

Chronic Stress as a Primary Deterrent of Adult Hippocampal Neurogenesis:
Mechanism, Consequences, and Implications

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November 10, 2013

Author Note

The purpose of this literature review is to fulfill the requirements of Dr. John Lakey's Psychology Senior Seminar course at the University of Evansville. I have chosen adult hippocampal neurogenesis as my topic because it is relevant to stem cell research, a matter of popular controversy that both intrigues me, and may be useful for my graduate school pursuits.

If there are any further questions about this review, I can be reached at jm519@evansville.edu.

Abstract

The hippocampus is one of just two areas in the adult central nervous system where new neurons are generated. Levels of neurogenesis are decreased under conditions of psychological stress, sleep deprivation, and the aging process, while they are increased with regular exercise and an enriched environment. Levels of neurogenesis have also been found to be decreased as a result of certain neuropathological disease including Alzheimer's disease, depression, and epilepsy. Chronic stress either directly or indirectly influences these environmental and disease related decreases in neurogenesis, supporting the argument that stress is a primary deterrent of neurogenesis.

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Introduction

Most of the neuronal precursors in the brain differentiate terminally during, or just following, prenatal development (Cameron, McEwen, & Gould, 1995). The dentate gyrus of the hippocampus, however, is just one of two locations in the mammalian central nervous system (CNS) that contains active neural stem cells in adulthood (Lie et al., 2005). Stem cells in the subgranular zone (SGZ) of the hippocampus proliferate, mature, and differentiate to become integrated hippocampal granule cells throughout the lifespan (Bracko et al., 2012; Eckenhoff & Rakic, 1988).

The extent to which new neurons proliferate and successfully integrate into the hippocampal neural network in adulthood is influenced by both environmental and genetic factors. Influential environmental factors include stress levels, the aging process, quality of sleep, amount of exercise, and the quality of one's social and intellectual environment (Cameron & Gould, 1994; Cameron & McKay, 1999; Guzman-Martin, Bashir, Suntosva, Szymusiak & McGinty, 2007; Nilsson, Perfilieva, Johansson, Orwar, & Eriksson, 1999; Pragg, Shubert, Zhao, & Gage, 2005). Several neuropathological issues including epilepsy, Alzheimer's disease, stroke, and depression, which occur as a result of both genetic predisposition and environmental triggers, are also associated with changes in the neurogenesis process (DeCarolis & Eisch, 2010; Dranozsky & Hen, 2006; Kuruba, Hattiangady, & Shetty, 2009; Liu, Solway, Messing & Sharp, 1998).

All environmental and pathological deterrents of hippocampal neurogenesis, including chronic stress, aging, sleep deprivation, epilepsy, Alzheimer's disease, and depression are positively correlated with chronic stress (Cameron & Gould, 1994; Cameron & McKay, 1999; DeCarolis & Eisch, 2010; Dranozsky & Hen, 2006; Guzman-Martin et al., 2007; Kuruba et al.,

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2009; Nilsson et al., 1999). Stroke induced ischemia is the exception to this pattern, in that it is associated with chronic stress, but results in increased, as opposed to reduced, neurogenesis (Liu et al., 1998). Aside from ischemia, however, overwhelming evidence implicates chronic stress as a factor in neurogenesis deterrence.

Chronic stress, whether acting directly or indirectly, is, arguably, the primary cause of reduced proliferation and hindered integration of newborn neurons in the adult hippocampus, which can lead to increased prevalence of depression and learning impairment (Nilsson et al., 1999; Sahay & Hen, 2007). Therefore, studying the link between stress and deterrence of hippocampal neurogenesis holds implications for the cognitive, psychological, and neuropathological well-being of adults.

Background

Purpose of Neurogenesis

The hippocampus plays a role in the regulation of motivation and rewards, higher-order cognitive function, and memory consolidation (Dobrossy et al., 2003; Dupret et al., 2007). The purpose of hippocampal neurogenesis, in particular, is to facilitate both spatial and episodic learning, and to promote mood stability (Nilsson et al., 1999; Sahay & Hen, 2008).

Spatial and Episodic Learning

Overwhelming evidence, much of which is centered on spatial learning, supports a critical role for hippocampal neurogenesis in memory consolidation (Nilsson et al., 1999). The dentate gyrus, where adult neurogenesis occurs, is thought to be involved in both spatial and episodic memory (Clelland et al., 2009). Nilsson et al. (1999) subjected rats to two different maze tasks, and found that ablation of hippocampal neurogenesis resulted in spatial

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discrimination impairments. It was clear that spatial and episodic learning of the maze was not as effective when no new hippocampal neurons were being produced, supporting the indispensability of neurogenesis in consolidating spatial memories. Involvement of neurogenesis in episodic memory can be deduced by the finding that those with episodic amnesia have hippocampal lesions, but has not yet been confirmed or elucidated (Tulving, 2002).

Mood Stability

Neurogenesis is reduced in depressed individuals, who, when compared with healthy individuals, show a reduction in both reward-induced pleasure and motivation (Sahay & Hen, 2008). Therefore, can be adduced that neurogenesis plays a role in regulation of the dopaminergic reward pathway, which is responsible for motivation and mood stabilization (Depue & Collins, 1999).

Mechanism of Neurogenesis

The hippocampal neurogenesis process consists of cell proliferation, learning and maturation, integration, and clearance (Dupret et al., 2007; Feng et al., 2001). When new information is presented, newly proliferated neurons in the hippocampus receive it (Dupret et al., 2007). Once they mature, neurons that have absorbed information integrate into the existing hippocampal network, while neurons that have not received information undergo apoptosis (Dupret et al., 2007). This apoptotic process is critical, as neurogenesis is inhibited when the normal apoptosis process that immature, unlearned cells undergo is blocked (Dupret et al., 2007). Furthermore, the process of new neurons integrating into the hippocampus clears out older sub networks, allowing integrated information to remain in the hippocampus for only about three weeks before being transferred to the cortex (Feng et al., 2001). Mood regulation, because it is

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linked to the reward-learning dopaminergic pathway, functions via this learning-consolidation mechanism (Depue & Collins, 1999).

According to Dobrossy et al. (2003), the acquisition phase of learning is associated with a static proliferative rate of neurogenesis, while the consolidation phase of learning is associated with a decrease in neurogenesis. Therefore, the rate of neurogenesis is not just influenced by, but controlled by, learning (Dobrossy et al., 2003; Dupret et al., 2007). The mechanism of learning-induced proliferation may be a learning triggered cascade of signaling events resembling that of development, when neurons are regularly dividing (Dupret et al, 2007).

Signal Regulation of Neurogenesis

The proliferation, maintenance, and fate of hippocampal neural stem cells is regulated on a molecular level by microenvironmental signals, generated by learning and other environmental or genetic influences (Lie et al., 2005). Different types of regulatory signaling in the microenvironment of the dentate gyrus include neurotransmitter signaling, growth factor signaling, steroid signaling, and general protein signaling. The following subsections are incomprehensive, exemplar signaling mechanisms that can influence division in the dentate gyrus.

Neurotransmitters

Various neurotransmitters are known to influence hippocampal neurogenesis, including the monoamines norepinephrine and serotonin, and glutamate, which will be further discussed to generally illustrate neurotransmitter regulation of hippocampal neurogenesis (Dranozsky & Hen, 2006).

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Excitation of the entorhinal cortex releases glutamate, the brain's primary excitatory neurotransmitter, which then activates N-methyl-D-aspartate (NMDA) receptors on the hippocampus (Stone et al., 2011). NMDA receptors appear to exhibit differential regulation of cell proliferation depending on the period of learning during which they are being activated. This differential regulation persists across the lifespan: from development to adulthood (Cameron & Gould, 1994; Cameron et al., 1995).

When stimulated during development, NMDA receptors promote both migration and survival of newly born neurons, but also apoptosis (Cameron & Gould, 1994). Studies on adults have yielded similar mixed results. According to Cameron et al. (1995), NMDA receptor activation in the adult brain decreases during the birth of new hippocampal neurons, and inhibiting NMDA receptors causes an abrupt increase in cell cycle progression. These results suggest that NMDA excitation has an inhibitory effect on adult hippocampal neurogenesis (Cameron et al., 1995). Alternatively, according to Stone et al. (2011), there is a causal relationship between stimulation of the entorhinal cortex, and increased neurogenesis, suggesting that activation of hippocampal NMDA receptors induces proliferation. The contradictory findings of these different studies may be a result of conducting the studies during different learning phases. It is likely that Cameron studied neurogenesis during the consolidation phase, when neurogenesis is thought to be inhibited, and Stone observed proliferation during the acquisition phase, when neurogenesis is stable. Regardless of whether glutamate signaling upregulates or downregulates neurogenesis, it clearly plays a critical regulatory role.

Growth Factors

The adult neural proliferation process somewhat mimics developmental proliferation, since neural cell division is not standard in adulthood. Therefore, many of the growth factors that

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are key to neural differentiation during development are active in the microenvironment of the adult dentate gyrus.

Vascular endothelial growth factor-A (VEGF), promotes initial proliferation of stem cells in the subgranular zone (Palmer, Willhoite & Gage, 2000). Insulin-like growth factor 2 (IGF2), also regulates hippocampal stem cell proliferation (Bracko et al., 2012). When compared to their immature progeny, neural stem cells were found to express IGF2 at significantly higher levels (Bracko et al., 2012). Additionally, stem cells derived from adult white matter, and exposed to fibroblast growth factor (FGF-2) generate new neurons both *in vivo* and *in vitro* (Palmer et al., 2000). Likewise, brain-derived neurotropic factor (BDNF) has been found to encourage both survival and differentiation of new-born hippocampal neurons (Palmer et al., 2000). This list only describes some of the growth factors responsible for regulating neurogenesis.

Steroids

Steroids, particularly corticosteroids, are also influential to the neurogenesis process. Chronic stress, which releases corticosteroids, a category of adrenal hormones consisting of glucocorticoids and mineralocorticoids most often referred to as glucocorticoids, alters levels of hippocampal neurogenesis (Dranozsky & Hen, 2006). Additionally, glucocorticoids are known to directly regulate proliferation as there are glucocorticoid receptors on the dentate gyrus (Snyder, Soumier, Brewer, Pickel & Cameron, 2012).

Other Proteins

Various, more extraneous proteins also act to regulate adult neurogenesis. For example, the Wnt protein, which is expressed in both developmental and adult mice, encourages hippocampal neurogenesis during each learning phase (Lie et al., 2005). Wnt proteins act as a

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key regulator in the stem cell proliferation process during embryotic development (Lie et al., 2005). Likewise, adult hippocampal progenitor cells express receptors for these Wnt proteins, and indeed, overexpression of a Wnt protein, called Wnt3, increases adult neurogenesis, while blocking its signaling reduces division (Lie et al., 2005).

Chronic Stress and Neurogenesis

Hippocampal neurogenesis is reduced as a result of chronic stress (Cameron & Gould, 1994). Uncoincidentally, there is a strong component of stress and glucocorticoid elevation in other, seemingly independent deterrents of neurogenesis, such as rapid eye movement (REM) sleep deprivation and aging (Cameron & McKay, 1999; Guzman-Marin et al., 2005).

Additionally, environmental influences known to alleviate stress, such as exercise and a positive, supportive social environment, have been shown to ameliorate the detrimental effects of high glucocorticoid levels on neurogenesis (Nilsson et al., 1999; Pragg et al., 2005). Furthermore, the onset of neuropathological issues known to reduce neurogenesis, including epilepsy and Alzheimer's disease, often occurs in conjunction with, or following, periods of stress (Christensen, Li, Vestergaard, & Olsen, 2007; Quervain et al., 2003). Therefore, chronic stress and the associated elevation of glucocorticoids could be argued to be the most influential deterrent of neurogenesis, whether acting directly or indirectly.

Environmental Influence

Sleep Deprivation

Chronic or extended sleep deprivation, as well as sleep fragmentation, decreases hippocampal neurogenesis, while acute, brief sleep deprivation does not (Guzman-Martin et al., 2007; Meerlo, Mistlberger, Jacob, Heller & McGinty, 2009). Rapid-eye movement (REM) sleep

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deprivation or disruption, in particular, as opposed to non-REM or slow wave sleep (SWS) deprivation, is linked to this decline (Guzman-Marin et al., 2007). These results could be interpreted to suggest that REM sleep promotes neurogenesis, but this is unlikely. Despite the fact that the exact mechanism by which sleep deprivation reduces neurogenesis in the adult hippocampus is unknown, there is strong evidence supporting glucocorticoid release, due to the stress of chronic sleep deprivation, as the cause of sleep deprivation associated diminution of neurogenesis (Meerlo et al., 2009). Additionally, as presence of glucocorticoids inhibits sleep onset, the relationship between sleep deprivation and elevated glucocorticoid levels seems to be bidirectional (Vgontzas et al., 2001). This dual directionality suggests that stress can act as either the direct or indirect cause of sleep deprivation-associated reductions in neurogenesis.

Mirescu, Peters, Noiman, and Gould (2006) found that inhibition of neurogenesis occurred during sleep deprivation only when levels of circulating corticosterone were elevated, and not when the steroid was clamped. This finding fortifies elevated corticosterone levels as the cause of neurogenesis depletion. It also explains why chronic, and not acute, deprivation is associated with a decrease in hippocampal neurogenesis, as the release of glucocorticoids only occurs when stress is chronic. Although it is possible that REM sleep also encourages neuronal proliferation, it is not the primary reason that deprivation reduces neurogenesis.

Aging

Aging, like sleep deprivation, is associated with a decreased rate of granule cell proliferation (Cameron & McKay, 1999). This decrease in proliferation is correlated with an increase in corticosteroid levels (Cameron & McKay, 1999). Circulating corticosteroid levels are higher with age due to both increased basal levels of corticosteroids as well as prolonged secretion of glucocorticoids throughout the lifetime (Cameron & McKay, 1999). Adults who

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have managed to maintain corticosteroid levels comparable to their younger counterparts do not show a decrease in hippocampal neurogenesis (Cameron & McKay, 1999). Therefore, it is not age itself, but its general association with increased corticosteroid levels, that creates the negative correlation between age and levels of neurogenesis.

Elderly animals not only show elevated amounts of corticosteroids, but are more susceptible to their detrimental effects. According to Bodnoff, et al. (1995) young rats are resilient to the effects of corticosteroids, in that the rate of dentate gyrus cell proliferation in youthful rats is not hindered by moderate amounts of corticosteroid exposure. In another study, however, if stress was sufficiently prolonged, young rats did show hippocampal dysfunction that was morphologically and physiologically similar to that of elderly rats, including a decrease in neurogenesis (Endo, Nishimura, & Kimura, 1995). These findings suggest that older animals, whether humans or rats, have two stress related reasons for their decrease in neurogenesis: greater corticosteroid levels, and a greater susceptibility to their affects.

Exercising

According to Pragg et al. (2005) both young and elderly rats show an increased extent of hippocampal neurogenesis as a result of exercise. As exercise reduces stress levels, and since high levels of glucocorticoids play a significant role in the neurogenesis reduction, it is highly likely that exercise-facilitated neurogenesis is due to a reduction of and reduced sensitivity to corticosteroids (Salmon, 2001). This explanation, however, does not address the increase in neurogenesis seen in young rats, who are fairly resilient to stress levels. Therefore, exercise may not only facilitate neurogenesis by reducing stress levels, but also through an ancillary mechanism, such as by increasing vasculature in the dentate gyrus (Pragg et al., 2005).

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Unfortunately, exercise is not enough to completely reduce the hippocampal effects of stress and aging. The exercise induced recovery rate of neurogenesis in elderly rats is only 50% of the rate seen in young, exercising mice (Pragg et al., 2005). This may be because only basal corticosteroid levels, and not decades of corticosteroid exposure, are decreased by exercise. Alternatively, vasculature is not found to be increased in elders, while it is in youngsters, potentially providing youngsters extra benefits of exercise (Pragg et al., 2005).

Experience and Environment

An intellectually and socially enriched environment also increases the survival rate of newly produced neurons in rats (Nilsson et al., 1999). A positive and supportive social environment, as well as an environment enriched with proper basic needs, do indeed reduce stress levels (Belz, Kennell, Czambel, Rubin, & Rhodes, 2003). An enriched environment or enhanced experience, however, is not likely to exert its neurogenesis promoting effects solely through the reduction of glucocorticoids (Nilsson et al., 1999).

The increase of neurogenesis resulting from environmental stimulation, is just that - stimulated by the environment. If there is no new learning to be done, whether this learning is social or cognitive, neurogenesis is less important. This is especially true for the aging brain, which is more often neglected than the young, budding mind (Nilsson et al, 1999). Therefore, an enriched environment helps maintain a healthy amount of neurogenesis, both through a reduction in glucocorticoids and promotion of proliferation.

Pathological and Psychological Influence

Although chronic stress is not directly responsible for annihilation of neurogenesis in the following neuropathological issues, it is an etiological factor of these often proliferation reducing maladies.

Epilepsy

Epilepsy, characterized by reoccurring seizures, reduces hippocampal neurogenesis, while rare, acute seizures promote neurogenesis (Kuruba et al., 2009). Seizures are thought to result from excessive neural connectivity and the subsequent random firing that activates the brain (Morgan & Soltesz, 2008). The opposing effects of acute and chronic seizures are characterized by differing molecular mechanisms.

Following acute seizures, neurogenesis is increased for three to four weeks before returning to baseline levels (Kuruba et al., 2009). Additionally, acute seizures are thought to increase the integration of these new neurons into preexisting hippocampal networks (Kuruba et al., 2009). At first glance, increased neurogenesis after seizures appears to be advantageous, in that dying neurons, deafferented granule cells and reactive glia are sending a variety of mitogenic factors, including Nerve Growth Factor (NGF), BDNF, FGF2 and Sonic hedgehog (Shh), to replace neurons lost during the seizure (Kuruba et al., 2009). This “neuroprotective” effect may in fact work a little too well, however, in that more connective neural fibers are sprouting from newborn neurons and forming synapses with the existing hippocampal neural system, over-connecting hippocampal networks (Liu et al., 1998). These new networks are activated during subsequent spontaneous seizures, exhibiting spontaneous bursts of action potentials that contribute to epilepsy (Kuruba et al., 2009). Therefore, it appears that the

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occurrence of one seizure, and the upregulation of hippocampal neurogenesis that follows, may facilitate the occurrence of more seizures, negating any advantageous effects of increased neurogenesis.

In contrast, when seizures become frequent, as they are in epileptics, neurogenesis is deterred, and neuronal survival and integration inhibited (Kuruba et al., 2009). Epileptics show a 64-81% decrease in neurogenesis, and less than 4% of neurons, compared to 80% in non-epileptic control subjects, differentiate (Kuruba et al., 2009). A decrease in hippocampal neurogenesis may prove favorable, as to avoid further increases in hyperconnectivity which may promote seizures, but also unfavorable, in that reductions in hippocampal neurogenesis are associated with depression and impaired learning (Sahay & Hen, 2007; Nilsson et al., 1999).

This decrease in neurogenesis is attributed to an unfavorable environment. One factor of this unfavorable environment is increased levels of a Wnt protein inhibitor, called Dickkopf-1 (Kuruba et al., 2009). As Wnt is a key protein expressed in both developing and adult brains that promotes neurogenesis, epilepsy appears to activate pathways that turn off neurogenesis (Lie et al., 2005). It is also plausible that negative feedback signals, via autocratic signaling, lead to a decrease the various mitogenic factors promoted as result of cell death.

The role of stress in epilepsy-induced reduction of neurogenesis, however, is indirect. The occurrence of a high stress event, likely to result in chronic stress, such as the loss of a child, is moderately correlated with increased risk of epilepsy (Christensen et al., 2007). A moderate correlation between an environmental influence, such as stress, and a disease, such as epilepsy, is quite significant, as diseases are a product of both genetic susceptibility and environmental trigger. Therefore, it is likely that epilepsy befalls most adults who are both exposed to chronic stress and genetically susceptible. Although reoccurring seizures, and not stress, are the main

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cause of epilepsy-induced reductions in neurogenesis, there is still an associated role for stress in the matter. Additionally, stress may be induced by the onset and existence of the disease, which would further exacerbate the unfavorable effects of the seizures on dentate cell proliferation.

Alzheimer's Disease

The hippocampus is one of the first brain structures affected by Alzheimer's disease (AD) (DeCarolis & Eisch, 2010). Whether AD deters or facilitates hippocampal neurogenesis remains controversial, but there is strong evidence to suggest that AD decreases the rate of hippocampal neurogenesis in the dentate gyrus, and causes abnormal granule cell maturation (DeCarolis & Eisch, 2010; Donovan et al., 2006). Understanding the true nature of this relationship will foster further development of AD therapies.

Alzheimer's disease is characterized by the conglomeration of A-Beta plaques, which trigger microglial activation, or the brain's immune response (Donovan et al., 2006). This immune response triggers inflammation in the brain, which seems to be largely responsible for the cognitive deficits of AD, as reduction of inflammation in AD models restores cognitive function (Donovan et al., 2006). Beta amyloid plaques found in the hippocampus in particular are directly associated with AD, suggesting that the disease exerts a strong pathological effect on the structure (Rodriguez et al., 2008).

There is controversy over the nature of the relationship between AD and neurogenesis. Results have varied; some studies suggesting a decrease, and other studies suggesting an increase in hippocampal neurogenesis in AD models (DeCarolis & Eisch, 2010). AD mouse models have revealed decreased neurogenesis in the subgranular zone of the dentate gyrus (Donovan et al., 2006). A decrease in neurogenesis is well supported by the idea that new neurons are more

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difficult to produce with age, which is associated with stress (Rodriguez et al., 2008). Additional effects seen in these models are a decrease in apoptosis, and abnormal maturation of these new neurons. A decrease in apoptosis may either be a biological attempt to preserve what exists, or merely due to the fact that less neurons are produced, so less neurons are available to die (Donovan et al., 2006). Abnormal development of juvenile granule cells is characterized by irregular shape as well as retarded cell differentiation and maturation (Donovan et al., 2006). This live, in vivo, model of AD is a much more credible source of results than a post-mortem human model of AD.

Post-mortem human models have revealed contrary results, suggesting that hippocampal neurogenesis is upregulated as a result of AD (Jin et al., 2004). This facilitation of neurogenesis is thought to compensate for the loss of cells due to AD (Jin et al., 2004). Doublecortin and TUC4, both neurogenesis markers, have been stained to reveal this increase (Jin et al., 2004). These markers, however, are indicative of immature neurons that may survive only briefly. Therefore, the methodology used in post-mortem human models is thought to reveal insignificant, short-lived populations of hippocampal neurons (Donovan et al., 2006).

Despite the fact that neurogenesis seems to be decreased in the dentate gyrus as a result of AD, in vivo mouse models have revealed increased neurogenesis in the outer granule cell layer (Donovan et al., 2006). This finding alone may compensate for the discrepancy between live animal and post-mortem human models, as methodological techniques could be skewing the population of cells that is stained. The difference in upregulation and downregulation of neurogenesis may be due to altered levels of growth factors, which play different roles in different places on the hippocampus (Donovan et al., 2006).

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Regardless of whether hippocampal neurogenesis is facilitated or deterred as a result of AD, an increase in hippocampal neurogenesis would be therapeutic, by counteracting the effects of AD either alone, or in conjunction with the body's natural neurogenesis increase. Cell replacement is a practical therapeutic possibility, as the aged brain had been found to be capable of integrating new neurons into the hippocampus (Jin et al., 2004). Pharmacological agents, on the other hand, are a currently applicable therapeutic agent (Tchantchou, Xu, Wu, Christen & Luo, 2007). Spinnewyn B. Ginkgo biloba extract (Ecb 761) is a dementia drug that increases cAMP response element-binding (CREB) protein phosphorylation, facilitating the cell cycle to promote neurogenesis (Tchantchou, et al., 2007). The drug may also act via inhibition of A-Beta oligomerization, which would prevent microglial activation and inflammation, and therefore increase the rate of hippocampal neurogenesis (Tchantchou, et al., 2007). Despite the fact that some amelioration for AD exists, further exploring its relationship to hippocampal neurogenesis would open up new, potentially curative possibilities.

Similarly to epilepsy, excess glucocorticoid exposure increases the likelihood of Alzheimer's disease onset, as the steroid increases neuronal vulnerability to insult, including that of AD neurotoxicity (Quervain et al., 2003). Additionally, AD is characterized by a general increase in circulating glucocorticoid levels (Quervain et al., 2003). Therefore, the effect of glucocorticoids is both direct, and potentially even the main cause of AD-induced reduction of neurogenesis, as well as indirect, in that stress increases vulnerability of disease onset. Therefore further exploration of the link between AD, neurogenesis and stress levels may eventually lead to a cure for dementia.

Stroke

Stroke causes ischemia, or restriction of blood supply to tissues. Reduced blood supply, which ordinarily carries nutrients to the brain, prevents glutamergic neurons from firing, as glutamine is not available. Activity of NMDA and α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) neurons is restricted as a result of ischemia, which drives an increase in hippocampal neurogenesis (Bernaneu & Sharp, 2000; Liu et al., 1998). This increase in neurogenesis lasts for one to two weeks post-ischemia, acting as the body's mechanism of recovery due to granule cell injury and death, facilitating cognitive improvement comparable to that of cell transplantation (Liu et al., 1998).

Additionally, BDNF and FGF, which facilitate neurogenesis, are enhanced following ischemia (Liu et al., 1998). These growth and mitogenic factors stimulate increased cell birth (Liu et al., 1998). Expression of FGF receptors is enhanced in the dentate gyrus, and production of FGF is increased in astrocytes, a type of glial cell, after ischemia (Liu et al., 1998). The mechanism of neurogenesis enhancement via these growth factors, post-ischemia, is likely parallel to other neurogenesis enhancing events, including development.

Aside from the natural boost in hippocampal neurogenesis which facilitates recovery, an enriched environment, as well as administration of selective serotonin reuptake inhibitors (SSRI) or lithium, can also play a healing role after stroke by increasing neurogenesis. Neuroblasts, or neuronal precursors, depleted during ischemia, were restored in the dentate gyrus due to an enriched environment, suggesting that the environment has pathological implications for stroke patients (Matsumori et al., 2006). Captivatingly, SSRIs, which are primarily used to alleviate depression, were also found to alleviate the cognitive symptoms of ischemia by enhancing newborn cell survival (Li et al., 2009). This finding strongly supports the hypothesis that SSRIs,

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and other monoamine enhancers used for depression, act by enhancing hippocampal neurogenesis. Lithium, when taken prior to the onset of ischemia, both increases neurogenesis and enhances survival rate of new neurons (Yan, Hou, Wu, Liu, & Zhou, 2007). Lithium, being a pharmacological remedy for bipolar disease, which involves depressive episodes, may act in a similar manner to monoamine reuptake inhibitors, enhancing neurogenesis.

Elevated levels of glucocorticoids both increase susceptibility to stroke and exacerbate stroke outcome. A battery of self-report and case studies have supported a significant role of severe emotional stress, which would likely trigger glucocorticoid release, in the occurrence of stroke (DeVries et al., 2001). Furthermore, exposure to high levels of glucocorticoids prior to or during ischemia increases the amount of stroke-induced cell death (DeVries et al., 2001). Stress-induced stroke, therefore, has an unexpected positive effect on hippocampal neurogenesis, similar to that of acute seizure. There is a strong possibility, however, that subsequent, repeated strokes, if the patient survived, would eventually lead to reduced neurogenesis, similar to the pattern seen in epilepsy. Therefore, the stress-induced occurrence of stroke appears to be a promoter of neurogenesis, but this effect may be short lived.

Mechanism of Deterrence

Chronic stress overexposes the brain to corticosteroids and mineralocorticoids (Cameron & McKay, 1999; Dranovsky & Hen, 2006). This stress exposure has deleterious effects on the entirety of the hippocampus, but especially impacts the neurogenesis in the dentate gyrus (Dranovsky & Hen, 2006). During episodes of chronic stress, the hypothalamus, which sits at the base of the brain and serves as the brain's regulator of the body's endocrine system, releases Corticotrophin Releasing Factor (CRF) (Dranovsky & Hen, 2006). CRF proceeds to stimulate the pituitary gland, a processes hanging from the hypothalamus, triggering the release of Adreno-

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Corticotrophic Hormone (ACTH) (Dranovsky & Hen, 2006). In turn, ACTH stimulates the adrenal cortex of the adrenal glands, which are located on top of the kidneys (Dranovsky & Hen, 2006). Finally, the adrenal cortex releases adrenal steroids into the bloodstream (Dranovsky & Hen, 2006).

The hippocampus contains a dense population of adrenal hormone receptors, through which glucocorticoid and mineralocorticoid signaling directly deter hippocampal neurogenesis (Dranovsky & Hen, 2006; Synder et al., 2012). Adrenal steroids appear to have a regulatory effect on hippocampal neurogenesis from birth, as an adrenalectomy leads to increased cell proliferation throughout the brain during the early postnatal phase. Therefore, the detrimental effects of adrenal steroids in adulthood neurogenesis may just be residual from their regulatory role in infancy. Alternatively, inhibitory effects of adrenal signaling may serve the same regulatory role in adulthood as they did during the postnatal phase, keeping neurogenesis in check. The latter is improbable, however, because chronic stress has taxing effects on the body, and would not likely be required for proper regulation of neurogenesis.

Intriguingly, stimulation of NMDA receptors, which can either inhibit or excite neurogenesis, is necessary for adrenal steroids to deter proliferation (Dranovsky & Hen, 2006). It is likely that excitation of inhibitory NMDA receptors would facilitate this decrease in proliferation. NMDA regulation of steroid effects could be the key to the increased susceptibility to stress effects with age, as aging alters the expression of NMDA receptors (Magnusson, Brim & Das, 2010).

It is uncertain whether glucocorticoids inhibit neurogenesis directly or indirectly on a molecular level, but it is certain that mineralocorticoids act indirectly. Within the dentate gyrus, neuronal precursors and mature cells, but not immature cells, contain glucocorticoid receptors

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(GR), while mineralocorticoid receptors are located only on mature cells (Dranovsky & Hen, 2006). Accordingly, glucocorticoids may exert their effects on neuronal precursor cells directly, work through activation of other mature neurons, or both, while mineralocorticoids may only deter neurogenesis through the mediation of mature cells.

The hippocampus does not just receive stress signals from the hypothalamus, but sends signals in return, forming an inhibitory feedback loop (Dranovsky & Hen, 2006). Steroid stimulation of the hippocampus causes inhibitory afferent neurons to signal to the hypothalamus to slow the release of the CRH (Dranovsky & Hen, 2006). This feedback loop helps to keep stress in check as well as preserve the learning process, as not only neurogenesis, but also the survival and cell fate of hippocampal neurons is hindered by an overabundance of corticosteroids and mineral steroids (Dranovsky & Hen, 2006).

Neurogenesis levels are a key factor in this hippocampal-hypothalamic feedback loop. After moderate stress, glucocorticoid levels are slower to recover in neurogenesis deficient mice than in normal mice, suggesting that weak or deficient neurogenesis prolongs the chronic stress response, as opposed to inhibiting it, as it would when neurogenesis levels are normal (Snyder et al., 2012).

In contrast to the effects of glucocorticoids on the hippocampus, norepinephrine, a neurotransmitter released as a result of acute stress, actually facilitates neurogenesis. Acute stress upregulates neural proliferation in the SGZ, and lesions of the noreadrenergic input to the dentate gyrus leads to decreased hippocampal cell division (Snyder et al., 2012). Additionally, the hippocampus appears to mediate the acute stress response (Snyder et al., 2012). Neurogenesis deficient mice show an increase in food avoidance and behavioral despair, as well as a decrease in sucrose preference, indicating hedonia, when exposed to acute stress (Snyder et al., 2012).

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Therefore, the relationship between hippocampal neurogenesis and acute stress is a positive one, as norepinephrine boosts hippocampal neurogenesis, and neurogenesis supports a healthier stress response. Therefore, the deleterious effects of stress on the hippocampus are exclusive to chronic stress and elevated levels of adrenal steroids only.

Consequences of Deterred Neurogenesis

Since neurogenesis functions to promote spatial and episodic learning, and to regulate mood, deficient neurogenesis can result in depression and impaired learning. Therefore, reduction of hippocampal neurogenesis is likely the mechanism by which stress undermines mood and cognition, at least in part.

As the function and mechanism of hippocampal neurogenesis in learning, and cognition in relation to obstructed neurogenesis has already been elucidated, only the role of stress and neurogenesis in depression will be explored here.

Depression

Ample evidence suggests that depression is a stress-induced, at least in part, psychophysiological ailment. Depression is characterized by a depletion in hippocampal neurogenesis, as an increase in neurogenesis is required for antidepressants, including tricyclics and SSRIs, to exert behavioral improvements (Sahay & Hen, 2007). The behavioral improvements of antidepressant drugs were prevented when proliferation of progenitor cells was blocked via irradiation (Warner and Schmidt, 2006). SSRIs and Tricyclic drugs prevent the reuptake of serotonin and norepinephrine, two monoamines which are depleted in depressed patients, respectively (Dranozsky & Hen, 2006). Lesions to both the raphe nucleus and locus coeruleus, the sources of serotonin and norepinephrine, result in decreased neurogenesis

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(Dranozsky & Hen, 2006). Therefore, these monoamines are important upregulators of hippocampal neurogenesis.

Despite the necessity of hippocampal neurogenesis in alleviating depression, decreased neurogenesis is just one malady of the depressive state. Antidepressants also act on the prefrontal cortex, amygdala, nucleus accumbens, and the hypothalamus-pituitary-adrenal axis of the brain and neuroendocrine system (Sahay & Hen, 2008). This multifunctional drug action supports the finding that ablation of hippocampal neurogenesis alone is not enough to induce, or even increase susceptibility to, a depressive state (Sahay & Hen, 2008). To induce depression, ablation of hippocampal neurogenesis must be accompanied by a genetic predisposition as well as an environmental stressor (Sahay & Hen, 2008). Therefore, depression is much more than just a function of decreased hippocampal neurogenesis. Especially for those who find relief in antidepressants, however, ablated neurogenesis is a significant neurological factor contributing to the disorder.

Both stress and depression appear to elicit similar neurogenesis suppression mechanisms via alterations to GABA, BDNF and IL-1 signaling. Stressful events early in life predispose individuals to later bouts of depression, by inhibiting the developmental expression of GABA receptors, which are critical for upregulating neurogenesis, and maintaining a stable mood (Earnheart et al., 2007). Stress also lowers BDNF signaling, which is required for neural proliferation in the dentate gyrus, and the administration of antidepressants compensates for this decrease by increase BDNF signaling, (Dranozsky & Hen, 2006). Additionally, IL-1 inflammatory signaling, elicited by stress and characteristic of depression, suppresses neurogenesis (Goshen et al., 2008). Mice exposed to stress, with either ablated IL-1 receptors, or an administered IL-1 antagonist, did not show the signs of depression that the control group

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exhibited (Goshen et al., 2008). Taken as a whole, these results suggest that stress significantly contributes to depression, through the depletion of hippocampal neurogenesis.

Implications and Conclusions

Indirect, disease mediated stress, or direct glucocorticoid stimulation of the dentate gyrus generally has a strong inhibiting impact on neurogenesis. Due to its involvement in almost every dentate proliferation reducing psychological, physiological, and neuropathological concern, stress could be considered the primary etiological factor in reduced adult hippocampal neurogenesis. As healthy levels of neurogenesis play a critical role in preventing depression as well as facilitating spatial and episodic memory formation, understanding and further exploring how and why elevated glucocorticoid levels work to reduce neurogenesis is critical for mental and neuropathological well-being. Merely recognizing the impact that stress plays in one's mental health also has health facilitating implications.

The presence of glucocorticoids in the blood stream directly inhibit hippocampal neurogenesis, via the abundance of glucocorticoid receptors present on the dentate gyrus (Snyder et al., 2012). Therefore, things such as aging, long-term sleep disturbance or deprivation, or chronic mental perception of stress elevate levels of glucocorticoids and reduce neurogenesis, and undermine one's mental health and agility (Cameron & McKay, 1999; Guzman-Martin et al., 2007). Additionally, stress induced neuropathological issues including epilepsy and Alzheimer's disease can undermine neurogenesis (DeCarolis & Eisch, 2010; Kuruba et al., 2009). Exercise or an enriched, socially supportive environment can ameliorate effects of perceived chronic stress, aging, sleep deprivation, Alzheimer's disease, epilepsy, and possibly stroke by reducing levels of, or sensitivity to, glucocorticoids, thereby preserving cognition as well as mood (Nilsson et al., 1999; Pragg et al., 2005). Consequently, exercise, lifelong learning, a steady group of friends,

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and general attempts to minimize stress are critical for maintaining adult brain wellness. The impact of stress on neurogenesis should be further explored to reveal alternative remedies to be implicated after neurogenesis reduction has occurred, as this malaise has many neuropathological as well as everyday implications.

References

- Belz, E.E., Kennell, J.S., Czambel, R.K., Rubin, R.T., & Rhodes, M.E. (2003). Environmental enrichment lowers stress-responsive hormones in singly housed male and female rats. *Pharmacology Biochemistry and Behavior*, 76, 481-486.
- Bernaneu, R., & Sharp, F.R. (2000). NMDA and AMPA/Kainate glutamate receptors modulate dentate neurogenesis and CA3 Synapsin-I in normal and ischemic hippocampus. *Journal of Cerebral Blood Flow and Metabolism*, 20, 1669-1680.
- Bodnoff, S.R., Humphreys, A.G., Lehman, J.C., Diamond, D.M., Rose, G.M. & Meaney, M.J. (1995). Enduring effects of chronic corticosterone treatment on spatial learning, synaptic plasticity, and hippocampal neuropathology in young and mid-aged rats. *The Journal of Neuroscience*, 15(1), 61-69.
- Bracko, O., Singer, T., Aigner, S., Knobloch, M., Winner, B., Ray, J., Clemenson, G.D., Suh, H., Couillard-Despres, S., Aigner, L., Gage, F.H., & Jessberger, S. (2012). Gene expression profiling of neural stem cells and their neuronal progeny reveals IGF2 as a regulator of adult hippocampal neurogenesis. *The Journal of Neuroscience*, 32(10), 3376-3387.
- Cameron, H., & Gould, E. (1994). Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. *Neuroscience*, 61(2), 203-209.
- Cameron, H., McEwen, B., & Gould, E. (1995). Regulation of adult neurogenesis by excitatory input and NMDA receptor activation in the dentate gyrus. *The Journal of Neuroscience*, 15(6), 4687-4692.

STRESS & HIPPOCAMPAL NEUROGENESIS

Cameron, H., & McKay, R. (1999). Restoring production of hippocampal neurons in old age.

Nature Neuroscience, 2(10), 894-897.

Christensen, J., Li, J., Vestergaard, M., & Olsen, J. (2007). Stress and epilepsy: A population-

based cohort study of epilepsy in parents who lost a child. *Epilepsy & Behavior*, 11, 324-

328.

Clelland, C., Choi, M., Romberg, C., Clemenson, G., Fragniere, A., Tyers, P., Jessberger, S.,

Saksida, L.M., Barker, R.A., Gage, R.A., & Bussey, T.J. (2009). A functional role for

adult hippocampal neurogenesis in spatial pattern perception. *Science*, 325(5937), 310-

213.

DeCarolis, N.A., & Eisch, A.J. (2010). Hippocampal neurogenesis as a target for the treatment of

mental illness: A critical evaluation. *Neuropharmacology*, 58(6), 884-893.

Depue, R.A., & Collins, P.F. (1999). Neurobiology of the structure of personality: Dopamine,

facilitation of incentive motivation, and extraversion. *Behavioral and Brain Sciences*, 22,

491-569.

Devries, A.C., Joh, H., Bernard, O., Hattori, K., Hurn, P.D., Traystman, R.J., & Alkayed, N.J.

(2001). Social stress exacerbates stroke outcome by suppressing Bcl-2 expression. *PNAS*,

98(20), 11824-11828.

Dobrossy, M.D., Drapeau, E., Aourousseau, C., Le Moal, M., Piazza, P.V. & Abrous, D.N.

(2003). Differential effects of learning on neurogenesis: learning increases or decreases

the number of newly born cells depending on their birth rate. *Molecular Psychiatry*, 8,

974-982.

STRESS & HIPPOCAMPAL NEUROGENESIS

- Donovan, M.H., Yazdani, U., Norris, R.B., Games, D., German, D.C. & Eisch, A.J. (2006). Decreased adult hippocampal neurogenesis in the PDAPP mouse model of Alzheimer's disease. *The Journal of Comparative Neurobiology*, 495, 70-83.
- Dranovsky, A., & Hen, R. (2006). Hippocampal neurogenesis: Regulation by stress and antidepressants. *Biological Psychiatry*, 59, 1136-1143.
- Dupret, D., Fabre, A., Dobrossy, D., Panatier, A., Rodriguez, J., Lamarque, S., Lemaire, V., Olier, S.H.R., Piazza, P., & Abrous, D.N. (2007). Spatial learning depends on both the addition and removal of new hippocampal neurons. *PLoS Biology*, 5 (8), 1683-1694.
- Eckenhoff, M., & Rakic, P (1988). Nature and fate of proliferative cells in the hippocampal dentate gyrus during the life span of the rhesus monkey. *The Journal of Neuroscience*, 8(8), 2729-2747.
- Endo, Y., Nishimura, J., & Kimura, F. (1995). Impairment of maze in rats following long-term glucocorticoid treatments. *Neuroscience Letters*, 203, 199-202.
- Earnheart, J.C., Schweizer, C., Crestani, F., Iwasato, T., Itohara, S., Mohler, H., & Luscher, B. (2007). GABAergic control of adult hippocampal neurogenesis in relation to behavior indicative of trait anxiety and depression states. *The Journal of Neuroscience*, 27 (14), 3845-3854.
- Feng, R., Rampon, C., Tang, Y., Shrom, D., Jin, J., Kiyin, M., Sopher, B., Martin, G.M., Kim, S., Langdon, R.B., Sisodia, S.S., & Tsien, J. Z. (2001). Deficient neurogenesis in forebrain-specific Presenilin-1 knockout mice is associated with reduced clearance of hippocampal memory traces, *Cell Press*, 32, 911-926.

STRESS & HIPPOCAMPAL NEUROGENESIS

- Goshen, I., Kreisel, T., Ben-Menachem-Zidon, O., Licht, T., Weidenfeld, J., Ben-Hur, T., & Yirmiya, R. (2008). Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. *Molecular Psychiatry*, *13*, 717-728.
- Guzman-Marin, R., Bashir, T., Suntsova, N., Szymusiak, R., & McGinty, D. (2007). Adult hippocampal neurogenesis is reduced by sleep fragmentation in the adult rat. *Neuroscience*, *148* (1), 325-333.
- Guzman-Marin, R., Suntsova, N., Methippara, M., Greiffenstein, R., Szymusiak, R., & McGinty, D. (2005). Sleep deprivation suppresses neurogenesis in the adult hippocampus of rats. *European Journal of Neuroscience*, *22*, 2111-2116.
- Jin, K., Peel, A., Mao, X., Xie, L., Cottrell, B., Henshall, D., & Greenberg, D. (2004). Increased hippocampal neurogenesis in Alzheimers disease. *PNAS*, *101*(1), 343-347.
- Kuruba, R., Hattiangady, B., & Shetty, A.K. (2009). Hippocampal neurogenesis and neural stem cells in temporal lobe epilepsy. *Epilepsy Behavior*, *14*, 65-73.
- Li, W., Cai, H., Wang, B., Chen, L., Zhou, Q., Luo, C., Liu, N., Ding, X., & Zhu, D. (2009). Chronic fluoxetine treatment improves ischemia-induced spatial cognitive deficits through increasing hippocampal neurogenesis after stroke. *Journal of Neuroscience Research*, *87*, 112-122.
- Lie, D., Colamarino, S., Song, H., Desire, L., Mira, H., Consiglio, A., Lein, E.S., Jessberger, S., Lansford, H., Dearie, A.R., & Gage, F.H. (2005). Wnt signaling regulates adult hippocampal neurogenesis. *Nature*, *437*(27), 1370-1375.

STRESS & HIPPOCAMPAL NEUROGENESIS

- Liu, J., Solway, K., Messing, R.O., & Sharp, F.R. (1998). Increased neurogenesis in the dentate gyrus after transient global ischemia in gerbils. *The Journal of Neuroscience*, *18*(19), 7768-7778.
- Matsumori, Y., Hong, S.M., Fan, Y., Kayama, T., Hsu, C.Y., Weinstein, P.R., & Liu, J. (2006). Enriched environment and spatial learning enhance hippocampal neurogenesis and salvages ischemic penumbra after focal cerebral ischemia. *Neurobiology of Disease*, *22*, 187-198.
- Magnusson, K.R., Brim, B.L., & Das, S.R. (2010). Selective vulnerabilities of *N*-methyl-D-aspartate (NMDA) receptors during brain aging. *Frontiers in Aging Neuroscience*.
- Mirescu, C., Peters, J., Noiman, L., & Gould, E. (2006). Sleep deprivation inhibits adult neurogenesis in the hippocampus by elevating glucocorticoids. *PNAS*, *103* (50), 19170-19175.
- Meerlo, P., Mistlberger, R., Jacob, B., Heller, H., & McGinty, D. (2009). New neurons in the adult brain: The role of sleep and consequences of sleep loss. *Sleep Medicine Review*, *13* (3), 187-194.
- Morgan, R.J., & Soltesz, I. (2008). Nonrandom connectivity of the epileptic dentate gyrus predicts a major role for neuronal hubs in seizures. *PNAS*, *105*(16), 6179–6184.
- Nilsson, M., Perfilieva, E., Johansson, U., Orwar, O., & Eriksson, P. (1999). Enriched environment increases neurogenesis in the adult rat dentate gyrus and improves spatial memory. *Journal of Neurobiology*, *39* (4), 569-578.

STRESS & HIPPOCAMPAL NEUROGENESIS

- Palmer, T.D., Willhoite, A.R., & Gage, F.H. (2000). Vascular niche for adult hippocampal neurogenesis. *The Journal of Comparative Neurology*, 425, 479-494.
- Pragg, H., Shubert, T., Zhao, C., & Gage, F. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *The Journal of Neuroscience*, 25(38), 8680-8685.
- Quervain, D., Poirier, R., Wollmer, M.P., Grimaldi, L., Tsolaki, M., Streffer, J., Hock, C., Nitsch, R., Mohajeri, M.H., & Papassotiropoulos, A. (2003). Glucocorticoid-related genetic susceptibility for Alzheimer's disease. *Human Molecular Genetics*, 13 (1), 47-52.
- Rodriguez, J.J., Jones, V.C., Tanuchi, M., Allan, S.M., Knight, E.M., LaFerla, F.M., Oddo, S., & Verkhratsky, A. (2008). Impaired adult neurogenesis in the dentate gyrus of a triple transgenic mouse model of Alzheimer's disease. *PlosOne*, 3(8), 1-7.
- Sahay, A., & Hen, R. (2008). Hippocampal neurogenesis and depression. *Novartis Foundation Symposium*, 289, 152-160.
- Sahay, A., & Hen., R. (2007). Adult hippocampal neurogenesis in depression. *Nature Neuroscience*, 10 (9), 1110-1115.
- Salmon, P. (2001) Effects of physical exercise on anxiety, depression, and sensitivity to stress: A unifying theory. *Clinical Psychology Review*, 21(1), 33-61.
- Snyder, J., Soumier, A., Brewer, M., Pickel, J., & Cameron, A. (2012). Adult hippocampal neurogenesis buffers stress responses and depressive behavior. *Nature*, 476(7361), 458-461.

STRESS & HIPPOCAMPAL NEUROGENESIS

- Stone, S.S.D., Teixeira, C.M., DeVito, L.M., Zaslavsky, K., Josselyn, S.A., Lozano, A.M., & Frankland, P.W. (2011). Stimulation of entorhinal cortex promotes adult neurogenesis and facilitates spatial memory. *The Journal of Neuroscience*, *31*(38), 13469-13484.
- Tchantchou, F., Yanan, X., Yanjue, W., Christen, Y., & Luo, Y. (2007). EGb 761 enhances adult hippocampal neurogenesis and phosphorylation of CREB in transgenic mouse model of Alzheimer's disease, *The FASEB Journal*, *21*, 2400-2407.
- Tulving, E. (2002). Episodic memory: from mind to brain. *Annual Review of Psychology*, *53*, 1-25.
- Vgontzas, A.N. Bixler, E.O., Wittman, A.M., Zachman, K., Lin, H., Vela-bueno, A., Kales, A., & Chrousos, J.P. (2001). Middle-aged men show higher sensitivity of sleep to the arousing effects of corticotropin-releasing hormone than young men: Clinical implications. *The Journal of Clinical Endocrinology and Metabolism*, *86*(4), 1489-1495.
- Warner-Schmidt, J.L., & Dunman, R.S. (2006). Hippocampal neurogenesis: Opposing effects of stress and antidepressant treatment. *Wiley InterScience*, *16*, 239-249.
- Yan, X., Hou, H., Wu, L., Liu, J., & Zhou, J. (2007). Lithium regulates hippocampal neurogenesis by ERK pathway and facilitates recovery of spatial learning and memory in rats after transient global cerebral ischemia. *Neuropharmacology*, *53*, 487-495.