University of Nevada, Reno

Neurogenesis, Neuroplasticity, and the Treatment of Brain Disorder

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Abstract

Brain disorders affect 2.4 billion individuals around the world (Worldometers, 2013). Many brain disorders such as stroke, Alzheimer's, and Parkinson's disease are characterized by the loss of functioning neurons (National Institute on Aging, 2014). The ability to generate new neurons (neurogenesis) represents a potential opportunity to create effective, targeted treatment for these patients. Until the 1960s it was not believed that neurogenesis could occur in the adult brain (Reynolds & Weiss, 1992). Since that time a multitude of research has been done regarding the causes of neurogenesis and neuroplasticity, but very little in the way of effective treatments for adult humans have resulted (Hannan, 2014). Current research into potential neurogenesis related treatments has focused primarily on the creation of drugs, but other options may be feasible for implementation now. Extensive literature review and interviews with practicing neurologists allow for the proposition of potentially effective neurogenesis relevant treatments for brain disorders, namely enriched environment and restricted diet.

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Introduction

Neuroplasticity refers to the ability of the brain to reorganize a given function over time, and is believed to be the basis of such important functions as learning and memory (Jones & Kleim, 2008). An important component of neuroplasticity is neurogenesis, or the ability of the brain to produce more neurons as needed (Kazanis, 2013). For the purposes of this thesis, a brain disorder refers to a disease or injury that physically affects neurons. The brain disorder either destroys neuronal tissue, (Berryhill, 2013), or alters the neurons so that those neurons no longer function in a typical fashion, (Lehmann, Brachman, Martinowich, Schloesser, & Herkenham, 2013). In disorders such as depression, this dysfunction is thought to be caused by a disruption in neurotransmitter functions (Blier, 2013), while in disorders such as stroke, neuronal tissue is lost (Zheng et al., 2013). The definition of a brain disorder is therefore broad, but this broadness is what makes the potential application of neurogenesis and neuroplasticity treatments so important and appealing as these treatments have the potential to function on a similarly broad level. Although naturally occurring plasticity in the nervous system may or may not result in improved function, the goal of neuroplasticity treatments is to improve or restore what has been lost (Zheng et al., 2013; Lehmann, Brachman, Martinowich, Schloesser, & Herkenham, 2013; Blier 2013).

One avenue for restoring function in patients with brain disorders is neurogenesis. There is solid evidence that neurogenesis occurs in the adult mammalian brain, and that these new neurons and the ability to produce them can persist well into old age (Rakic, 2002). The evidence for neurogenesis is mainly restricted to the hippocampus and olfactory bulb, but current research has revealed that other parts of the brain, including

the cerebellum, may be involved as well (Ponti, Peretto, & Bonfanti, 2008). These results indicate that neurogenesis has the potential to aid in the treatment of brain disorders that occur in a variety of locations in the brain, and in patients of various ages. For the purposes of this thesis, the focus will be on adult patients. Adult patients were chosen as they have had the least amount of research done with regards to the use of neurogenesis and neuroplasticity related treatments (Bellenchi, Volpicelli, Piscopo, Perrone-Capano, & di Porzio, 2013).

Despite the large body of research into neuroplasticity, very little has been done to utilize the results obtained from neuroplasticity studies to formulate treatments for adult patients with brain damage (Hannan, 2014). Although extensive research has been done to determine the role of neuroplasticity in addiction (Olsen, 2011), mood disorders (Drevets, 2004), and stroke (Font, Arboix & Krupinski, 2010), conditions that stand to benefit the most from the development of novel treatments, these studies have not translated into applied therapies, even though researchers (including Olsen, 2011, Drevets, 2004, and Font, Arboix & Krupinski, 2010) suggest that increased understanding of neuroplasticity should be applied to the formulation of treatments for humans.

This thesis aims to bridge the gap between research on neurogenesis, neuroplasticity and treatments of brain disorders in adults, and to propose potential practical application of therapies that could conceivably be implemented at the current time to treat these brain disorders, specifically enriched environment and diet. Three main objectives will be undertaken: 1) to identify and explain the historical context and knowledge of neuroplasticity, and to demonstrate how this knowledge has shaped the ideas about the workings of the brain and the treatment of brain disorders; 2) to review

current research in neuroplasticity and its implications in the understanding of the human brain; and 3) to discuss how current research into neuroplasticity could be applied to the treatment of brain disorder patients, and how research and treatment modalities should be altered for better patient outcomes. Potential treatments are identified through literature research, as well as from discussions with several neurologists from The Cleveland Clinic in Las Vegas, who specialize in treating brain disorders.

The significance of determining potential treatments for these brain disorders is staggering. It is estimated that one in three people, or approximately 2.4 billion individuals (Worldometers, 2013), will suffer from a brain disorder sometime in their life (One Mind for Research, 2013). Any treatment that has the potential to improve the outcome for these individuals will have an immensely beneficial impact on their lives. Current research has identified several methods shown to improve neuroplasticity and associated neurogenesis such as exercise (Ruan et al., 2013; Winter et al., 2007) and enriched environment (Hannan, 2014; Laviola, Hannan, Macri, Solinas, & Jaber, 2008). These improvements appear to lead to improved functional results in animal models. Furthermore, all the treatment approaches that may be applicable to humans are identified by the neurologists interviewed as being implementable from a practical standpoint. These treatment approaches include using an enriched environment, and components of an enriched environment such as exercise and tactile stimulation to promote neurogenesis, as well as diet changes. These options are particularly appealing as potential treatments due to their ease of implementation, widespread availability, and relatively low cost.

Historical Context

For decades, scientists generally believed that the adult brain is "hard-wired" and that once the adult is past a certain age, no new cells were generated, and the brain could not significantly change (Kazanis, 2013; Colucci-D'Amato, Bonavita, & di Porzio, 2006). Thus, if an adult were to lose his or her sight the visual cortex would go dark as well. Studies such as those performed by Hubel and Wiesel (1970), who demonstrated that ocular dominance columns in the lowest neocortical visual area, V1, were largely immutable after the critical period in development, reinforced the idea that brain plasticity was possible only during early development. This belief dates back to the earliest days of Neurology, when the Nobel-prize winning histologist Ramon y Cajal stated, 'Once development was ended, the fonts of growth and regeneration of the axons and dendrites dried up irrevocably' in the 19th century (Colucci-D'Amato, Bonavita, & di Porzio, 2006).

It is widely accepted now that brain plasticity occurs beyond this critical period (Bellenchi et al., 2013). Merzenich outlined one of the first experiments that demonstrated this adult plasticity during interviews with his biographer (D. Boulton, 2004, Interview with M. Merzenich). Merzinch’s first encounter with adult plasticity came when he was engaged in a postdoctoral study. They observed that in the brain when one peripheral nerve was cut the nerve subsequently regenerated. The scientists micro-mapped the hand maps of monkey brains before and after cutting a peripheral nerve and sewing the ends together. Afterwards, the hand map in the brain that was expected to be jumbled was nearly normal (Merzenich et al., 1983). Merzenich asserted that "if the brain map could normalize its structure in response to abnormal input, the prevailing view that

we are born with a hardwired system had to be wrong. The brain had to be plastic" (D. Boulton, 2004, Interview with M. Merzenich).

Perhaps the first evidence that adult neurogenesis was possible occurred in the 1960s, when evidence of neurogenesis was found in brains of adult rats with lesions (Altman, 1962). Even with this evidence, the debate continued until the early 1990s. Most researchers agree that the issue was finally settled in 1992 when researchers showed that isolated adult mammalian neural cells could undergo neurogenesis (Banks, Bernick, Cummings, & Le, 2014, personal interview; Banks, Bernick, Cummings, & Le, 2013, personal interview; Kazanis, 2013; Reynolds & Weiss, 1992).

Although neurologists now agreed that adult neurogenesis was possible, many believed that it occurred only in certain areas of the brain; specifically the hippocampus and olfactory bulbs (Belzung & Wigmore, 2013). Neurogenesis in these areas has been shown in multiple species and in multiple situations. Birds have been shown to have neurogenesis in the hippocampus related to food-caching over the winter (Pravosudov & Clayton, 2002), and increases in the size of the human hippocampus has been demonstrated in individuals that perform complex memory and spatial tasks routinely (Maguire et al., 2000), and rats have demonstrated neurogenesis in the olfactory bulb after lesions (Kazanis, 2013)

Neuroanatomical and neurophysiological studies have changed this picture substantially over the last twenty years. Importantly, plasticity has been demonstrated not only in the brains of children, adolescents, and younger adults, but also in middle-aged adults and more recently in the elderly. For instance, elderly patients who were taught to juggle showed an increase in gray matter in certain parts of the brain using voxel based

morphometry (Boyke, Driemeyer, Gaser, Buchel, & May, 2008). Functional magnetic resonance imaging (fMRI) is being widely used to study recovery of function in patients with several neurologic conditions, including Alzheimer's, multiple sclerosis, and stroke. FMRIs have demonstrated cortical changes occurring after injuries of different etiologies to the central nervous system. These changes appear to be limited to the extent of damage but can greatly contribute to the limitations of clinical consequences of brain damage. Conversely, the failure of the brains plastic properties of the cerebral cortex may be responsible for the accumulation of "fixed" neurological deficits (Filippi, & Rocca, 2006).

Mechanism of Neurogenesis

Neurogenesis and neuroplasticity have now been shown throughout the adult human brain (Alvarez-Buylla, Garcia-Verdugo, & Tramontin, 2001; Gage, 2000; McKay, 1997). The mechanisms for how neurogenesis and neuroplasticity occur are not fully understood. Two main theories have been presented (figure 1). The first (theory A) is that very early in humans' embryonic development two pools of stem cells arise from the neuroepithelium, one to make glial cells and one to make neuronal cells. The second theory (theory B) states that only one type of progenitor stem cell is needed. Under the influence of currently unknown factors this stem cell produces radial glial cells and then astrocytes. Along this path the cell may instead be shunted into a glial or a neuron cell (Alvarez-Buylla, Garcia-Verdugo, &Tramontin, 2001).

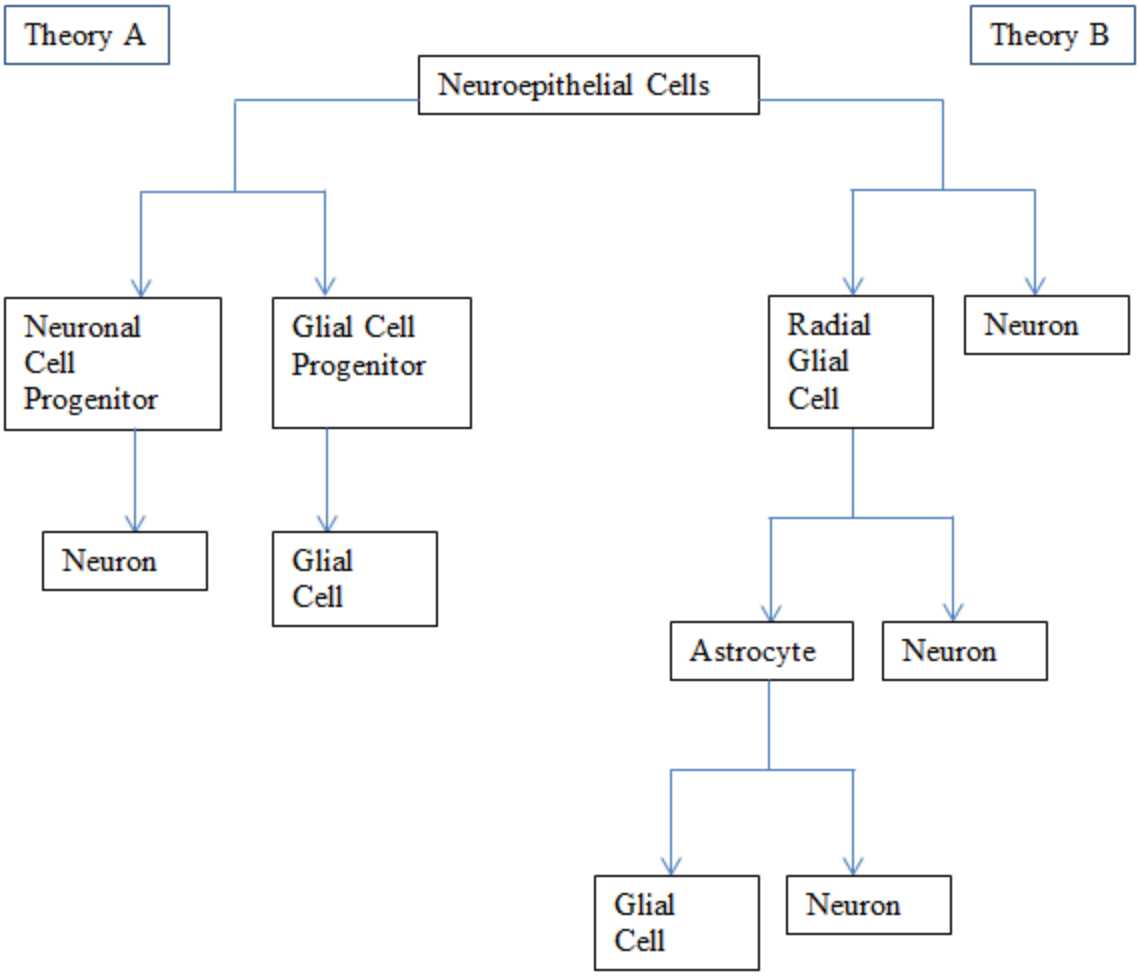

Figure 1. Diagram of the two common theories of neurogenesis in the adult mammalian brain (Alvarez-Buylla et al., 2001). Theory A states that early in embryonic development committed glial and neuronal progenitors are created, and all neurons and glial cells originate from these progenitors. Theory B states that neuroepithelial cells differentiate into radial glial cells and then astrocytes, while retaining the ability to become neurons at any step.

While this thesis is focused on the production of neurons as the functional unit of brain function and neuroplasticity, it is important to note that neurogenesis also has the potential to increase other necessary cells in the brain, which may aid brain function after brain disorders.

Mechanism of Neuroplasticity

There appear to be three major kinds of neuroplasticity that occur in the mammalian brain: neurologists refer to these as homologous area adaptation, cross-modal reassignment, and map expansion (Grafman, 2000). Briefly, homologous area adaptation occurs most commonly in children and adolescents, and involves the shifting of a function from one area of the brain to a corresponding similar area, usually after injury (Chugani, Muller, & Chugani, 1996). For instance, if an area of the brain that affects speech is damaged in the left hemisphere, this function may be moved to the same area of the brain in the right hemisphere. Homologous area adaption is thought to be quite rare, and exact figures regarding occurrence are not known.

Cross-modal reassignment involves the use of areas of the brain that have not previously been receiving input being modified to receive input and is often seen in patients with certain sensory deficits such as blindness. For instance, patients who have been blind since birth or very early childhood have visual cortices that receive little if no input from the visual system. However, scans of the brain while reading braille show brain activity in these visual cortex areas (Cohen et al., 1997).

Map expansion refers to the ability of an area of the brain to expand in response to its needs. For example, a larger hippocampus has been linked through extensive research to a greater memory. In London cab drivers, who must memorize a complex city and multiple alternate routes to each destination, the hippocampus is enlarged compared to control subjects (Maguire et al., 2000). Stringed instrument players show a larger right motor area, which is thought to be linked to their critical use of their left hand while playing (Bangert & Schlaug, 2006).

For the purpose of creating treatments based on neuroplasticity, map expansion is the form of neuroplasticity this thesis is focused on. Underlying map expansion is neurogenesis, which can be influenced and controlled. Though homologous area adaptation, cross-modal reassignment may also be influenced by various interventions, it is not currently clear how. However there is a correlational link between map expansion and neurogenesis (Belzung & Wigmore, 2013).

Three Common Brain Disorders: Alzheimer's disease, Parkinson's disease, and Stroke. Who do they impact and how do they affect the Brain?

The exact mechanism for each brain disorder is often different, however the end result is the same; the destruction of brain tissue. Brain disorders include some very common and well known disorders such as Alzheimer's disease, Parkinson's disease, and stroke. Brain disorders are problematic when the loss of brain tissue causes a resulting loss of function. Although it would be impractical to review all possible brain disorders, an overview of some common problems is helpful for understanding, and to clarify the need for the types of neurogenesis and neuroplasticity targeted treatments this thesis outlines.

Alzheimer's affects approximately 20 percent of individuals over the age of 75. Over the age of 85 this number jumps to 40 percent. It is estimated that 5 million Americans have Alzheimer's disease and is the leading cause of dementia among people over 60. Alzheimer's is defined as "a degenerative brain disease of unknown cause that is the most common form of dementia, that usually starts in late middle age or in old age, that results in progressive memory loss, impaired thinking, disorientation, and changes in personality and mood, that leads in advanced cases to a profound decline in cognitive and

physical functioning, and that is marked histologically by the degeneration of brain neurons especially in the cerebral cortex and by the presence of neurofibrillary tangles and plaques containing beta-amyloid" (Merriam-Webster Medical Dictionary, 2014). Alzheimer's is characterized by memory loss, forgetfulness, a decline in cognitive abilities, and eventually the inability to perform tasks of everyday living (National Institute on Aging, 2014). Alzheimer's is characterized by a loss of neurons, specifically in the hippocampus (Alzheimer's Association, 2014). As the hippocampus is one area of the adult human brain where neurogenesis is particularly active, the fact that many of the negative symptoms associated with Alzheimer's is due to a loss of neurons in the hippocampus makes Alzheimer's an ideal target for treatments based on neurogenesis.

The exact cause of Alzheimer's disease is not known, which is one of the reasons why effective treatments or a cure for the disease has yet to be developed. Figure 2 shows a comparison between a healthy (neuro-typical) brain and a brain affected by Alzheimer's.

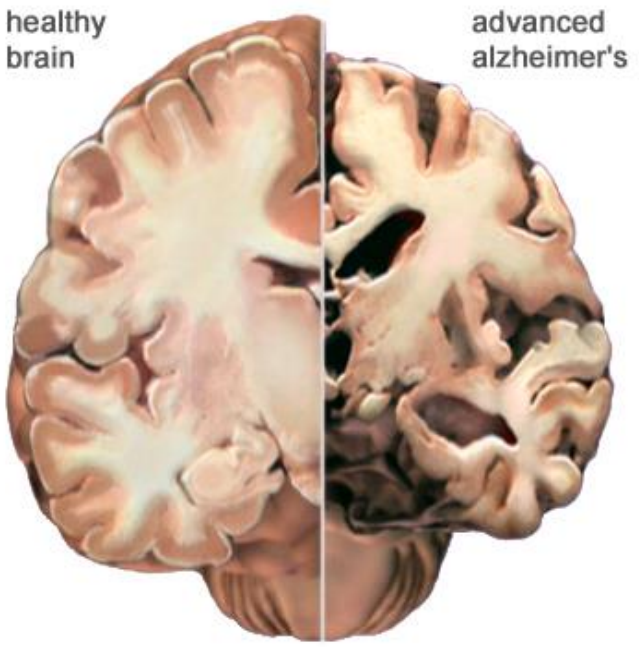

Figure 2. Image of a healthy brain compared to a brain affected by Alzheimer's brain. The Alzheimer's brain shows a loss of overall brain mass, a shriveled appearance, and an enlargement of the ventricles, all of which may be attributed to loss of neurons and neurons and neural tissue. This image is used with permission from http://www.alz.org/braintour/healthy_vs_alzheimers.asp ©2014 Alzheimer's Association. www.alz.org. All rights reserved. Illustrations by Stacy Jannis

Parkinson's disease is defined as" a chronic progressive neurological disease chiefly of later life that is linked to decreased dopamine production in the substantia nigra and is marked especially by tremor of resting muscles, rigidity, slowness of movement, impaired balance, and a shuffling gait" (Merriam-Webster Medical Dictionary, 2014). Parkinson's is also characterized by a loss of neurons, specifically those related to movement. Figure 3 shows the loss of neurons in the substantia nigra that is seen in Parkinson's patients. Parkinson's disease affects approximately 60 thousand Americans each year (National Institute of Health, 2014). Patients affected with Parkinson's experience difficulties with movement and tremors that eventually impair their ability to perform everyday activities. There is no cure for Parkinson's, and no effective long-term

treatments. Neurogenesis and neuroplasticity targeted treatments are potentially especially suited for these patients, as it is known that a primary cause of the disease is a loss of specific neurons. Replacing these neurons could be an effective treatment.

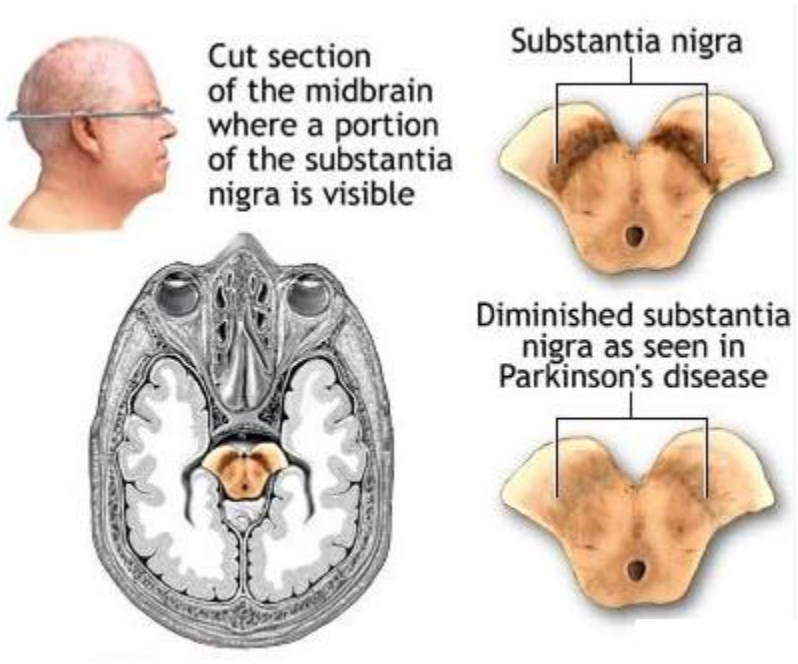

Figure 3. An image showing of the loss of neurons in the brain of Parkinson's disease patients. The loss of color is due to the loss of dopaminergic neurons in the substantia nigra. http://www.healthcentral.com/ency/408/guides/000051_1.html

Stroke is occurs when the "blood supply to part of your brain is interrupted or severely reduced, depriving brain tissue of oxygen and food. Within minutes, brain cells begin to die" (Mayo Clinic, 2014). The disruption of blood flow may be due to a block in a blood vessel that prevents blood from reaching the area or a hemorrhage (figure 4), but with either mechanism the result is the loss of brain tissue (figure 5). A stroke affects the patient differently depending on what area of the brain is destroyed. In the United States, stroke is the fourth leading cause of death and a major cause of disability. There are

approximately 7 million stroke survivors in America, living with various degrees of disability (National Stroke Association, 2009).

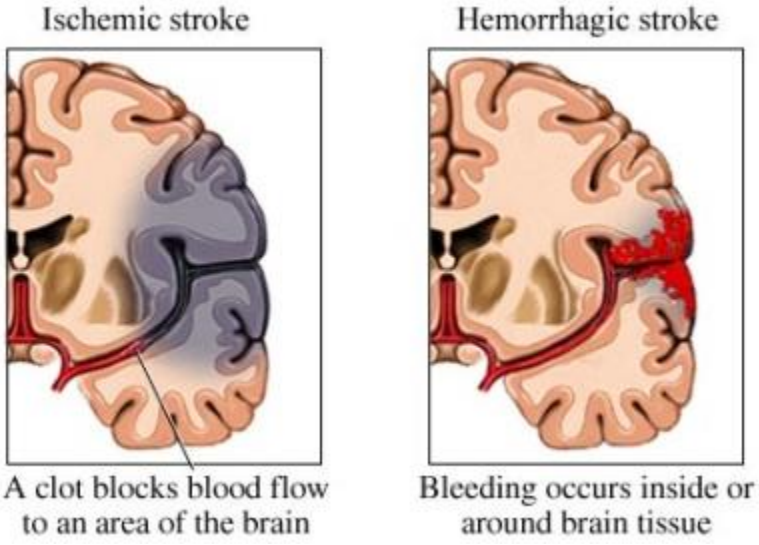

Figure 4. The two caused of strokes. Both types of stroke result in the death of brain tissue (shown in gray).

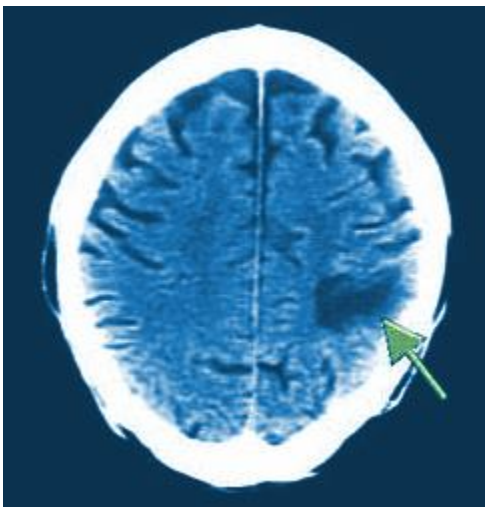

Figure 5. A CT image of the brain of a stroke victim. The arrow points to the area of the brain that has been destroyed by the stroke. http://www.strokecenter.org/patients/stroke-diagnosis/imaging-tests/ct-scan/

Current Treatments for Alzheimer's disease, Parkinson's disease, and Stroke

Medicine currently has no widely used treatments that target the underlying causes of many brain disorders, including Alzheimer's disease, Parkinson's disease, and Stroke. There is no specific treatment for patients after a stroke has occurred, beyond supportive, symptom specific treatments such as speech therapy for difficulty speaking (Banks, Bernick, Cummings, & Le, 2014, personal interview; Banks, Bernick, Cummings, & Le, 2013, personal interview).

Alzheimer's Disease

Alzheimer's is treated with two main classes of drugs: cholinesterase inhibitors, and glutamate regulators. Cholinesterase inhibitors include Aricept, Exelon, and Razadyne. These medications work by inhibiting the breakdown of the neurotransmitter acetylcholine, which is implicated in learning and memory though its function is not fully understood. Side effects of cholinesterase inhibitors include nausea, vomiting, loss of appetite, and increased frequency of bowel movements. These medications work on approximately 50 percent of patients, and when the medications do work they only delay the worsening symptoms for six months to a year before the medications become ineffective. Why the medications become ineffective is thought to be linked to the loss of neurons (Banks, Bernick, Cummings, & Le, 2014, personal interview; Banks, Bernick, Cummings, & Le, 2013, personal interview; Alzheimer's Association, 2012).

Namenda is the only approved glutamate regulating medication that is used to treat Alzheimer's. Glutamate is a neurotransmitter that is linked to memory and learning, though its exact function is not well understood. The effectiveness of Namenda is on par with the cholinesterase inhibitors, in that it works for approximately half of the

individuals taking it, and then only for a short time. The side effects of Namenda include headaches, constipation, confusion, and dizziness (Banks, Bernick, Cummings, & Le, 2014, personal interview; Banks, Bernick, Cummings, & Le, 2013; Alzheimer's Association, 2012).

The other currently approved medications focus on symptoms that are related to the diagnoses of Alzheimer's, namely conditions such as depression, anxiety, insomnia which are very common in patients with Alzheimer's. According to the neurologists interviewed, these are treated on a symptom by symptom basis with a variety of medications such as antidepressants and sedatives (Banks, Bernick, Cummings, & Le, 2014, personal interview; Banks, Bernick, Cummings, & Le, 2013; Alzheimer's Association, 2012). These additional medications carry their own risks; selective serotonin reuptake inhibitors (SSRIs) such as Fluoxetine are routinely given to patients to minimize depressive symptoms. Relatively few studies have been done regarding the use of SSRIs in brain disorder patients, but one study is particularly worrying. Kieth et al. (2007) demonstrated a decrease in rats' recovery regarding spatial memory tasks when they were given fluoxetine after a hippocampal lesion compared to untreated rats with the same lesion.

Parkinson’s Disease

Parkinson's disease may be treated with a multitude of medications; however, similar to Alzheimer's medications, they are usually effective only for a short period of time. These medications include L-Dopa, dopamine agonists, MAO-B inhibitors, Catechol O-methyltransferase (COMT) inhibitors, and anticholinergics (Mayo Clinic,

2014; Banks, Bernick, Cummings, & Le, 2014, personal interview; Banks, Bernick, Cummings, & Le, 2013, personal interview).

L-Dopa is a precursor to dopamine and is converted to dopamine once in the brain. As Parkinson's destroys the dopaminergic neurons and thus reduces dopamine, L-Dopa serves to improve symptoms by increasing dopamine. The effectiveness of L-Dopa declines as the disease progresses, and the neurons available to respond to the dopamine decrease. COMT inhibitors are given to augment the effects of L-Dopa by blocking an enzyme that breaks down dopamine. Dopamine agonists also affect the dopamine pathways by mimicking the effects of dopamine and activating the same neurons (Banks, Bernick, Cummings, & Le, 2014, personal interview; Banks, Bernick, Cummings, & Le, 2013, personal interview).

MAO-B inhibitors work by inhibiting the brain enzyme monoamine oxidase B (MAO-B). The MAO-B enzyme metabolizes brain dopamine, so inhibiting its function increases the dopamine available in the brain. These medications can cause nausea, headaches, and increased risk of hallucinations. They also prevent the patient from taking medications for depression and pain, symptoms often seen in Parkinson's patients, as these medications have potentially serious interactions (Banks, Bernick, Cummings, & Le, 2014, personal interview; Banks, Bernick, Cummings, & Le, 2013, personal interview).

Parkinson's disease may also be treated with deep brain stimulation, a surgical intervention in which an electrode is inserted into the brain and connected to a generator that is implanted in the chest. This expensive and invasive procedure has the potential for many complications, so deep brain stimulation is used only when L-Dopa and other

medications have failed. Deep brain stimulation is most effective at stabilizing tremors. Deep brain stimulation does not halt the progression of the disease (Mayo Clinic, 2014).

Stroke

Though we understand for the most part what causes a stroke, the only options for treatment currently are rehabilitation programs based on patient's specific symptoms. For instance, patients with strokes that have occurred in the area of the brain responsible for speech often show speech deficits, which may be treated with visits to speech therapists. Problems walking due to strokes in motor control areas are treated with compensatory physical therapy, and walking aids such as canes and walkers (Banks, Bernick, Cummings, & Le, 2013, personal interview).

If an individual having a stroke can be diagnosed and treated in an Emergency Room within four hours of stroke onset then there are some surgical options depending on exactly how the stroke is occurring, such as an angioplasty to remove clots. The administration of tissue plasminogen activator (tPA) also removes blood clots. By removing these clots blood flow, and thus oxygen and nutrient flow, in the brain is restored, preventing further tissue damage. No current stroke treatments affect the tissue that has already been destroyed prior to intervention (Banks, Bernick, Cummings, & Le, 2013, personal interview).

Why Can Neurogenesis and Neuroplasticity offer Better Treatments for Brain Disorder Patients?

An effective neurogenesis/neuroplasticity related treatment would do more than just mediate the symptoms of brain disorders; it may solve the problem by replacing the neurons that were lost. Aside from potentially replacing neurons destroyed by brain

disorders, neurogenesis and neuroplasticity have the potential to be helpful to brain disorder patients in other ways. Although there are many specific, experimental positive correlations seen between neurogenesis, neuroplasticity, and function to be discussed in the treatment section, experiments examining the use of stem cell therapies provides insight into the effectiveness of neurogenesis by demonstrating the benefits of nonspecific additions of neurons.

The majority of research examining the benefits of stem cells and brain disorders has focused on Parkinson's disease. Human embryonic mesencephalic tissue transplants, which are rich in neuroblasts, have demonstrated the effectiveness of neuronal replacement in Parkinson's disease patients. In these patients the neuroblasts formed dopaminergic neurons that reinnervate the affected striatum areas, integrated fully, and maintained a regulated dopamine release. Patients showed a marked clinical improvement and the most improved were able to discontinue L-Dopa and live independently again. Even more tellingly, there was a direct correlation between the number of successfully grown dopaminergic neurons and symptom relief (Lindvall & Bjorklund, 2011; Lindvall & Kokaia, 2010).

Methods for Identifying Proposed Treatments

To examine treatments and ideas an extensive literature review of peer-reviewed journal articles was completed. As this thesis aims to identify treatments that could be currently implemented, this review focused on studies that produced the most beneficial results with the most practical and applicable methods. The review was also strongly guided by the neurologist interviews, whose extensive experience in treating patients with

brain disorders allowed them to judge what types of treatments are likely to be acceptable to patients, and relatively easily implemented by the largest number of people.

Four practicing neurologists from the Cleveland Clinic Lou Ruvo Center for brain health in Las Vegas, Nevada were interviewed. They were selected due to their extensive knowledge and practical experience in the treatment of brain disorders. The mission of Cleveland Clinic is "the pursuit of more effective treatments for brain diseases" (Cleveland Clinic, 2014), so these neurologists are uniquely suited for discussions about how current research and understandings of neurogenesis and neuroplasticity may be used to modify treatment options for patients with brain disorders. These physicians were also chosen in part due to their willingness to review and discuss proposed treatment options. Preliminary requests concerning interviews or questionnaire completion made to over twenty other practicing neurologists prior to this thesis were answered negatively or not at all.

The technique of qualitative interviews that was performed with the neurologist is utilized often in many fields such as sociology and psychology. It is also gaining more and more acceptance in medical fields (Gill, Stewart, Treasure, & Chadwick, 2008). It is argued that these types of interviews provide a more nuanced and deeper understanding into the topic being discussed than can be obtained from purely qualitative methods such as standardized questionnaires.

Current Research on using Neurogenesis and Neuroplasticity for the Treatment of Brain Disorders

Much of the current research into neurogenesis and neuroplasticity have focused on the effects of increasing neurogenesis and neuroplasticity in the brains of both healthy

animals and animals with various brain disorders (for example see Kazanis, 2013; Ruan et al., 2013; Taupin, 2006). Very few studies have been conducted that look at applying this knowledge to the treatment of brain disorders in humans, even though most studies agree that this application is the next logical step. Those studies that are underway focus almost entirely on the use of drugs to target neurogenesis, with few exceptions such as the use of electrical stimulation. Some of the most promising treatments currently being researched include the use of electrical stimulation, nicotine, and Inosine (Adkins, Hsu, & Jones, 2008; Adkins, Boychuk, Remple, & Kleim, 2006;).

The use of electrical stimulation holds promise in particular for enhancing behavioral recovery following a stroke. Studies in rats with infarcts on the sensorimotor cortex indicate that the efficacy of rehabilitation of motor functions is proved by coupling it with cortical stimulation through electrodes positioned over peri-infarct areas (Adkins, Boychuk, Remple, & Kleim, 2006). First the minimum amount of current to elicit movement is found by placing the electrodes and passing increasing amounts of current through the electrodes until movement occurs. Finding the correct electrode location and current required is an important step as it allows the researcher to determine if the electrode is in a viable location and is capable of performing the desired forelimb movement. Current at a sub-threshold level is then given during daily training of behavioral tasks requiring skilled forelimb usage. The details as to the underlying neural causes of functional effects are not well known. Research suggests that there is an increase in the surface density of layer V dendritic processes, and a greater density of synapses with multisynaptic buttons (Adkins, Hsu, & Jones, 2008). This increase in neuronal dendrites and multisynaptic buttons is a feature of neuroplasticity, indicating

that electrical stimulation is capable of producing neuroplasticity (Adkins, Boychuk, Remple, & Kleim, 2006).

From a pharmacological standpoint, various studies have looked at the effects of stimulants on recovery from brain injury, often with mixed results (for example Wagner & Zitelli, 2013; Gonzalez et al. 2005). One of the more promising and immediately applicable results seen is in relation to nicotine. Gonzalez et al. (2005) showed significant improvement in skilled forelimb movements in adult rats that were positively correlated with changes in dendritic length and spine density. The increase in dendritic length and spine density indicates that nicotine caused growth and changes in these neurons that are linked to neuroplasticity (Grundey et al., 2012a, 2012b). Nicotine can be given in slow-release nicotine patches already available, a benefit of nicotine as a potential treatment. If clinical trials show nicotine treatment to be applicable to humans, the treatment is already available widely and relatively cheaply. Unexpectedly, nicotine exposure prior to cerebral injury negates the effect. This severely limits the proportion of people that may be aided by this treatment. Also, although animals treated with nicotine showed an initial improvement in skilled forelimb movement, they seem to have impaired new motor skill learning, an important potential problem (Gonzalez et al. 2005).

Inosine, a purine nucleoside currently undergoing trials, is a promising pharmacological intervention that produces improvements equal to that of enriched environment animals (Smith et al., 2007). Rats with traumatic brain injury in the area of the sensorimotor cortex that controls forelimb function were given Inosine or placed in an enriched environment. The rats' motor skills were tested using the staircase test, limb-use asymmetry test, tapered beam, and ladder walking test. In particular, the staircase test

tests skilled forelimb movement, as it involves reaching and grasping food pellets at increasing reaching difficulty, and requires corticospinal neurons to perform (Kolb, 2013; Smith et al., 2007). A rat's performance on the staircase test is positively correlated to neurogenesis and neuroplasticity as the uninjured corticospinal neurons axons grew through the midline and into the damaged territory. The more this axon growth occurred, the better the functional recovery. Rats receiving Inosine or placed in enriched environment had five times the amount of corticospinal neuron axon growth compared to controls. Although the enriched environment group recovered more quickly, after 28 days there was no functional difference between the two sets of animals in skilled forelimb movement (Smith et al., 2007).

Why the majority of studies looking at the treatment of brain disorders in current research are focused on drug therapies instead of alternate treatments that have been shown to be effective is an area of speculation that is outside the scope of this thesis, however it is important to note that drug therapies take years to develop and approve, and currently are producing mixed results in patient outcomes. There are treatment options that are available on a widespread, relatively cheap basis, right now.

Potential Treatment Options

Enriched Environment

The standard definition of an enriched environment is “a combination of complex inanimate and social stimulation” (Rosenzweig, Bennett, Hebert, & Morimoto, 1978). The components of an enriched environment from an experimental standpoint include larger living spaces with more opportunities for play and exercise. An important component of an enriched environment is the opportunity to encounter multiple forms of

stimuli including visual, auditory, and tactile stimuli (Laviola et al., 2008). An example of enriched environment in animal studies is shown in figure 6.

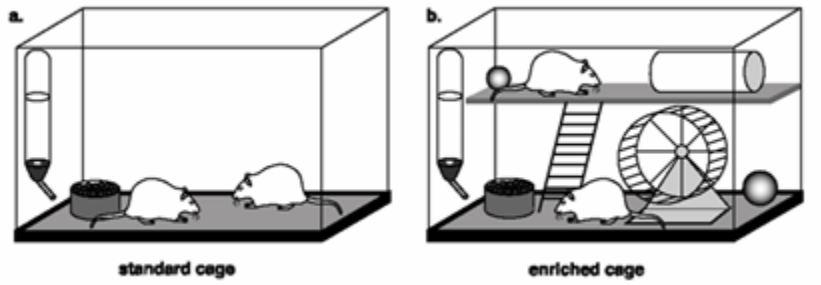

Figure 6. A standard cage (a) compared to an enriched cage (b). The enriched cage offers more usable space, a varity of toys for stimulation, and the running wheel for voluntary exercise. http://science.education.nih.gov/supplements/nih4/self/guide/info-brain.htm

Above all other proposed treatment options an enriched environment appears to cause the largest increase in neurogenesis and neuroplasticity, and to have the largest impact of performance of animals with brain disorders (Smith et al., 2007). For instance, Inosine was identified by the neurologists interviewed as the most promising drug for brain injuries on the horizon (Banks, Bernick, Cummings, & Le, 2014, personal interview; Banks, Bernick, Cummings, & Le, 2013, personal interview). Comparing the growth of new neurons and the increase in complexity of existing neurons in rats who were placed in enriched environment or given Inosine found that those in an enriched environment recovered functionality faster, and showed more neuron growth and plasticity than those that received Inosine (Smith et al., 2007). Reviews of studies done in wild-type rats show that the most effective was to change both brain and behavior is to place the rats in an enriched environment for a month or longer (for example Hannan, 2014; Jones & Kleim, 2008). Environmental enrichment has been shown to improve neurogenesis and

neuroplasticity in rodent models that have been affected by stroke, Parkinson's disease, Alzheimer's disease, traumatic brain injury, epilepsy, multiple sclerosis, depression, schizophrenia, and autism spectrum disorders and to improve these rodent's functions at various cognitive tasks (Hannan, 2014; Laviola et al., 2008). Rats kept in an enriched environment for a month or longer have an approximately 5 percent increase in brain weight as well as generalized increases in synapse number, astrocyte numbers and complexity, and angiogenesis. Improved ability on a wide range of cognitive and motor tasks is also typical (Kolb & Whishaw, 1998). Studies from literally dozens of laboratories have also shown this experience to be the most successful treatment strategy for optimizing functional recovery from a variety of forms of experimental brain damage including cortical ablation, cortical ischemia, and head trauma (Biernaskie & Corbett, 2001; Johansson, 1996; Will & Kelche, 1992).

For instance rats with brain lesions that affect the functionality of one forelimb show a thirty percent increase in that forelimb's functionality when those rats are placed in an enriched environment for four weeks compared with brain lesion rats in standard housing. Examination of the brains of the rats using the Golgi-Cox procedure (which stains only dendrites and cell soma) show that the rats placed in enriched environment after brain lesions had enhanced dendritic complexity and length both within and without the lesion. This increase in dendritic complexity and length throughout the brain suggests that enriched environment is capable of augmenting the adult rats' intrinsic neoplastic capabilities not just in injured brain areas, but in noninjured, functionally connecting brain tissue, as well as improving the brain injured rats functional outcome (Biernaskie & Corbett, 2001).

How enriched environment causes increase neurogenesis and neuroplasticity is not well known. It has been hypothesized that changes in gene expression may increase the synthesis of neurotropic factors, which in turn facilitate synaptic plasticity (Johansson, 2011).

Applying Enriched Environment to Humans

This treatment could easily be applied to humans. Of course, when discussing practical applications of animal research in humans, it must always be asked what the equivalent treatment would be. It can be argued that the life of a caged rat is, in fact, deprived, thus the movement to an enriched environment is equivalent to the "normal" environment of the vast majority of humans. However, it is worth noting that most people post brain injury find themselves in simple, unchanging environments, either in the hospital or at home, with a marked decrease in social interaction. This sort of environment is comparable to the standard housing, or unenriched environment compared to the normal active person with a full work/school life, and social life. This static environment is really a form of deprivation.

"Dementia Village" as it is called, is a small town on the outskirts of Denmark, Holland that is populated entirely by dementia patients and staffed entirely by caretakers. Patients wander around the walled town that is split into themed areas such as crafts, cultures, religion, and urban areas. Music and art is present in abundance. Patients visit restaurants, movie theaters, hairdressers, et cetera, who are trained to interact effectively and compassionately with dementia patients. Although the rate of neurogenesis has not been measured in these patients, the environment they live in meets the criteria of an enriched environment. The patients encounter multiple forms of stimulation across

multiple sensory modalities, and get plenty of unrestricted exercise as they are allowed to freely move about the village. Medical staff working with these patients report that compared to typical dementia patients, those that live in "Dementia Village" live longer, require fewer medications, eat better, and experience slowed cognitive decline (Jenkins & Smythe, 2013; Tinker, 2013). This improvement in patient outcome suggests that enriched environment in humans is a viable and effective treatment option.

Subsets of Enriched Environment

Exercise

A multitude of studies shows that increased exercise in animals leads to improved recovery from traumatic brain injury (Grealy, Johnson, & Rushton, 1999), delays the onset of neurodegenerative diseases (Adlard, Perreau, Pop, & Cotman, 2005), improves age related declines in memory (van Praag, Shubert, Zhao, & Gage, 2005), enhances cognition (Winter et al., 2007), and reduces the negative effects of depression (van Praag, 2008).

The experiments performed by Grealy, Johnson, and Rushton (1999) are particularly interesting as the researchers used adult human brain injury patients and treated them with exercise and virtual reality. Participants were asked to use a recumbent bike and given a virtual reality headset that simulated either cycling a bicycle around a course or racing against virtual riders. The virtual reality helmets provided new and changing sensory stimuli via changing visual and auditory scenes, and the recumbent bikes provided exercise, both components of enriched environment. Thirteen brain injury patients were compared with control brain injury patients on tests of movement, reaction time, learning, attention, and information processing. After just one session the

experimental group showed significant improvements in movement and reaction times. After four weeks (between 13-17 exercise sessions per participant) all other tested areas were significantly improved.

Similarly, experiments such as those performed by Winter et al. (2007) demonstrate the positive effects of exercise on human participants. 27 healthy males were asked to undergo periods of intense exercise involving sprints, low intensity exercise involving low impact running, or no exercise. The participants were tested after their exercise bouts on learning and retaining novel vocabulary. The participants who underwent exercise showed increased speed of vocabulary learning, and increased retention at one week and eight months. Participants who underwent more intense exercise improved the most, then low intensity exercise, and finally the no exercise group. The ability to improve performance in healthy brains as well as injured brains suggests that exercise could be a valuable treatment option in brain disorder patients, not just improving the areas of the brain that were injured but the nonaffected areas as well, potentially providing greater recovery.

Adlard, Perreau, Pop, & Cotman, (2005) examined mice bred to have a double mutant amyloid precursor protein, which causes these mice to have Alzheimer's. These mice were housed in cages either with a running wheel or without a running wheel. Those mice that had the opportunity for exercise showed more voluntary exercise. The mice were not compelled to exercise on the wheel; it was simply there to provide the opportunity to exercise. Mice with access to the running wheel showed decreased amyloid-ß plaques in the frontal cortex and the hippocampus. The mice with access to exercise showed improvements in cognitive tasks such as the Morris water maze. As the

loss of ability to perform cognitive tasks is one of the most distressing side effects of brain disorders (Banks, Bernick, Cummings, & Le, 2014, personal interview; Banks, Bernick, Cummings, & Le, 2013), any treatment that improves cognitive abilities could have a positive impact on the lives of brain disorder patients.

Research into why exercise is so beneficial has focused on everything from changes in neurotransmitters to neurotrophins (Neeper, Gomez-Pinilla, Choi, & Cotman, 1995). Recently that relationship between neurogenesis and exercise has been explored. Greatly increased neurogenesis is seen, specifically in the hippocampus, with exercise (van Praag, 2008). Comparisons of the brains of young and old mice that were given access to a running wheel for forty-five days demonstrate this neurogenesis and neuroplasticity. Neurogenesis was measured using immunohistochemistry for BrdU and immunofluorescent triple labeling for BrdU, neuronal nuclei (NeuN), and S100β which allows for the determination of quantity and type of new cells in the brain. Green fluorescent protein (GFP)-expressing retrovirus allows for the determination of dendritic length and density to measure neuroplasticity. Both the young and old mice in the exercise group showed significant increases in neurogenesis and neuroplasticity compared to aged-matched controls. While the young group showed more neurogenesis that the old group, there was no significant difference in the amount of plasticity found. Additionally, the old mice learned and remembered the morris water maze better than the controls (van Praag, Shubert, Zhao, & Gage, 2005). This suggests that exercise can promote neurogenesis and neuroplasticity in the adult brain, and improve functional ability.

Exercise is an important component in enriched environments. Animals that are housed in enriched environments show greater frequency and duration of voluntary exercise. In rats, those in enriched environments have been shown to perform upwards 40 percent more exercise than their standard housing cohorts (Lehmann et al., 2013). It is arguable that researchers who test exercise as a form of neurogenesis promotion are actually testing a subset of enriched environment, though this is not conclusive.

A recent study using voxel-based morphometry (VBM) technique examined novice golfers between the age of 40 and 60. These golfers underwent 40 hours of golf training, after which they showed an increase in gray matter in relevant sensorimotor regions. Furthermore, those that reported that they trained more intensely, showed the largest increase in gray matter (Bezzola, Mérillat, Gaser, & Jäncke, 2011).

Constraint induced movement therapy (CIMT) is a treatment currently in use that also supports the idea that neurogenesis will aid brain disorder patients. CIMT forces stroke patients to use their impaired arm by restraining their other arm. It has been demonstrated that this provides improved functional recovery, though it was not known how. Tests in rats have demonstrated that focal lesions followed by CIMT show greater neurogenesis than control rats using doublecortin immunohistochemistry. However, comparing CIMT rats to rats who were placed in non-CIMT rehabilitation and were given target exercise programs that involved usage of the affected limb showed even greater functional recovery and increased neurogenesis, perhaps because their ability to exercise overall was not hampered by restraints (Livingston-Thomas, McGuire, Doucette, & Tasker, 2014).

Tactile Stimulation

Tactile stimulation is often prominently featured in the enriched environment, and includes the opportunity to touch and be touched by a variety of textures and in a variety of manners (Laviola et al., 2008). Massage therapy has often been used as a supportive treatment for brain injured patients, although the mechanism of action as to why this seemed helpful was unknown (Banks, Bernick, Cummings, & Le, 2014, personal interview; Banks, Bernick, Cummings, & Le, 2013, personal interview). Research into even relatively small amounts of tactile stimulation, in which rats were given body massages for 15 minutes, three times a day for 2-3 weeks, showed dramatic recovery in tests of spatial navigation and skilled forelimb movements in rats after frontal of posterior parietal injuries (Kolb & Gibb, 2010). In adulthood there were changes in the cortical pyramidal neurons. More specifically, the animals with injuries who did not receive tactile stimulation showed an extensive atrophy of the cortical pyramidal neurons, while those with the stimulation showed a reversal of such atrophy, in correlation with functional recovery. These results are particularly promising. Although not as extensive as the results of the enriched environment studies, it is eminently more practical for clinical use. The results are not trivial and 45 minutes a day is greatly reduced from 24 hours a day.

How enriched environments improve neurogenesis is not yet fully understood. Exercise has been shown to increase levels of brain-derived neurotropic factor (BDNF). BDNF is a trophic factor that appears to be vital in neurogenesis and neuroplasticity (Lee, Duan, & Mattson, 2002). In transgenic mice that are blocked from producing BDNF hippocampal neurogenesis does not occur at all (Lee et al., 2002). And in mice with

augmented BDNF neurogenesis is increased (Henry, Hughes, & Connor, 2007). However, exercise is only one component of enriched environment. Furthermore, the benefit of exercise by itself for brain injuries does not equal that of enriched environment (Ruan et al., 2013). Additional, yet unknown, factors must be involved.

Discussion of Enriched Environment as a Treatment for Brain Disorder

A possible criticism of using enriched environment as a form of neurogenesis promotion is the potentially contradictory results in its effectiveness. Though the vast majority of researchers have found that enriched environment increases neurogenesis and its associated neuroplasticity (as outlined above), there are some studies that do not show these effects (Gobbo & O'Mara, 2005; Huang, Huang, Wu, & Boucheron, 2006). However, these contradictory results come with some very important caveats. For instance Gobbo & O'Mara (2005) compared the effect of exercise on neurogenesis and the effect of an enriched environment on neurogenesis without the exercise component, and found that the enriched environment alone did not produce functional recovery after brain injury that exceeded the recovery of the rats that received exercise. Exercise is a critical part of an enriched environment, so removing exercise from the study condition reduces the validity of these results. Additionally, many other enriched environment studies found no beneficial cognitive effects or neurogenesis effects in very specific areas of the brain. However, these studies often found improvements in other areas. For example, Huang et al. (2006) found mice that are bred to be missing a specific protein substrate in the brain (Neurogranin) did not gain new Neurogranin with enriched environment. Neurogranin is implicated in the neuroplasticity as it plays a role in long-term potentiation. However, they find an improvement in cognitive function and learning

in these mice, so while it did not demonstrate the exact mechanism of neuroplasticity the researchers were looking for, it did demonstrate others. In the end, the vast majority of research supports the idea that enriched environment improves neurogenesis and neuroplasticity.

In the majority of enriched environment experiments, the animals were kept in the environment 24 hours a day. This could be accomplished by modifying hospital's wards that specifically look after patients with brain disorders by including more stimulation. Simple additions such as having textured cloths to play with or some form of simple exercise machine such as treadmill or arm bike for those who cannot walk would be vastly beneficial, and at least partially fulfill some of the requirements of an enriched environment.

Another potential criticism of enriched environment as a treatment for brain disorder is the cost. However, in 2010 the cost of treating just one brain disorder, Alzheimer's, in just one country, the United States, was approximately $170 billion (Williams, 2010). The cost is already quite large. Implementing treatments based on enriched environments does not necessarily need to be exorbitantly costly. Merely increasing a patient's opportunity to exercise and access to materials that provide stimulation will be beneficial, as will incorporating other elements of enriched environment, such as tactile stimulation in the form of massage therapy.

Diet

The final treatment that I will discuss here is potentially the simplest to implement into the current treatment programs of brain disorder patients, and can be immediately implemented. Several studies indicate that diet is important for stimulating recovery after

early cortical injury. Dabydeen et al (2008) conducted a study where human neonates with perinatal brain damage were randomly allocated to receive either a high (120 percent recommended average intake) or average (100 percent recommended average intake) calorie and protein diet. The effect on recovery was so dramatic that the study was terminated before completion so that all the infants could be placed on a higher energy diet. For obvious reasons, direct anatomical measurements of synaptic growth could not be done in such a study. However, non-invasive imaging showed that axonal diameters in the corticospinal tract were increased, as well as the length and width, which is associated with neuroplasticity and neurogenesis. As the degree of recovery was positively correlated with the amount of growth in these axons, it is suggested that the improvement in these brain damages patients was related to this growth.

In adults, this trend is reversed. High-caloric intake diets have been shown to slow down neurogenesis and neuroplasticity, especially if the majority of those calories come from fats (Park & Lee, 2011; Lindqvist et al., 2006). Rats fed a diet in which forty-five percent of the calories came from fat had decreased new neuron proliferation in the hippocampus and decreased BDNF compared to controls (Park & Lee, 2011). Diets that are restricted in fat also shown to increase the longevity of neuronal cells; as well as reduce many other non-brain disorder related diseases and infirmities (Swindell, 2009). It is thought that dietary restriction acts as a mild stressor on the body, which in turn causes an increase in BDNF.

N−3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in fish and other foods, is linked to decreased cognitive decline in elderly men (van Gelder, Tijhuis, Kalmijn, & Kromhout, 2007). 210 men aged 70 to 89 years were given

the mini-mental state examination (MMSE), widely used to test global cognitive function, over a period of five years. The men who consumed approximately 380 mg of EPA and DHA a day sowed a significant decrease in cognitive decline compared to the men who consumed less EPA and DHA. This statistically significant decrease in cognitive decline remained even when the authors adjusted the results for age, education, caloric intake, alcohol consumption, smoking status, physical activity, baseline cognitive functioning, dietary antioxidants, intake of fatty acids, and depressive symptoms.

Many more studies have shown the positive effects of diet on neurogenesis and neuroplasticity in rodents, and diets role in altering mood and cognitive performance. There are many aspects of diet that may be manipulated to have differing effects on neurogenesis, neuroplasticity, and cognitive function. Table 1 outlines identified multiple components of diet, and how those components affect neurogenesis in the adult hippocampus.

Diet	**Study models**	**Effect on AHN**	**References**
Caloric restriction/dietary restriction	Rat	Increased survival	(Kushida et al., 2008)
	Mouse	Increased survival	(Bondolfi, Ermini, Long, Ingram, & Jucker, 2004; Kitamura, Mishina, & Sugiyama, 2006; Lee, Duan, & Mattson, 2002; Lee, Seroogy, & Mattson, 2002)
Omega 3 fatty acids	Rat	Increased (DHA)	(Kawakita, Hashimoto, & Shido, 2006)
Flavonoids	Rat, chronically stressed	Increased proliferation	(An et al., 2008)
Blueberry	Rat	Increased proliferation	(Casadesus et al., 2004)

Diet	**Study models**	**Effect on AHN**	**References**
Curcumin low concentrations	Mouse	Increased proliferation	(Kim et al., 2008)
Retinoic acid excess	Mouse	Decreased proliferation	(Crandall et al., 2004)
Vitamin A deficiency	Rat	Decreased proliferation (rescued with retinoic acid)	(Bonnet et al., 2008)
Thiamine deficiency	Mouse	Decreased proliferation/survival	(Zhao et al., 2008)
Zinc deficiency	Rat male	Decreased proliferation/survival	(Corniola, Tassabehji, Hare, Sharma, & Levenson, 2008)
Folate deficiency	Mouse	Inhibited proliferation	(Kronenberg et al., 2008)
Increased homocysteine	Mouse	Inhibited proliferation	(Kruman, Mouton, Emokpae, Cutler, & Mattson, 2005; Rabaneda et al., 2008)
High fat	Male rat	Decreased proliferation	(Lindqvist et al., 2006)
	Female rat	No change	
Soft diet	Rat	Decreased proliferation	(Aoki, Kimoto, Hori, & Toyoda, 2005)
Caffeine			
At physiologically relevant doses	Mouse	Decreased proliferation	(Wentz & Magavi, 2009)
At supraphysiological doses	Mouse	Increased proliferation/decreased survival	(Wentz & Magavi, 2009)
Low doses, chronically	Rat	Decreased proliferation	(Han et al., 2007)
Ethanol	Rat	Decreased proliferation	(He, Nixon, Shetty, & Crews, 2005; Nixon & Crews, 2002)
	Mouse	Decreased proliferation	(Stevenson et al., 2009)

Table 1. Modulation of adult hippocampal neurogenesis (AHN) by diet. Diet affects AHN in many ways.

Table 2 shows how different components of diet have been experimentally linked to the modulation of learning and memory and depressive behavior.

Diet	**Effect on learning and memory**	**Effect on depressive behavior**	**Study models**	**References**
Caloric/dietary restriction	Enhanced spatial learning in aged rats		Rat	Stewart, Mitchell, & Kalant, (1989).
	Enhanced cognitive performance in females only		Rat	(Martin et al., 2007)
	Increased learning and motor performance		Mouse	(Ingram, Weindruch, Spangler, Freeman, & Walford, 1987)
	Increased learning consolidation		Mouse	(Fontán-Lozano et al., 2007)
Omega 3 fatty acids		Improved (EPA)	Human	(Jazayeri et al., 2008)
		Delayed onset of depressive periods	Human (bipolar)	(Stoll et al., 1999)
		Decreased	Human (bipolar)	(Osher, Bersudsky, & Belmaker, 2005)
		No benefit 6 g/day EPA	Human (bipolar)	(Keck et al., 2006)
		Improvement with 1 g/day EPA	Human (bipolar)	(Frangou, Lewis, & McCrone, 2006)
		Various effects with various	Human	For review:(Appleton, Rogers, & Ness,

Diet	Effect on learning and memory	Effect on depressive behavior	Study models	References
		concentrations of various fatty acids		2010)
	Improved spatial memory		Mouse Alzheimer model	(Hooijmans et al., 2009)
	Improved acquisition and retention in a T-maze foot shock avoidance test		Mouse Senescence - Accelerated	(Petursdottir, Farr, Morley, Banks, & Skuladottir, 2008)
Flavonoids		Improved	Rat	(Dimpfel, 2009)
	Improved			For review: (Vauzour, Vafeiadou, Rodriguez-Mateos, Rendeiro, & Spencer, 2008)
Blueberry	Increased spatial memory		Rat	(Williams et al., 2008)
Polyphenol/flavonoids/ berry	Positive impact		Various animals	For review: (Willis, Shukitt-Hale, & Joseph, 2009)
		Improved	Rat	(Willis et al., 2009)
Curcumin	Improved cognitive performance		Human	(Ng et al., 2006)
Retinoic acid excess		Increased	Mouse adult	(O'Reilly, Shumake, Bailey, Gonzalez-Lima, & Lane, 2009)
Vitamin A/retinoid deficiency	Impaired spatial learning and		Rat adult	(Cocco et al., 2002)

Diet	**Effect on learning and memory**	**Effect on depressive behavior**	**Study models**	**References**
	memory			
	Impaired relational memory		Mouse adult	(Etchamendy et al., 2003)
Zinc		Improved	Rodents	For review: (Szewczyk et al., 2008)
		Improved	Human	For review:(Szewczyk et al., 2008)
		Improved	Human	(Nowak, Siwek, Dudek, Zieba, & Pilc, 2003)
High fat	Decreased spatial learning		Rat	(Molteni, Barnard, Ying, Roberts, & Gómez-Pinilla, 2002)
	Decreased learning and memory and Increased risk for dementia		Rat	(Winocur & Greenwood, 2005)
High sugar	Impaired spatial learning		Rat	(Stranahan et al., 2008)
Low glucose (extracellular)	Impaired memory		Rat aged	(Gold, 2005)
Soft diet	Impairment of learning ability and memory		Rat Alzheimer model	(Kushida et al., 2008)
Caffeine	Improved object recognition		Mouse	(Costa et al., 2008)
		Reduced risk	Human	(Smith, 2009)
Ethanol	Improved associative		Mouse male	(Robles & Sabriá, 2008)

Diet	Effect on learning and memory	Effect on depressive behavior	Study models	References
	learning with moderate chronic consumption			
	Deficits		Human	(Parsons, 1998)

Table 2. The modulation of learning and memory and depressive behavior by diet. EPA stands for eicosapentaenoic acid.

Discussion of Diet as a Treatment for Brain Disorder

There appear to be no criticisms related to the use of a high caloric diet in neonates from a research or scientific standpoint. The issue of cost and availability could potentially be raised, which are beyond the scope of this thesis to solve. However, where it can be implemented it seems clear that it should be.

In adults the difficulties that come with a restricted diet are mainly those of willpower and social pressure. While not trivial in themselves, an individual with a brain disorder and those caring for them must make their own cost-benefit analysis to determine whether the difficulties of maintaining a low calorie, low fat diet are worth the benefits.

The shear breadth of research involving the multiple components of diet and how they can be manipulated to produce differing outcomes in neurogenesis and patient functionality demonstrate the flexibility of diet modification as a potential treatment for patients with brain disorder. Treatment flexibility is a key component for patient compliance (Banks, Bernick, Cummings, & Le, 2014, personal interview; Banks, Bernick, Cummings, & Le, 2013, personal interview), so diet modification has the potential to be

effective in a wide range of brain disorder patients, especially those that have difficulty maintaining a less flexible treatment plan. The variety in dietary targets for modification mean that as a treatment dietary modification may be applied to almost everyone, from a variety of cultural backgrounds, without difficulty, further emphasizing the practicality of implementing dietary modification as a treatment option for brain disorder patients.

Conclusions

With 2.4 billion individuals worldwide diagnosed with brain disorders (Worldometers, 2013), the need for effective treatments is dire. The vast body of research that supports the positive benefits of an enriched environment, suggesting that enriched environment is a potentially valuable tool to aid in the rehabilitation and recovery of patients with brain disorders. The effectiveness of segments of enriched environment suggests that it is a potentially valuable tool to aid in the rehabilitation and recovery of patients with brain disorders. The effectiveness of segments of enriched environment such as exercise and tactile stimulation offers further evidence of the positive benefits in pursuing enriched environment as a treatment modality. The fact that segments of enriched environment can be effective on their own also means that it is a treatment that may be implemented flexibly, and relatively cheaply. Cost of treatment is a barrier for many people, so any way to bring this cost down will be beneficial.

The evidence for the benefits of dietary modification it is still compelling. The wide range of dietary modifications that have been experimentally demonstrated to have beneficial effects on neurogenesis, neuroplasticity, and functionality demonstrate the flexibility and practicality in dietary modifications as a treatment for brain disorder. The variety of dietary targets for modifications allows for customization to the needs and

abilities of the patient. Furthermore, the cost of implementing some of the modifications, such as dietary restriction almost nonmonetary in nature; it is more a matter of willpower and social pressure. Though these are not trivial costs in themselves, it means that there are few barriers to implementing dietary restrictions as part of a treatment plan now.

Much of the work related to neurogenesis and neuroplasticity has been conducted with animal models, so there is always difficulty in applying such results to humans. Both of the proposed treatments (enriched environment and dietary modification) have been experimentally shown to enhance neurogenesis, neuroplasticity, and cognitive function in both healthy animals and animals in brain disorders. Similarly, human studies have shown that enriched environment and dietary modifications cause decreases in cognitive decline, and improvement in cognitive function, even when controlling for other factors (Szewczyk et al., 2008; Ng et al., 2006; van Gelder, Tijhuis, Kalmijn, & Kromhout, 2007; Winter et al. 2007). This suggests that enriched environment and dietary modifications produce similar neurogenesis and neuroplasticity effects in human brains as they do in animal models. Studies using imaging techniques like fMRIs are supporting that fact (Filippi, & Rocca, 2006). As the cause of many brain disorders is directly related to the loss of neurons in the brain, the promotion of neurogenesis allows for truly effective treatments of brain disorders.

What is important to keep in mind in reviewing all this information is how it can be applied to humans. Identifying and understanding the mechanisms of neuroplasticity will help us to aim our rehabilitation strategies at the appropriate targets. Notably, the enriched environment provides a useful standard against which to compare other treatments. Although it is unclear how it would translate in the human arena, there are

few treatments that are as effective. That being said there are some that are at least nearly as effective, and it may be that a combination of therapies is the most effective of all. Research into this area must be focused on identifying those mechanisms that produce beneficial effects and understanding why they work. Once we understand why treatments work, the development of new and more effective treatments becomes far more attainable.

References

Adkins, D. L., Boychuk, J., Remple, M. S., & Kleim, J. A. (2006). Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord. *Journal of Applied Physiology, 101*(6), 1776-1782. doi: 10.1152/japplphysiol.00515.2006

Adkins, D. L., Hsu, J. E., & Jones, T. A. (2008). Motor cortical stimulation promotes synaptic plasticity and behavioral improvements following sensorimotor cortex lesions. *Experimental Neurology, 212*(1), 14-28. doi: 10.1016/j.expneurol.2008.01.031

Adlard, P. A., Perreau, V. M., Pop, V., & Cotman, C. W. (2005). Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. *Journal of Neuroscience*, *25*(17), 4217-4221. doi: 10.1523/jneurosci.0496-05.2005

Altman, J. (1962). Are new neurons formed in the brains of adult mammals? Science, 135(3509), 1127-1128.

Alvarez-Buylla, A., Garcia-Verdugo, J., & Tramontin, A. (2001). A unified hypothesis on the lineage of neural stem cells. *Nature Reviews Neuroscience, 2*(4), 287-293. doi: 10.1038/35067582

Alzheimer's Association, (2014). Healthy brain vs alzheimer's brain. *Alzheimer's and the Brain.* Retrieved 18 March, 2014, from http://www.alz.org/braintour/healthy_vs_alzheimers.asp

Alzheimer's Association, (2012). FDA approved treatments for alzheimers. *Medications for Memory Loss.* Retreived 18 March, 2014 from http://www.alz.org/national/documents/topicsheet_treatments.pef

Alzheimer's disease. (2014). *Merriam-Webster Medical Dictionary*. Retrieved March 30, 2014, from http://www.merriam-webster.com/medical/alzheimer's+disease

Bangert, M., & Schlaug, G. (2006). Specialization of the specialized in features of external human brain morphology. *European Journal of Neuroscience*, *24*(6), 1832-1834. doi: 10.1111/j.1460-9568.2006.05031.x

Bellenchi, G. C., Volpicelli, F., Piscopo, V., Perrone-Capano, C., & di Porzio, U. (2013). Adult neural stem cells: an endogenous tool to repair brain injury?. *Journal of Neurochemistry, 124*(2), 159-167. doi: 10.1111/jnc.12084

Belzung, C., & Wigmore, P. (2013). Neurogenesis and Neural Plasticity (Vol. 15): Springer.

Berryhill, M., (2013). Chapter 7 lecture slides. *Psy 432 Human Memory and Learning.* Lecture conducted at University of Nevada, Reno, Reno, Nevada

Bezzola, L., Mérillat, S., Gaser, C., & Jäncke, L. (2011). Training-induced neural plasticity in golf novices. *Journal of Neuroscience, 31*(35), 12444-12448. doi: 10.1523/JNEUROSCI.1996-11.2011

Biernaskie, J., & Corbett, D. (2001). Enriched rehabilitative training promotes improved forelimb motor function and enhanced dendritic growth after focal ischemic injury. *Journal of Neuroscience, 21*(14), 5272-5280.

Blier, P. (2013). Neurotransmitter targeting in the treatment of depression. *Journal of Clinical Psychiatry, 74 Supplement 2,* 19-24. doi: 10.4088/JCP.12084su1c.04

Boulton, D. (20004). Interview with M. Merzenich. Retrieved from http://www.childrenofthecode.org/interviews/merzenich.htm

Boyke, J., Driemeyer, J., Gaser, C., Buchel, C., & May, A. (2008). Training-induced brain structure changes in the elderly. *Journal of Neuroscience, 28*(28), 7031-7035. doi: 10.1523/jneurosci.0742-08.2008

Chugani, H. T., Muller, R. A., & Chugani, D. C. (1996). Functional brain reorganization in children. Brain & Development, 18(5), 347-356. doi: 10.1016/0387-7604(96)00032-0

Cleveland Clinic. (2014). *Lou ruvo center for brain health*. Retrieved from http://my.clevelandclinic.org/neurological_institute/lou-ruvo-brain-health/default.aspx

Cohen, L. G., Celnik, P., PascualLeone, A., Corwell, B., Faiz, L., Dambrosia, J., . . . Hallett, M. (1997). Functional relevance of cross-modal plasticity in blind humans. *Nature, 389*(6647), 180-183. doi: 10.1038/38278

Colucci-D'Amato, L., Bonavita, V., & di Porzio, U. (2006). The end of the central dogma of neurobiology: stem cells and neurogenesis in adult CNS. *Neuroligical Science, 27*(4), 266-270. doi: 10.1007/s10072-006-0682-z

Dabydeen, L., Thomas, J. E., Aston, T. J., Hartley, H., Sinha, S. K., & Eyre, J. A. (2008). High-energy and -protein diet increases brain and corticospinal tract growth in term and preterm infants after perinatal brain injury. *Pediatrics, 121*(1), 148-156. doi: 10.1542/peds.2007-1267

Drevets, W.C. (2004). Neuroplasty in mood disorders. *Dialogues in Clinical Neuroscience. 6*(2), 199-216. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181795/?tool=pmcentrez&report=abstract

Filippi, M., & Rocca M.A., (2006). Functional mri to study brain plasticity in clinical neurology. *Neurological Sciences,* 27(1), 24-26. doi: 10.1007/s10072-006-0541-y

Font, M.A., Arboix, A., & Krupinski, J. (2010). Angiogenesis, neurogenesis and neuroplasticity in ischemic stroke. *Current Cardiology Reviews., 6*(3), 238-244. doi: 10.2174/157340310791658802

Gage, F. (2000). Mammalian neural stem cells. *Science, 287*(5457), 1433-1438. doi: 10.1126/science.287.5457.1433

Gill, P., Stewart, K., Treasure, E., & Chadwick, B. (2008). Methods of data collection in qualitative research: interviews and focus groups. *British Dental Journal*, 204, 291-295. doi: 10.1038/bdj.2008.192

Gobbo, O. L., & O'Mara, S. M. (2005). Exercise, but not environmental enrichment, improves learning after kainic acid-induced hippocampal neurodegeneration in association with an increase in brain-derived neurotrophic factor. *Behavioral Brain Research*, *159*(1), 21-26. doi: 10.1016/j.bbr.2004.09.021

Gonzalez, C. L., Gharbawie, O. A., Whishaw, I. Q., & Kolb, B. (2005). Nicotine stimulates dendritic arborization in motor cortex and improves concurrent motor skill but impairs subsequent motor learning. *Synapse, 55*(3), 183-191. doi: 10.1002/syn.20106

Grafman, J. (2000). Conceptualizing functional neuroplasticity. *Journal of Communication Disorders, 33*(4), 345-356. doi: http://dx.doi.org/10.1016/S0021-9924(00)00030-7

Grealy, M. A., Johnson, D. A., & Rushton, S. K. (1999). Improving cognitive function after brain injury: the use of exercise and virtual reality. *Archives of Physical Medicine and Rehabilitation, 80*(6), 661-667.

Grundey, J., Thirugnanasambandam, N., Kaminsky, K., Drees, A., Skwirba, A. C., Lang, N., . . . Nitsche, M. A. (2012a). Neuroplasticity in cigarette smokers is altered under withdrawal and partially restituted by nicotine exposition. *Journal of Neuroscience, 32*(12), 4156-4162. doi: 10.1523/jneurosci.3660-11.2012

Grundey, J., Thirugnanasambandam, N., Kaminsky, K., Drees, A., Skwirba, A. C., Lang, N., . . . Nitsche, M. A. (2012b). Rapid effect of nicotine intake on neuroplasticity in non-smoking humans. *Frontiers in Pharmacology, 3,* 186. doi: 10.3389/fphar.2012.00186

Hannan, A. J. (2014). Review: Environmental enrichment and brain repair: harnessing the therapeutic effects of cognitive stimulation and physical activity to enhance experience-dependent plasticity. *Neuropathology and Applied Neurobiology, 40*(1), 13-25. doi: 10.1111/nan.12102

Henry, R. A., Hughes, S. M., & Connor, B. (2007). AAV-mediated delivery of BDNF augments neurogenesis in the normal and quinolinic acid-lesioned adult rat brain. *European Journal of Neuroscience, 25*(12), 3513-3525. doi: 10.1111/j.1460-9568.2007.05625.x

Huang, F. L., Huang, K. P., Wu, J., & Boucheron, C. (2006). Environmental enrichment enhances neurogranin expression and hippocampal learning and memory but fails to rescue the impairments of neurogranin null mutant mice. *Journal of Neuroscience*, *26*(23), 6230-6237. doi: 10.1523/jneurosci.1182-06.2006

Hubel, D.H., & Wiesel, T.N., (1970). The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *The Journal of Physiology. 206*(2), 419-436. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed

Ingram, D. K., Weindruch, R., Spangler, E. L., Freeman, J. R., & Walford, R. L. (1987). Dietary restriction benefits learning and motor performance of aged mice. *Journal of Gerontology, 42*(1), 78-81.

Jenkins, C., & Smythe, A. (2013). Reflections on a visit to a dementia care village. *Nursing Older People, 25*(6), 14-19.

Johansson, B. B. (1996). Environmental influence on outcome after experiment brain infarction. *Acta Neurochirurgica Supplement*, 66, 63-67.

Johansson, B. B. (2011). Current trends in stroke rehabilitation. A review with focus on brain plasticity. *Acta Neurologica Scandinavia, 123*(3), 147-159. doi: 10.1111/j.1600-0404.2010.01417.x

Jones, T. A., & Kleim, J. A. (2008). Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *Journal of Speech, Language, and Hearing Research*, 51, 225-239.

Kazanis, I. (2013). Neurogenesis in the adult mammalian brain: How much do we need, how much do we have?. *Current Topics in Behavioral Neuroscience,* 15, 3-29. doi: 10.1007/7854_2012_227

Keith J., Wu, Y., Epp J.R., & Sutherland R.J. (2007). Fluoxetine and the dendate gyrus: memory, recovery of function, and electrophysiology. *Behavioral Pharmacology*, 18, 521-531

Kolb, B., & Gibb, R. (2010). Tactile stimulation after frontal or parietal cortical injury in infant rats facilitates functional recovery and produces synaptic changes in adjacent cortex. *Behavioral Brain Research, 214*(1), 115-120. doi: 10.1016/j.bbr.2010.04.024

Kolb, B., & Whishaw, I. Q. (1998). Brain plasticity and behavior. *Annual Review of Psychology*, 49, 43-64. doi: 10.1146/annurev.psych.49.1.43

Laviola, G., Hannan, A. J., Macrì, S., Solinas, M., & Jaber, M. (2008). Effects of enriched environment on animal models of neurodegenerative diseases and psychiatric disorders. *Neurobiology of Disease, 31*(2), 159-168. doi: http://dx.doi.org/10.1016/j.nbd.2008.05.001

Lee, J., Duan, W., & Mattson, M. P. (2002). Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. *Journal of Neurochemestry , 82*(6), 1367-1375.

Lehmann, M. L., Brachman, R. A., Martinowich, K., Schloesser, R. J., & Herkenham, M. (2013). Glucocorticoids orchestrate divergent effects on mood through adult neurogenesis. *Journal of Neuroscience, 33*(7), 2961-2972. doi: 10.1523/jneurosci.3878-12.2013

Lindvall, O., & Bjorklund, A. (2011). Cell therapeutics in parkinson's disease. *Neurotherapeutics, 8*(4), 539-548. doi: 10.1007/s13311-011-0069-6

Lindvall, O., & Kokaia, Z. (2010). Stem cells in human neurodegenerative disorders -- time for clinical translation? *Journal of Clinical Investigation, 120*(1), 29-40. doi: 10.1172/jci40543

Livingston-Thomas, J. M., McGuire, E. P., Doucette, T. A., & Tasker, R. A. (2014). Voluntary forced use of the impaired limb following stroke facilitates functional recovery in the rat. *Behavioural Brain Research*, 261, 210-219. doi: 10.1016/j.bbr.2013.12.032

Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S., & Frith, C. D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Science U S A*, *97*(8), 4398-4403. doi: 10.1073/pnas.070039597

Martin, B., Pearson, M., Kebejian, L., Golden, E., Keselman, A., Bender, M., . . . Mattson, M. P. (2007). Sex-dependent metabolic, neuroendocrine, and cognitive responses to dietary energy restriction and excess. *Endocrinology*, *148*(9), 4318-4333. doi: 10.1210/en.2007-0161

Mayo Clinic. (2014). Treatments and drugs. *Parkinson ’s Disease.* Retrieved from http://www.mayoclinic.org/diseases-conditions/parkinsons-disease.basics/treatment/com-20028488

McKay, R. (1997). Stem cells in the central nervous system. *Science*, *276*(5309), 66-71. doi: 10.1126/science.276.5309.66

Merzenich, M. M., Kaas, J. H., Wall, J. T., Sur, M., Nelson, R. J., & Felleman, D. J. (1983). Progression of change following median nerve section in the cortical representation of the hand in areas 3b and 1 in adult owl and squirrel monkeys. *Neuroscience*, *10*(3), 639-665.

National Institute of Health. (2014). Parkinson’s disease. *NIHSeniorHealth.* Retrieved 18 March, 2014, from

http://nihseniorhealth.gov/parkinsonsdisease/whatcausesparkinsonsdisease/01.htm
1

National Institute on Aging. (2014). About alzheimer's disease: Alzheimer's basics. *Alzheimer's Disease Education and Referral Center.* Retrieved 1 March, 2014, from http://www.nia.nih.gov/alzheimers.topics/alzheimers-basics

National Stroke Association. (2009). Stroke 101: fact sheet. *National Stroke Association*. Retrieved 1 March, 2014, from http://www.stroke.org/site/PageServer?pagename=library_factsheets

Neeper, S. A., Gomez-Pinilla, F., Choi, J., & Cotman, C. (1995). Exercise and brain neurotrophins. *Nature, 373*(6510), 109. doi: 10.1038/373109a0

Olsen, C.M. (2011). Natural rewards, neuroplasticity, and non-drug addictions. *Neuropharmacology, 61*(7), 1109-1122. doi: 10.1016/j.neuropharm.2011.03.010

One Mind for Research. (2013). *Learn more about brain diseases.* Retrieved from http://1mind4research.org/brain-disorders

Park, H. R., & Lee, J. (2011). Neurogenic contributions made by dietary regulation to hippocampal neurogenesis. *Nutrition and Physical Activity in Aging, Obesity, and Cancer*, 1229, 23-28. doi: 10.1111/j.1749-6632.2011.06089.x

Parkinson's disease. (2014, January 1). *Merriam-Webster Medical Dictionary*. Retrieved March 30, 2014, from http://www.merriam-webster.com/medical/parkinson%27s+disease?show=0&t=1397854697

Ponti, G., Peretto, P., & Bonfanti, L. (2008). Genesis of neuronal and glial progenitors in the cerebellar cortex of peripuberal and adult rabbits. *Plos One, 3*(6), 19. doi: 10.1371/journal.pone.0002366

Pravosudov, V. V., & Clayton, N. S. (2002). A test of the adaptive specialization hypothesis: population differences in caching, memory, and the hippocampus in black-capped chickadees (Poecile atricapilla). *Behavioral Neuroscience*, *116*(4), 515-522.

Rakic, P. (2002). Adult neurogenesis in mammals: an identity crisis. *Journal of Neuroscience*, *22*(3), 614-618.

Reynolds, B. A., & Weiss, S. (1992). Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. *Science, 255*(5052), 1707-1710.

Rosenzweig, M. R., Bennett, E. L., Hebert, M. & Morimoto, H. (1978). Social grouping cannot account for cerebral effects of enriched environments. *Brain Research, 153*(3), 563–576.

Ruan, L., Lau, B. W., Wang, J., Huang, L., Zhuge, Q., Wang, B., . . . So, K. F. (2013). Neurogenesis in neurological and psychiatric diseases and brain injury: From bench to bedside. *Progress in Neurobiology*, *115*, 116-37. doi: 10.1016/j.pneurobio.2013.12.006.

Smith, J. M., Lunga, P., Story, D., Harris, N., Le Belle, J., James, M. F., . . . Fawcett, J. W. (2007). Inosine promotes recovery of skilled motor function in a model of focal brain injury. *Brain, 130*, 915-925. doi: 10.1093/brain/awl393

Stewart, J., Mitchell, J., Kalant, N., (1989). The effects of life-long food restriction on spatial memory in young and aged Fischer 344 rats measured in the eight-arm radial and the Morris water mazes. *Neurobiology of Aging, 10*, 669–675

Swindell, W. R. (2009). Genes and gene expression modules associated with caloric restriction and aging in the laboratory mouse. *BMC Genomics, 10*, 585. doi: 10.1186/1471-2164-10-585

Taupin, P. (2006). Adult neurogenesis and neural stem cells in mammals Retrieved from WorldCat Adult neurogenesis and neural stem cells in mammals Philippe Taupin 2006 English Internet Resource Computer File 1 online resource (ix, 208 p.) : ill. New York : Nova Biomedical Books, ; ISBN: 9781616685768 (electronic bk.) 161668576X (electronic bk.) WorldCat database Retrieved from http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&AN=315716 Retrieved from Materials specified: EBSCOhost http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&AN=315716

Tinker, B. (2013). *'Dementia* village' inspires new care. CNN. Retrieved 18 March, 2014, from http://www.cnn.com/2013/07/11/world/europe/wus-holland-dementia-village/

van Gelder, B. M., Tijhuis, M., Kalmijn, S., & Kromhout, D. (2007). Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. *American Journal of Clinical Nutrition, 85*(4), 1142-1147.

van Praag, H. (2008). Neurogenesis and exercise: Past and future directions. *Neuromolecular Medicine, 10*(2), 128-140. doi: 10.1007/s12017-008-8028-z

van Praag, H., Shubert, T., Zhao, C., & Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *Journal of Neuroscience, 25*(38), 8680-8685. doi: 10.1523/jneurosci.1731-05.2005

Wagner, A. K., & Zitelli, K. T. (2013). A Rehabilomics focused perspective on molecular mechanisms underlying neurological injury, complications, and recovery after severe TBI. *Pathophysiology, 20*(1), 39-48.

Will, B., & Kelch, C. (1992). Environmental approaches to recovery of function from brain damage: a review of animal studies (1998 to 1991). *Advances in Experimental Medicine and Biology, 325,* 79-103.

Williams, T. (2010). Alzheimer's disease to cost the United States $20 trillion over next forty years. In Alzheimer's Association (Ed.). Retrieved from 18 March, 2014, from http://www.alz.org/documents_custom/final_trajectory_report_release-emb_5-11-10.pdf

Winter, B., Breitenstein, C., Mooren, F. C., Voelker, K., Fobker, M., Lechtermann, A., . . . Knecht, S. (2007). High impact running improves learning. *Neurobiology, Learning, and Memory*, *87*(4), 597-609. doi: 10.1016/j.nlm.2006.11.003

Worldometers. (2013). *Current world population.* Retrieved from http://www.worldometers.info/world-population/

Zheng, W., ZhuGe, Q., Zhong, M., Chen, G., Shao, B., Wang, H., . . . Jin, K. (2013). Neurogenesis in Adult Human Brain after Traumatic Brain Injury. *Journal of Neurotrauma*, *30*(22), 1872-1880. doi: 10.1089/neu.2010.1579