioning, and contextual fear conditioning (Ming and Song, 2011). Although the majority of studies assessing adult neurogenesis has focused on the SVZ/MOB and DG, evidence has accumulated suggesting that adult neurogenesis also occurs in other non-traditional neurogenic brain regions (Fowler et al., 2008; see reviews Gould, 2007; Migaud et al., 2010). In particular, adult-generated neurons have been reported in the neocortex (Altman, 1962; Bernier et al., 2002; Cameron and Dayer, 2008; Dayer et al., 2005; Gould et al., 1999c; Gould et al., 2001), piriform cortex (Bernier et al., 2002), and striatum (Bedard et al., 2002; Bedard et al., 2006). Furthermore, numerous limbic structures such as the amygdala (Figure 2), hypothalamus, and medial preoptic area—brain regions essential to mediating social behaviors—have been reported to display adult-generated neurons (Akbari et al., 2007; Bernier et al., 2002; Fowler et al., 2002; Huang et al., 1998; Kokoeva et al., 2005; Lieberwirth et al., 2012; Okuda et al., 2009). Although various researchers have observed new neurons in these non-traditional brain regions, it should be noted that other researchers did not (Bhardwaj et al., 2006; Koketsu et al., 2003; Kornack and Rakic, 2001). Interestingly, correlative studies have shown that the social environment can influence the rate of adult neurogenesis within the limbic system. For example, positive social interactions (such as mating) increase, whereas negative interactions (such as social isolation; Figure 2) decrease the number of adult-generated limbic system neurons (for review see Lieberwirth and Wang, 2012). As these studies are correlational, future studies are needed to assess the causal link between adult-generated neurons in the limbic system and social behavior.

Although numerous studies have focused on various aspects of the functional significance of adult-generated cells, the present review will only focus on adult neurogenesis in the hippocampus and its associated learning-memory functions. We will discuss various external (such as exercise) and internal (such as steroid hormones) factors influencing the distinct stages—cell proliferation, cell survival, and neuronal differentiation—of adult neurogenesis in the DG. In addition, we will highlight the different mammalian animal models (including laboratory as well as field animal models) that have been used to study hippocampal neurogenesis. Finally, as the DG is involved in spatial learning and memory functions (Broadbent et al., 2004; Galani et al., 1998; Riedel et al., 1999), we will also summarize the evidence indicating the potential involvement of adult-generated hippocampal neurons in behaviors displayed in the laboratory as well as naturally-occurring behaviors that require special learning and memory.

2. Adult neurogenesis in the hippocampus

2.1. Evidence of hippocampal neurogenesis across diverse species including humans

The occurrence of adult neurogenesis has been documented in a large variety of species covering a large range of animal classes, including fish (Pisces) (Byrd and Brunjes, 2001; Fernández et al., 2011), amphibians (Amphibia) (Raucci et al., 2006), reptiles (Reptila) (Font et al., 2001; Pérez-Cañellas and García-Verdugo, 1996), birds (Aves) (Alvarez-Buylla and Nottebohm, 1990; Alvarez-Buylla and Kirn, 1997; Ling et al., 1997), and mammals (Mammalia) (Fowler et al., 2008; Gould et al., 2000). Specifically, hippocampal adult neurogenesis has been observed in all mammalian species studied to date [hedgehogs (Bartkowska et al., 2009); marsupials (Harman et al., 2002); moles (Bartkowska et al., 2009); rodents including guinea pigs (Altman and Das, 1967), mice (Carlen et al., 2002; Kempermann et al., 1997; Kempermann et al., 2003), rats (Altman and Das, 1965; Cameron et al., 1993; Kaplan and Hinds, 1977), squirrels (Barker et al., 2005), and voles (Fowler et al., 2002; Galea and McEwen, 1999; Lieberwirth et al., 2012); rabbits (Gueneau et al., 1982); sheep (Brus et al., 2010; Hawken et al., 2009); tree shrews (Gould et al., 1997); several bat species (Amrein et al., 2007; Gatome et al., 2009); non-human primates (Gould et al., 1999b; Kornack and Rakic, 1999); and even humans (Eriksson et al., 1998; Knoth et al., 2010; Kukekov et al., 1999)]. Although substantial numbers of new cells are generated, only a small subset of these cells survives, matures into neurons, and integrates into the existing neuronal circuit (Cameron and McKay, 2001; Kempermann et al., 2003; von Bohlen Und Halbach, 2007). Interestingly, numerous studies have identified environmental and endogenous factors that influence hippocampal adult neurogenesis—suggesting that hippocampal adult neurogenesis may be an adaptive process to respond to environmental and/or internal challenges (Lledo et al., 2006).

2.2. A variety of factors influence hippocampal neurogenesis

2.2.1. Environmental factors—Previous research has indicated that various environmental factors influence the distinct stages of hippocampal neurogenesis including cell proliferation, neuronal differentiation, and/or survival. In particular, increased environmental complexity (relative to standard housing)—enhancing the opportunities for social, cognitive, sensory, and motor stimulation (Nithianantharajah and Hannan, 2006; van

Praag et al., 2000)—has been shown to increase hippocampal cell survival in mice and rats, without affecting hippocampal cell proliferation (Bruehl-Jungerman et al., 2005; Kempermann et al., 1997; Kempermann et al., 1998; Nilsson et al., 1999; Olson et al., 2006; van Praag et al., 1999b). Increased environmental complexity also significantly enhances neuronal differentiation in the murine DG (Brown et al., 2003; Kempermann et al., 1998; Kempermann et al., 2002; Tashiro et al., 2007). Voluntary physical activity (via wheel running) also heightens hippocampal adult neurogenesis by increasing cell proliferation, neuronal differentiation, as well as cell survival in the adult mouse (Brown et al., 2003; Stranahan et al., 2006; van Praag et al., 1999a; van Praag et al., 1999b; van Praag et al., 2005; Zhao et al., 2006). As increased environmental complexity consists of various components (including social, cognitive, sensory, and motor stimulation), van Praag and colleagues (1999a) separately investigated the components of environmental complexity and found that only one component—physical activity—is associated with enhanced hippocampal neurogenesis. There is evidence that voluntary physical activity and a complex environment increase vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF), which, in turn, positively influence hippocampal neurogenesis (Adlard et al., 2004; Cao et al., 2004; During and Cao, 2006; Fabel et al., 2003; Farmer et al., 2004).

Furthermore, increased environmental complexity enhances the number of learning opportunities as compared to standard housing (Leuner and Gould, 2010). Interestingly, learning also has beneficial effects on hippocampal neurogenesis (Gould et al., 1999d). In particular, hippocampal-dependent learning tasks, such as eye-blink conditioning, spatial navigation learning, and conditioned food preference, alter adult neurogenesis in the DG. Eye-blink conditioning and spatial navigation learning in the Morris water maze increase hippocampal cell proliferation (Dupret et al., 2007; Van der Borgh et al., 2005) and survival (Ambrogini et al., 2000; Döbrössy et al., 2003; Epp et al., 2011; Gould et al., 1999a; Leuner et al., 2004; Leuner et al., 2006). Similarly, acquiring conditioned food preference, a hippocampus-dependent learning task, enhances cell survival in the rat DG (Olariu et al., 2005). In contrast, hippocampal-independent learning tasks (such as short-delay eye-blink conditioning, cued water maze training, and active shock avoidance) do not alter hippocampal neurogenesis (Gould et al., 1999a). However, the classification of learning tasks as hippocampus-dependent or hippocampus-independent does not completely account for the learning-induced effects on hippocampal adult neurogenesis (reviewed by Shors, 2008). Data from previous studies suggest that the stimulatory effect of learning on hippocampal adult neurogenesis depends on task difficulty (Leuner et al., 2006; Waddell and Shors, 2008) and depth of learning (Dalla et al., 2007; Leuner et al., 2004).

In contrast to the enhancement of neurogenesis due to exposure to a complex environment, voluntary physical activity, and learning, stress (due to both physical and psychosocial stressors) negatively affects adult neurogenesis in the DG (for review see Mirescu and Gould, 2006). For example, a physical stressor such as forced swimming results in the reduction of hippocampal cell proliferation in rats (Heine et al., 2004; Veenema et al., 2007). Acute foot shock reduces cell proliferation in male, but not female, rats (Malberg and Duman, 2003; Shors et al., 2007). Chronic, but not acute, restraint stress reduces both hippocampal cell proliferation and survival (Pham et al., 2003). Cell proliferation is also

reduced in response to chronic unpredictable stress (Heine et al., 2004). Similarly to physical stressors, psychosocial stressors, such as the exposure to an aggressive conspecific, predator odor, or social isolation, reduce hippocampal neurogenesis (reviewed by Lieberwirth and Wang, 2012). In particular, acute as well as chronic social defeat stress reduces hippocampal cell proliferation and survival in marmoset monkeys (*Callithrix jacchus*), mice, rats, and tree shrews (*Tupaia belangeri*) (Czeh et al., 2001; Czeh et al., 2002; Czeh et al., 2007; Gould et al., 1997; Gould et al., 1998; Mitra et al., 2006; Simon et al., 2005; Thomas et al., 2007; Van Bokhoven et al., 2011; van der Hart et al., 2002; Yap et al., 2006). Hippocampal cell proliferation and survival are also reduced in response to predator odor exposure in male rats (Falconer and Galea, 2003; Tanapat et al., 2001). Furthermore, social isolation reduces hippocampal cell proliferation and cell survival in prairie voles (*Microtus ochrogaster*) and rats (Fowler et al., 2002; Lieberwirth et al., 2012; Spritzer et al., 2011). It should be noted that contrary to aversive social experiences (e.g., exposure to social defeat, resident-intruder, and social isolation), non-stressful social interactions including exposure to male pheromones, maternal experience, and interactions with conspecific pups increase hippocampal neurogenesis in mice, prairie voles, and rats (Furuta and Bridges, 2009; Mak et al., 2007; Ruscio et al., 2008) (for reviews see Gheusi et al., 2009; Lieberwirth and Wang, 2012).

Researchers have also focused on the effects of the administration of psychotropic drugs on hippocampal neurogenesis. As such, the chronic use of drugs of abuse including alcohol, cocaine, opioids, ecstasy, and nicotine negatively affect hippocampal neurogenesis by reducing cell proliferation and survival (Abrous et al., 2002; Dominguez-Escriba et al., 2006; Duman et al., 2001; Eisch et al., 2000; He et al., 2005; Hernandez-Rabaza et al., 2006; Herrera et al., 2003; Nixon and Crews, 2002; Yamaguchi et al., 2005). On the other hand, the exposure to antidepressants increase hippocampal cell proliferation and neuronal differentiation (Malberg et al., 2000).

2.2.2. Endogenous factors—In addition to environmental factors, various intrinsic factors (such as developmental morphogens, neurotrophic factors, neurotransmitters, and steroids) have been reported to influence hippocampal neurogenesis (Grote and Hannan, 2007; Jang et al., 2008; Lledo et al., 2006; Schinder and Gage, 2004; Vaidya et al., 2007; Zhao et al., 2008). In particular, data from previous studies have shown that morphogens including Notch, Shh, Wnts, and BMPs play a regulatory role in the maintenance, activation, and neural differentiation of adult neural precursors (for review see Ming and Song, 2011). By experimentally manipulating the levels of neurotrophic factors, such as BDNF, ciliary neurotrophic factor (CNTF), insulin-like growth factor-1 (IGF-1) and VEGF, it has been shown that such neurotrophic factors increase hippocampal cell proliferation. For example, the site-specific chronic infusion of BDNF into the DG increases adult neurogenesis in rats (Scharfman et al., 2005). Similarly, central CNTF administration increases the cell proliferation and neuronal differentiation in the murine DG (Emsley and Hagg, 2003). Additionally, the peripheral as well as central administration of IGF-1 enhances the proliferation and neuronal differentiation in the DG of mice and rats (Åberg et al., 2000; Lichtenwalner et al., 2001). Hippocampal cell proliferation is also upregulated in response to central administration or viral-vector-induced expression of VEGF (Cao et al., 2004; Jin et

al., 2002). On the contrary, the genetic knockdown of TrkB—the high affinity receptor for BDNF—or the knockdown of CNTF cause a significant reduction in hippocampal neurogenesis (Bergami et al., 2008; Müller et al., 2009).

In addition to morphogens and neurotrophic factors, various types of neurotransmitters have been shown to influence hippocampal neurogenesis. For example, the activation of the gamma amino butyric acid (GABA) neurotransmitter system, the main inhibitory neurotransmitter, regulates adult hippocampal neurogenesis. On one hand, GABA system activation downregulates cell proliferation, on the other hand GABA system activation seems to accelerate the synaptic integration of adult-generated hippocampal neurons (Ge et al., 2007). Interestingly, the activation of the glutamate neurotransmitter system, the main excitatory neurotransmitter, negatively affects hippocampal neurogenesis. For example, the administration of an agonist to the NMDA subtype of the glutamate receptors reduces hippocampal neurogenesis by inhibiting cell proliferation (Cameron et al., 1995). Administering a NMDA receptor antagonist or lesioning the perforant path, the main glutamatergic input to the DG, results in an increase in hippocampal cell proliferation in rats, tree shrews (*Tupaia belangeri*), and gerbils (Bernabeu and Sharp, 2000; Cameron et al., 1995; Cameron et al., 1998; Gould et al., 1997). Another neurotransmitter that has been shown to influence hippocampal neurogenesis is serotonin. Serotonin upregulates hippocampal neurogenesis, whereas the inhibition of serotonin synthesis and the lesioning of the raphe nuclei, site of serotonin neurons, downregulate hippocampal neurogenesis (Brezun and Daszuta, 1999; Gould, 1999; Radley and Jacobs, 2002).

Lastly, hippocampal neurogenesis is also modulated by steroids, including both corticosteroids and gonadal steroids. Corticosteroids, such as glucocorticoids that are naturally released during the stress response, reduce hippocampal neurogenesis (Cameron and Gould, 1994; Gould and Tanapat, 1999; Wong and Herbert, 2005). Similarly, the administration of glucocorticoids decreases hippocampal cell proliferation in adult rats (Ambrogini et al., 2002; Cameron and Gould, 1994; Gould et al., 1992). On the contrary, reducing corticosteroid levels (via adrenalectomy) increases hippocampal cell proliferation and can even restore the age-related decline of hippocampal neurogenesis, which is observed due to high levels of corticosteroids (Cameron and Gould, 1994; Cameron and McKay, 1999; Gould et al., 1992; Rodriguez et al., 1998). Adrenalectomy accompanied by corticosterone replacement does not lead to an increase in hippocampal cell proliferation (Gould et al., 1992; Rodriguez et al., 1998). Similarly to adrenalectomy, the blockade of glucocorticoid receptors can normalize a stress-induced reduction of hippocampal adult neurogenesis (Oomen et al., 2007). In addition, naturally occurring differences in the stress response have been shown to influence hippocampal cell proliferation. Specifically, highly reactive rats show significantly reduced hippocampal cell proliferation compared to low reactive rats (Lemaire et al., 1999).

Similarly to the modulating effects of corticosteroids, gonadal steroids have been shown to affect hippocampal cell proliferation. In particular, hippocampal proliferation in female rats and meadow voles (*Microtus pennsylvanicus*) fluctuates corresponding to ovarian steroid changes across the course of the estrous and breeding cycle (Galea and McEwen, 1999; Ormerod and Galea, 2001; Pawluski et al., 2009; Tanapat et al., 1999). Acute estrogen

administration (within 4 hours) upregulates cell proliferation in the DG of female meadow voles and rats, whereas acute estrogen administration suppresses cell proliferation after 48 hours (Ormerod and Galea, 2001; Ormerod et al., 2003; Tanapat et al., 1999). Gonadal steroids have also been shown to affect hippocampal cell survival. In particular, neuronal survival in the male rat DG is enhanced by chronic androgen exposure (Spritzer and Galea, 2007). Hippocampal cell survival in the male meadow vole also seems to fluctuate corresponding to the seasonal changes of androgens (Ormerod and Galea, 2003).

3. Hippocampal adult neurogenesis and its behavioral significance

As the DG plays an essential role in learning and memory functions (such as converting short-term into long-term memories as well as spatial memory) (Broadbent et al., 2004; Burgess et al., 2002; Deacon et al., 2002a; Galani et al., 1998; Riedel et al., 1999) and hippocampal adult neurogenesis seems to be regulated by environmental factors and experience (Lledo et al., 2006; Zhao et al., 2008), researchers have investigated the functional significance of hippocampal adult-generated neurons. In the following section, we will review studies that focused on spatial learning and memory behaviors displayed by laboratory animals in the laboratory (using behavioral tests such as the Morris water maze or Barnes maze; Figure 3) or displayed by field animal species that naturally display spatial learning and memory behaviors (such as food hoarding).

3.1. Studying hippocampal adult neurogenesis using laboratory animals

3.1.1. Rats—One traditional animal model that has been used to study the functional implications of adult neurogenesis and its link to spatial learning has been the rat model. Hippocampus-dependent spatial learning (e.g., Morris water maze) has been reported to increase hippocampal neurogenesis (Epp et al., 2007; Gould et al., 1999a). Interestingly, the time and the proficiency of spatial learning seem to play a specific role. In particular, spatial learning increases the survival of 1-week old neurons, whereas younger and older neurons at the time of spatial learning are not more likely to survive (Ambrogini et al., 2000; Ambrogini et al., 2004; Dupret et al., 2007; Epp et al., 2007; Gould et al., 2000). Hippocampal cell proliferation seems to be upregulated only during the late, but not early, phase of spatial learning (Döbrössy et al., 2003; Dupret et al., 2007). Furthermore, high, but not low, proficiency spatial learning enhances hippocampal adult neurogenesis (Sisti et al., 2007). Such time- and proficiency-related enhancement of hippocampal neurogenesis suggests that the surviving adult-generated hippocampal neurons might play a role in these newly acquired spatial memories.

Further support of the involvement of newly generated cells in spatial learning comes from the observation that the reduction of adult neurogenesis causes impairments in spatial learning. In particular, the age-dependent reduction of hippocampal neurogenesis has been linked to impairments in learning the Morris water maze task (Drapeau et al., 2003; Driscoll et al., 2006). It is of interest to note that aged-impaired rats, which exhibit a lower level of adult neurogenesis than aged-unimpaired rats, show spatial memory impairments, whereas the aged-unimpaired rats do not show such impairments. Abolishing hippocampal adult neurogenesis by using low dose irradiation—an effective and rapid, but irreversible, method

to reduce the number of young hippocampal neurons (Mizumatsu et al., 2003; Tada et al., 2000; Wojtowicz, 2006)—causes deficits in long-term retention, but not acquisition, in the Morris water maze (Snyder et al., 2005; Wojtowicz et al., 2008) and spatial working memory in the T-maze (Madsen et al., 2003). However, the ablation of adult neurogenesis using an anti-mitotic agent (such as methylazoxymethanol acetate, MAM) does not seem to affect spatial learning (Shors et al., 2002). One possible explanation for these apparently contradictory results is that spatial learning may only require a very small percentage of newly-generated cells (Moser et al., 1995; Snyder and Cameron, 2012). MAM-treatment, which does not fully ablate adult neurogenesis, may allow for a greater number of adult-generated hippocampal neurons than exist during senescence (Dupret et al., 2005; Shors et al., 2002). Another possible explanation is that the test of spatial memory must be sufficiently difficult to detect small changes in performance. For example, ablation of adult-generated hippocampal neurons leads to a deficit in the Morris water maze only if a long-delay time is used (Snyder et al., 2005; Zhang et al., 2008).

Whereas factors that reduce adult hippocampal neurogenesis impair spatial learning, factors that enhance adult neurogenesis seem to increase spatial learning. For example, increased environmental complexity enhances hippocampal adult neurogenesis as well as spatial learning in the Morris water maze (Nilsson et al., 1999). Increased environmental complexity can even ameliorate the stress-induced reduction in hippocampal cell proliferation as well as the spatial learning deficits (Veena et al., 2009). In sum, research in rats provides evidence that newly-generated hippocampal neurons play a role in spatial learning and memory.

3.1.2. Mice—In addition to rats, another traditional animal model to study the functional implications of adult neurogenesis is the mouse model. Similarly to findings in rats, hippocampus-dependent spatial learning enhances hippocampal adult neurogenesis in mice (Nilsson et al., 1999; Trouche et al., 2009). Furthermore, these adult-generated hippocampal neurons tend to incorporate into neuronal networks supporting spatial memory (Kee et al., 2007; Tashiro et al., 2007; Trouche et al., 2009). The reduction of adult neurogenesis causes impairments in spatial learning. Specifically, the age-dependent reduction of hippocampal neurogenesis has been linked to impairments in learning the Morris water maze task (van Praag et al., 2005). Experimentally abolishing hippocampal adult neurogenesis by using low dose irradiation also causes spatial memory deficits in the Barnes maze (Raber et al., 2004). Similarly, irradiation impairs the performance of mice in the Morris water maze, the radial arm maze, and a two-choice spatial discrimination task (Ben Abdallah et al., 2013; Clelland et al., 2009) (but see Raber et al., 2004). Correspondingly, the ablation of adult neurogenesis using temozolomide (TMZ), a DNA-alkylating agent, results in impaired performance in the Morris water maze task (Garthe et al., 2009; Garthe et al., 2013).

Whereas factors that reduce adult hippocampal neurogenesis impair spatial learning, factors that enhance adult neurogenesis seem to increase spatial learning. For example, running (via voluntary wheel running) enhances hippocampal adult neurogenesis as well as spatial learning in the Morris water maze (van Praag et al., 1999a; van Praag et al., 2005). Voluntary wheel running can even ameliorate the age-dependent reduction in hippocampal cell proliferation as well as the spatial learning deficits (van Praag et al., 2005). It should be

noted that ablation studies in rats have been limited to the use of low dose irradiation and anti-mitotic treatment—techniques that lack specificity as well as have unwanted side effects (Brüel-Jungferman et al., 2007; Dupret et al., 2005; Schinder and Gage, 2004; Tada et al., 2000; Winocur et al., 2006). In mice, however, ablation of adult neurogenesis can also be achieved by using genetic tools, which allow for the reversible ablation of specific neurons. Several transgenic mouse lines have been developed, which allow the precise induction of death of neuronal precursors in the hippocampus. Using a transgenic mouse model to precisely induce the ablation of nestin-positive hippocampal neural precursors causes spatial deficits in the Morris water maze (Deng et al., 2009; Dupret et al., 2008). Similarly, the removal of TLX-positive neural precursors and the removal of NSE-positive cells also leads to spatial deficits in the Morris water maze and the Barnes maze, respectively (Imayoshi et al., 2008; Zhang et al., 2008). Interestingly, the ablation of GFAP-positive progenitor cells does not result in spatial deficits in the Morris water maze or the Y maze (Saxe et al., 2006). Although it could be argued that these GFAP-progenitor cells may not play a role in spatial learning and memory, it should be noted that the specific training protocol for the Morris water maze may be important to observe spatial learning and memory deficits induced by ablating adult hippocampal neurogenesis (Zhang et al., 2008). Using a transgenic technique that allows the ablation of previously-tagged adult-generated neurons, Arruda-Carvalho et al. (2011) ablated time-specifically neurons before or after Morris water maze learning. The authors observed that ablating adult-generated hippocampal neurons after memory formation, but not before, causes significant deficits in the Morris water maze task. In sum, various studies have shown a potential link between adult-generated hippocampal neurons in mice and spatial learning and memory behavior.

3.1.3. Other species—In addition to the traditional rat and mouse models to assess the functional implications of hippocampal neurons in spatial learning and memory, researchers have been assessing the presence of hippocampal adult neurogenesis in various non-traditional laboratory species, including guinea pigs (Altman and Das, 1967); rabbits (Gueneau et al., 1982); rodents such as California mice (*Peromyscus californicus*) (Glasper et al., 2011), meadow voles (Galea and McEwen, 1999; Ormerod and Galea, 2003), prairie voles (Fowler et al., 2002; Lieberwirth et al., 2012; Ruscio et al., 2008), and squirrels (Barker et al., 2005); sheep (Brus et al., 2010; Hawken et al., 2009); tree shrews (*Tupaia belangeri*) (Gould et al., 1997); and non-human primates (Gould et al., 1999b; Kornack and Rakic, 1999). Comparative research of the long-tailed wood mouse (*Apodemus sylvaticus*) and the bank vole (*Clethrionomys glareolus*) shows that wood mice have higher levels of hippocampal neurogenesis (Amrein et al., 2004b) and superior spatial learning capabilities (Galsworthy et al., 2005) than bank voles—providing correlational evidence that newly generated hippocampal neurons may play a functional role in spatial learning and memory. However, the causal relationship between adult-generated hippocampal neurons and spatial learning using non-traditional animal models has not yet been systematically investigated.

3.2. Studying hippocampal adult neurogenesis using field animal models

Numerous researchers have studied the potential link of hippocampal adult neurogenesis and its functional implications in spatial learning and memory using traditional laboratory animals such as rats and mice. However, using such animal models has various limitations

and this approach cannot determine whether adult-generated neurons promote survival and reproductive fitness in natural populations (Barnea, 2010; Boonstra et al., 2001). Laboratory animals live in a highly controlled environment and are often exposed to inappropriate environmental stimuli—conditions that are not reflective of the natural environment (Barker et al., 2005). Standard laboratory housing is characterized by the surplus of food and water, unusually close proximity between conspecifics, environmental simplicity, and physical inactivity (Nottebohm, 2002). Further, naturally-occurring environmental stimuli such as predators, competition, and seasonal cues are usually absent. In turn, such impoverished and unnatural housing conditions may negatively impact the brain, in particular the DG (Gould and Gross, 2002). Indeed animals living in an enriched environment, either in the wild or in a relatively complex laboratory environment, display higher rates of hippocampal neurogenesis than laboratory animals living in standard laboratory housing (Amrein et al., 2004a; Barnea and Nottebohm, 1994; Epp et al., 2009; Kempermann et al., 1997; Kempermann et al., 1998; Kempermann et al., 2002; Nilsson et al., 1999; Nottebohm, 2002; Tarr et al., 2009).

In addition to the unnatural housing conditions, spatial learning/memory in laboratory animals is often assessed using tests such as the Morris water maze and Barnes maze (Paul et al., 2009). Although these tests measure spatial learning reliably, they have various limitations. One of the limitations is that these tests require extensive training. For example, rodents must be trained in the Morris water maze for 5-10 days with 4-6 trials per day (Morgan, 2009; Paul et al., 2009). Furthermore, these tests are rather stressful due to the requirement of negative reinforcers (such as water immersion, intense light, or loud noise) (Van Sluyters and Obernier, 2004) as well as food or water deprivation (Hyde et al., 1998). As the exposure to stressful stimuli reduces hippocampal neurogenesis (for review see Mirescu and Gould, 2006), such stressors might act as a confound in assessing the link between spatial learning and hippocampal neurogenesis.

For the above-mentioned reasons, various researchers have focused on establishing field animal models to assess the functional implications of hippocampal adult neurogenesis in spatial learning (Boonstra et al., 2001; Nottebohm, 2002). Such field models focus on studying animals in their natural habitat and rely on naturally displayed behaviors. Indeed, this approach eliminates various confounds associated with laboratory studies, namely the unnatural, controlled laboratory environment and the use of stress-inducing spatial tasks that often require extensive training. To this date, field studies have mainly focused on assessing hippocampal adult neurogenesis in animal species that display food hoarding behaviors, including bird species such as the black-capped chickadee (*Parus atricapillus*) (Barnea and Nottebohm, 1994; Barnea and Nottebohm, 1996; Chancellor et al., 2011; Hoshoooley and Sherry, 2004; Hoshoooley et al., 2006; Hoshoooley and Sherry, 2007) and mountain chickadee (*Poecile gambeli*) (Freas et al., 2012; LaDage et al., 2010), as well as rodent species such as the eastern grey squirrel (*Sciurus carolinensis*) (Barker et al., 2005; Lavenex et al., 2000a; Lavenex et al., 2000b), red squirrel (*Tamiasciurus hudsonicus*) (Johnson et al., 2010), Siberian chipmunk (*Tamias sibiricus*) (Pan et al., 2013), and yellow-pine chipmunk (*Tamias amoenus*) (Barker et al., 2005). It is of importance to note that both avian and mammalian hippocampal formations originate from the reptilian dorsomedial cortex. Through evolution, the mammalian hippocampus developed structures such as the dentate gyrus and Ammon's

horn—structures that seem to be lacking in the avian hippocampus. Instead the avian hippocampus has a V-shaped layer of densely packed neurons and a dorsomedial zone surrounding the V shape that can be seen as the mammalian equivalent to the hippocampus proper and dentate gyrus, respectively (reviewed in Lee, et al. 1998). Furthermore, both avian and mammalian hippocampi share cell types such as pyramidal and granule cells and these cells display similarities in connectivity to brain regions such as the septum and brain stem (but note the direct projections to the hypothalamus is absent in birds) It should be noted that although there are differences in the avian and mammalian hippocampus, there is homology in terms of anatomy, physiology (e.g., existence of adult neurogenesis), neurochemistry (e.g., similarity in occurrence of neuropeptides and neurotransmitters), function (specifically the involvement in spatial learning and memory), and postnatal plasticity (e.g., display of adult neurogenesis) (Colombo and Broadbent, 2000; Lee et al., 1998; Shiflett et al., 2004). In regards to differences of avian and mammalian adult hippocampal neurogenesis specifically, one main difference is that avian neurogenesis appears to be seasonally regulated (Barnea and Nottebohm, 1994; Smulders et al., 2000), whereas neurogenesis in most mammals lacks such seasonal fluctuations (but see Galea and McEwen, 1999; Lavenex et al., 2000a).

Food hoarding (caching) is a behavior that is characterized by storing food in locations concealed from other conspecifics and members of other species. Food is either larder or scatter hoarded. Larder hoarding refers to the food storage in one or few large stores (larders), whereas scatter hoarding refers to the formation of a large number of food storage sites (small hoards) (Vander Wall, 1990). Creating larder or small hoard food caches is an important adaptation to seasonal and unpredictable changes in food availability (Pravosudov and Clayton, 2002; Pravosudov and Smulders, 2010; Vander Wall, 1990). Relocating such caches in times of low food availability seems to be a hippocampus-dependent learning task as indicated by lesion studies. For example, lesions of the hippocampus disrupt the ability of Eurasian nutcrackers (*Nucifraga caryocatactes*), black-capped chickadees (*Parus atricapillus*), and dark-eyed juncos (*Junco hyemalis*) to relocate their caches (Hampton and Shettleworth, 1996; Krushinskaya, 1966; Sherry and Vaccarino, 1989). Similarly, cytotoxic lesions of the hippocampus cause deficits in food hoarding in mice (Deacon et al., 2002b). Furthermore, researchers have reported a link between hoarding behavior and hippocampal size (for review see Clayton and Lee, 1998; Krebs et al., 1989; Krebs et al., 1996; Lucas et al., 2004; Sherry and Hoshoooley, 2010). Comparing the hippocampal sizes of 23 bird species in 13 passerine families and subfamilies that differ in their food-storing behavior shows that food-storing birds have larger hippocampi than non-food-storing species (Sherry et al., 1989). In addition, food-storing bird species, which rely more extensively on stored food—such as the Clark's nutcracker (*Nucifraga columbiana*), have larger hippocampi than food-storing species that rely less on stored food—such as the gray-breasted jay (*Aphelocoma ultramarina*), the scrub jay (*Aphelocoma coerulescens*), and the pinyon jay (*Gymnorhinus cyanocephalus*) (Basil et al., 1996). In addition, bird species that store more food, store food for longer, or both have larger hippocampi than species that store less food or store food for a lesser duration (Hampton et al., 1995; Healy and Krebs, 1992; Healy and Krebs, 1996). Similarly to the findings in birds, the DG size of the Merriam's kangaroo rat (*Dipodomys merriami*), which relies extensively on stored food, is larger than the DG of the bannertail

kangaroo rat (*Dipodomys spectabilis*), which relies less on stored food (Jacobs and Spencer, 1994). Due to the link between the DG and hoarding behavior, it is not surprising that researchers have started to investigate the potential involvement of adult-generated DG neurons in hoarding behavior.

The first study to investigate the potential link of hippocampal adult neurogenesis and spatial learning in natural populations was conducted in bird species that display food hoarding behavior. Specifically, black-capped chickadees (*Parus atricapillus*) showed a peak of adult-generated hippocampal neurons in fall—the season, in which hoarding behavior is highest (Barnea and Nottebohm, 1994). Such seasonal recruitment suggests that the adult-generated hippocampal neurons may play a role in the acquisition of new spatial memories.

Interestingly, there were no seasonal differences in cell proliferation—suggesting that the seasonal difference in neuronal recruitment observed by Barnea and Nottebohm (1994) is likely due to an enhancement in survival (Hoshooley and Sherry, 2004). Comparing neuronal recruitment in black-capped chickadees (*Parus atricapillus*; food storing bird species) to the neuronal recruitment in the house sparrow (*Passer domesticus*; non-food storing bird species) allows the assessment about whether the increased neuronal recruitment in fall plays a role in food storing behavior. Indeed, black-capped chickadees (*Parus atricapillus*) show significantly greater hippocampal neuronal recruitment than house sparrows (*Passer domesticus*)—suggesting that the degree of hippocampal neurogenesis may be associated with spatial memory requirements of food-caching behavior (Hoshooley and Sherry, 2007). It should be noted that the authors did not observe seasonally fluctuating recruitment of adult-generated hippocampal neurons in chickadees (*Parus atricapillus*) as seen in Barnea and Nottebohm's study (1994). This discrepancy between studies may be due to differences in methodology (e.g., examination of wild vs. captive chickadees).

Additional support for the role of adult-generated hippocampal neurons in spatial memory comes from a study assessing a possible link between environmental harshness and adult neurogenesis (Chancellor et al., 2011). Environmental harshness is believed to cause a greater reliance on cached food, which, in turn might influence the rate of hippocampal neurogenesis (Pravosudov et al., 2015). The comparison of the number of adult-generated neurons in black-capped chickadees (*Parus atricapillus*) along an environmental gradient revealed that chickadees from harsh environments with more reliance on cached food have higher rates of hippocampal neurogenesis than birds from milder environments with less reliance on cached food (Chancellor et al., 2011). Therefore, this study provides evidence of the role of adult-generated hippocampal neurons in spatial memory. Further support of this link comes from an experiment conducted by LaDage et al. (2010)—assessing the effect of restricting food caching behavior in captivity on adult hippocampal neurogenesis in mountain chickadees (*Poecile gambeli*). The results showed that food caching behavior influenced adult hippocampal neurogenesis in captivity. Specifically, the mountain chickadees (*Poecile gambeli*), which were allowed to display food caching behavior, had significantly more new hippocampal neurons than the ones, which were denied to display food caching behavior.

Besides food hoarding avian species, food caching mammalian species, in particular rodents, have also been studied to assess the possible functional link of hippocampal adult

neurogenesis and spatial memory. Contrary to the seasonal fluctuations observed in black-capped chickadees (*Parus atricapillus*) (Barnea and Nottebohm, 1994), the adult scatter-hoarding eastern gray squirrel (*Sciurus carolinensis*) does not display seasonal changes in cell proliferation (Lavenex et al., 2000a). Due to the absence of seasonal fluctuations of cell proliferation, Barker et al. (2005) assessed the potential link between adult-generated neurons and spatial memory by comparing levels of adult neurogenesis between scatter and larder hoarders. It was predicted that scatter hoarders, which rely more heavily on spatial memory than larder hoarders, should have a higher rate of hippocampal adult neurogenesis. Indeed, the eastern gray squirrel (*Sciurus carolinensis*), a scatter hoarder, displays a higher number of newly-generated cells, but not a higher number of young neurons than does the yellow pine chipmunk (*Tamias amoenus*), a larder hoarder. Interestingly, such differences are not observed between scatter hoarding (in eastern North America) and larder hoarding (in western North America) subpopulations of red squirrels (*Tamiasciurus hudsonicus*) (Johnson et al., 2010). Despite these seemingly contradictory findings, which may be in part due to methodological shortcomings (such as not assessing cell turnover), these studies provide evidence for significant differences of adult neurogenesis across species with different food storing behaviors.

In addition to assessing the link between hippocampal adult neurogenesis and spatial memory using natural populations in the field, this link has also been investigated using natural populations in semi-natural enclosures. For example, the display of hoarding behavior, which shows large individual variations in these semi-natural enclosures in Siberian chipmunk (*Tamias sibiricus*), is associated with enhanced hippocampal cell proliferation (Pan et al., 2013) (Figure 4). It is of interest to note that only males, but not females, display this association between food hoarding and cell proliferation. Such sex differences may be due to less use of spatial memory via less cached seed retrieval by females or sex differences in spatial use patterns. However, there are no significant correlations between the level of hoarding behavior and cell survival. It is possible that the seed distribution and hoarding paradigm in this experiment was not vigorous enough to increase hippocampal cell survival. Although research has shown that food-caching animals may represent an excellent model to investigate the relationship between adult hippocampal neurogenesis and spatial memory, it should be noted that the studies mentioned above only show a correlational link between hoarding and hippocampal adult neurogenesis. Future research needs to be conducted to further elucidate the complex functional link between adult-generated hippocampal neurons and spatial memory as well as study the cause and effect relationship between hoarding behavior and hippocampal adult neurogenesis.

4. Conclusion

The well-documented evidence reviewed here suggests that adult neurogenesis in the hippocampus can be influenced by both environmental and endogenous factors. In addition, data also indicate a possible link between hippocampal adult neurogenesis and spatial learning and memory. Various environmental factors related to spatial learning and memory have been shown to enhance adult neurogenesis in the DG, whereas the reduction of hippocampal neurogenesis causes deficits in spatial learning and memory tasks. Although data from laboratory studies have contributed significantly to our understanding of adult

neurogenesis and its functions, it will also be important to study adult neurogenesis and its functions in free-living animals. Studies utilizing natural populations displaying natural spatial learning and memory behaviors (such as hoarding) will provide a better understanding about whether adult-generated DG neurons promote survival and reproductive fitness in natural populations (Barnea, 2010; Boonstra et al., 2001).

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Abbreviations

BDNF	brain-derived neurotrophic factor
BrdU	5-bromo-3'-deoxyuridine
CldU	chlorodeoxyuridine
CNTF	ciliary neurotrophic factor
DG	dentate gyrus of the hippocampus
GABA	gamma amino butyric acid
IdU	iododeoxyuridine
IGF-1	insulin-like growth factor-1
MAM	methylazoxymethanol acetate
MCM-2	minichromosome marker-2
MOB	main olfactory bulb
PCNA	proliferating cell nuclear antigen
SVZ	subventricular zone
TMZ	temozolomide
VEGF	vascular endothelial growth factor

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Figure 1.

Confocal microscopy images illustrating adult-generated cells (labeled with BrdU, red) in the dentate gyrus of the hippocampus in male rats. The majority of BrdU-labeled cells also co-expressed neuronal markers (NeuN and TuJ1), but not a glial marker (GFAP). Scale bar=10 μ m. (Adapted from Leuner et al., 2010).

Figure 2.

Confocal microscopy images illustrating adult-generated cells (labeled with BrdU, red) which express a neuronal phenotype (labeled with NeuN, green) in the dentate gyrus (DG) of the hippocampus (A, B, C, D, and E) and the amygdala (AMY) (F, G, H, and I) in female prairie voles. The white box in Panel A indicates the area of the DG with high magnification (B–D). Arrows indicate cells double-labeled for BrdU/NeuN. Arrowheads indicate the double-labeled cell shown in the magnified image in the DG (E) and AMY (I). 3D co-localization of BrdU and NeuN is demonstrated using views along the y–z axis (right) and x–z axis (below). Scale bar=20 μ m (A–D and F–H) or 5 μ m (E and I). (J) Female prairie voles that were socially isolated for 6 weeks had significantly lower percentages of BrdU-labeled cells that co-expressed NeuN in the granular cell layer (GCL) of the DG and AMY, compared to control females that were continuously housed with the female cage mates. * p < 0.05. Error bars represent SEM. (Adapted from Lieberwirth et al., 2012).

Morris Water Maze

Barnes Maze

Radial Maze

T Maze

Figure 3. Schematic drawings of commonly used behavioral tasks in rodent research for hippocampus-dependent spatial learning and memory. These tasks include Morris water maze, Barnes maze, Radial arm maze, and T-maze.

Figure 4.

Seed hoarding and newly-generated cells in the dentate gyrus (DG) of the hippocampus in Siberian chipmunks in semi-natural enclosures. Hoarding animals hoarded significantly more seeds than their non-hoarding counterparts (A) and showed large individual differences in seed-hoarding behavior (B). (C) Photomicrographs illustrating BrdU-labeled cells in the DG of hoarding animals. Scale bar=50 μm. The insert in Panel C shows BrdU-labeled cells in the DG with scale bar=10 μm. (D) Hoarding animals had a higher density of BrdU-labeled cells in the DG than the control and non-hoarding animals ($p < 0.01$). Alphabetic letters indicate the results of the post-hoc test. Error bars represent SEM. (Adapted from Pan et al., 2013).