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Review

Depression, Antidepressants, and Neurogenesis: A Critical Reappraisal

Nicola D Hanson[1], Michael J Owens*[,1] and Charles B Nemeroff[2]

[1]Laboratory of Neuropsychopharmacology, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA; [2]Department of Psychiatry and Behavioral Sciences, University of Miami School of Medicine, Miami, FL, USA

The neurogenesis hypothesis of depression posits (1) that neurogenesis in the subgranular zone of the dentate gyrus is regulated negatively by stressful experiences and positively by treatment with antidepressant drugs and (2) that alterations in the rate of neurogenesis play a fundamental role in the pathology and treatment of major depression. This hypothesis is supported by important experimental observations, but is challenged by equally compelling contradictory reports. This review summarizes the phenomenon of adult hippocampal neurogenesis, the initial and continued evidence leading to the development of the neurogenesis hypothesis of depression, and the recent studies that have disputed and/or qualified those findings, to conclude that it can be affected by stress and antidepressants under certain conditions, but that these effects do not appear in all cases of psychological stress, depression, and antidepressant treatment.

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INTRODUCTION

It is by now well understood that prolonged or intense stress can have physiologically deleterious effects on the brain. These effects, which are especially pronounced in the hippocampus, include neuronal atrophy, neurotoxicity, and neuroendangerment (making neurons more susceptible to other insults) (Sapolsky, 1996). They are largely linked to elevated concentrations of glucocorticoids, through multiple mechanisms that are still not entirely clear. Glucocorticoids in the hippocampus seem to serve an allostatic regulation function, alternately facilitating and protecting against damaging effects of excitatory amino-acid neurotransmitters to maintain stability in response to changing conditions (McEwen, 2001; Lee *et al*, 2002). Glucocorticoids also play important roles in better-characterized hippocampal processes, such as the modulation of neuronal excitability involved in learning and memory. Other molecular conduits, including serotonin (5-HT) and NMDA receptors, have also been implicated in stress-induced hippocampal damage.

*Correspondence: Dr MJ Owens, Laboratory of Neuropsychopharmacology, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 100 Woodruff Circle, Suite 4000, Atlanta, GA 30322, USA. Tel: +1 404 727 4059, Fax: +1 404 727 3233, E-mail: mowens@emory.edu

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These detrimental influences of stress on the general neuronal health and plasticity in the hippocampus extend to the regulation of granule cell generation in that region. For the vast majority of the twentieth century, neurobiology was dogmatic in the belief that neurogenesis does not occur during adulthood in the mammalian brain. The first evidence of newly generated central nervous system (CNS) neurons in adulthood was reported in 1965, when Altman and Das (1965) used ^{3}H-thymidine to label proliferating cells in the subgranular zone (SGZ) of the rat dentate gyrus. The resulting daughter cells became morphologically identical to mature granule cells; later studies confirmed that these new cells were indeed neurons (Kaplan and Hinds, 1977). The presence of the highly polysialated form of neural cell adhesion molecule (PSA-NCAM or NCAM-H), which is only found in immature neurons, provided additional evidence that neurogenesis occurs in the adult dentate gyrus (Seki and Arai, 1993). The existence of adult-generated neurons in the human hippocampus was demonstrated some years later (Eriksson *et al*, 1998).

In addition to the adult neurogenesis seen in the dentate gyrus, the subventricular zone (SVZ) of the lateral ventricle is now known to be a second site of adult neurogenesis. Neuroblasts produced in this region travel along the rostral migratory stream to differentiate into interneurons of the olfactory bulb (reviewed in Garcia-Verdugo *et al*, 1998). However, unlike nascent hippocampal neurons, these cells are largely unresponsive to stress or psychoactive drugs, with the exceptions of a few reports of increased neurogen-

esis by atypical antipsychotic drugs (Wakade *et al*, 2002; Green *et al*, 2006; Nasrallah *et al*, 2010). Thus, neurogenesis of the SVZ will not be addressed further in this review. In addition, some reports show a small number of adult-generated GABAergic interneurons in the neocortex of rodents and non-human primate, although negative reports regarding this region are equally as compelling (reviewed in Cameron and Dayer, 2008). Moreover, strong evidence exists that this is unlikely to occur in humans (Bhardwaj *et al*, 2006). Figure 1 shows areas of adult neurogenesis in the rat brain.

TIMELINE AND MARKERS OF HIPPOCAMPAL NEUROGENESIS

The SGZ of the dentate gyrus contains Type-1 radial-glia-like stem cells, which express the astrocytic marker glial fibrillary acidic protein (GFAP) as well as the intermediate filament protein nestin (Seri *et al*, 2001). Their population size and proliferation rate are relatively constant; these are likely the true stem cells of the region (Kempermann *et al*, 2004; Zhao *et al*, 2008; Bonaguidi *et al*, 2011). These cells exhibit morphology of radial glia and divide asymmetrically, producing a Type-2 daughter cell, while maintaining the parent Type-1 cell. Type-2 and, later, Type-3 cells are GFAP-negative and much more proliferative than Type-1 cells, and their proliferation rates are acutely variable. Type-2 cells express nestin and, as they develop, the microtubule-associated protein doublecortin (DCX) and the polysialated form of neural cell adhesion molecule (PSA-NCAM). Type-3 cells continue to express DCX, but no longer express nestin (Encinas *et al*, 2006). Type-3 cells are generally referred to as neuroblasts, while Type-2 cells are called lineage-determined progenitor cells or neural progenitor cells (NPCs). During the Type-3 stage, cells shift the orientation of new processes from horizontal (parallel to the granule cell layer) to vertical (perpendicular) and begin radial migration into the granule cell layer (Encinas *et al*, 2006). When the maturing cell exits the cell cycle, about 3 days after the original division, it reaches the Type-4 cell stage. These immature granule cells begin to express the calcium-binding protein calretinin and neuronal nuclei protein (NeuN), and project axons toward the CA3 region. Survival of the newborn cell population is largely regulated during this stage via variable rates of apoptosis (Zhao *et al*, 2008). Approximately 2–3 weeks after exiting the cell cycle, they cease expressing calretinin and instead express calbindin, a marker of mature granule cells (Kempermann *et al*, 2004). At this point, the new neurons enter a critical period of enhanced synaptic plasticity in which their electrophysiological properties resemble those of neurons in the classic early postnatal critical period in juvenile animals (Ge *et al*, 2007). This phase occurs approximately 4–6 weeks after the original cell division, resulting in a total of up to 7 weeks required for newborn cells to become functionally indistinguishable from the older granule cell population (Zhao *et al*, 2008). Figure 2 shows the stages of neurogenesis within the dentate gyrus.

Dividing cell populations have traditionally been studied using nucleotide analogs: originally ^{3}H-thymidine, and later bromodeoxyuridine (BrdU) or, less often, iododeoxyuridine or chlorodeoxyuridine. When made available via systemic injection, these molecules are incorporated into replicating DNA in place of thymidine, resulting in labeled cells that can be visualized using autoradiography or immunocytochemistry. Some concerns have been raised that BrdU might have cytotoxic effects or otherwise disrupt normal proliferation or maturation processes, but no deleterious actions of BrdU at doses well above those commonly used in labeling protocols have been shown (Hancock *et al*, 2009). One notable disadvantage of BrdU is that it only labels cells that are in the S-phase of the cell cycle (when DNA replication occurs). BrdU is metabolized and/or excreted within approximately 2 h following injection. Because progenitor cells in the dentate gyrus have been determined to have a cell cycle time of 24.7 h (Cameron and McKay, 2001), only a portion of the entire population of cycling cells

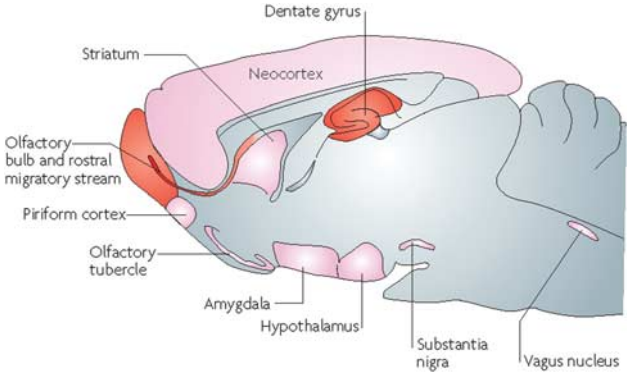

Figure 1 Areas of neurogenesis in the adult rat brain. Red – confirmed neurogenesis; pink – possible neurogenesis. (reproduced from Gould, 2007).

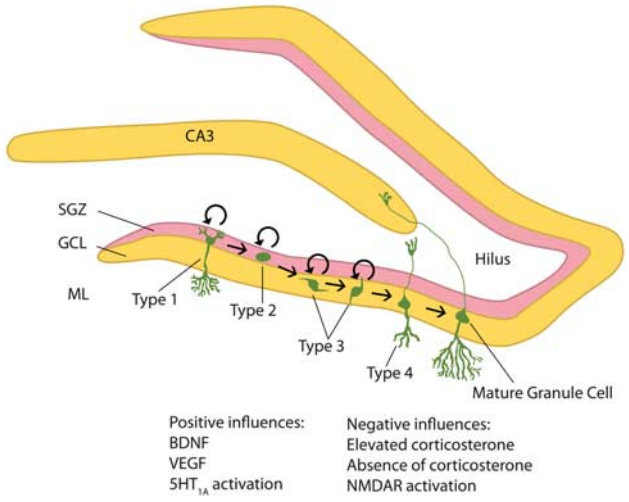

Figure 2 Stages of neurogenesis in the dentate gyrus. Type-1 cells (radial-glia-like stem cells) in the subgranular zone divide asymmetrically, maintaining their population while producing Type-2 daughter cells (neural progenitor cells). These continue to divide symmetrically as they mature into Type-3 cells (neuroblasts) and migrate into the granule cell layer. Type-4 cells, which have ceased mitosis, extend axons toward the CA3, leading to the development of mature granule cells that integrate with the mossy fiber pathway. SGZ, subgranular zone; GCL, granule cell layer; ML, molecular layer.

is labeled. Although changes in the number of BrdU-labeled cells accurately represent changes in the total number of currently cycling cells, a single pulse will not yield an estimate of the true total cycling population. Many investigators attempt to solve this problem by using repeated pulses, maintaining BrdU availability over at least a full cell cycle. However, because BrdU-labeled DNA is passed on to daughter cells, this adds the complication of allowing those cells labeled early in the availability period to complete mitosis following labeling, resulting in doubling of the labeled cell number. In contrast, those labeled late in the period will not have time to complete mitosis and will only result in single labeled cells. This distorts the makeup of the targeted cell population, confounding interpretation of the results. The number of cells labeled by a single pulse of a nucleotide analog peaks at 1 week, marking the shift of most of the population from the proliferative Type-2 and -3 stages to the non-proliferative Type-4, at which time cells are subjected to a high rate of apoptosis. At 4 weeks post-labeling, virtually all labeled cells in the granule cell layer express neuron-specific enolase, identifying them as mature neurons; the small number that express GFAP are likely Type-1 progenitor cells (Cameron *et al*, 1993b).

In recent years, the endogenous protein marker Ki-67 has emerged as an alternative target for the labeling of proliferating cells. This protein is expressed in the nucleus during all phases of the cell cycle, although its function is unclear (Kee *et al*, 2002). It can be easily visualized using immunocytochemistry and eliminates the issues surrounding incorporation periods, as well as any stress associated with injection procedures. Because staining for Ki-67 identifies all cycling cells, rather than only those currently in the S-phase, counts of Ki-67-labeled cells are approximately twofold higher than BrdU-labeled cells in the same experimental situation. However, relative expression patterns of Ki-67 and BrdU incorporation have been found to be highly correlated under a number of conditions, validating the use of either method according to convenience. It is common to study multiple stages of the neurogenic process in a single animal by injecting BrdU 3–4 weeks before being killed to identify long-term cell survival, and also labeling Ki-67, DCX, nestin, or other markers to examine particular stages of proliferation and development.

IMPORTANCE OF NEUROGENESIS IN HIPPOCAMPAL FUNCTION

The number of granule cell neurons generated each month in the dentate gyrus is approximately 6% of the total population (Cameron and McKay, 2001). The magnitude of this continuous production of new neurons indicates that they play an important role in hippocampal function, for which several possible hypotheses have been proposed. Computational network theories suggest that new neurons lend advantages in the temporary storage and processing of new memories (Deisseroth *et al*, 2004; Wiskott *et al*, 2006). It has repeatedly been reported that young granule cells display characteristics very different from mature ones, such as reduced threshold to induction of long-term potentiation (LTP) and an excitatory response to GABAergic input (Wang *et al*, 2000; Snyder *et al*, 2001; Ge *et al*, 2006). In fact, calcium signaling resulting from the activation of GABA receptors has been found to promote activity-dependent differentiation and regulate synaptic integration of these neuronal precursor cells (Tozuka *et al*, 2005; Ge *et al*, 2006).

A large body of literature supports a bidirectional relationship between learning and neurogenesis. Participation in learning tasks, particularly those involving hippocampal-dependent spatial memory formation (ie, place recognition or maze tasks) or exposure to enriched or novel environments, which facilitate spatial learning, are associated with increased rates of hippocampal neurogenesis (Leuner *et al*, 2006). The most compelling arguments indicate a specific role in spatial pattern separation: mice subjected to site-specific x-ray irradiation to ablate hippocampal cell proliferation develop significant impairment in the low spatial separation component of a challenging memory task, but function normally when presented with larger spatial separations and in other tasks of general spatial learning and memory (Clelland *et al*, 2009). Others report that the same irradiation treatment produces mice with normal spatial learning in the Morris water maze, but impairments in the Barnes maze, which requires distinguishing a single escape tunnel from 40 possible locations and necessitates finer spatial separation assessment than the Morris maze (Raber *et al*, 2004). (Any discussion of experimental ablation of neurogenesis via x-ray irradiation must mention that this method has an important drawback: it is not possible to control for other, non-neurogenic effects of the treatment. More details on hippocampal irradiation are included in the section 'The neurogenesis hypothesis of depression' below.) Interestingly, rats that primarily use a hippocampus-dependent place strategy in the Morris water maze exhibit lower rates of NPC proliferation than those rats, which use a non-hippocampus-dependent cue strategy, although they do not differ in survival rates of newborn neurons (Epp and Galea, 2009).

There is a compelling body of evidence that young granule cells are more responsive than their older counterparts to learning involving fear or anxiety. Survival and fos-activation within young granule cells are increased in animals exposed to a Morris water maze, but not in swim controls, which experience the stressful condition of the swim without the spatial learning component of hidden platforms (Gould *et al*, 1999; Snyder *et al*, 2009). In addition, inhibition of hippocampal neurogenesis using x-ray irradiation showed that the presence of immature neurons at the time of training is required for learning in the water maze (Snyder *et al*, 2005). Context-dependent fear conditioning also seems to be neurogenesis-dependent, because freezing is reduced in animals subject either to x-ray irradiation or to genetic ablation of neurogenesis, whereas cue-dependent fear conditioning and non-stressed spatial learning are unaffected (Saxe *et al*, 2006). Moreover, the formation of a fear association during training, but not the unconditioned stressor or the expression of fear, has been reported to significantly reduce proliferation of neurogenic cells of the dentate gyrus (Pham *et al*, 2005).

Apart from those memory functions that have been specifically linked to new granule cells, it is plausible that the continual alteration of hippocampal circuitry throughout adulthood has gradual long-term effects on interactions with those other brain regions intricately connected with the hippocampus. The limbic-hypothalamic-pituitary-adrenal axis encompasses inputs from the amygdala and prefrontal cortex to the hippocampus, which, via the subiculum, inhibits the paraventricular nucleus (PVN) of the hypothalamus. In addition to this direct pathway between the hippocampus and PVN, an indirect pathway involves excitatory input from the hippocampus to the bed nucleus of the stria terminalis, which provides inhibition to the PVN. The parvocellular neurons of the PVN secrete corticotropin-releasing factor (CRF) onto the anterior lobe of the pituitary gland via the median eminence and portal vessels, resulting in the release of adrenocorticotropic hormone into the general circulation and ultimately stimulating the production of glucocorticoids by the adrenal cortex. Under acute stress conditions, activity of this circuit and the resulting production of glucocorticoids increase dramatically. Negative feedback regulation occurs via glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) at several components of the system, including direct inhibition of CRF-secreting cells as well as on hippocampal neurons (reviewed in Lopez *et al*, 1999).

High glucocorticoid concentrations have been reported to negatively influence the proliferation rate of hippocampal NPCs; this rate is increased by adrenalectomy and decreased by acute corticosterone administration (Cameron and Gould, 1994). However, NPCs do not themselves express either GRs or MRs (Cameron *et al*, 1993a), indicating that this effect must be mediated by an indirect pathway. This pathway most likely involves NMDA receptor-mediated excitatory signaling of the perforant path from the entorhinal cortex via the subiculum. NPC proliferation can be increased by lesion of the perforant pathway or by administration of NMDA receptor antagonists, which block the effect of corticosterone, and proliferation can be decreased by the administration of NMDA itself (Cameron *et al*, 1995). Interestingly, NMDA blockade also increases rates of cell death of both mature and newborn granule cells (Gould *et al*, 1994). Corticosterone concentrations exhibit a U-shaped dose-response relationship with rates of granule cell death: complete removal of corticosterone via adrenalectomy results in cell loss, as do elevated concentrations commensurate with acute stress, meaning that low basal concentrations are optimal for survival. However, this relationship is complicated by the observation that the neurogenic effects of fluoxetine (discussed below in 'Antidepressants and neurogenesis') require the occurrence of diurnal corticosterone rhythms (Huang and Herbert, 2006). It is also notable that the age-related decreases in rates of both hippocampal cell proliferation and spontaneous neuronal death parallel the age-related increase in glucocorticoid secretion (Heine *et al*, 2004); however, a causal relationship has not been defined.

5-HT and the 5-HT_{1A} receptor in particular also play a seminal role in hippocampal responses to stress. 5-HT_{1A} receptors are highly colocalized with GR and MR on GABAergic interneurons, which receive serotonergic innervations from the median and dorsal raphe (Patel and Zhou, 2005). 5-HT release increases sharply in the presence of acute stress, therefore inhibiting the inhibitory influence of the hippocampus onto the PVN (Keeney *et al*, 2006). Hippocampal 5-HT_{1A} receptor expression and binding density are decreased by chronic stress; this decrease can be attenuated or blocked by antidepressant administration and appears to be mediated by glucocorticoids (Lopez *et al*, 1998). Simple increases or decreases in 5-HT transmission do not appear to directly affect NPC proliferation because neither acute 5-HT spikes nor depletion affect proliferation rate (Jha *et al*, 2006). In contrast, a 5-HT_{2A} receptor antagonist reduces proliferation acutely and increases it when given chronically, and chronic administration of a 5-HT_{1A} receptor agonist increases proliferation (Santarelli *et al*, 2003; Jha *et al*, 2008). The NPC proliferation rates of 5-HT_{1A} knockout mice are identical to wild-type mice at baseline and with imipramine-induced increase, but do not exhibit an increase in response to fluoxetine treatment (Santarelli *et al*, 2003).

ROLE OF NEUROTROPHIC FACTORS

Neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF), have been shown to play a role in the regulation of neurogenesis in the hippocampus. Neurotrophins are believed to largely affect cell survival via inhibition of apoptotic pathways (Manji *et al*, 2000). Direct infusion of BDNF into the hippocampus dramatically increases the number of newborn neurons, even contralateral to the injection site, which suggests that this effect does not result exclusively from a direct action upon NPCs or immature neurons (Scharfman *et al*, 2005). Similarly to central injection, chronic peripheral administration of BDNF has been found to increase survival of newborn cells of the dentate gyrus, via an unknown but necessarily indirect mechanism (Schmidt and Duman, 2010). In slice cultures, BDNF application enhances excitatory synaptic activity of CA1 pyramidal cells, offering a possible indirect pathway and tying BDNF-TrkB signaling to hippocampal learning and memory processes (Tyler and Pozzo-Miller, 2001). However, evidence supporting a direct pathway has also been reported, in that both NPCs and immature neurons do express TrkB, and conditional deletion of the *TrkB* gene in these cells negatively affects their proliferation, survival, axonal and dendritic growth, and ability to develop LTP, as well as abolishing the effects of imipramine and fluoxetine on proliferation and survival (Sairanen *et al*, 2005; Bergami *et al*, 2008; Li *et al*, 2008). BDNF heterozygote mice show decreased rates of granule cell proliferation and survival, as well as loss of the upregulation of neurogenesis by exposure to an enhanced environment (Sairanen *et al*, 2005; Rossi *et al*, 2006). In human populations, healthy subjects carrying the met allele of the val66met BDNF gene polymorphism have been found to have smaller hippocampal and parahippocampal volumes than those with the more common val/val genotype, providing further support for BDNF's importance in maintaining normal cell populations (Bueller *et al*, 2006; Montag *et al*, 2009).

In addition to its role in the regulation of neurogenesis, BDNF has been found to have its own antidepressant-like effects. Direct bilateral infusion of BDNF into the dentate

gyrus decreases the expression of learned helplessness and decreases immobility in the forced swim test (Shirayama *et al*, 2002). Chronic peripheral administration likewise has anxiolytic and antidepressant effects (Schmidt and Duman, 2010). Transgenic mice overexpressing BDNF in the forebrain (including the cortex and amygdala as well as the hippocampus) show improved performance in the forced swim and protection against CA3 dendritic atrophy induced by chronic stress, but also exhibit increased anxious behavior in an open field and increased amygdalar spine density (Govindarajan *et al*, 2006). In addition, depressive-like behavior and resistance to the behavioral effects of desipramine and citalopram result from localized knockdown of BDNF in the dentate gyrus, but not of knockdown in CA1 or CA3 (Adachi *et al*, 2008; Taliaz *et al*, 2010).

Evidence that hippocampal BDNF may be involved in the regulation of neurogenesis includes the observation that BDNF expression is similarly responsive to chronic stress and antidepressant treatments. In rats, restraint stress, either acute or chronic, decreases BDNF mRNA expression in the dentate gyrus and CA3 of the hippocampus, an effect that can be mimicked with corticosterone administration. However, corticosterone is not essential for this decrease; it is still observed in adrenalectomized animals with or without glucocorticoid replacement (Smith *et al*, 1995a, b). Chronic unpredictable stress and forced swim have also been seen to significantly decrease hippocampal BDNF expression (Shi *et al*, 2010; First *et al*, 2011); however, some experimenters report paradoxical increases in BDNF expression soon after exposures to acute stress (Larsen *et al*, 2010; Shi *et al*, 2010). Increased expression of hippocampal (particularly dentate gyrus) BDNF occurs in response to electroconvulsive shock or chronic treatment with any of several classes of antidepressant drugs (Nibuya *et al*, 1995; Altar *et al*, 2003; Czubak *et al*, 2009; Musazzi *et al*, 2009; Gersner *et al*, 2010), but also has been seen to time-dependently decrease after antidepressant treatment (Alboni *et al*, 2010). In summary, although the literature regarding BDNF's relationship with neurogenesis largely shows positive interactions, a consensus is not entirely clear.

There is also evidence that vascular endothelial growth factor (VEGF) regulates neurogenesis. VEGF's receptor (Flk-1) is expressed on adult hippocampal NPCs (Yang *et al*, 2003). Central VEGF infusion increases cell proliferation and increases the number of immature (DCX-expressing) neurons in the SGZ (Jin *et al*, 2002; Warner-Schmidt and Duman, 2007). Likewise, VEGF knockout mice show decreases in both cell proliferation and numbers of immature neurons (Sun *et al*, 2006), and viral-mediated VEGF overexpression increases proliferation and survival of new neurons, as well as improving performance in a Morris water maze and a passive avoidance learning task (Cao *et al*, 2004). As is the case with BDNF, this evidence links VEGF to neurogenesis-associated memory enhancement without ruling out additional effects of non-neurogenic processes such as increased microvasculature and blood flow.

STRESS AND NEUROGENESIS

Psychological stress has been reported to impair many aspects of hippocampal neurogenesis: decreasing proliferation rate of NPCs, decreasing survival of neuroblasts and immature neurons, and decreasing growth and development of new neurons. Although ischemic and oxidative stressors have also been found to negatively influence neurogenesis, they will not be discussed here. The stress experiments reviewed in this section are summarized in Table 1.

Restraint or immobilization is a classic stressor that has been repeatedly demonstrated to inhibit proliferation, in some reports after only a single session and in others requiring repeated treatment, and also to reduce survival rate of new cells (Pham *et al*, 2003; Vollmayr *et al*, 2003; Duric and McCarson, 2006; Koo and Duman, 2008). Reduced hippocampal volume was produced in one experiment utilizing a chronic paradigm of prolonged (6 h daily) restraint (Lee *et al*, 2009). Chronic unpredictable stress or chronic mild stress paradigms, often considered to be a more valid model of human major depression, have also been used to produce deficits in both proliferation and survival, although those including only mild stressors have produced somewhat less consistent results (Heine *et al*, 2005; Jayatissa *et al*, 2006; Lee *et al*, 2006; Xu *et al*, 2007; Silva *et al*, 2008; Jayatissa *et al*, 2010). A more naturally relevant stressor, exposure to the odor of a natural predator, has been reported to reduce proliferation with only a single exposure (Tanapat *et al*, 2001).

Experiments involving social stress take advantage of male rats' propensity toward establishing dominance hierarchies within a colony to examine social subordination as a chronic low-intensity stress condition. The most elaborate social stress studies involve extensive burrow systems in which animals can be monitored for home environment behavior, such that the effects of inhabiting various levels of a stable hierarchy can be compared between individual animals. In an experiment involving groups of four cohabitating rats, the dominant animal showed significantly higher numbers of surviving immature neurons than the subordinates, although the rate of NPC proliferation was unchanged (Kozorovitskiy and Gould, 2004). A long-standing model using a colony of tree shrews, which form intense and long-lasting dominance hierarchies that are particularly stressful for the subordinate, shows dramatically decreased proliferation, dramatically increased adrenal weights, and decreased hippocampal volume (Lucassen *et al*, 2001; Simon *et al*, 2005). The social defeat model (also called the resident-intruder model) restricts psychosocial stress into discrete episodes of conflict: the experimental animal (called the intruder) is only exposed to a larger dominant animal in its home territory (the resident) for short sessions, which can be performed on acute or chronic timelines (Heinrichs *et al*, 1992; Pulliam *et al*, 2009). In some variations, the intruder is left in visual and olfactory contact with the resident (eg, separated by a mesh barrier) for a period extending beyond the physical interaction. Reports of the effects of social defeat stress on neurogenesis vary: some studies have demonstrated significant negative effects on cell proliferation and/or neuronal survival, while others have not found such effects (Czeh *et al*, 2002; Thomas *et al*, 2007). In addition, social isolation has been reported to intensify deleterious effects of other stressors (Stranahan *et al*, 2006).

Studies involving variations of electric foot or tail shock have attempted to tease apart the importance of

Table 1 Effects of Exposure to Stressors

Reference	Sex	Stressor	Duration	Proliferation	Short survival	Long survival
Physiologically based stressors						
Keilhoff *et al* (2006)	M	Olfactory bulbectomy	N/A		–	
Jha *et al* (2006)	M	PCPA injection	5 d	–		–
	M	5,7-DHT infusion	N/A	0		0
Cameron and Gould (1994)	M	Cort injection	2 d	–		
Ekstrand *et al* (2008)	M	Cort injection	7 d	–		
Tanapat *et al* (2001)	M	Predator odor	3 h	–	–	0
Hill *et al* (2006)	M	Predator odor	1 h	–		
Thomas *et al* (2006)	M	Predator odor	20 m	0		
Duric and McCarson (2006)	M	Inflammatory pain	1	0		
			2 w	–		
Kraus *et al* (2010)	M	Noise trauma	2 h	–	–	
Guzman-Marin *et al* (2007)	M	Sleep fragmentation	1 d	0		
			4 or 7 d	–		
Mueller *et al* (2008)	M	Sleep fragmentation	4 d	–		
Socially based stressors						
Czeh *et al* (2002)	M	Social defeat	18 d	–		–
Kozorovitskiy and Gould (2004)	M	Social stress	3 d	0	–	
Thomas *et al* (2007)	M	Social defeat	20 m	0	–	–
Hanson *et al* (2011b)	M	Resident-intruder	3 w	0	0	0
Inescapable environmental stressors						
Heine *et al* (2005)	M	Chronic unpredictable stress	3 w	–		
Jayatissa *et al* (2006)	M	Chronic mild stress	6 w	–		
Lee *et al* (2006)	M	Chronic mild stress	3 w	0		–
Xu *et al* (2007)	M	Chronic unpredictable stress	3 w	–		
An *et al* (2008)	M	Chronic unpredictable stress	4 w	–		
Silva *et al* (2008)	M	Chronic mild stress	14 d		–	
Pham *et al* (2003)	M	Restraint	2 or 6 h	0		
			21 d	–		0
			6 w			0
Vollmayr *et al* (2003)	M	Restraint	45 m	–		
Luo *et al* (2005)	M	Restraint	1 w	–		
Rosenbrock *et al* (2005)	M	Restraint	3 h	0		
			2 w	–		
Duric and McCarson (2006)	M	Restraint	45 m	0		
Xu *et al* (2006)	M	Restraint	2 w	–		
Hanson *et al* (2011b)	M	Restraint	2 h	0		
Stranahan *et al* (2006)	M	Forced swim	10 d	–		
Malberg and Duman (2003)	M	Inescapable footshock	1 h	–		0
Vollmayr *et al* (2003)	M	Inescapable footshock	1 h	0	–	0
Westenbroek *et al* (2004)	M	Inescapable footshock	1 w	0		
			3 w		–	
	F	Inescapable footshock	1 w	0		
Pham *et al* (2005)	M	Unconditioned footshock	5 m	0		
Bland *et al* (2006)	M	Inescapable tail shock	1 h	–		–
Shors *et al* (2007)	M	Inescapable footshock	30 m	–		
	F	Inescapable footshock	30 m	0		
Chen *et al* (2006)	M	Inescapable tail shock	1 w	–		
Dagyte *et al* (2009)	M	Inescapable footshock	20 m	0		
			3 w	–		0
Hanson *et al* (2011b)	M	Inescapable tail shock	1 or 3 d	0		

Table 1 Continued

Reference	Sex	Stressor	Duration	Proliferation	Short survival	Long survival
Learning-associated stressors						
Malberg and Duman (2003)	M	Escapable footshock	1 h	0		
Pham *et al* (2005)	M	Context learning (footshock)	5 m	–	0	
Van der Borght *et al* (2005)	M	Active shock avoidance	1 d	0	0	
			4 d	0	0	
Bland *et al* (2006)	M	Escapable tail shock	1 h	0		0
Shors *et al* (2007)	M	Escapable footshock	30 m	–		
	F	Escapable footshock	30 m	0		
Mohapel *et al* (2006)	M	Water maze	4 d	0	0	
			2 w	–	–	
Aztiria *et al* (2007)	M	Water maze	7 d		–	

Abbreviations: PCPA, *para*-chlorophenylalanine; 5,7-DHT, 5,7-dihydroxytryptamine; N/A, not applicable.
All listed results regard adult rats. Short survival = 7–14 days; long survival = 21–28 days. 0, no effect, −, decrease, +, increase.

stress-related factors such as fear conditioning and behavioral control. A single session of footshock, either inescapable or as part of avoidance conditioning, has been in some cases enough to reduce NPC proliferation by 50%, regardless of whether animals develop learned helplessness behavior (Malberg and Duman, 2003; Vollmayr *et al*, 2003). This suggests that any stressor can inhibit neurogenesis when administered at sufficient intensity and duration. However, a report involving tail shock found that a single session reduced proliferation only in those rats developing learned helplessness (Chen *et al*, 2006). Studies of yoked pairs, in which one animal controls the duration of shock for both partners, have observed all the possible potential outcomes, namely, that both escapable and inescapable conditions result in decreased proliferation, that only the inescapable condition does so, or that neither has any effect on proliferation (Westenbroek *et al*, 2004; Bland *et al*, 2006; Shors *et al*, 2007). Further complicating the story is the fact that virtually all experiments in this area are performed on male animals only; when females are included they often show very different results, such as increased proliferation when males demonstrate a decrease, or no effect when males show a large one (Westenbroek *et al*, 2004; Shors *et al*, 2007).

As noted above, a particularly interesting series of experiments revealed that proliferation was only decreased by inescapable shock when the protocol timeline allowed contextual fear associations to occur, suggesting strongly that the important factor is not stress or fear itself, but the emotionally charged learning that takes place under stressful conditions (Pham *et al*, 2005). However, another study using a similar active avoidance protocol that should allow for contextual conditioning found no change in proliferation or survival rates, even when substantial learning had occurred (Van der Borght *et al*, 2005). In addition, several reports indicate that proliferation is decreased in animals exposed to stressful conditions, regardless of whether these animals develop depressive-like behaviors, such as learned helplessness or reduced sucrose consumption (Malberg and Duman, 2003; Vollmayr *et al*, 2003; Jayatissa *et al*, 2009, 2010), which imply that behavioral adaptations are not necessarily related to alterations in neurogenesis.

Stressful experiences in prenatal and early life, which have lasting effects on behavioral stress response into adulthood, have similarly lasting effects on both basal neurogenesis and its response to stress. Maternally separated rats show decreased NPC proliferation and immature neuron survival, but do not show normal stress-related suppression of these processes (Mirescu *et al*, 2004). Likewise, adult offspring of dams subjected to restraint stress during gestation show suppressed proliferation and survival, which can be rescued to normal levels by daily handling during the early postnatal period (Lemaire *et al*, 2006).

Taken as a whole, the literature on effects of stress on the processes of neurogenesis is somewhat discordant. A generally negative impact on NPC proliferation and survival is apparent, with a trend toward more intense and prolonged stressors producing more reliable and robust downregulation. The existence of numerous reports of validated, profound stress procedures, which produce no alterations in neurogenesis, however, prevent complete acceptance of this model. Clearly, stress is a factor in the regulation of neurogenesis, but other factors such as novelty, fear, learning, and spatial representation, which color these stressful experiences significantly modify the impact of the stress itself.

ANTIDEPRESSANTS AND NEUROGENESIS

A number of antidepressant drugs have been shown to positively influence various aspects of neurogenesis (summarized in Table 2). NPC proliferation rate and immature neuron survival rate have been upregulated by 14 or more days of treatment with the selective 5-HT reuptake inhibitor (SSRI) fluoxetine, but not by shorter treatment regimens (Malberg *et al*, 2000; Kodama *et al*, 2004; Huang and Herbert, 2006; Marcussen *et al*, 2008), although this effect has not been universally observed (Cowen *et al*, 2008; David *et al*, 2009; Hanson *et al*, 2011a). Similar results have been seen in experiments involving the SSRIs citalopram or escitalopram (Jaako-Movits *et al*, 2006; Jayatissa *et al*, 2006; Mnie-Filali *et al*, 2007; Bjornebekk *et al*, 2010). The tricyclic antidepressant imipramine, although less frequently used in studies of neurogenesis, has been shown to positively

impact both proliferation and survival (Keilhoff *et al*, 2006; Surget *et al*, 2008). In addition, other classes of drugs that are not clinically approved but have shown antidepressant properties in laboratory animals, such as CRF_1 antagonists and V_{1B} antagonists, have shown a similar ability to rescue proliferation rate from a stress-induced deficit, although not to increase it under non-stressed conditions (Alonso *et al*, 2004; Surget *et al*, 2008). The mood stabilizers lithium and valproate have been shown to markedly enhance both proliferation and survival (Chen *et al*, 2000; Hao *et al*, 2004;

Table 2 Effects of Antidepressant Treatments Under Non-stressed Conditions

Reference	Sex	Treatment and dose (mg/kg per day)	Duration	Proliferation	Short survival	Long survival
Electroconvulsive shock						
Madsen *et al* (2000)	M	Electroconvulsive shock	1 d	0/+		
Malberg *et al* (2000)	M	Electroconvulsive shock	10 d	+		+
Hellsten *et al* (2002)	M	Electroconvulsive shock	1 d			0
			5 d			+
SSRIs						
Malberg *et al* (2000)	M	Fluoxetine (5)	1 or 5 d	0		
			2 or 4 w	+		+
Kodama *et al* (2004)	M	Fluoxetine (5)	1 w	0		
			3 w	+		+
Huang and Herbert (2006)	M	Fluoxetine (7)	2 w	+	+	
Jaako-Movits *et al* (2006)	M	Citalopram (10)	4 w	0		0
Jayatissa *et al* (2006)	M	Escitalopram (5)	4 w	+		
Mnie-Filali *et al* (2007)	M	Escitalopram (10)	2 w	+		
Cowen *et al* (2008)	M	Fluoxetine (5)	25 d	0		0
Marcussen *et al* (2008)	M	Fluoxetine (10)	5 d	0		
			4 w	+		+
Pinnock *et al* (2009)	M	Fluoxetine (2.5 or 5)	2 w	0		
	M	Fluoxetine (10)	2 w	+		
Su *et al* (2009)	M	Fluoxetine (5)	3 w	0		0
Sui *et al* (2009)	M	Fluoxetine (5)	2 w	+		
			4 w	+		+
Castro *et al* (2010)	M	Fluoxetine (10)	5 w	+	+	
Bjornebekk *et al* (2010)	F	Escitalopram (25)	45 d			+
Hanson *et al* (2011a)	M	Fluoxetine (11)	3 w	0		
SNRIs						
Malberg *et al* (2000)	M	Reboxetine (40)	1 d	0		
Xu *et al* (2006)	M	Venlafaxine (2.5)	3 w	0		
	M	Venlafaxine (5)	3 w	+		
Larsen *et al* (2007)	M	Tesofensine (3)	5 d	0		
Mostany *et al* (2008)	M	Venlafaxine (40)	2 w	+		
Other monoaminergics						
Malberg *et al* (2000)	M	Tranylcypromine (10)	14 d	+		
Keilhoff *et al* (2006)	M	Imipramine (5)	15 d		+	
Other treatments						
Bai *et al* (2003)	M	LY451616 (0.025–0.125)	1 d	0		
			3 w	+		
Banasr *et al* (2006)	M	Agomelatine (40)	1, 3, 6 w	0		+
Hanson *et al* (2011a)	M	R121919 (30)	3 w	0		
Czeh *et al* (2002)	M	Transcranial magnetic stimulation	18 d	0		0
Grassi Zucconi *et al* (2006)	M	Sleep deprivation	1 d	+	+	+

All listed results regard adult rats. Short survival = 7–14 days; long survival = 21–28 days. 0, no effect; −, decrease; +, increase.

Silva *et al*, 2008; Hanson *et al*, 2011a). It is not known whether issues of dosing equivalency between various labs and individual experiments are responsible for the observed differences across drugs within the same class.

Non-drug treatments that have behavioral antidepressant effects also positively affect neurogenesis. A single electroconvulsive seizure (ECS), purportedly analogous to the electroconvulsant therapy used clinically to treat major depression, causes a profound increase in the number of new neurons surviving up to 2 months afterward. With multiple sessions, NPC proliferation rate also shows a dramatic increase, greater than that observed with fluoxetine (Madsen *et al*, 2000; Malberg *et al*, 2000). ECS has even been able to restore some degree of neurogenesis after disruption by x-ray irradiation, as well as restoring the corresponding deficits in contextual fear conditioning (Warner-Schmidt *et al*, 2008). A home-cage environment enriched to encourage exploratory behavior, as discussed above in 'Importance of neurogenesis in hippocampal function', promotes neurogenesis in a spatial learning context. Enriched environment can also relieve stress-induced depressive and anxious behaviors, a benefit that has been seen to involve or even require neurogenesis (Kronenberg *et al*, 2003; Veena *et al*, 2009; Schloesser *et al*, 2010). Exercise, either forced or voluntary, likewise has been shown to both increase NPC proliferation and decrease depressive and anxious behaviors (Olson *et al*, 2006; Yi *et al*, 2009; Brandt *et al*, 2010).

As is the case with stress-induced downregulation of neurogenesis, antidepressant-induced upregulation of neurogenesis forms a trend, rather than a reliable association. Numerous demonstrations have been made of varying types of antidepressant treatments notably increasing NPC proliferation and survival, but a substantial number of negative findings have been reported as well, particularly in the context of multi-drug experiments where some but not all treatments show significant effects.

THE NEUROGENESIS HYPOTHESIS OF DEPRESSION

Based on evidence described that hippocampal neurogenesis is (1) downregulated under stressful conditions, including those that result in laboratory animal models of depressive-like behaviors, and (2) upregulated by antidepressant drugs and other antidepressant treatments, the hypothesis emerged that neurogenesis and other related aspects of hippocampal plasticity are integrally involved in the pathophysiology of major depressive disorder (MDD) and its effective treatment. Some experiments have even suggested that neurogenesis is necessary for the behavioral effects of antidepressants, particularly hedonic or novelty-associated effects (Santarelli *et al*, 2003; David *et al*, 2009). Clinical evidence supporting this hypothesis includes reports of reduced hippocampal volume in MRI or post-mortem studies of MDD patients. Meta-analysis of 32 publications found that volume is significantly reduced with greater than one lifetime major depressive episode or greater than 2 years of illness, suggesting that the observed atrophy is resultant from the burden of illness rather than being a pre-existing risk factor (McKinnon *et al*, 2009). Evidence has even been found for increased proliferation of NPCs in antidepressant-treated vs -untreated MDD (Boldrini *et al*, 2009). However, discrepant reports have appeared, and there is evidence that reduced hippocampal volume may be associated with a history of child abuse and neglect or confounded by comorbid post-traumatic stress disorder in depressed women (Stein *et al*, 1997; Gilbertson *et al*, 2002; Vythilingam *et al*, 2002).

Nevertheless, the hypothesis has been recently subjected to serious criticisms. Many factors other than decreased neuron number could account for hippocampal volume changes: tissue from MDD patients has been found to have increased granule cell and pyramidal cell density, presumably from decreased neurophil, and the possibility of altered fluid content also exists (Stockmeier *et al*, 2004). The effects of chronic stress or experimentally elevated corticosterone concentrations on dendritic atrophy and loss of synapses have been well documented in laboratory animals (Sousa *et al*, 2000; Vyas *et al*, 2002; Tata and Anderson, 2010). This atrophy can be reversed by the administration of antidepressants of multiple classes, and in fact, the behavioral effects of chronic stress and antidepressants in the sucrose consumption test and forced swim test have been found to be associated more closely with the complexity of the dendritic arbor of granule and pyramidal cells than with neurogenesis (Bessa *et al*, 2009). In addition, fluoxetine and paroxetine have been seen to induce mature granule cells to revert to an immature phenotype, wherein expression of c-fos and calretinin are decreased and calbindin increased to early postmitotic levels. Such changes in the expression of maturation-associated proteins might result in experimental mistaking of these granule cells for truly newborn ones. Synaptic plasticity in SSRI-treated granule cells is also altered to resemble patterns seen in immature neurons, including enhanced LTD and suppressed LTP (Kobayashi *et al*, 2010). This 'dematuration' of older granule cells to more plastic functional states may allow many of the putative cognitive processing functions of newborn neurons to be performed without requiring a high volume of new cell generation as has been proposed previously (Deisseroth *et al*, 2004; Wiskott *et al*, 2006).

Another counterargument to the hypothesis is the finding that experimental disruption of neurogenesis does not produce depression-like behavior, nor does it render animals more sensitive to the behavioral effects of chronic stress (Surget *et al*, 2008; Jayatissa *et al*, 2009). In addition, there are now reports of antidepressants at behaviorally active or clinically relevant doses that exert no effect upon NPC proliferation or immature neuron number (see Table 2). Another complication arises when comparing studies using x-ray irradiation to block neurogenesis and those using the chemical agent methylazoxymethanol (MAM): while both methods interrupt cell proliferation in targeted areas, MAM does not block the effects of antidepressant drugs (cf. Surget *et al*, 2008; Bessa *et al*, 2009). Thus, it seems likely that some of the effects of hippocampal x-ray irradiation are due less to deficits in neurogenesis than to other alterations caused by the radiation.

To summarize, initial evidence regarding the effects of psychological stress and antidepressant drugs on adult neurogenesis in laboratory animals led to the development of the neurogenesis hypothesis of depression, which has

supportive evidence in many experimental settings. However, the emergence of contradictory reports and failed replications requires a revision of this hypothesis to state that neurogenesis in the adult dentate gyrus *can be* regulated by stress and antidepressants *under certain as-yet-undefined conditions*, but that this regulation is not an intrinsic property of all psychological stress, depression, and antidepressant treatments. It seems most likely that neurogenesis is only one, more visible aspect of a complex array of neuroplastic functions that occur in the adult hippocampus, and that the various factors involved in this neuroplastic environment are responsive to external influences, which often accompany but are not inherently linked with the pathophysiology and pharmacological treatment of depression and depression-like behaviors.

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