IN VIVO MRI STUDIES OF STRUCTURAL CHANGES IN THE MOUSE BRAIN FOLLOWING FORCED TREADMILL TRAINING

Brocke Addison

Integrated Program in Neuroscience

McGill University, Montreal

August 2014

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science in Neuroscience

Table of Contents

Abstract 4

Acknowledgements 5

Introduction 6

History 7

Activity-dependent structural plasticity 9

Exercise 11

Methods 13

Mice 13

Exercise training procedures 13

In vivo MRI acquisition 14

MRI processing 14

Measuring ROI-based cortical thickness 15

Measuring ROI-based volume 16

Statistics and analysis 16

Results 17

Longitudinal cortical thickness measurements 17

Longitudinal volume measurements 18

Volume measurements of hippocampus 19

Volume measurements of amygdala 20

Discussion 21

Exercise induces large structural volume changes 21

Exercise induces no detectable change in cortical thickness 21

Cellular physiology underlying volume change in hippocampus 22

Cellular physiology underlying volume change in amygdala 23

Conclusions and current work 25

Works Cited ii

Abstract

Introduction

Environmental enrichment and exercise are known to promote brain plasticity. The cellular underpinnings associated with plasticity related changes to brain structure remain unknown. Anatomical changes of volume and biochemistry occurring in the brain following forced treadmill training are well documented in both animal and human literature, but little is known about the underlying physiology of how one is connected to the other. The objective of this study was therefore to perform longitudinal *in vivo* scans following exercise and to investigate these underlying cellular mechanisms.

Methods

3-month-old CD1 male littermate mice were randomly assigned to two groups. One group (n =15) was exposed to 6 weeks of forced treadmill (FT) at escalating speeds, increasing 1cm/sec per week beginning at 24cm/sec. A control group (n = 12) received no treadmill exposure (NX) for the same 6-week interval.

Mice were spatially normalized to an anatomical template (PERMITS™, Biospective Inc.), providing extracted mean values of volume in 7 different cortical and subcortical regions. All scans were obtained from a 7T Bruker Pharmascan system. Baseline scans were obtained following a weeklong training at low speed (15cm/sec) for all mice. A second scan was obtained from each mouse following the 6-week interval of either forced treadmill or no exercise. Upon completion of the final scan, all animals were sacrificed for histological examination.

Results

Analysis of volume measurements taken from baseline and post-exercise scans revealed that 6 weeks of forced treadmill led to a significantly larger increase in hippocampal volume in FT mice (13.74%) compared to the increase in NX controls (4.13%) ($t(24) = 8.36$, $p < 0.0001$). Analysis of the amygdala showed an increase in volume in the FT group (6.21%) compared to a decrease in amygdala volume in the NX controls (-1.39%) ($t(24) = 3.8$, $p < 0.001$). Explored group differences in cortical thickness and volume for 5 other regions revealed no significant distinction.

Conclusions

We observed a significant increase in both hippocampal and amygdala volume of mice following forced treadmill compared to controls. The cellular physiology that underlies these increases is being investigated and will reveal a better understanding of how these regions change after exercise training and how the brain changes in response to activity.

Introduction:

The brain changes in response to the environment (Hubel, 1963; Martin, 2000; Buonomano, 1998). After development, activity-dependent plastic changes occur within the brain to maintain survival and create a behavioral and physiological equilibrium with a dynamic environment. This ability to learn and adapt rapidly has been essential to human evolution and our primacy in nature (Wexler, 2011).

Tissues in the body increase their own blood perfusion based on activity, which if persistent, can result in hypertrophy of the cells (Kumar, 2009). When functional regions of the brain are more active, they require a larger supply of nutrients and signaling molecules, which increases blood perfusion in that region (Churchill, 2002). This increase can lead to the growth of cells, vascular development and an increase in capillary growth. (Kumar, 2009; Churchill, 2002). If the activity involved also includes learning or motor training, development of the synaptic network and associated cellular components can occur, leading to changes in communication and signaling, electrical activity, neuronal morphology, axonal and dendritic remodeling and protein composition. If these structural changes occur in the brain on a large scale, they can be observed and measured through structural magnetic resonance imaging (MRI)(Zatorre, 2012).

History

The first speculation that brain tissue was plastic and could be altered through behavior began in the works of psychologist William James. In 1890, James published *The Principles of Psychology*, a seminal work that established a foundation from which both fields of psychology and neuroscience would arise. In this book, he first describes organic matter as being 'plastic' and suggests the possibilities that brain tissue is capable of changing its physiology in response to the environment:

"Two elementary brain processes have been active together or in immediate succession, one of them, on reoccurring, tends to propagate its excitement into the other" (James, 1890).

The predominant theory of brain tissue at the time James wrote his *Principles of Psychology* was the 'diffuse nerve net' or reticular theory endorsed by the Nobel Prize laureate Camille Golgi and followers. This theory described the nervous system as a single diffuse network (Berlucchi, 2009). This theory was soon replaced with 'Neuron theory' proposed and encouraged by Santiago Ramon y Cajal in the final decade of the 19th century. Cajal discovered the axonal growth cone and determined that brain tissue was not a continuous diffuse network but composed of discrete, specialized cells that somehow communicate with one another (Finger, 2000). In 1893, the Italian psychiatrist Eugenio Tanzi, proposed that waves of excitation in the brain could cross distances that we now call synaptic clefts. He speculated that if these waves were repeated within a neural pathway through behavioral conditioning or learning, this could lead to

hypertrophy of associated neurons within this path and reduce resistance, making the crossing between neurons easier (Berlucchi, 2009). Building off this idea, Cajal expanded the theory that pathways in the brain changed over time, adding his belief that these networks required the creation of new pathways through growth of dendritic arborization and axonal branching and that this could be directly associated to the addition or loss of mental faculties (Azmitia, 2007). This speculation could be investigated and confirmed following the pioneering work of Charles Sherrington, in which he revealed the existence of the synapse between neurons and the unidirectionality along neural pathways (Pearce, 2004). Karl Lashley, a student of the prominent creator of behaviorist psychology James B. Watson, explored these theories of activity-dependent plasticity by examining changes in the cortex following behavioral training or changes in behavior following lesions to the cortex. He discovered that memories were not localized in the brain, but were spread out through networks in the cortex. He designed two theories that have become integral to the study of neuroplasticity: The theories of mass action and equipotentiality. The theory of mass action suggests the quality of learning depends on the amount of cortex available; damage to the cortex results in lower quality of performance dependent on the amount of tissue destroyed. The theory of equipotentiality describes cortical tissue as being capable of taking over function from any surrounding tissue. If cortical tissue is damaged within a region, surrounding tissue can take over the functional loss of that lesion (Josselyn, 2010). Lashley's discoveries were important to plasticity because they revealed that the brain was highly malleable and could be shaped on a larger scale than ever conceived.

Early research into neuroplasticity revealed many findings about how the brain structurally organizes itself and develops, but by the mid 20th century these theories were poorly connected and accepted universally until 1949 when Donald Hebb published *The Organization of Behavior* (Berlucchi, 2009). Hebb proposed that conditioning in the brain, specifically learned tasks, occurs through the strengthening of weak or nonexistent synapses through chemical modification or changes in electrical properties (Hebb, 1949).

"…when an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency as one of the cells firing B is increased." (Hebb, 1949).

This concept of Hebbian plasticity established that learning and training alters the brain through repeated stimulation that develops neural pathways, strengthening communication at the synapse between neurons in a network. The field of activity-dependent plasticity, the idea that experience, training and environmental stimuli can shape the organization of brain tissue grew from these studies (Berlucchi, 2009).

Activity-Dependent Structural Plasticity

Numerous studies have observed significant structural changes in response to activity/experience (Maguire, 2000; Bermudez, 2009; Schneider, 2002, Draganski, 2004), disease (Jubault, 2010), genetic variations (Egon, 2003) and maturity (Chen, 2011; Erickson, 2011). One of the earliest landmark studies investigating the role of activity in brain reorganization examined the size of hippocampus within London taxi drivers

(Maguire, 2000). A large increase in the posterior hippocampus and decrease in the anterior hippocampus in taxi drivers compared to non-taxi drivers was observed. These changes in volume are regarded as being related to the drivers' dependence on spatial navigation for traversing the city efficiently (Maguire, 2000). This structural change was observed to be duration dependent, as time spent as a taxi driver was positively correlated with growth in the right posterior hippocampus and negatively correlated with growth in the anterior hippocampus (Maguire, 2000). A further study (Maguire, 2006) confirmed these results in comparison with bus drivers. Taxi drivers again exhibited an increase in gray matter in the right posterior hippocampus where as bus drivers did not. Bus drivers drive planned routes in repetition and therefore do not require spatial memory to perform and lack the structural alteration to the hippocampus (Maguire, 2006). In 2004, the May lab published a paper that revealed how repeated training could be used to directly alter brain structure. They trained participants to juggle over a 3-month period following a baseline scan. After this 3 month training, both participants and non-juggling controls were scanned again and these scans were compared to baseline. An increase in gray matter was discovered in the mid-temporal area (hMT/V5) and the left posterior intra-parietal sulcus in those that were taught to juggle (Draganski, 2004). A decrease in this change in gray matter was noted from a third scan following a 3 month period with no training or practice, but not significantly, leaving open the question of how long these effects persist (Draganski, 2004). These studies indicate that training and experience can impact the structural organization of the brain, however neither study provided any biological conclusion as to how and why these changes occurred.

A similar finding was uncovered more recently in mice using variations of the Morris water maze task. In 2011, Lerch et al. detailed how activity-dependent brain restructuring occurs within mice and how it can be measured through MRI. A task dependent increase in volume was discovered after mice were trained in either a spatially oriented swim maze task or a cued swim maze task. Mice trained to use spatial navigational cues posted around the maze to discover a platform showed a 3.1% increase in hippocampal volume as measured through high resolution MRI. Mice trained to use non-spatial cues to locate the platform, such as a 4-inch marker, had a 1.9% increase in the striatum, but no change in the hippocampus (Lerch, 2011). The hippocampal increase in volume was also significantly correlated with GAP-43 staining expression, an axonal growth cone marker, indicating a change in neuronal morphology may have contributed to these observed volume changes (Lerch, 2011).

Exercise

Exercise provides a robust model for investigating changes in brain shape and volume following activity. Voluntary access to wheel running or forced treadmill leads to extensive, global changes to the brain including neurogenesis (Van Praag, 1999; Van praag, 2005; Li, 2013), angiogenesis (Swain, 2003; Kleim, 2002), astrocytosis (Li, 2005) and cortical thickness (Anderson, 2002).

Numerous studies have provided observations of exercise driven changes in the brain, but few connect the cellular and biochemical mechanisms that underlie these changes. We

were interested in designing an assay to induce a structural brain change within a mouse brain measurable *in vivo* through MRI. This experiment consisted of three aims:

Aim 1 – Establish if six weeks of forced treadmill at escalating speed per week would induce an MRI detectable reorganization in brain structure in a living mouse.

Aim 2 – Understand the cellular mechanisms that underlie MRI detectable changes in brain structure

Aim 3 – Examine how structural brain reorganization changes in aging and cognitively impaired mice

In order to investigate if we could induce a structural brain change detectable by MRI, we trained mice on a 5-lane treadmill for 6 weeks to induce a change in brain shape measurable through MRI. Several studies (Soya, 2007; Lin 2012, Liu, 2009) characterized forced treadmill as an appropriate platform for this induction. We expected that by using a simple motor task like the treadmill, we could induce discrete and bilateral changes in structure within the brain, which could then be investigated histologically.

Methods:

Mice:

27 male (aged 90 days) CD1 mice (Charles River, Senneville, QC) littermates were used in these experiments. Animals were housed 3 – 4 per cage in standard housing conditions. Mice were housed under a 12-h light: 12-h dark schedule and fed standard laboratory chow and water ad libitum. Experiments were approved by the Animal Ethics Committee of the Montreal Neurological Institute and McGill University, and were conducted in accordance with the guidelines of the Canadian Council on Animal Care (CCAC).

Exercise Training Procedures:

Exercise testing was conducted on a 5-lane treadmill for mice (Harvard Apparatus, Saint Laurent, Quebec), located in a behavioral testing room approved by the Animal Ethics Committee of the Montreal Neurological Institute and McGill University.

All mice were initially trained together for 7 days under low speeds (15cm/sec) for 15 minutes per day to familiarize all mice to the treadmill procedure. Following this training, the mice were split into two groups: exercise and sedentary control. Mice in the exercise group (n = 15) were forced to run on a treadmill each day (09:30am +/- 60 minutes) for 60 minutes, 6 days a week, at escalating speeds beginning at 24cm/sec on

week 1 and increasing 1cm/sec per week to 29cm/sec on week 6. The added distance of one centimeter increases total distance in 60 minutes by 36 meters per week (1cm/sec = 36 meters/60mins). We measured front right footfalls with slow motion video and found an average increase of 8.75% in total footfalls with each additional cm/sec per week.

In vivo MRI Acquisition:

Mice were anesthetized with an induction dose of 4–5% sevoflurane and secured in an MRI compatible bed. All MRI studies were performed under 2.5–3% sevoflurane in medical air and animals were allowed to breathe spontaneously without mechanical ventilation. Respiration rate and body temperature were continuously monitored using an MR-compatible system (Small Animal Instruments Inc., Stony Brook, NY) and the temperature was maintained at 37 ± 0.2 °C throughout the study using a feedback-regulated warming system (Small Animal Instruments Inc., Stony Brook, NY). All MR images were obtained from a 7T Bruker Pharmascan system (Bruker Biospin, Ettlingen, Germany) using a 28-mm inner- diameter, quadrature volume resonator (RAPID MR International, Columbus, OH). Anatomical images were acquired using a 3D balanced Steady-State Free Precession (b-SSFP) sequence with repetition time (TR) = 5. 2 ms, echo time (TE) = 2. 6 ms, flip angle = 30°, matrix size = 128 × 128 × 64, field-of-view = 1. 8 × 1. 8 × 0. 9 cm, spatial resolution = 140 × 140 × 140 μm, number of phase-cycles = 4, number of averages = 4, and acquisition time = 35 min. The phase- cycled images were combined using the sum-of-squares reconstruction method in order to minimize banding artifacts (Bangerter et al., 2004).

MRI Processing:

An unbiased, symmetric, customized template was generated using the anatomical scans from the 27 CD1 male mice using an iterative process (Fonov et al., 2011; Lau et al., 2008). Prior to template generation, each reconstructed image volume underwent image non-uniformity correction using the N3 algorithm (Sled et al., 1998), brain masking, and linear spatial normalization utilizing a 12-parameter affine transformation (Collins et al., 1994) to map individual images from native coordinate space to reference space. Briefly, the template generation process involved an iterative (coarse-to-fine resolution) estimation of the nonlinear transformation to match each MRI scan to the evolving average of the population (Grand'maison et al., 2013). The final anatomical template (population average) was generated with an isotropic voxel resolution of 0.06 mm. This customized template was parcellated into an atlas, including the following neocortical and subcortical regions: anterior cingulate cortex, entorhinal cortex, motor cortex, posterior cingulate cortex, retrosplenial cortex, somatosensory cortex 1, somatosensory cortex 2, hippocampus and amygdala, using the Montreal Neurological Institute (MNI) DISPLAY software package (http://www.bic.mni.mcgill.ca).

Measuring ROI-based Cortical Thickness

For cortical thickness measurements, the cortical mask with inside, outside, interhemispheric, and resistive boundaries was nonlinearly aligned with each subject using the template-to-subject transformation. Streamlines running from the inner to outer boundaries of the cortex were defined using Laplace's equation and their length was used as the measure of cortical thickness (Lerch et al., 2008). The mean cortical thickness was computed from an intermediate surface for each of the pre-defined ROIs from the

spatially normalized thickness maps. Whole cortical volume was also computed from the transformed cortical mask for each subject.

Measuring ROI-based Volume

Regional volumes were measured using a fully automated, atlas-based segmentation method. Briefly, ROI labels from a parcellated atlas were mapped to each subject image volume in native space by nonlinear registration (Collins, 1995).

Statistics and Analysis

Statistical analysis was performed using GraphPad Prism Software (http://www.graphpad.com/scientific-software/prism/). ROI-based measures from the left and right hemispheres were combined, and quantitative results are expressed as mean ± standard deviation of the effect of interest. Specifically, a Student's two-tailed t-tests were used for group comparisons. The data was adjusted for multiple comparisons using the Bonferroni correction and $p < 0.05$ was considered significant.

Results:

3-month old male CD1 mice (EX, n = 15) were trained on a 5-lane treadmill at escalating weekly speeds to induce structural changes detectable by MRI. Volume and cortical thickness measurements were compared to a sedentary control (SC, n = 12) that experienced no added training or handling. All animals were scanned at 3-months for baseline comparison. After 6 weeks of treadmill training, all mice were scanned again, and neuroanatomic volume and cortical thickness were measured for multiple regions for comparison.

Longitudinal cortical thickness measurements from CD1 mice

The initial investigation into structural changes following forced treadmill was to examine cortical thickness changes in regions associated with learning and exercise. From the cortical mask aligned to each subject, we attained mean cortical thickness from each of the predetermined ROIs. Examination and statistical testing on these measurements revealed no significant distinctions between exercised mice and sedentary controls (**Fig. 1**). These results indicate that 6 weeks of forced treadmill had no significant effect on cortical thickness compared to sedentary controls.

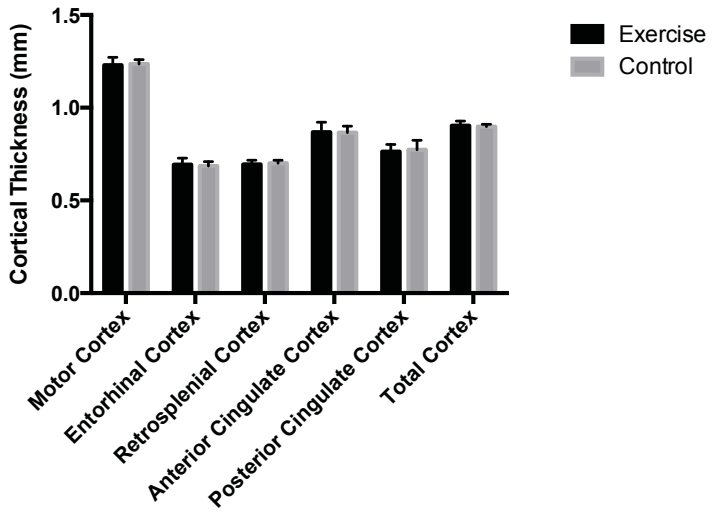

Figure. 1. Regional MRI cortical thickness measures from 3-month old male CD1 mice following 6 weeks of forced treadmill. No differences were found between exercised mice and controls at $p < 0.05$ significance.

Longitudinal volume measurements from CD1 mice

The next investigation to discover if 6 weeks of forced treadmill influenced brain structure measured the total volume of 12 regions, specifically: Lateral Ventricles, Striatum, Thalamus, Hippocampus, Amygdala, Motor Cortex, Entorhinal Cortex, Retrosplenial Cortex, Anterior Cingulate Cortex, Posterior Cingulate Cortex, Somatosensory Cortex 1, and Somatosensory Cortex 2 (**Table. 1 + Fig. 2**). This analysis revealed a significant increase of total volume in both the amygdala ($t(24) = 3.059$, $p = 0.03$) and hippocampus ($t(24) = 3.417$, $p = 0.013$) within the EX group compared to SC, after an unpaired, two tailed t-test corrected for multiple comparisons. No other regions were significant at $p < 0.05$.

Regions	Grouping	Baseline Volume (mm^3)	Post Exercise Volume (mm^3)	t Value (EX vs. SC, Post Exercise)	Corrected p-value
Lateral Ventricles	Exercise Group	5.89	6.6	0.24	0.82
	Sedentary Control	6.61	6.55		
Somatosensory 1	Exercise Group	13.77	13.4	0.02	0.98
	Sedentary Control	14.25	13.4		
Somatosensory 2	Exercise Group	8.5	7.76	0.56	0.58
	Sedentary Control	8.07	7.61		
Striatum	Exercise Group	22.3	23.21	1.72	0.1
	Sedentary Control	21.7	22.36		
Thalamus	Exercise Group	20.17	20.7	1	0.33
	Sedentary Control	19.84	20.24		
Motor Cortex	Exercise Group	13.95	13.4	0.25	0.8
	Sedentary Control	13.65	13.55		
Hippocampus	Exercise Group	28.37	32.27	3.42	0.012*
	Sedentary Control	28.51	29.7		
Amygdala	Exercise Group	13.54	14.34	3.06	0.03*
	Sedentary Control	13.58	13.39		
Entorhinal Cortex	Exercise Group	10.22	10.38	1.32	0.2
	Sedentary Control	10	9.98		
Retrosplenial Cortex	Exercise Group	8.46	8.82	0.45	0.65
	Sedentary Control	8.69	8.38		
Anterior Cingulate Cortex	Exercise Group	1.22	1.28	0.27	0.79
	Sedentary Control	1.19	1.25		
Posterior Cingulate Cortex	Exercise Group	1.23	1.12	0.39	0.69
	Sedentary Control	1.25	1.15		
Total Intracranial Volume	Exercise Group	509.8	536.64	1.47	0.16
	Sedentary Control	508.4	519.3		

Table. 1. Volume data from all regions and groups. An unpaired T-test was performed on post exercise values (EX vs. SC) to compare volume change following 6 weeks of treadmill or no exercise. Corrected $p < 0.05$ was considered significant.

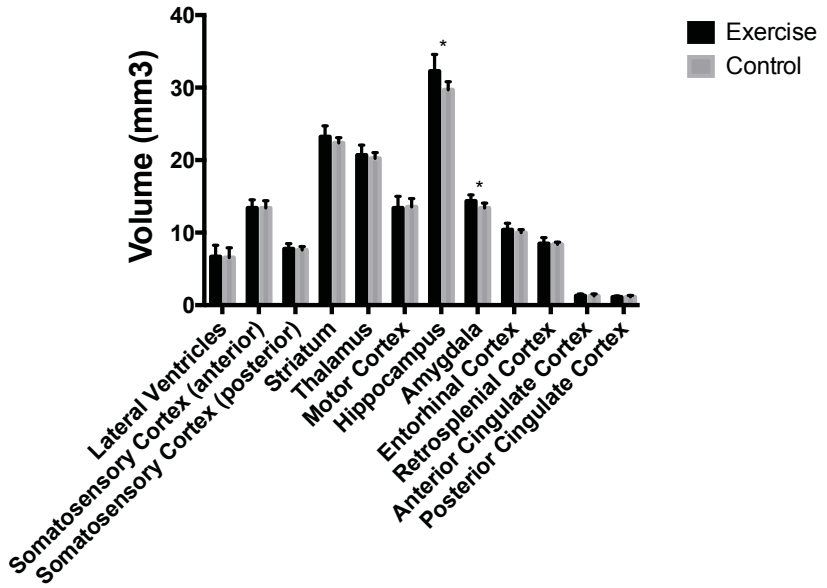

Figure. 2. Regional MRI volume measures from 3-month old male CD1 mice following 6 weeks of forced treadmill (exercise) and sedentary controls (controls). Both the amygdala ($t(24) = 3.059$, $p = 0.03$) and hippocampus ($t(24) = 3.417$, $p = 0.013$) had increased total volume after correcting for multiple comparisons. * indicates $p < 0.05$.

Volume measurements of hippocampus in mice after forced treadmill

Analysis of the hippocampus revealed a significant increase in volume ($t(24) = 3.417$, $p = 0.013$) of mice following 6 weeks of forced treadmill compared to sedentary controls (**Fig. 3**). Mean hippocampal volume measured at baseline was 28.37mm^3 in EX group. Measurements following exercise revealed an increase of 3.9mm^3 to 32.27, or a 13.7% increase in volume from baseline. Controls increased from 28.51mm^3 at baseline to 29.7, an increase of 1.19mm^3, a 4.1% increase.

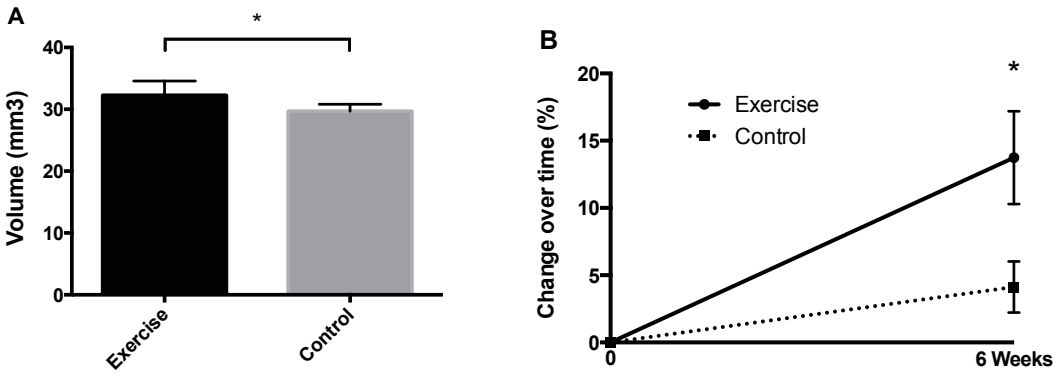

Figure. 3. Raw MRI volume measures of hippocampus (A) and % change over time (B) from 3-month old male CD1 mice following 6 weeks of forced treadmill (exercise) and sedentary controls (controls). * indicates $p < 0.05$.

Volume Measurements of amygdala in mice after forced treadmill

Analysis of the amygdala complex revealed a significant increase in volume ($t(24) = 3.059$, $p = 0.03$) of mice following 6 weeks of forced treadmill compared to sedentary controls (**Fig. 4**). Mean amygdala volume measured at baseline was 28.52mm^3 in SC group, which increased by 1.17mm^3 to 29.69mm^3, or a 4.1% increase in volume following a 6-week sedentary period. Controls showed a decrease in volume from 13.58 to 13.39mm^3 after 6 weeks or a loss of 1.4%.

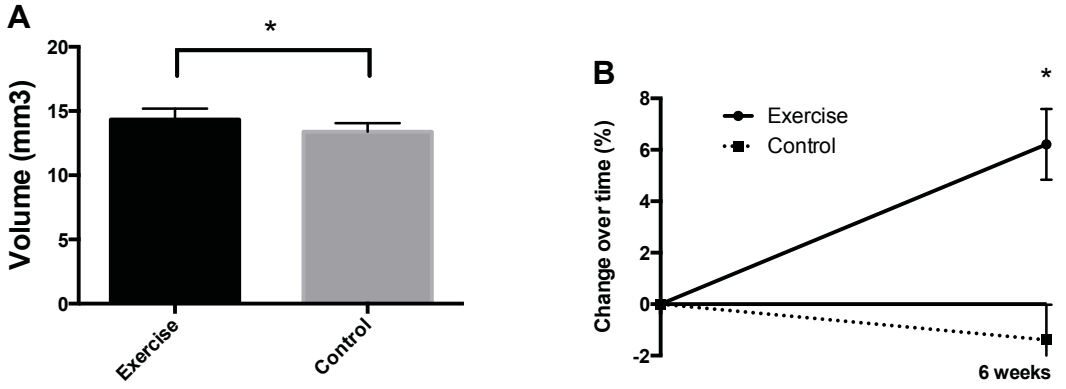

Figure. 4. Raw MRI volume measures of amygdala complex (A) and % change over time (B) from 3-month old male CD1 mice following 6 weeks of forced treadmill (exercise) and sedentary controls (controls). * indicates $p < 0.05$.

Discussion:

Exercise induces large structural volume changes

These results establish that forced treadmill at escalating speeds can induce an MRI detectable reorganization in brain structure in mice. Six weeks of forced treadmill led to a 9.6% increase in hippocampal volume over sedentary controls and a 7.6% larger increase in volume of the amygdala over controls, which showed a non-significant reduction in volume from baseline. Despite these large alterations in brain shape, no significant decrease in total intracranial volume was discovered, nor a volumetric decrease in any of the examined regions, suggesting this increase may have been compensated for globally in small cellular changes. Such significant increases in volume were unexpected as evidence previous characterized increases less then 2% in humans following exercise (Erickson 2011).

Exercise induced no detectable change in cortical thickness

There are numerous studies observing an increase in angiogenesis within the motor cortical regions following exercise (Swain, 2003; Kleim, 2002, Van Praag, 2005). We were interested in investigating whether this increase in vasculature was affecting the thickness of the cortex within regions associated with exercise and training. Of the 6 regions chosen, no change in thickness was measured from baseline. Finding no change in thickness conflicts with Anderson et al., that found female rats given voluntary access to wheel running increased cortical thickness in a small region of the motor cortex (Anderson et al. 2002). This conflict is likely due to differences in methodology, as they

performed thickness measurements on post mortem sliced and stained tissue that, rather than MRI and cortical masking. Measuring thickness on post mortem tissue that has been sliced, processed and stained often distorts and reshapes the tissue, allowing for more inaccurate measurements. The effect differences between using wheel vs. treadmill likely had a large impact, as well as using females vs. males or rats vs. mice.

Cellular physiology underlying volume change in hippocampus

We are currently performing histological investigation to uncover the cellular changes associated with the increase in hippocampal volume. A large number of studies have observed changes in the hippocampus following various methods of exercise (Erickson, 2010; Van Praag, 1999; Van Praag, 2005; Kitamura, 2003; O'Callaghan, 2007; Adlard, 2004; Adlard, 2005; Liu, 2009; Neeper, 1996). Hippocampal changes in animals following one week or more of wheel running or forced treadmill include an increase in neurogenesis (Van praag, 1995; Van praag, 2005; Kitamura, 2003), enhanced LTP (O'Callaghan, 2007), increased BDNF (Liu, 2009; Adlard, 2005; Kitamura, 2003; Neeper, 1996; Berchtold, 2005), increased glutamate receptors (Lou, 2008; Kitamura, 2003; Dietrich, 2005; Farmer, 2004), increases in dendritic and axonal remodeling (Lin, 2012; Olson, 2006), and gliogenesis (Li, 2005; Ehniger, 2003). Increases in BDNF within the hippocampus following exercise correlate highly with increased neurogenesis in the dentate gyrus as well as better performance in memory tasks (Van praag, 2005; O'Callaghan, 2007; Liu, 2009). BDNF, injected directly into the dentate gyrus increases neurogenesis (Scharfman, 2005). Cultured hippocampal neurons that receive acute and gradual increases in BDNF result in neurite branching and dendritic spine development,

through the activation of its trkB receptor pathway. Damage that occurs in the hippocampus following chronic periods of stress is also mediated through the actions of glucocorticoids on BDNF (Schaaf, 1998). These observations led us to believe the volume increase observed within the hippocampus is likely due to an increase in expression of BDNF following regular exercise. BDNF is shown to increase neurogenesis (Sharfman, 2005) and dendritic remodeling in the hippocampus, through an activity-dependent mechanism (Kellner, 2014). This activity-dependent increase in BDNF within the hippocampus can be mediated by glutamate signaling through the phospholipase C signaling pathways (Canossa, 2001). Glutamate activation is shown to directly stimulate BDNF in hippocampal neurons, providing a mechanism for activity-dependent BDNF release (Hartmann, 2001). Glutamate receptors and mediators, such as GluR1, GluR2/3, SAP-97 and GRIP-1 are increased in mouse cortical tissue following exercise (Dietrich, 2005; Real, 2010), and forced treadmill directly enhanced LTP in the dentate gyrus (O'Callaghan, 2007) and increased NMDAR1 mRNA expression in the hippocampus, which was directly associated with enhanced BDNF expression (Lou, 2008). Taken together, it appears long-term exercise training may trigger large changes of glutamate signaling in the hippocampus, enhancing LTP and synaptic remodeling. This increased glutamate signaling increases BDNF within the hippocampus, increasing neurogenesis, axonal and dendritic remodeling and spine density. It is possible that through these actions, exercise is increasing hippocampal volume.

Cellular physiology underlying volume change in amygdala

The volume increase within the amygdala complex following forced treadmill is due most likely to the effects of stress/fear rather than through training. Direct comparisons between forced treadmill and voluntary wheel running indicate the treadmill provides a larger stress and fear component, due likely to the shock received for noncompliance and the absence of choice. Wheel access provides an enrichment novelty that mice have freedom to utilize, whereas the treadmill is a forced activity. Both wheel running and treadmill improve performance in water maze tasks, as well as enhanced expression of BDNF-trkB signaling within the hippocampus, but only the treadmill improved performance on the passive/avoidance test (Liu, 2009), which involves shocking an animal as it moves from a brightly lit chamber to darkness, then measuring its latency to enter the darkness upon testing after an extended period. This test is recognized as measuring fear memory. As well, only treadmill enhanced BDNF-trkB signaling in the amygdala (Liu, 2009). If forced treadmill is viewed as a model of fear conditioning, a mechanism for amygdala growth becomes clear. Fear conditioning induces behavioral LTP in the amygdala (Rattiner, 2005). As well, BDNF mRNA expression is elevated in the basolateral amygdala in the period just following fear conditioning (Rattiner, 2004). Volume growth within the amygdala complex following forced treadmill is likely a reflection of enhanced synaptic activity and BDNF expression due to fear learning, leading to increased dendritic spine density and neurite growth. It would not be expected that hippocampal growth was due to a fear conditioning as chronic restraint stress simultaneously increases dendritic spine density and growth in the basolateral amygdala (BLA) while causing dendritic atrophy within the hippocampus (Lakshminarasimhan, 2012). Consideration of fear conditioning as a cause of amygdala increase should be

noted as conflicting to hippocampal findings as fear conditioning leads to atrophy within the hippocampus (Lakshminarasimhan, 2012). These findings of chronic restraint stress were also associated with an increase in BDNF in the BLA, and reduced BDNF in the hippocampus (Lakshminarasimhan, 2012).

Current/Future Work

The work described here indicates that 6 weeks of forced treadmill induces a nearly 10% larger increase in hippocampal volume and nearly a 6% larger increase in amygdala volume compared to sedentary controls. Evidence suggests this growth may be due to glutamate signaling, LTP enhancement and BDNF expression within the regions, leading to increased neurogenesis, neurite remodeling and an increase in dendritic spine density. Histological investigation is on going to confirm or reject this speculation.

Using the template created by averaging all the MRI sections from all mice, we can reconstruct stained sections to fit within the regions structurally altered and quantify all markers within. Immunostaining and 3D reconstruction of stained sections for stereology may indicate how these volume changes are occurring structurally. Markers of neuronal density such as the neuronal nuclear antigen NeuN, for astrocytosis using glial fibrillary acidic protein (GFAP) and neuronal morphology like GAP43, an axonal growth cone can be stained for and reconstructed to count total signal within a single region such as the complete hippocampus. Markers for glutamate receptors, BDNF and trkB and plasticity can be measured as well to reveal how these structural changes are mediated.

Having established that exercise from forced treadmill at escalating speeds can induce a structural brain change, this platform can be used to understand how the brain structurally reorganizes in various transgenic models and circumstances.

Forced treadmill on aging and cognitively impaired mice

The forced treadmill platform will be utilized to understand how exercise influences brain structure in an aging mouse model with amyloidosis to investigate how Alzheimer's disease might affect plasticity and training. Twenty-nine male mice aged 10 – 12 months, with an overexpression of the Swedish (670/671KM→NL) and Indiana (717V→F) mutations of human APP will been scanned at baseline and trained under the same treadmill protocol as the CD1 mice to induce structural changes in the brain. Following training, all mice will be scanned again and sacrificed to analyze for volume and cortical thickness measures, corresponding histology and 3D reconstruction for stereology as previously described. By understanding how aged animals with amyloidosis are being affected by exercise, we can observe how structural plasticity changes over time and how it is affected under pathological circumstances.

Forced treadmill on Brainbow mice

An interesting model to investigate how forced treadmill effects neural pathways and specific cell types is the Brainbow mouse. Developed by the labs of Jeff Lichtman and Joshua Sanes at Harvard, the Brainbow mouse was first presented in a 2007 Nature paper (Livet, 2007). Brainbow mice utilize the Cre-Lox recombination to splice specifically

targeted DNA sections, inserting randomly arranged fluorescent protein genes that are divided by loxP sites. In the presence of the Cre recombinase, this inserted transgene undergoes an excision event that promotes expression of these fluorescent genes. These sites have multiple copies of the transgene allowing for each neuron to express one of a wide variety of fluorescent combinations and emit a distinctive hue (Livet, 2007). The ability to fluorescently label neuron types in mice that are forced to run at escalating speeds would allow us to visualize the distinct changes in neural pathways associated with structural reorganization of the brain.

Platforms for inducing structural change

Forced treadmill requires little behavioral training and cognitive functioning for the mouse. Most mice adapt to the 60-minute protocol within the first 10 days and maintain a consistent pace through the 6-week experimental period. This simplistic training may limit the amount of tissue structurally affected. To investigate how other regions are reorganized structurally, it is necessary to train under different protocols that utilize more or specialized brain functioning.

The Barnes maze can be utilized to measure spatial learning and memory and how the brain reshapes in response to a more cognitive task. Mice are placed in the center of a large circular field with bright lights above and 20 indentions surrounding the circumference. One of these 20 indentions opens to a dark chamber where the mouse can escape the light, as mice are nocturnal and bright lighting is a strong aversion. Navigational markers are placed on walls surrounding the table to provide the mouse

with spatial cues. Latency to find the dark chamber is measured and shorter durations are accepted as learning the maze. Training on the Barnes maze targets more cognitive and spatial mapping regions of the brain and are likelier to induce structural changes in regions more associated with spatial memory and learning, as well as having a more global effect on the brain as the animal attempts to 'solve' a task under aversive pressure.

Environmental Enrichment was the first assay used to analyze structural brain changes and could be a valuable tool for inducing changes in cortical structure (Diamond, 2001). In the 1960's, Marion Diamond and colleagues revealed that rats living under enriched conditions for 30 days had greater cortical thickness than rats in standard or impoverished living conditions (Kerch, 1960). Environmental enrichment was defined as 12 animals living together in a large cage that contained 5 – 6 objects to play with or climb upon (e.g., wheels, ladders, small mazes). These objects were changed twice a week to maintain novelty (Krech, 1960). These were compared to standard housing conditions with three animals to a small cage with no objects and impoverished conditions with a single housed animal with no objects. Under these conditions, environmental enrichment led to an increase in cortical thickness globally which was associated to increased nerve cell size, dendritic lengthening and an increase in dendritic spine density (Krech, 1960). Environmental enrichment has also been associated with increased astrocytosis (Ehniger, 2003), improved spatial memory and maze performance (Leggio, 2005), dendritic spine development (Leggio, 2005; Mora, 2007), improved outcomes for many diseases

affecting the nervous system (Nithianantharajah, 2006) and a decrease in spontaneous apoptosis within the hippocampus (Young, 1999). Enrichment has long lasting, global effects, but little is known about the cellular physiology underlying these structural changes. Early studies measured a change in cortical thickness as measured by analyzing stained tissue on slides. This assay could be used to induce structural reorganization in the cortex that could be measured *in vivo* with more accurate MRI technology and histological 3D reconstruction for cellular analysis to better understand how the environment effects neurophysiology.

Conclusion

In this investigation, it was shown that 6 weeks of forced treadmill at escalating speeds led to an increase of almost 10% in hippocampal volume and an increase of almost 6% in amygdala volume compared to sedentary controls. Ongoing histological investigation will reveal the cellular changes that occurred with these increases in volume. The significance of these investigations will become clearer once the cellular physiology is revealed. Studies like these advance techniques in noninvasive examination within living animals. Studies performed non-invasively *in vivo* have great potential in a clinical setting. Development of these tools improves diagnoses and aids in the understanding of how disease begins and manifests, which can lead to early prevention methods for neurological disorders such as Alzheimer's disease, Parkinson's disease, Multiple Sclerosis and various brain related cancers. With a better understanding of structural reorganization in response to the environment, we gain insight into cognition and how the human brain has evolved into the most complex object in the known universe.

Works Cited

Abel, T., Havekes, R., Saletin, J. M., & Walker, M. P. (2013). Sleep, plasticity and memory from molecules to whole-brain networks. *Current Biology : CB*, *23*(17), R774–88. doi:10.1016/j.cub.2013.07.025

Adlard, P. a, & Cotman, C. W. (2004). Voluntary exercise protects against stress-induced decreases in brain-derived neurotrophic factor protein expression. *Neuroscience*, *124*(4), 985–92. doi:10.1016/j.neuroscience.2003.12.039

Adlard, P. a, Perreau, V. M., & Cotman, C. W. (2005). The exercise-induced expression of BDNF within the hippocampus varies across life-span. *Neurobiology of Aging*, *26*(4), 511–20. doi:10.1016/j.neurobiolaging.2004.05.006

Akbik, F., Cafferty, W. B. J., & Strittmatter, S. M. (2012). Myelin associated inhibitors: a link between injury-induced and experience-dependent plasticity. *Experimental Neurology*, *235*(1), 43–52. doi:10.1016/j.expneurol.2011.06.006

Akers, K. G., Martinez-Canabal, a., Restivo, L., Yiu, a. P., De Cristofaro, a., Hsiang, H.-L., … Frankland, P. W. (2014). Hippocampal Neurogenesis Regulates Forgetting During Adulthood and Infancy. *Science*, *344*(6184), 598–602. doi:10.1126/science.1248903

Alon, U. (2009a). How to choose a good scientific problem. *Molecular Cell*, *35*(6), 726–8. doi:10.1016/j.molcel.2009.09.013

Amedi, A., Raz, N., Pianka, P., Malach, R., & Zohary, E. (2003). Early "visual" cortex activation correlates with superior verbal memory performance in the blind. *Nature Neuroscience*, *6*(7), 758–66. doi:10.1038/nn1072

Anderson, B. J., Eckburg, P. B., & Relucio, K. I. (2002). Alterations in the thickness of motor cortical subregions after motor-skill learning and exercise. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *9*(1), 1–9. doi:10.1101/lm.43402

Arshavsky, Y. I. (2006). "The seven sins" of the Hebbian synapse: can the hypothesis of synaptic plasticity explain long-term memory consolidation? *Progress in Neurobiology*, *80*(3), 99–113. doi:10.1016/j.pneurobio.2006.09.004

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry--the methods. *NeuroImage*, *11*(6 Pt 1), 805–21. doi:10.1006/nimg.2000.0582

Azmitia, E. C. (2007). Cajal and brain plasticity: Insights relevant to emerging concepts of mind. *Brain Research Reviews*, *55*(2), 395–405. doi:10.1016/j.brainresrev.2007.01.010

Badhwar, A., Lerch, J. P., Hamel, E., & Sled, J. G. (2013). Impaired structural correlates of memory in Alzheimer's disease mice. *NeuroImage. Clinical*, *3*, 290–300. doi:10.1016/j.nicl.2013.08.017

Badre, D., & Wagner, A. D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia*, *45*(13), 2883–901. doi:10.1016/j.neuropsychologia.2007.06.015

Bao, S., Chan, V. T., & Merzenich, M. M. (2001). Cortical remodelling induced by activity of ventral tegmental dopamine neurons. *Nature*, *412*(6842), 79–83. doi:10.1038/35083586

Barrickman, N. L., Bastian, M. L., Isler, K., & van Schaik, C. P. (2008). Life history costs and benefits of encephalization: a comparative test using data from long-term studies of primates in the wild. *Journal of Human Evolution*, *54*(5), 568–90. doi:10.1016/j.jhevol.2007.08.012

Barth, A. L., & Kuhlman, S. J. (2013). The many layers of specification and plasticity in the neocortex. *Neuron*, *79*(5), 829–31. doi:10.1016/j.neuron.2013.08.021

Basser, P. J., & Evren, Ö. (2009). Introduction to Diffusion MR, 3–10.

Bavelier, D., Green, C. S., Han, D. H., Renshaw, P. F., Merzenich, M. M., & Gentile, D. a. (2011). Brains on video games. *Nature Reviews. Neuroscience*, *12*(12), 763–8. doi:10.1038/nrn3135

Becker, J. A., Hedden, T., Carmasin, J., Maye, J., Rentz, D. M., Putcha, D., … Johnson, K. a. (2011). Amyloid-β associated cortical thinning in clinically normal elderly. *Annals of Neurology*, *69*(6), 1032–42. doi:10.1002/ana.22333

Belarbi, K., Burnouf, S., Fernandez-Gomez, F.-J., Laurent, C., Lestavel, S., Figeac, M., … Blum, D. (2011). Beneficial effects of exercise in a transgenic mouse model of Alzheimer's disease-like Tau pathology. *Neurobiology of Disease*, *43*(2), 486–94. doi:10.1016/j.nbd.2011.04.022

Belmonte, M. K., Cook, E. H., Anderson, G. M., Rubenstein, J. L. R., Greenough, W. T., Beckel-Mitchener, a, … Tierney, E. (2004). Autism as a disorder of neural information processing: directions for research and targets for therapy. *Molecular Psychiatry*, *9*(7), 646–63. doi:10.1038/sj.mp.4001499

Benowitz, L. I., & Routtenberg, a. (1997). GAP-43: an intrinsic determinant of neuronal development and plasticity. *Trends in Neurosciences*, *20*(2), 84–91. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9023877

Berchtold, N. C., Chinn, G., Chou, M., Kesslak, J. P., & Cotman, C. W. (2005). Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. *Neuroscience*, *133*(3), 853–61. doi:10.1016/j.neuroscience.2005.03.026

Berlucchi, G. (2002). The origin of the term plasticity in the neurosciences: Ernesto Lugaro and chemical synaptic transmission. *Journal of the History of the Neurosciences*, *11*(3), 305–9. doi:10.1076/jhin.11.3.305.10396

Berlucchi, G., & Buchtel, H. a. (2009). Neuronal plasticity: historical roots and evolution of meaning. *Experimental Brain Research*, *192*(3), 307–19. doi:10.1007/s00221-008-1611-6

Berrios, G. (n.d.). Cotards syndrome: analysis of 100 cases. *1997*.

Beth, A., Paul, D., Kathryn, C., & Adam, S. (2011). Effect of Exercise Training on Hippocampal Volume in Humans : A Pilot Study, *i*.

Bickart, K. C., Wright, C. I., Dautoff, R. J., Dickerson, B. C., & Barrett, L. F. (2011a). Amygdala volume and social network size in humans. *Nature Neuroscience*, *14*(2), 163–4. doi:10.1038/nn.2724

Bickart, K. C., Wright, C. I., Dautoff, R. J., Dickerson, B. C., & Barrett, L. F. (2011b). Amygdala volume and social network size in humans. *Nature Neuroscience*, *14*(2), 163–4. doi:10.1038/nn.2724

Biedermann, S., Fuss, J., Zheng, L., Sartorius, A., Falfán-Melgoza, C., Demirakca, T., … Weber-Fahr, W. (2012). In vivo voxel based morphometry: detection of increased hippocampal volume and decreased glutamate levels in exercising mice. *NeuroImage*, *61*(4), 1206–12. doi:10.1016/j.neuroimage.2012.04.010

Biology, M., & Solver, P. (n.d.). *Molecular Biology Problem Solver*.

Boccaletti, S., Latora, V., Moreno, Y., Chavez, M., & Hwang, D. (2006). Complex networks: Structure and dynamics. *Physics Reports*, *424*(4-5), 175–308. doi:10.1016/j.physrep.2005.10.009

Bock, O. (2013). Cajal, Golgi, Nansen, Schäfer and the neuron doctrine. *Endeavour*, *37*(4), 228–34. doi:10.1016/j.endeavour.2013.06.006

Bouzas-rodriguez, J., Cabrera, J. R., Delloye-bourgeois, C., Ichim, G., Delcros, J., Raquin, M., … Mehlen, P. (2010). Neurotrophin-3 production promotes human neuroblastoma cell survival by inhibiting TrkC-induced apoptosis, *120*(3). doi:10.1172/JCI41013DS1

Boyke, J., Driemeyer, J., Gaser, C., Büchel, C., & May, A. (2008). Training-induced brain structure changes in the elderly. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *28*(28), 7031–5. doi:10.1523/JNEUROSCI.0742-08.2008

Bradbury, E. J., King, V. R., Simmons, L. J., Priestley, J. V, & McMahon, S. B. (1998). NT-3, but not BDNF, prevents atrophy and death of axotomized spinal cord projection neurons. *The European Journal of Neuroscience*, *10*(10), 3058–68. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9786200

Bruel-Jungerman, E., Laroche, S., & Rampon, C. (2005). New neurons in the dentate gyrus are involved in the expression of enhanced long-term memory following environmental enrichment. *The European Journal of Neuroscience*, *21*(2), 513–21. doi:10.1111/j.1460-9568.2005.03875.x

Bueller, J. a, Aftab, M., Sen, S., Gomez-Hassan, D., Burmeister, M., & Zubieta, J.-K. (2006). BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. *Biological Psychiatry*, *59*(9), 812–5. doi:10.1016/j.biopsych.2005.09.022

Buonomano, D. V, & Merzenich, M. M. (1998). CORTICAL PLASTICITY : From Synapses to Maps.

Buonomano, D. V, & Merzenich, M. M. (1998). Cortical plasticity: from synapses to maps. *Annual Review of Neuroscience*, *21*, 149–86. doi:10.1146/annurev.neuro.21.1.149

Burgess, N., Maguire, E. a, & O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron*, *35*(4), 625–41. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12194864

Burghardt, P. R., Fulk, L. J., Hand, G. a, & Wilson, M. a. (2004). The effects of chronic treadmill and wheel running on behavior in rats. *Brain Research*, *1019*(1-2), 84–96. doi:10.1016/j.brainres.2004.05.086

Busch, V., Schuierer, G., Bogdahn, U., & May, A. (n.d.). Changes in grey matter induced by training Newly honed juggling skills show up as a transient feature on a brain-imaging scan ., 311–312.

Bussey, T. J., Holmes, a, Lyon, L., Mar, a C., McAllister, K. a L., Nithianantharajah, J., … Saksida, L. M. (2012). New translational assays for preclinical modelling of cognition in schizophrenia: the touchscreen testing method for mice and rats. *Neuropharmacology*, *62*(3), 1191–203. doi:10.1016/j.neuropharm.2011.04.011

Bussey, T. J., Padain, T. L., Skillings, E. a, Winters, B. D., Morton, a J., & Saksida, L. M. (2008). The touchscreen cognitive testing method for rodents: how to get the best out of your rat. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *15*(7), 516–23. doi:10.1101/lm.987808

Butz, M., Wörgötter, F., & van Ooyen, A. (2009). Activity-dependent structural plasticity. *Brain Research Reviews*, *60*(2), 287–305. doi:10.1016/j.brainresrev.2008.12.023

Buzsáki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science (New York, N.Y.)*, *304*(5679), 1926–9. doi:10.1126/science.1099745

Buzsáki, G., Logothetis, N., & Singer, W. (2013). Scaling brain size, keeping timing: evolutionary preservation of brain rhythms. *Neuron*, *80*(3), 751–64. doi:10.1016/j.neuron.2013.10.002

Calabrese, R. L. (2007). Motor networks: shifting coalitions. *Current Biology : CB*, *17*(4), R139–41. doi:10.1016/j.cub.2006.12.007

Carbonell, F., Charil, A., Zijdenbos, A. P., Evans, A. C., & Bedell, B. J. (2014). β-Amyloid is associated with aberrant metabolic connectivity in subjects with mild cognitive impairment. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, (February), 1–11. doi:10.1038/jcbfm.2014.66

Carmody, R. N., & Wrangham, R. W. (2009). The energetic significance of cooking. *Journal of Human Evolution*, *57*(4), 379–91. doi:10.1016/j.jhevol.2009.02.011

Cerovic, M., d'Isa, R., Tonini, R., & Brambilla, R. (2013). Molecular and cellular mechanisms of dopamine-mediated behavioral plasticity in the striatum. *Neurobiology of Learning and Memory*, *105*, 63–80. doi:10.1016/j.nlm.2013.06.013

Chae, C.-H., & Kim, H.-T. (2009). Forced, moderate-intensity treadmill exercise suppresses apoptosis by increasing the level of NGF and stimulating phosphatidylinositol 3-kinase signaling in the hippocampus of induced aging rats. *Neurochemistry International*, *55*(4), 208–13. doi:10.1016/j.neuint.2009.02.024

Champagne, F. a, & Curley, J. P. (2005). How social experiences influence the brain. *Current Opinion in Neurobiology*, *15*(6), 704–9. doi:10.1016/j.conb.2005.10.001

Chang, F. F., & Greenough, W. T. (1982). Lateralized effects of monocular training on dendritic branching in adult split brain rats, *232*, 283–292.

Chavis, P., & Westbrook, G. (2001). Integrins mediate functional pre- and postsynaptic maturation at a hippocampal synapse. *Nature*, *411*(6835), 317–21. doi:10.1038/35077101

Chen, M. J., & Russo-Neustadt, A. a. (2005). Exercise activates the phosphatidylinositol 3-kinase pathway. *Brain Research. Molecular Brain Research*, *135*(1-2), 181–93. doi:10.1016/j.molbrainres.2004.12.001

Chen, Z. J., He, Y., Rosa-Neto, P., Gong, G., & Evans, A. C. (2011). Age-related alterations in the modular organization of structural cortical network by using cortical thickness from MRI. *NeuroImage*, *56*(1), 235–45. doi:10.1016/j.neuroimage.2011.01.010

Chiang, M., Barysheva, M., Shattuck, D. W., Lee, A. D., Avedissian, C., Klunder, A. D., … Paul, M. (2009). GENETICS OF BRAIN FIBER ARCHITECTURE AND, *29*(7), 2212–2224. doi:10.1523/JNEUROSCI.4184-08.2009.GENETICS

Chomsky, N. (2002). The Faculty of Language. *Science (New York, N.Y.)*.

Churchill, J. D., Galvez, R., Colcombe, S., Swain, R. a, Kramer, A. F., & Greenough, W. T. (2002). Exercise, experience and the aging brain. *Neurobiology of Aging*, *23*(5), 941–55. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12392797

Cohen, J. E., Lee, P. R., Chen, S., Li, W., & Fields, R. D. (2011). MicroRNA regulation of homeostatic synaptic plasticity. doi:10.1073/pnas.1017576108/-/DCSupplemental.www.pnas.org/cgi/doi/10.1073/pnas.1017576108

Collins, D. L., Holmes, C. J., Peters, T. M., & Evans, A. C. (1996). Automatic 3-D Model-Based Neuroanatomical Segmentation, *208*(1995), 190–208.

Collins, D. L., Zijdenbos, A. P., Kollokian, V., Sled, J. G., Kabani, N. J., Holmes, C. J., & Evans, A. C. (1998). Digital Brain Phantom, *17*(3), 463–468.

Colom, R., Quiroga, M. Á., Solana, A. B., Burgaleta, M., Román, F. J., Privado, J., … Karama, S. (2012). Structural changes after videogame practice related to a brain network associated with intelligence. *Intelligence*, *40*(5), 479–489. doi:10.1016/j.intell.2012.05.004

Cortés-Mendoza, J., Díaz de León-Guerrero, S., Pedraza-Alva, G., & Pérez-Martínez, L. (2013). Shaping synaptic plasticity: the role of activity-mediated epigenetic regulation on gene transcription. *International Journal of Developmental Neuroscience : The Official Journal of the International Society for Developmental Neuroscience*, *31*(6), 359–69. doi:10.1016/j.ijdevneu.2013.04.003

Costa, D. a, Cracchiolo, J. R., Bachstetter, A. D., Hughes, T. F., Bales, K. R., Paul, S. M., … Potter, H. (2007). Enrichment improves cognition in AD mice by amyloid-related and unrelated mechanisms. *Neurobiology of Aging*, *28*(6), 831–44. doi:10.1016/j.neurobiolaging.2006.04.009

Cotman, C. W., & Berchtold, N. C. (2002). Exercise : a behavioral intervention to enhance brain health and plasticity, *25*(6), 295–301.

Cotman, C. W., Berchtold, N. C., & Christie, L.-A. (2007). Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends in Neurosciences*, *30*(9), 464–72. doi:10.1016/j.tins.2007.06.011

Crick, F. (n.d.). Function of Dream Sleep. *Function of Dream Sleep*.

Crick, F. (1988). @ Neural Edelmanism.

Cruikshank, S. J., & Weinberger, N. M. (1996). Evidence for the Hebbian hypothesis in experience-dependent physiological plasticity of neocortex: a critical review. *Brain Research. Brain Research Reviews*, *22*(3), 191–228. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8957560

Daniel H. Geschwind1, and P. R. (2013). Cortical Evolution: Judge the Brain by Its Cover. Neuron.

Davidson, R. J., Jackson, D. C., & Kalin, N. H. (2000). Emotion , Plasticity , Context , and Regulation : Perspectives From Affective Neuroscience, *126*(6), 890–909.

Dayan, E., & Cohen, L. G. (2011). Neuroplasticity subserving motor skill learning. *Neuron*, *72*(3), 443–54. doi:10.1016/j.neuron.2011.10.008

Debruyne, H. (n.d.). Cotards syndrome: a review. *2009*.

Deci, E. L., & Ryan, R. M. (2013). The " What " and " Why " of Goal Pursuits : of Behavior Human Needs and the Self-Determination, *11*(4), 227–268.

Deng, W., Saxe, M. D., Gallina, I. S., & Gage, F. H. (2009). Adult-born hippocampal dentate granule cells undergoing maturation modulate learning and memory in the brain. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *29*(43), 13532–42. doi:10.1523/JNEUROSCI.3362-09.2009

Desimone, R., & Duncan, J. (1995). NEURAL MECHANISMS OF SELECTIVE VISUAL, 193–222.

Dhenain, M., Ruffins, S. W., & Jacobs, R. E. (2001). Three-dimensional digital mouse atlas using high-resolution MRI. *Developmental Biology*, *232*(2), 458–70. doi:10.1006/dbio.2001.0189

Diamond, M. C. (2001). Response of the brain to enrichment. *Anais Da Academia Brasileira de Ciências*, *73*(2), 211–20. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11404783

Diamond, M. C., Rosenzweig, M. R., Edward, L., Lindner, B., & Lyon, L. (n.d.). IMPOVERISHMENT ON RAT CEREBRAL CORTEX The first part of this paper deals with rat brain anatomy as affected by variations of starting age and of duration of exposure to enriched (com- cortical depth measurements and weights of brain samples are compared , *3*(1), 47–64.

Dickerson, B. C., & Wolk, D. a. (2012a). MRI cortical thickness biomarker predicts AD-like CSF and cognitive decline in normal adults. *Neurology*, *78*(2), 84–90. doi:10.1212/WNL.0b013e31823efc6c

Dickerson, B. C., & Wolk, D. a. (2012b). MRI cortical thickness biomarker predicts AD-like CSF and cognitive decline in normal adults. *Neurology*, *78*(2), 84–90. doi:10.1212/WNL.0b013e31823efc6c

Dickerson, B. C., & Wolk, D. A. (2012c). ARTICLES MRI cortical thickness biomarker predicts AD-like CSF and cognitive decline in normal adults.

Dietrich, M. O., Mantese, C. E., Porciuncula, L. O., Ghisleni, G., Vinade, L., Souza, D. O., & Portela, L. V. (2005). Exercise affects glutamate receptors in postsynaptic densities from cortical mice brain. *Brain Research*, *1065*(1-2), 20–5. doi:10.1016/j.brainres.2005.09.038

Ditye, T., Kanai, R., Bahrami, B., Muggleton, N. G., Rees, G., & Walsh, V. (2013). Rapid changes in brain structure predict improvements induced by perceptual learning. *NeuroImage*, *81*, 205–12. doi:10.1016/j.neuroimage.2013.05.058

Doyon, J., & Benali, H. (2005). Reorganization and plasticity in the adult brain during learning of motor skills. *Current Opinion in Neurobiology*, *15*(2), 161–7. doi:10.1016/j.conb.2005.03.004

Draganski, B., Gaser, C., Kempermann, G., Kuhn, H. G., Winkler, J., Büchel, C., & May, A. (2006). Temporal and spatial dynamics of brain structure changes during extensive learning. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *26*(23), 6314–7. doi:10.1523/JNEUROSCI.4628-05.2006

Draganski, B., & Kherif, F. (2013). In vivo assessment of use-dependent brain plasticity--beyond the "one trick pony" imaging strategy. *NeuroImage*, *73*, 255–9; discussion 265–7. doi:10.1016/j.neuroimage.2012.08.058

Draganski, B., & May, a. (2008). Training-induced structural changes in the adult human brain. *Behavioural Brain Research*, *192*(1), 137–42. doi:10.1016/j.bbr.2008.02.015

Edelman, G. M. (1993). Neural Darwinism: selection and reentrant signaling in higher brain function. *Neuron*, *10*(2), 115–25. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8094962

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., … Weinberger, D. R. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*, *112*(2), 257–69. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12553913

Eggermont, L., Swaab, D., Luiten, P., & Scherder, E. (2006). Exercise, cognition and Alzheimer's disease: more is not necessarily better. *Neuroscience and Biobehavioral Reviews*, *30*(4), 562–75. doi:10.1016/j.neubiorev.2005.10.004

Ehninger, D., & Kempermann, G. (2003). Regional effects of wheel running and environmental enrichment on cell genesis and microglia proliferation in the adult murine neocortex. *Cerebral Cortex (New York, N.Y. : 1991)*, *13*(8), 845–51. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12853371

Engel, a K., Fries, P., & Singer, W. (2001). Dynamic predictions: oscillations and synchrony in top-down processing. *Nature Reviews. Neuroscience*, *2*(10), 704–16. doi:10.1038/35094565

Erickson, K. I., Colcombe, S. J., Wadhwa, R., Bherer, L., Peterson, M. S., Scalf, P. E., … Kramer, A. F. (2007). Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiology of Aging*, *28*(2), 272–83. doi:10.1016/j.neurobiolaging.2005.12.012

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Heo, S., Mclaren, M., … Kramer, A. F. (2011). NIH Public Access, *30*(15), 5368–5375. doi:10.1523/JNEUROSCI.6251-09.2010.BDNF

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Morris, K. S., White, S. M., … Kramer, A. F. (2011). NIH Public Access, *19*(10), 1030–1039. doi:10.1002/hipo.20547.Aerobic

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., … Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(7), 3017–22. doi:10.1073/pnas.1015950108

Evans, A., & Boucher, M. (2007). A Discrete Diffrenthil.

Evans, A. C., Janke, A. L., Collins, D. L., & Baillet, S. (2012). Brain templates and atlases. *NeuroImage*, *62*(2), 911–22. doi:10.1016/j.neuroimage.2012.01.024

Farmer, J., Zhao, X., van Praag, H., Wodtke, K., Gage, F. H., & Christie, B. R. (2004). Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. *Neuroscience*, *124*(1), 71–9. doi:10.1016/j.neuroscience.2003.09.029

Fields, R. D. (2014). Neuroscience. Myelin--more than insulation. *Science (New York, N.Y.)*, *344*(6181), 264–6. doi:10.1126/science.1253851

Finger, Stanley (2000). "Chapter 13: Santiago Ramon y Cajal. From nerve nets to neuron doctrine". *Minds behind the brain: A history of the pioneers and their discoveries*. New York: Oxford University Press. pp. 197–216. ISBN 0-19-508571-X.

Fischl, B., & Dale, a M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(20), 11050–5. doi:10.1073/pnas.200033797

Foster, N. E. V, & Zatorre, R. J. (2010). Cortical structure predicts success in performing musical transformation judgments. *NeuroImage*, *53*(1), 26–36. doi:10.1016/j.neuroimage.2010.06.042

Foundations, N., & Cognitive, O. F. (n.d.). *Neurological Foundations of Cognitive Neuroscience*.

Fu, M., & Zuo, Y. (2011). Experience-dependent structural plasticity in the cortex. *Trends in Neurosciences*, *34*(4), 177–187. doi:10.1016/j.tins.2011.02.001

Fuchs, E., Flügge, G., Ohl, F., Lucassen, P., Vollmann-Honsdorf, G. K., & Michaelis, T. (2001). Psychosocial stress, glucocorticoids, and structural alterations in the tree shrew hippocampus. *Physiology & Behavior*, *73*(3), 285–91. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11438353

Ganguly, K., & Poo, M.-M. (2013). Activity-dependent neural plasticity from bench to bedside. *Neuron*, *80*(3), 729–41. doi:10.1016/j.neuron.2013.10.028

Gascon, E., Vutskits, L., & Kiss, J. Z. (2010). Structure and Function of the Neural Cell Adhesion Molecule NCAM, *663*, 127–136. doi:10.1007/978-1-4419-1170-4

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, a, … Rapoport, J. L. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nature Neuroscience*, *2*(10), 861–3. doi:10.1038/13158

Giorgio, a, Watkins, K. E., Chadwick, M., James, S., Winmill, L., Douaud, G., … James, a C. (2010). Longitudinal changes in grey and white matter during adolescence. *NeuroImage*, *49*(1), 94–103. doi:10.1016/j.neuroimage.2009.08.003

Giorgio, A., Santelli, L., Tomassini, V., Bosnell, R., Smith, S., De Stefano, N., & Johansen-Berg, H. (2010). Age-related changes in grey and white matter structure throughout adulthood. *NeuroImage*, *51*(3), 943–51. doi:10.1016/j.neuroimage.2010.03.004

Gong, G., He, Y., & Evans, A. C. (2011a). Brain connectivity: gender makes a difference. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *17*(5), 575–91. doi:10.1177/1073858410386492

Gong, G., He, Y., & Evans, A. C. (2011b). Brain connectivity: gender makes a difference. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *17*(5), 575–91. doi:10.1177/1073858410386492

Gong, G., He, Y., & Evans, A. C. (2011c). Brain connectivity: gender makes a difference. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *17*(5), 575–91. doi:10.1177/1073858410386492

Gottmann, K., Mittmann, T., & Lessmann, V. (2009). BDNF signaling in the formation, maturation and plasticity of glutamatergic and GABAergic synapses. *Experimental Brain Research*, *199*(3-4), 203–34. doi:10.1007/s00221-009-1994-z

Grand'maison, M., Zehntner, S. P., Ho, M.-K., Hébert, F., Wood, A., Carbonell, F., … Bedell, B. J. (2013). Early cortical thickness changes predict β-amyloid deposition in a mouse model of Alzheimer's disease. *Neurobiology of Disease*, *54*, 59–67. doi:10.1016/j.nbd.2013.02.005

Gray, J. D., Milner, T. a, & McEwen, B. S. (2013). Dynamic plasticity: the role of glucocorticoids, brain-derived neurotrophic factor and other trophic factors. *Neuroscience*, *239*, 214–27. doi:10.1016/j.neuroscience.2012.08.034

Greenough, W. T., Larson, J. R., & Withers, G. S. (1985). Effects of unilateral and bilateral training in a reaching task on dendritic branching of neurons in the rat motor-sensory forelimb cortex. *Behavioral and Neural Biology*, *44*(2), 301–14. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2415103

Griesbach, G. S., Hovda, D. a, Molteni, R., Wu, a, & Gomez-Pinilla, F. (2004). Voluntary exercise following traumatic brain injury: brain-derived neurotrophic factor upregulation and recovery of function. *Neuroscience*, *125*(1), 129–39. doi:10.1016/j.neuroscience.2004.01.030

Griffin, E. W., Bechara, R. G., Birch, A. M., & Kelly, A. M. (2009). Exercise enhances hippocampal-dependent learning in the rat: evidence for a BDNF-related mechanism. *Hippocampus*, *19*(10), 973–80. doi:10.1002/hipo.20631

Grodzinsky, Y., & Nelken, I. (2014). Neuroscience. The neural code that makes us human. *Science (New York, N.Y.)*, *343*(6174), 978–9. doi:10.1126/science.1251495

Grogan, a, Parker Jones, O., Ali, N., Crinion, J., Orabona, S., Mechias, M. L., … Price, C. J. (2012). Structural correlates for lexical efficiency and number of languages in non-native speakers of English. *Neuropsychologia*, *50*(7), 1347–52. doi:10.1016/j.neuropsychologia.2012.02.019

Grubb, M. S., & Burrone, J. (2010). Activity-dependent relocation of the axon initial segment fine-tunes neuronal excitability. *Nature*, *465*(7301), 1070–4. doi:10.1038/nature09160

Hamzei, F., Glauche, V., Schwarzwald, R., & May, A. (2012). Dynamic gray matter changes within cortex and striatum after short motor skill training are associated with their increased functional interaction. *NeuroImage*, *59*(4), 3364–72. doi:10.1016/j.neuroimage.2011.10.089

Hardy, B. J. D., & Muschenheim, C. (1934). (Aldrich (2), Cobet, (6), 817–831.

Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science (New York, N.Y.)*, *297*(5580), 353–6. doi:10.1126/science.1072994

Hebb, Donald O. (1949) *The Organization of Behavior*. Wiley: New York, NY.

Hébert, F., Grand'maison, M., Ho, M.-K., Lerch, J. P., Hamel, E., & Bedell, B. J. (2013). Cortical atrophy and hypoperfusion in a transgenic mouse model of Alzheimer's disease. *Neurobiology of Aging*, *34*(6), 1644–52. doi:10.1016/j.neurobiolaging.2012.11.022

Heinrichs, S. C., Leite-Morris, K. a, Guy, M. D., Goldberg, L. R., Young, A. J., & Kaplan, G. B. (2013). Dendritic structural plasticity in the basolateral amygdala after fear conditioning and its extinction in mice. *Behavioural Brain Research*, *248*, 80–4. doi:10.1016/j.bbr.2013.03.048

Helfer, J. L., Goodlett, C. R., Greenough, W. T., & Klintsova, A. Y. (2009). The effects of exercise on adolescent hippocampal neurogenesis in a rat model of binge alcohol exposure during the brain growth spurt. *Brain Research*, *1294*, 1–11. doi:10.1016/j.brainres.2009.07.090

Herholz, S. C., & Zatorre, R. J. (2012). Musical training as a framework for brain plasticity: behavior, function, and structure. *Neuron*, *76*(3), 486–502. doi:10.1016/j.neuron.2012.10.011

Heyn, P., Abreu, B. C., & Ottenbacher, K. J. (2004). The effects of exercise training on elderly persons with cognitive impairment and dementia: A meta-analysis. *Archives of Physical Medicine and Rehabilitation*, *85*(10), 1694–1704. doi:10.1016/j.apmr.2004.03.019

Hihara, S., Notoya, T., Tanaka, M., Ichinose, S., Ojima, H., Obayashi, S., … Iriki, A. (2006). Extension of corticocortical afferents into the anterior bank of the intraparietal sulcus by tool-use training in adult monkeys. *Neuropsychologia*, *44*(13), 2636–46. doi:10.1016/j.neuropsychologia.2005.11.020

Hitti, F. L., & Siegelbaum, S. a. (2014). The hippocampal CA2 region is essential for social memory. *Nature*, *508*(7494), 88–92. doi:10.1038/nature13028

Hobson, J. A. (2009). REM sleep and dreaming: towards a theory of protoconsciousness. *Nature Reviews. Neuroscience*, *10*(11), 803–13. doi:10.1038/nrn2716

Holtmaat, a, De Paola, V., Wilbrecht, L., & Knott, G. W. (2008). Imaging of experience-dependent structural plasticity in the mouse neocortex in vivo. *Behavioural Brain Research*, *192*(1), 20–5. doi:10.1016/j.bbr.2008.04.005

Holtmaat, A., Randall, J., & Cane, M. (2013). Optical imaging of structural and functional synaptic plasticity in vivo. *European Journal of Pharmacology*, *719*(1-3), 128–36. doi:10.1016/j.ejphar.2013.07.020

Hölzel, B. K., Carmody, J., Vangel, M., Congleton, C., Yerramsetti, S. M., Gard, T., & Lazar, S. W. (2011a). Mindfulness practice leads to increases in regional brain gray matter density. *Psychiatry Research*, *191*(1), 36–43. doi:10.1016/j.pscychresns.2010.08.006

Hölzel, B. K., Carmody, J., Vangel, M., Congleton, C., Yerramsetti, S. M., Gard, T., & Lazar, S. W. (2011b). Mindfulness practice leads to increases in regional brain gray matter density. *Psychiatry Research*, *191*(1), 36–43. doi:10.1016/j.pscychresns.2010.08.006

Horn, K. E., Glasgow, S. D., Gobert, D., Bull, S., Girgis, J., Tremblay, M., … Kennedy, T. E. (2012). DCC expression by neurons regulates synaptic plasitcity in the adult brain. *Cell Reports*, 1–42.

Horn, K. E., Glasgow, S. D., Gobert, D., Bull, S.-J., Luk, T., Girgis, J., … Kennedy, T. E. (2013). DCC expression by neurons regulates synaptic plasticity in the adult brain. *Cell Reports*, *3*(1), 173–85. doi:10.1016/j.celrep.2012.12.005

Horn, K. E., & Kennedy, T. E. (2012). Putting flesh on the bones: DCC combines membrane insertion with cytoskeletal reorganization to promote chemoattraction (commentary on Cotrufo et al.). *The European Journal of Neuroscience*, *36*(9), 3151. doi:10.1111/ejn.12011

Hoveida, R., Alaei, H., Oryan, S., Parivar, K., & Reisi, P. (2011). Treadmill running improves spatial memory in an animal model of Alzheimer's disease. *Behavioural Brain Research*, *216*(1), 270–4. doi:10.1016/j.bbr.2010.08.003

Huang, E. J., & Reichardt, L. F. (2001). Neurotrophins: roles in neuronal development and function. *Annual Review of Neuroscience*, *24*, 677–736. doi:10.1146/annurev.neuro.24.1.677

Intlekofer, K. a, & Cotman, C. W. (2013). Exercise counteracts declining hippocampal function in aging and Alzheimer's disease. *Neurobiology of Disease*, *57*, 47–55. doi:10.1016/j.nbd.2012.06.011

Investigation, B. P. (n.d.). *No Title*.

Isler, K., & van Schaik, C. (2006). Costs of encephalization: the energy trade-off hypothesis tested on birds. *Journal of Human Evolution*, *51*(3), 228–43. doi:10.1016/j.jhevol.2006.03.006

Isler, K., & van Schaik, C. P. (2009). The Expensive Brain: a framework for explaining evolutionary changes in brain size. *Journal of Human Evolution*, *57*(4), 392–400. doi:10.1016/j.jhevol.2009.04.009

Jacobi, S., Soriano, J., Segal, M., & Moses, E. (2009). BDNF and NT-3 increase excitatory input connectivity in rat hippocampal cultures. *The European Journal of Neuroscience*, *30*(6), 998–1010. doi:10.1111/j.1460-9568.2009.06891.x

James, William. (1890) *The Principles of Psychology*. New York City, NY: Henry Holt and Company.

Ji, Y., Lu, Y., Yang, F., Shen, W., Tang, T. T.-T., Feng, L., … Lu, B. (2010). Acute and gradual increases in BDNF concentration elicit distinct signaling and functions in neurons. *Nature Neuroscience*, *13*(3), 302–9. doi:10.1038/nn.2505

Johansen-Berg, H., Baptista, C. S., & Thomas, A. G. (2012). Human structural plasticity at record speed. *Neuron*, *73*(6), 1058–60. doi:10.1016/j.neuron.2012.03.001

Jones, E. G. (2011). Cajal's debt to Golgi. *Brain Research Reviews*, *66*(1-2), 83–91. doi:10.1016/j.brainresrev.2010.04.005

Josselyn, Sheena. (2010) Continuing the search for the engram. *Journal of Psychiatry Neuroscience*. 35(4): 221 – 228.

Jubault, T., Gagnon, J.-F., Karama, S., Ptito, A., Lafontaine, A.-L., Evans, A. C., & Monchi, O. (2011). Patterns of cortical thickness and surface area in early Parkinson's disease. *NeuroImage*, *55*(2), 462–7. doi:10.1016/j.neuroimage.2010.12.043

Kahn, D., & Gover, T. (2010). *Consciousness in dreams*. *International review of neurobiology* (Vol. 92, pp. 181–95). Elsevier Inc. doi:10.1016/S0074-7742(10)92009-6

Kang, D.-H., Jo, H. J., Jung, W. H., Kim, S. H., Jung, Y.-H., Choi, C.-H., … Kwon, J. S. (2013). The effect of meditation on brain structure: cortical thickness mapping and diffusion tensor imaging. *Social Cognitive and Affective Neuroscience*, *8*(1), 27–33. doi:10.1093/scan/nss056

Karni, a, Meyer, G., Rey-Hipolito, C., Jezzard, P., Adams, M. M., Turner, R., & Ungerleider, L. G. (1998). The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(3), 861–8. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=33809&tool=pmcentrez&rendertype=abstract

Kellner, Y., Gödecke, N., Dierkes, T., Thieme, N., Zagrebelsky, M., & Korte, M. (2014). The BDNF effects on dendritic spines of mature hippocampal neurons depend on neuronal activity. *Frontiers in Synaptic Neuroscience*, *6*(March), 5. doi:10.3389/fnsyn.2014.00005

Kempermann, G., Fabel, K., Ehninger, D., Babu, H., Leal-Galicia, P., Garthe, A., & Wolf, S. a. (2010). Why and how physical activity promotes experience-induced brain plasticity. *Frontiers in Neuroscience*, *4*(December), 189. doi:10.3389/fnins.2010.00189

Kempermann, G., Gast, D., & Gage, F. H. (2002). Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. *Annals of Neurology*, *52*(2), 135–43. doi:10.1002/ana.10262

Kerr, a L., Steuer, E. L., Pochtarev, V., & Swain, R. a. (2010). Angiogenesis but not neurogenesis is critical for normal learning and memory acquisition. *Neuroscience*, *171*(1), 214–26. doi:10.1016/j.neuroscience.2010.08.008

Keshavan, V., & Tandon, N. (2012). How to give an effective presentation. *Asian Journal of Psychiatry*, *5*(4), 360–1. doi:10.1016/j.ajp.2012.09.013

Kilgard, M. P., & Merzenich, M. M. (1998). Cortical map reorganization enabled by nucleus basalis activity. *Science (New York, N.Y.)*, *279*(5357), 1714–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9497289

Kim, J. S., Singh, V., Lee, J. K., Lerch, J., Ad-Dab'bagh, Y., MacDonald, D., … Evans, A. C. (2005). Automated 3-D extraction and evaluation of the inner and outer cortical surfaces using a Laplacian map and partial volume effect classification. *NeuroImage*, *27*(1), 210–21. doi:10.1016/j.neuroimage.2005.03.036

Kim, S.-E., Ko, I.-G., Kim, B.-K., Shin, M.-S., Cho, S., Kim, C.-J., … Jee, Y.-S. (2010). Treadmill exercise prevents aging-induced failure of memory through an increase in neurogenesis and suppression of apoptosis in rat hippocampus. *Experimental Gerontology*, *45*(5), 357–65. doi:10.1016/j.exger.2010.02.005

Kitamura, T., Mishina, M., & Sugiyama, H. (2003). Enhancement of neurogenesis by running wheel exercises is suppressed in mice lacking NMDA receptor ε1 subunit. *Neuroscience Research*, *47*(1), 55–63. doi:10.1016/S0168-0102(03)00171-8

Kleim, J. a, Barbay, S., Cooper, N. R., Hogg, T. M., Reidel, C. N., Remple, M. S., & Nudo, R. J. (2002). Motor learning-dependent synaptogenesis is localized to functionally reorganized motor cortex. *Neurobiology of Learning and Memory*, *77*(1), 63–77. doi:10.1006/nlme.2000.4004

Kleim, J. a, Cooper, N. R., & VandenBerg, P. M. (2002). Exercise induces angiogenesis but does not alter movement representations within rat motor cortex. *Brain Research*, *934*(1), 1–6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11937064

Kleim, J. a, Hogg, T. M., VandenBerg, P. M., Cooper, N. R., Bruneau, R., & Remple, M. (2004). Cortical synaptogenesis and motor map reorganization occur during late, but not early, phase of motor skill learning. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *24*(3), 628–33. doi:10.1523/JNEUROSCI.3440-03.2004

Kleim, J. a, Markham, J. a, Vij, K., Freese, J. L., Ballard, D. H., & Greenough, W. T. (2007). Motor learning induces astrocytic hypertrophy in the cerebellar cortex. *Behavioural Brain Research*, *178*(2), 244–9. doi:10.1016/j.bbr.2006.12.022

Kleim, J. A., Markham, J. A., Vij, K., Freese, J. L., Ballard, D. H., & Greenough, W. T. (2008). NIH Public Access, *178*(2), 244–249. doi:10.1016/j.bbr.2006.12.022.Motor

Klein, D., Mok, K., Chen, J.-K., & Watkins, K. E. (2013). Age of language learning shapes brain structure: A cortical thickness study of bilingual and monolingual individuals. *Brain and Language*, 1–5. doi:10.1016/j.bandl.2013.05.014

Klintsova, A. Y., Dickson, E., Yoshida, R., & Greenough, W. T. (2004). Altered expression of BDNF and its high-affinity receptor TrkB in response to complex motor learning and moderate exercise. *Brain Research*, *1028*(1), 92–104. doi:10.1016/j.brainres.2004.09.003

Kolb, B., Cioe, J., & Comeau, W. (2008). Contrasting effects of motor and visual spatial learning tasks on dendritic arborization and spine density in rats. *Neurobiology of Learning and Memory*, *90*(2), 295–300. doi:10.1016/j.nlm.2008.04.012

Kozorovitskiy, Y., Gross, C. G., Kopil, C., Battaglia, L., McBreen, M., Stranahan, A. M., & Gould, E. (2005). Experience induces structural and biochemical changes in the adult primate brain. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(48), 17478–82. doi:10.1073/pnas.0508817102

Kramer, A. F., & Erickson, K. I. (2007). Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. *Trends in Cognitive Sciences*, *11*(8), 342–8. doi:10.1016/j.tics.2007.06.009

Krech D, Rosenzweig MR and Bennett EL. (1960). Effects of environmental complexity and training on brain chemistry. *J Comp Physiol Psychol* 53: 509- 519

Kronenberg, G., Bick-Sander, A., Bunk, E., Wolf, C., Ehninger, D., & Kempermann, G. (2006). Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. *Neurobiology of Aging*, *27*(10), 1505–13. doi:10.1016/j.neurobiolaging.2005.09.016

Kuczewski, N., Porcher, C., Lessmann, V., Medina, I., & Gaiarsa, J.-L. (2009). Activity-dependent dendritic release of BDNF and biological consequences. *Molecular Neurobiology*, *39*(1), 37–49. doi:10.1007/s12035-009-8050-7

Kuhn, S. (2014). Positive Association of Video Game Playing with Left Frontal Cortical Thickness in Adolescents. *Plosone*.

Kühn, S., Gleich, T., Lorenz, R. C., Lindenberger, U., & Gallinat, J. (2013). Playing Super Mario induces structural brain plasticity: gray matter changes resulting from training with a commercial video game. *Molecular Psychiatry*, (August), 1–7. doi:10.1038/mp.2013.120

Kwon, H.-B., & Sabatini, B. L. (2011). Glutamate induces de novo growth of functional spines in developing cortex. *Nature*, *474*(7349), 100–104. doi:10.1038/nature09986

Lakshminarasimhan, H., & Chattarji, S. (2012). Stress leads to contrasting effects on the levels of brain derived neurotrophic factor in the hippocampus and amygdala. *PloS One*, *7*(1), e30481. doi:10.1371/journal.pone.0030481

Lange-Asschenfeldt, C., & Kojda, G. (2008). Alzheimer's disease, cerebrovascular dysfunction and the benefits of exercise: from vessels to neurons. *Experimental Gerontology*, *43*(6), 499–504. doi:10.1016/j.exger.2008.04.002

Lazarov, O., Robinson, J., Tang, Y.-P., Hairston, I. S., Korade-Mirnics, Z., Lee, V. M.-Y., … Sisodia, S. S. (2005). Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. *Cell*, *120*(5), 701–13. doi:10.1016/j.cell.2005.01.015

Leasure, J. L., & Jones, M. (2008). Forced and voluntary exercise differentially affect brain and behavior. *Neuroscience*, *156*(3), 456–65. doi:10.1016/j.neuroscience.2008.07.041

Ledoux, J. E. (2000). Emotion Circuits in the Brain, 155–184.

Lee, K. J., Park, I. S., Kim, H., Greenough, W. T., Pak, D. T. S., & Rhyu, I. J. (2013). Motor skill training induces coordinated strengthening and weakening between neighboring synapses. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *33*(23), 9794–9. doi:10.1523/JNEUROSCI.0848-12.2013

Leggio, M. G., Mandolesi, L., Federico, F., Spirito, F., Ricci, B., Gelfo, F., & Petrosini, L. (2005). Environmental enrichment promotes improved spatial abilities and enhanced dendritic growth in the rat. *Behavioural Brain Research*, *163*(1), 78–90. doi:10.1016/j.bbr.2005.04.009

Lerch, J. P., Carroll, J. B., Dorr, A., Spring, S., Evans, A. C., Hayden, M. R., … Henkelman, R. M. (2008). Cortical thickness measured from MRI in the YAC128 mouse model of Huntington's disease. *NeuroImage*, *41*(2), 243–51. doi:10.1016/j.neuroimage.2008.02.019

Lerch, J. P., & Evans, A. C. (2005). Cortical thickness analysis examined through power analysis and a population simulation. *NeuroImage*, *24*(1), 163–73. doi:10.1016/j.neuroimage.2004.07.045

Lerch, J. P., Yiu, A. P., Martinez-Canabal, A., Pekar, T., Bohbot, V. D., Frankland, P. W., … Sled, J. G. (2011). Maze training in mice induces MRI-detectable brain shape changes specific to the type of learning. *NeuroImage*, *54*(3), 2086–95. doi:10.1016/j.neuroimage.2010.09.086

Li, H., Liang, A., Guan, F., Fan, R., Chi, L., & Yang, B. (2013). Regular treadmill running improves spatial learning and memory performance in young mice through increased hippocampal neurogenesis and decreased stress. *Brain Research*, *1531*, 1–8. doi:10.1016/j.brainres.2013.07.041

Li, J., Ding, Y.-H., Rafols, J. a, Lai, Q., McAllister, J. P., & Ding, Y. (2005). Increased astrocyte proliferation in rats after running exercise. *Neuroscience Letters*, *386*(3), 160–4. doi:10.1016/j.neulet.2005.06.009

Li, W., Wu, B., Avram, A. V, & Liu, C. (2012). Magnetic susceptibility anisotropy of human brain in vivo and its molecular underpinnings. *NeuroImage*, *59*(3), 2088–97. doi:10.1016/j.neuroimage.2011.10.038

Li, X., Yang, Z., & Zhang, A. (2009). The effect of neurotrophin-3/chitosan carriers on the proliferation and differentiation of neural stem cells. *Biomaterials*, *30*(28), 4978–85. doi:10.1016/j.biomaterials.2009.05.047

Lillard, A. S., & Erisir, A. (2011). Old dogs learning new tricks: Neuroplasticity beyond the juvenile period. *Developmental Review*, *31*(4), 207–239. doi:10.1016/j.dr.2011.07.008

Lim, Y. Y., Villemagne, V. L., Laws, S. M., Ames, D., Pietrzak, R. H., Ellis, K. a, … Maruff, P. (2013). BDNF Val66Met, Aβ amyloid, and cognitive decline in preclinical Alzheimer's disease. *Neurobiology of Aging*, *34*(11), 2457–64. doi:10.1016/j.neurobiolaging.2013.05.006

Lin, T.-W., Chen, S.-J., Huang, T.-Y., Chang, C.-Y., Chuang, J.-I., Wu, F.-S., … Jen, C. J. (2012). Different types of exercise induce differential effects on neuronal adaptations and memory performance. *Neurobiology of Learning and Memory*, *97*(1), 140–7. doi:10.1016/j.nlm.2011.10.006

Liu, C. (2010). Susceptibility tensor imaging. *Magnetic Resonance in Medicine : Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, *63*(6), 1471–7. doi:10.1002/mrm.22482

Liu, C., Li, W., Johnson, G. A., & Wu, B. (2011). High-field (9.4 T) MRI of brain dysmyelination by quantitative mapping of magnetic susceptibility. *NeuroImage*, *56*(3), 930–8. doi:10.1016/j.neuroimage.2011.02.024

Liu, C., Li, W., Wu, B., Jiang, Y., & Johnson, G. A. (2012). 3D fiber tractography with susceptibility tensor imaging. *NeuroImage*, *59*(2), 1290–8. doi:10.1016/j.neuroimage.2011.07.096

Liu, H., Zhao, G., Cai, K., Zhao, H., & Shi, L. (2011). Treadmill exercise prevents decline in spatial learning and memory in APP/PS1 transgenic mice through improvement of hippocampal long-term potentiation. *Behavioural Brain Research*, *218*(2), 308–14. doi:10.1016/j.bbr.2010.12.030

Liu, Y.-F., Chen, H., Wu, C.-L., Kuo, Y.-M., Yu, L., Huang, A.-M., … Jen, C. J. (2009a). Differential effects of treadmill running and wheel running on spatial or aversive learning and memory: roles of amygdalar brain-derived neurotrophic factor and synaptotagmin I. *The Journal of Physiology*, *587*(Pt 13), 3221–31. doi:10.1113/jphysiol.2009.173088

Liu, Y.-F., Chen, H., Wu, C.-L., Kuo, Y.-M., Yu, L., Huang, A.-M., … Jen, C. J. (2009b). Differential effects of treadmill running and wheel running on spatial or aversive learning and memory: roles of amygdalar brain-derived neurotrophic factor and synaptotagmin I. *The Journal of Physiology*, *587*(Pt 13), 3221–31. doi:10.1113/jphysiol.2009.173088

Livet, J., Weissman, T. a, Kang, H., Draft, R. W., Lu, J., Bennis, R. a, … Lichtman, J. W. (2007). Transgenic strategies for combinatorial expression of fluorescent proteins in the nervous system. *Nature*, *450*(7166), 56–62. doi:10.1038/nature06293

Lledo, P.-M., Alonso, M., & Grubb, M. S. (2006). Adult neurogenesis and functional plasticity in neuronal circuits. *Nature Reviews. Neuroscience*, *7*(3), 179–93. doi:10.1038/nrn1867

Lopez-Larson, M. P. (2012). ALTERED PREFRONTAL AND INSULAR CORTICAL THICKNESS, *220*(1), 164–172. doi:10.1016/j.bbr.2011.02.001.ALTERED

Lou, S., Liu, J., Chang, H., & Chen, P. (2008). Hippocampal neurogenesis and gene expression depend on exercise intensity in juvenile rats. *Brain Research*, *1210*, 48–55. doi:10.1016/j.brainres.2008.02.080

Lövdén, M., Bodammer, N. C., Kühn, S., Kaufmann, J., Schütze, H., Tempelmann, C., … Lindenberger, U. (2010). Experience-dependent plasticity of white-matter microstructure extends into old age. *Neuropsychologia*, *48*(13), 3878–83. doi:10.1016/j.neuropsychologia.2010.08.026

Lövdén, M., Wenger, E., Mårtensson, J., Lindenberger, U., & Bäckman, L. (2013). Structural brain plasticity in adult learning and development. *Neuroscience and Biobehavioral Reviews*, *37*(9 Pt B), 2296–310. doi:10.1016/j.neubiorev.2013.02.014

Luo, L. (2002). Actin cytoskeleton regulation in neuronal morphogenesis and structural plasticity. *Annual Review of Cell and Developmental Biology*, *18*, 601–35. doi:10.1146/annurev.cellbio.18.031802.150501

Lynch, M. A., Introduction, I., Erk, B., Potentiation, L., Age, D., & Cognition, E. (2004). Long-Term Potentiation and Memory, 87–136.

Lyttelton, O., Boucher, M., Robbins, S., & Evans, A. (2007). An unbiased iterative group registration template for cortical surface analysis. *NeuroImage*, *34*(4), 1535–44. doi:10.1016/j.neuroimage.2006.10.041

MacDonald, D., Kabani, N., Avis, D., & Evans, a C. (2000). Automated 3-D extraction of inner and outer surfaces of cerebral cortex from MRI. *NeuroImage*, *12*(3), 340–56. doi:10.1006/nimg.1999.0534

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 Sciences of the United States of America*, *97*(8), 4398–403. doi:10.1073/pnas.070039597

Maguire, E. A., Woollett, K., & Spiers, H. J. (2006). London Taxi Drivers and Bus Drivers : A Structural MRI and Neuropsychological Analysis, *m*, 1091–1101. doi:10.1002/hipo

Malenka, R. C., Bear, M. F., & Alto, M. P. (2004). LTP and LTD: An Embarrassment of Riches. *Neuron*, *44*, 5–21.

Malinow, R., & Malenka, R. C. (2002). AMPA receptor trafficking and synaptic plasticity. *Annual Review of Neuroscience*, *25*, 103–26. doi:10.1146/annurev.neuro.25.112701.142758

Manning, L. (2008). Do some neurological conditions induce brain plasticity processes? *Behavioural Brain Research*, *192*(1), 143–8. doi:10.1016/j.bbr.2008.04.001

Manuscript, A. (2011). NIH Public Access, *70*(5), 304–322. doi:10.1002/dneu.20765.Post-synaptic

Manuscript, A., Juvenile, C., Produces, S., Dendritic, C., Remodeling, A., & Rats, F. (2013). NIH Public Access, *37*(1), 39–47. doi:10.1016/j.psyneuen.2011.04.015.Chronic

Markham, J. a, & Greenough, W. T. (2004). Experience-driven brain plasticity: beyond the synapse. *Neuron Glia Biology*, *1*(4), 351–63. doi:10.1017/s1740925x05000219

Markham, J. a, Herting, M. M., Luszpak, A. E., Juraska, J. M., & Greenough, W. T. (2009). Myelination of the corpus callosum in male and female rats following complex environment housing during adulthood. *Brain Research*, *1288*, 9–17. doi:10.1016/j.brainres.2009.06.087

Martin, S. J., Grimwood, P. D., & Morris, R. G. M. (2000). S YNAPTIC P LASTICITY AND M EMORY : An Evaluation of the Hypothesis, (Hebb 1949), 649–711.

Matsuda, N., Lu, H., Fukata, Y., Noritake, J., Gao, H., Mukherjee, S., … Poo, M.-M. (2009). Differential activity-dependent secretion of brain-derived neurotrophic factor from axon and dendrite. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *29*(45), 14185–98. doi:10.1523/JNEUROSCI.1863-09.2009

May, A. (2008). Chronic pain may change the structure of the brain. *Pain*, *137*(1), 7–15. doi:10.1016/j.pain.2008.02.034

May, A. (2011). Experience-dependent structural plasticity in the adult human brain. *Trends in Cognitive Sciences*, *15*(10), 475–82. doi:10.1016/j.tics.2011.08.002

May, A., Driemeyer, J., Boyke, J., Gaser, C., & Bu, C. (2008). Changes in Gray Matter Induced by Learning — Revisited, *3*(7), 1–5. doi:10.1371/Citation

Maya-Vetencourt, J. F., Tiraboschi, E., Greco, D., Restani, L., Cerri, C., Auvinen, P., … Castrén, E. (2012). Experience-dependent expression of NPAS4 regulates plasticity in adult visual cortex. *The Journal of Physiology*, *590*(Pt 19), 4777–87. doi:10.1113/jphysiol.2012.234237

McCloskey, D. P., Adamo, D. S., & Anderson, B. J. (2001). Exercise increases metabolic capacity in the motor cortex and striatum, but not in the hippocampus. *Brain Research*, *891*(1-2), 168–75. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11164820

McEwen, B. S. (1998). Protective and Damaging Effects of Stress Mediators, 171–179.

Mcewen, B. S. (1999). STRESS AND HIPPOCAMPAL.

Merzenich, M. M., Jenkins, W. M., Johnston, P., Schreiner, C., Miller, S. L., Tallal, P., … Jan, N. (2013). Training All use subject to JSTOR Terms and Conditions Temporal Processing Deficits of Language-Learning Impaired Children Ameliorated by Training, *271*(5245), 77–81.

Merzenich, M. M., Nelson, R. J., Stryker, M. P., Cynader, M. S., Schoppmann, a, & Zook, J. M. (1984). Somatosensory cortical map changes following digit amputation in adult monkeys. *The Journal of Comparative Neurology*, *224*(4), 591–605. doi:10.1002/cne.902240408

Meyer, M., Liem, F., Hirsiger, S., Jäncke, L., & Hänggi, J. (2013). Cortical Surface Area and Cortical Thickness Demonstrate Differential Structural Asymmetry in Auditory-Related Areas of the Human Cortex. *Cerebral Cortex (New York, N.Y. : 1991)*. doi:10.1093/cercor/bht094

Miller, E. K., & Cohen, J. D. (2001a). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*, 167–202. doi:10.1146/annurev.neuro.24.1.167

Miller, E. K., & Cohen, J. D. (2001b). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*, 167–202. doi:10.1146/annurev.neuro.24.1.167

Miller, F. D., & Kaplan, D. R. (2001). Cellular and Molecular Life Sciences Neurotrophin signalling pathways regulating neuronal apoptosis, *58*, 1045–1053.

Milliken, G. W. (1996). Use-Dependent Primary Motor Alterations of Movement Representations Cortex of Adult Squirrel Monkeys in of Physiology and, *16*(2), 785–807.

Mischel, W., Ebbesen, E. B., & Zeiss, a R. (1972). Cognitive and attentional mechanisms in delay of gratification. *Journal of Personality and Social Psychology*, *21*(2), 204–18. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/5010404

Mitra, R., & Sapolsky, R. M. (2008). Acute corticosterone treatment is sufficient to induce anxiety and amygdaloid dendritic hypertrophy. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(14), 5573–8. doi:10.1073/pnas.0705615105

Molendijk, M. L., van Tol, M.-J., Penninx, B. W. J. H., van der Wee, N. J. a, Aleman, a, Veltman, D. J., … Elzinga, B. M. (2012). BDNF val66met affects hippocampal volume and emotion-related hippocampal memory activity. *Translational Psychiatry*, *2*(1), e74. doi:10.1038/tp.2011.72

Molteni, R., Ying, Z., & Gomez-Pinilla, F. (2002). Differential effects of acute and chronic exercise on plasticity-related genes in the rat hippocampus revealed by microarray. *European Journal of Neuroscience*, *16*(6), 1107–1116. doi:10.1046/j.1460-9568.2002.02158.x

Mora, F., Segovia, G., & del Arco, A. (2007). Aging, plasticity and environmental enrichment: structural changes and neurotransmitter dynamics in several areas of the brain. *Brain Research Reviews*, *55*(1), 78–88. doi:10.1016/j.brainresrev.2007.03.011

Morris, G. P., Clark, I. a, Zinn, R., & Vissel, B. (2013). Microglia: a new frontier for synaptic plasticity, learning and memory, and neurodegenerative disease research. *Neurobiology of Learning and Memory*, *105*, 40–53. doi:10.1016/j.nlm.2013.07.002

Morris, R. G. M. (2013). NMDA receptors and memory encoding. *Neuropharmacology*, *74*, 32–40. doi:10.1016/j.neuropharm.2013.04.014

Münte, T. F., Altenmüller, E., & Jäncke, L. (2002). The musician's brain as a model of neuroplasticity. *Nature Reviews. Neuroscience*, *3*(6), 473–8. doi:10.1038/nrn843

Nagy, Z., Lagercrantz, H., & Hutton, C. (2011). Effects of preterm birth on cortical thickness measured in adolescence. *Cerebral Cortex (New York, N.Y. : 1991)*, *21*(2), 300–6. doi:10.1093/cercor/bhq095

Natt, O., Watanabe, T., Boretius, S., Radulovic, J., Frahm, J., & Michaelis, T. (2002). High-resolution 3D MRI of mouse brain reveals small cerebral structures in vivo. *Journal of Neuroscience Methods*, *120*(2), 203–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12385770

Neeper, S. a, Gómez-Pinilla, F., Choi, J., & Cotman, C. W. (1996). Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Research*, *726*(1-2), 49–56. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8836544

Nejad, A. (2004). Co-existence of lycanthropy and Cotard's syndrome in a single case.

Nesler, K. R., Sand, R. I., Symmes, B. a, Pradhan, S. J., Boin, N. G., Laun, A. E., & Barbee, S. a. (2013). The miRNA pathway controls rapid changes in activity-dependent synaptic structure at the Drosophila melanogaster neuromuscular junction. *PloS One*, *8*(7), e68385. doi:10.1371/journal.pone.0068385

Nichol, K., Deeny, S. P., Seif, J., Camaclang, K., & Cotman, C. W. (2009). Exercise improves cognition and hippocampal plasticity in APOE epsilon4 mice. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *5*(4), 287–94. doi:10.1016/j.jalz.2009.02.006

Nichol, K. E., Parachikova, A. I., & Cotman, C. W. (2007). Three weeks of running wheel exposure improves cognitive performance in the aged Tg2576 mouse. *Behavioural Brain Research*, *184*(2), 124–32. doi:10.1016/j.bbr.2007.06.027

Nithianantharajah, J., & Hannan, A. J. (2006). Enriched environments, experience-dependent plasticity and disorders of the nervous system. *Nature Reviews. Neuroscience*, *7*(9), 697–709. doi:10.1038/nrn1970

Nudelman, A. S. (2011). Neuronal Activity Rapidly Induces Transcription of the CREB-Regulated MicroRNA-132, In Vivo, *20*(4), 492–498. doi:10.1002/hipo.20646.Neuronal

Numakawa, T., Adachi, N., Richards, M., Chiba, S., & Kunugi, H. (2013). Brain-derived neurotrophic factor and glucocorticoids: reciprocal influence on the central nervous system. *Neuroscience*, *239*, 157–72. doi:10.1016/j.neuroscience.2012.09.073

O'Callaghan, R. M., Ohle, R., & Kelly, A. M. (2007). The effects of forced exercise on hippocampal plasticity in the rat: A comparison of LTP, spatial- and non-spatial learning. *Behavioural Brain Research*, *176*(2), 362–6. doi:10.1016/j.bbr.2006.10.018

Oest, M., Meyer, T., Backens, M., & Schneider-axmann, T. (2014). Hippocampal Plasticity in Response to Exercise in Schizophrenia, *67*(2), 133–143.

Oliff, H. S., Berchtold, N. C., Isackson, P., & Cotman, C. W. (1998). Exercise-induced regulation of brain-derived neurotrophic factor (BDNF) transcripts in the rat hippocampus. *Brain Research. Molecular Brain Research*, *61*(1-2), 147–53. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9795193

Olson, A. K., Eadie, B. D., Ernst, C., & Christie, B. R. (2006). Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways. *Hippocampus*, *16*(3), 250–60. doi:10.1002/hipo.20157

Ota, K. (2014). REDD1 is essential for stress-induced synaptic loss and depressive behavior . *Nature Neuroscience* .

Palomero-Gallagher, N., Vogt, B. a, Schleicher, A., Mayberg, H. S., & Zilles, K. (2009). Receptor architecture of human cingulate cortex: evaluation of the four-region neurobiological model. *Human Brain Mapping*, *30*(8), 2336–55. doi:10.1002/hbm.20667

Pantev, C., & Herholz, S. C. (2011). Plasticity of the human auditory cortex related to musical training. *Neuroscience and Biobehavioral Reviews*, *35*(10), 2140–54. doi:10.1016/j.neubiorev.2011.06.010

Parasoglou, P., Berrios-Otero, C. a, Nieman, B. J., & Turnbull, D. H. (2013). High-resolution MRI of early-stage mouse embryos. *NMR in Biomedicine*, *26*(2), 224–31. doi:10.1002/nbm.2843

Park, H., & Poo, M. (2013). Neurotrophin regulation of neural circuit development and function. *Nature Reviews. Neuroscience*, *14*(1), 7–23. doi:10.1038/nrn3379

Park, H., Yang, J., Seo, J., & Lee, J. (2013). Dimensionality reduced cortical features and their use in predicting longitudinal changes in Alzheimer's disease. *Neuroscience Letters*, *550*, 17–22. doi:10.1016/j.neulet.2013.06.042

Pascual-Leone, A., Amedi, A., Fregni, F., & Merabet, L. B. (2005). The plastic human brain cortex. *Annual Review of Neuroscience*, *28*, 377–401. doi:10.1146/annurev.neuro.27.070203.144216

Pearce, J. M. (2004). "Sir Charles Scott Sherrington (1857-1952) and the synapse". *Journal of neurology, neurosurgery, and psychiatry* **75** (4): 544. PMC 1739021. PMID 15026492. edit

Pearn, J. (n.d.). Jules Cotard (1840–1889) His life and the unique syndrome which bears his name . *2003*.

Pezawas, L., Verchinski, B. a, Mattay, V. S., Callicott, J. H., Kolachana, B. S., Straub, R. E., … Weinberger, D. R. (2004). The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *24*(45), 10099–102. doi:10.1523/JNEUROSCI.2680-04.2004

Pietropaolo, S., Sun, Y., Li, R., Brana, C., Feldon, J., & Yee, B. K. (2008). The impact of voluntary exercise on mental health in rodents: a neuroplasticity perspective. *Behavioural Brain Research*, *192*(1), 42–60. doi:10.1016/j.bbr.2008.03.014

Polley, D. B., Steinberg, E. E., & Merzenich, M. M. (2006). Perceptual learning directs auditory cortical map reorganization through top-down influences. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *26*(18), 4970–82. doi:10.1523/JNEUROSCI.3771-05.2006

Priel, A., Tuszynski, J. a, & Woolf, N. J. (2010). Neural cytoskeleton capabilities for learning and memory. *Journal of Biological Physics*, *36*(1), 3–21. doi:10.1007/s10867-009-9153-0

Qin, W., Liu, Y., Jiang, T., & Yu, C. (2013). The development of visual areas depends differently on visual experience. *PloS One*, *8*(1), e53784. doi:10.1371/journal.pone.0053784

Ra, S. M., Kim, H., Jang, M. H., Shin, M. C., Lee, T. H., Lim, B. V., … Kim, S. S. (2002). Treadmill running and swimming increase cell proliferation in the hippocampal dentate gyrus of rats. *Neuroscience Letters*, *333*(2), 123–6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12419496

Raichle, M. E., MacLeod, a M., Snyder, a Z., Powers, W. J., Gusnard, D. a, & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(2), 676–82. doi:10.1073/pnas.98.2.676

Rajasekharan, S., & Kennedy, T. E. (2009). Protein family review The netrin protein family, 1–8.

Rakic, P. (1995). A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. *Trends in Neurosciences*, *18*(9), 383–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7482803

Rakic, P. (2002). the evidence, *3*(January).

Ramirez, S., Liu, X., Lin, P.-A., Suh, J., Pignatelli, M., Redondo, R. L., … Tonegawa, S. (2013). Creating a false memory in the hippocampus. *Science (New York, N.Y.)*, *341*(6144), 387–91. doi:10.1126/science.1239073

Rampon, C., Jiang, C. H., Dong, H., Tang, Y. P., Lockhart, D. J., Schultz, P. G., … Hu, Y. (2000). Effects of environmental enrichment on gene expression in the brain. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(23), 12880–4. doi:10.1073/pnas.97.23.12880

Raviola, E., & Mazzarello, P. (2011). The diffuse nervous network of Camillo Golgi: facts and fiction. *Brain Research Reviews*, *66*(1-2), 75–82. doi:10.1016/j.brainresrev.2010.09.005

Raznahan, A., Shaw, P., Lalonde, F., Stockman, M., Wallace, G. L., Greenstein, D., … Giedd, J. N. (2011). How does your cortex grow? *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *31*(19), 7174–7. doi:10.1523/JNEUROSCI.0054-11.2011

Reagan, L. P., Hendry, R. M., Reznikov, L. R., Piroli, G. G., Wood, G. E., McEwen, B. S., & Grillo, C. a. (2007). Tianeptine increases brain-derived neurotrophic factor expression in the rat amygdala. *European Journal of Pharmacology*, *565*(1-3), 68–75. doi:10.1016/j.ejphar.2007.02.023

Real, C. C., Ferreira, A. F. B., Hernandes, M. S., Britto, L. R. G., & Pires, R. S. (2010). Exercise-induced plasticity of AMPA-type glutamate receptor subunits in the rat brain. *Brain Research*, *1363*, 63–71. doi:10.1016/j.brainres.2010.09.060

Rebola, N., Srikumar, B. N., & Mulle, C. (2010a). Activity-dependent synaptic plasticity of NMDA receptors. *The Journal of Physiology*, *588*(Pt 1), 93–9. doi:10.1113/jphysiol.2009.179382

Rebola, N., Srikumar, B. N., & Mulle, C. (2010b). Activity-dependent synaptic plasticity of NMDA receptors. *The Journal of Physiology*, *588*(Pt 1), 93–9. doi:10.1113/jphysiol.2009.179382

Recanzone, G. H., Schreiner, C. E., & Merzenich, M. M. (1993). Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *13*(1), 87–103. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8423485

Rhyu, I. J. (2012). Effects of Aerobic Exercise Training on Cognitive Function and Cortical Vascularity in Monkeys, *167*(4), 1239–1248. doi:10.1016/j.neuroscience.2010.03.003.Effects

Rhyu, I. J., Bytheway, J. a, Kohler, S. J., Lange, H., Lee, K. J., Boklewski, J., … Cameron, J. L. (2010). Effects of aerobic exercise training on cognitive function and cortical vascularity in monkeys. *Neuroscience*, *167*(4), 1239–48. doi:10.1016/j.neuroscience.2010.03.003

Rimol, L. M., Nesvåg, R., Hagler, D. J., Bergmann, O., Fennema-Notestine, C., Hartberg, C. B., … Dale, A. M. (2012). Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder. *Biological Psychiatry*, *71*(6), 552–60. doi:10.1016/j.biopsych.2011.11.026

Rizos, E. N., Papathanasiou, M., Michalopoulou, P. G., Mazioti, a, Douzenis, a, Kastania, a, … Lykouras, L. (2011). Association of serum BDNF levels with hippocampal volumes in first psychotic episode drug-naive schizophrenic patients. *Schizophrenia Research*, *129*(2-3), 201–4. doi:10.1016/j.schres.2011.03.011

Rogalski, E., Cobia, D., Harrison, T. M., Wieneke, C., Weintraub, S., & Mesulam, M.-M. (2011a). Progression of language decline and cortical atrophy in subtypes of primary progressive aphasia. *Neurology*, *76*(21), 1804–10. doi:10.1212/WNL.0b013e31821ccd3c

Rogalski, E., Cobia, D., Harrison, T. M., Wieneke, C., Weintraub, S., & Mesulam, M.-M. (2011b). Progression of language decline and cortical atrophy in subtypes of primary progressive aphasia. *Neurology*, *76*(21), 1804–10. doi:10.1212/WNL.0b013e31821ccd3c

Ron de Kloet, E. (2014). From Receptor Balance to Rational Glucocorticoid Therapy. *Endocrinology*, (May), en20141048. doi:10.1210/en.2014-1048

Rosenzweig, M. R., & Bennett, E. L. (1996). Psychobiology of plasticity: effects of training and experience on brain and behavior. *Behavioural Brain Research*, *78*(1), 57–65. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8793038

Roth, G., & Dicke, U. (2005). Evolution of the brain and intelligence. *Trends in Cognitive Sciences*, *9*(5), 250–7. doi:10.1016/j.tics.2005.03.005

Sabuncu, M. R., Desikan, R. S., Sepulcre, J., Yeo, B. T. T., Liu, H., Schmansky, N. J., … Fischl, B. (2011). The dynamics of cortical and hippocampal atrophy in Alzheimer disease. *Archives of Neurology*, *68*(8), 1040–8. doi:10.1001/archneurol.2011.167

Sagi, Y., Tavor, I., Hofstetter, S., Tzur-Moryosef, S., Blumenfeld-Katzir, T., & Assaf, Y. (2012). Learning in the fast lane: new insights into neuroplasticity. *Neuron*, *73*(6), 1195–203. doi:10.1016/j.neuron.2012.01.025

Sahay, A., Scobie, K. N., Hill, A. S., O'Carroll, C. M., Kheirbek, M. a, Burghardt, N. S., … Hen, R. (2011). Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature*, *472*(7344), 466–70. doi:10.1038/nature09817

Sanchez, M. M., Das, D., Taylor, J. L., Noda, a, Yesavage, J. a, & Salehi, a. (2011). BDNF polymorphism predicts the rate of decline in skilled task performance and hippocampal volume in healthy individuals. *Translational Psychiatry*, *1*(10), e51. doi:10.1038/tp.2011.47

Sapolsky, R. M. (2014). Glucocorticoids and Hippocampal Atrophy in Neuropsychiatric Disorders, *57*, 925–935.

Sauvageot, C. (2002). Molecular mechanisms controlling cortical gliogenesis. *Current Opinion in Neurobiology*, *12*(3), 244–249. doi:10.1016/S0959-4388(02)00322-7

Schaaf, M. J., de Jong, J., de Kloet, E. R., & Vreugdenhil, E. (1998). Downregulation of BDNF mRNA and protein in the rat hippocampus by corticosterone. *Brain Research*, *813*(1), 112–20. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9824681

Scharfman, H., Goodman, J., Macleod, A., Phani, S., Antonelli, C., & Croll, S. (2005). Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. *Experimental Neurology*, *192*(2), 348–56. doi:10.1016/j.expneurol.2004.11.016

Schneider, P., Scherg, M., Dosch, H. G., Specht, H. J., Gutschalk, A., & Rupp, A. (2002). Morphology of Heschl's gyrus reflects enhanced activation in the auditory cortex of musicians. *Nature Neuroscience*, *5*(7), 688–94. doi:10.1038/nn871

Scholz, J., Klein, M. C., Behrens, T. E. J., & Johansen-Berg, H. (2009). Training induces changes in white-matter architecture. *Nature Neuroscience*, *12*(11), 1370–1. doi:10.1038/nn.2412

Schulte-Herbrüggen, O., Chourbaji, S., Ridder, S., Brandwein, C., Gass, P., Hörtnagl, H., & Hellweg, R. (2006). Stress-resistant mice overexpressing glucocorticoid receptors display enhanced BDNF in the amygdala and hippocampus with unchanged NGF and serotonergic function. *Psychoneuroendocrinology*, *31*(10), 1266–77. doi:10.1016/j.psyneuen.2006.09.008

Schultz, W. (1997). A Neural Substrate of Prediction and Reward. *Science*, *275*(5306), 1593–1599. doi:10.1126/science.275.5306.1593

Science, S. M., Winter, N., Griffin, A., & Hauser, J. R. (2013). The Voice of the Customer Author (s): Abbie Griffin and John R . Hauser THE VOICE OF THE CUSTOMER, *12*(1), 1–27.

Sehgal, M., Song, C., Ehlers, V. L., & Moyer, J. R. (2013). Learning to learn - intrinsic plasticity as a metaplasticity mechanism for memory formation. *Neurobiology of Learning and Memory*, *105*, 186–99. doi:10.1016/j.nlm.2013.07.008

Sehm, B., Taubert, M., Conde, V., Weise, D., Classen, J., Dukart, J., … Ragert, P. (2014). Structural brain plasticity in Parkinson's disease induced by balance training. *Neurobiology of Aging*, *35*(1), 232–9. doi:10.1016/j.neurobiolaging.2013.06.021

Seifert, C. L., Magon, S., Staehle, K., Zimmer, C., Foerschler, A., Radue, E.-W., … Sprenger, T. (2012). A case-control study on cortical thickness in episodic cluster headache. *Headache*, *52*(9), 1362–8. doi:10.1111/j.1526-4610.2012.02217.x

Selkoe, D. J. (2001). Alzheimer ' s Disease : Genes , Proteins , and Therapy. *Physiological Reviews*, *81*(2), 741–766.

Shi, Y., & Ethell, I. M. (2006). Integrins control dendritic spine plasticity in hippocampal neurons through NMDA receptor and Ca2+/calmodulin-dependent protein kinase II-mediated actin reorganization. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *26*(6), 1813–22. doi:10.1523/JNEUROSCI.4091-05.2006

Sled, J. G., Zijdenbos, a P., & Evans, a C. (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Transactions on Medical Imaging*, *17*(1), 87–97. doi:10.1109/42.668698

Smith, M. a, Makino, S., Kvetnansky, R., & Post, R. M. (1995). Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *15*(3 Pt 1), 1768–77. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7891134

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–55. doi:10.1002/hbm.10062

Soffié, M., Hahn, K., Terao, E., & Eclancher, F. (1999). Behavioural and glial changes in old rats following environmental enrichment. *Behavioural Brain Research*, *101*(1), 37–49. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10342398

Song, S., Miller, K. D., & Abbott, L. F. (2000). Competitive Hebbian learning through spike-timing-dependent synaptic plasticity, 919–926.

Soya, H., Nakamura, T., Deocaris, C. C., Kimpara, A., Iimura, M., Fujikawa, T., … Nishijima, T. (2007). BDNF induction with mild exercise in the rat hippocampus. *Biochemical and Biophysical Research Communications*, *358*(4), 961–7. doi:10.1016/j.bbrc.2007.04.173

Spontaneous, S., Engert, F., & Bonhoeffer, T. (1999). Dendritic spine changes associated with hippocampal long-term synaptic plasticity, *399*(May).

St. James, D. (2012). Seven deadly speaker sins. *Currents in Pharmacy Teaching and Learning*, *4*(3), 217–218. doi:10.1016/j.cptl.2012.04.007

Stahnisch, F. W., & Nitsch, R. (2002). Santiago Ram ó n y Cajal ' s concept of neuronal plasticity : the ambiguity lives on, *25*(11), 589–591.

Stein, M., Federspiel, A., Koenig, T., Wirth, M., Strik, W., Wiest, R., … Dierks, T. (2012). Structural plasticity in the language system related to increased second language proficiency. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *48*(4), 458–65. doi:10.1016/j.cortex.2010.10.007

Su, M. Y., Jao, J. C., & Nalcioglu, O. (1994). Measurement of vascular volume fraction and blood-tissue permeability constants with a pharmacokinetic model: studies in rat muscle tumors with dynamic Gd-DTPA enhanced MRI. *Magnetic Resonance in Medicine : Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, *32*(6), 714–24. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7869893

Sublette, M. E., Baca-Garcia, E., Parsey, R. V, Oquendo, M. a, Rodrigues, S. M., Galfalvy, H., … Mann, J. J. (2008). Effect of BDNF val66met polymorphism on age-related amygdala volume changes in healthy subjects. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *32*(7), 1652–5. doi:10.1016/j.pnpbp.2008.06.009

Suri, D., & Vaidya, V. a. (2013). Glucocorticoid regulation of brain-derived neurotrophic factor: relevance to hippocampal structural and functional plasticity. *Neuroscience*, *239*, 196–213. doi:10.1016/j.neuroscience.2012.08.065

Swain, R. ., Harris, a. ., Wiener, E. ., Dutka, M. ., Morris, H. ., Theien, B. ., … Greenough, W. . (2003). Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. *Neuroscience*, *117*(4), 1037–1046. doi:10.1016/S0306-4522(02)00664-4

Sweatt, J. D. (2009). *Alzheimer ' s Disease. Mechanisms of Memory* (Second Edi., pp. 292–319). Elsevier Inc. doi:10.1016/B978-0-12-374951-2.00012-3

Takagi, S., Obata, K., & Tsubokawa, H. (2002). GABAergic input contributes to acti v ity-dependent change in cell v olume in the hippocampal CA1 region, *44*, 315–324.

Takeuchi, H., Sekiguchi, A., Taki, Y., Yokoyama, S., Yomogida, Y., Komuro, N., … Kawashima, R. (2010). Training of working memory impacts structural connectivity. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *30*(9), 3297–303. doi:10.1523/JNEUROSCI.4611-09.2010

Tallal, P., Miller, S. L., Bedi, G., Byma, G., Wang, X., Nagarajan, S. S., … Merzenich, M. M. (1996). Language comprehension in language-learning impaired children improved with acoustically modified speech. *Science (New York, N.Y.)*, *271*(5245), 81–4. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8539604

Taubert, M., Draganski, B., Anwander, A., Müller, K., Horstmann, A., Villringer, A., & Ragert, P. (2010). Dynamic properties of human brain structure: learning-related changes in cortical areas and associated fiber connections. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *30*(35), 11670–7. doi:10.1523/JNEUROSCI.2567-10.2010

Taubert, M., Lohmann, G., Margulies, D. S., Villringer, A., & Ragert, P. (2011). Long-term effects of motor training on resting-state networks and underlying brain structure. *NeuroImage*, *57*(4), 1492–8. doi:10.1016/j.neuroimage.2011.05.078

Ten Brinke, L. F., Bolandzadeh, N., Nagamatsu, L. S., Hsu, C. L., Davis, J. C., Miran-Khan, K., & Liu-Ambrose, T. (2014). Aerobic exercise increases hippocampal volume in older women with probable mild cognitive impairment: a 6-month randomised controlled trial. *British Journal of Sports Medicine*, *i*, 1–8. doi:10.1136/bjsports-2013-093184

The Mendeley Support Team. (2011a). Getting Started with Mendeley. *Mendeley Desktop*. London: Mendeley Ltd. Retrieved from http://www.mendeley.com

The Mendeley Support Team. (2011b). Getting Started with Mendeley. *Mendeley Desktop*. London: Mendeley Ltd. Retrieved from http://www.mendeley.com

Thomas, C., & Baker, C. I. (2013). Teaching an adult brain new tricks: a critical review of evidence for training-dependent structural plasticity in humans. *NeuroImage*, *73*, 225–36. doi:10.1016/j.neuroimage.2012.03.069

Thorns, J., Jansma, H., Peschel, T., Grosskreutz, J., Mohammadi, B., Dengler, R., & Münte, T. F. (2013). Extent of cortical involvement in amyotrophic lateral sclerosis -- an analysis based on cortical thickness. *BMC Neurology*, *13*(1), 148. doi:10.1186/1471-2377-13-148

Tohka, J., Zijdenbos, A., & Evans, A. (2004). Fast and robust parameter estimation for statistical partial volume models in brain MRI. *NeuroImage*, *23*(1), 84–97. doi:10.1016/j.neuroimage.2004.05.007

Trachtenberg, J. T., Chen, B. E., Knott, G. W., Feng, G., Sanes, J. R., Welker, E., & Svoboda, K. (2002). Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. *Nature*, *420*(6917), 788–94. doi:10.1038/nature01273

Tronel, S., Fabre, A., Charrier, V., Oliet, S. H. R., Gage, F. H., & Abrous, D. N. (2010). Spatial learning sculpts the dendritic arbor of adult-born hippocampal neurons. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(17), 7963–8. doi:10.1073/pnas.0914613107

Tropea, D., Van Wart, A., & Sur, M. (2009). Molecular mechanisms of experience-dependent plasticity in visual cortex. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *364*(1515), 341–55. doi:10.1098/rstb.2008.0269

Tuoc, T. C., Pavlakis, E., Tylkowski, M. A., & Stoykova, A. (2014). Control of cerebral size and thickness. *Cellular and Molecular Life Sciences : CMLS*. doi:10.1007/s00018-014-1590-7

Uda, M., Ishido, M., Kami, K., & Masuhara, M. (2006). Effects of chronic treadmill running on neurogenesis in the dentate gyrus of the hippocampus of adult rat. *Brain Research*, *1104*(1), 64–72. doi:10.1016/j.brainres.2006.05.066

Um, H.-S., Kang, E.-B., Koo, J.-H., Kim, H.-T., Jin-Lee, Kim, E.-J., … Cho, J.-Y. (2011). Treadmill exercise represses neuronal cell death in an aged transgenic mouse model of Alzheimer's disease. *Neuroscience Research*, *69*(2), 161–73. doi:10.1016/j.neures.2010.10.004

Ungerleider, L. (2002). Imaging Brain Plasticity during Motor Skill Learning. *Neurobiology of Learning and Memory*, *78*(3), 553–564. doi:10.1006/nlme.2002.4091

Van Haren, N. E. M., Schnack, H. G., Cahn, W., van den Heuvel, M. P., Lepage, C., Collins, L., … Kahn, R. S. (2011a). Changes in cortical thickness during the course of illness in schizophrenia. *Archives of General Psychiatry*, *68*(9), 871–80. doi:10.1001/archgenpsychiatry.2011.88

Van Haren, N. E. M., Schnack, H. G., Cahn, W., van den Heuvel, M. P., Lepage, C., Collins, L., … Kahn, R. S. (2011b). Changes in cortical thickness during the course of illness in schizophrenia. *Archives of General Psychiatry*, *68*(9), 871–80. doi:10.1001/archgenpsychiatry.2011.88

Van Praag, H., Kempermann, G., & Gage, F. H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nature Neuroscience*, *2*(3), 266–70. doi:10.1038/6368

Van Praag, H., Kempermann, G., & Gage, F. H. (2000). Neural consequences of environmental enrichment. *Nature Reviews. Neuroscience*, *1*(3), 191–8. doi:10.1038/35044558

Van Praag, H., Shubert, T., Zhao, C., & Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *25*(38), 8680–5. doi:10.1523/JNEUROSCI.1731-05.2005

Vaynman, S., Ying, Z., & Gomez-Pinilla, F. (2004). Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *The European Journal of Neuroscience*, *20*(10), 2580–90. doi:10.1111/j.1460-9568.2004.03720.x

Vaynman, S., Ying, Z., & Gómez-Pinilla, F. (2004). Exercise induces BDNF and synapsin I to specific hippocampal subfields. *Journal of Neuroscience Research*, *76*(3), 356–62. doi:10.1002/jnr.20077

Vogt, B. A., Berger, G. R., & Derbyshire, S. W. G. (2003). Structural and functional dichotomy of human midcingulate cortex, *18*, 3134–3144. doi:10.1046/j.1460-9568.2003.03034.x

Voss, U., Holzmann, R., Tuin, I., & Hobson, J. A. (2009). Lucid dreaming: a state of consciousness with features of both waking and non-lucid dreaming. *Sleep*, *32*(9), 1191–200. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2737577&tool=pmcentrez&rendertype=abstract

Voss, W., Vanpatter, M., Pontifex, M. B., Raine, L. B., & Konkel, A. (2014). NIH Public Access, 172–183. doi:10.1016/j.brainres.2010.08.049.A

Wenger, E., Schaefer, S., Noack, H., Kühn, S., Mårtensson, J., Heinze, H.-J., … Lövdén, M. (2012). Cortical thickness changes following spatial navigation training in adulthood and aging. *NeuroImage*, *59*(4), 3389–97. doi:10.1016/j.neuroimage.2011.11.015

Wexler, B. E. (2011). Culture and Neural Frames of Cognition and Communication. doi:10.1007/978-3-642-15423-2

Williams, M. R., Chaudhry, R., Perera, S., Pearce, R. K. B., Hirsch, S. R., Ansorge, O., … Maier, M. (2013). Changes in cortical thickness in the frontal lobes in schizophrenia are a result of thinning of pyramidal cell layers. *European Archives of Psychiatry and Clinical Neuroscience*, *263*(1), 25–39. doi:10.1007/s00406-012-0325-8

Wong, P. C. M., Warrier, C. M., Penhune, V. B., Roy, A. K., Sadehh, A., Parrish, T. B., & Zatorre, R. J. (2010). NIH Public Access, *18*(4), 828–836. doi:10.1093/cercor/bhm115.Volume

Woolf, C. J., & Salter, M. W. (2014). Neuronal Plasticity : Increasing the Gain Pain, *288*(5472), 1765–1768.

Woollett, K., & Maguire, E. a. (2011). Acquiring "the Knowledge" of London's layout drives structural brain changes. *Current Biology : CB*, *21*(24), 2109–14. doi:10.1016/j.cub.2011.11.018

Wr, R. R. N., Dqg, Q., Deryh, F., Dssurdfk, D., Irxqg, Q. R. W., Dq, I., … Hdv, I. R. U. (n.d.). %xvvh\ 0rxvh 7rxfk 6fuhhq &kdpehu 3dfndjh 0rgho, 5–9.

Young, D., Lawlor, P. a, Leone, P., Dragunow, M., & During, M. J. (1999). Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. *Nature Medicine*, *5*(4), 448–53. doi:10.1038/7449

Yuede, C. M., Zimmerman, S. D., Dong, H., Kling, M. J., Bero, A. W., Holtzman, D. M., … Csernansky, J. G. (2009). Effects of voluntary and forced exercise on plaque deposition, hippocampal volume, and behavior in the Tg2576 mouse model of Alzheimer's disease. *Neurobiology of Disease*, *35*(3), 426–32. doi:10.1016/j.nbd.2009.06.002

Zagrebelsky, M., & Korte, M. (2014). Form follows function: BDNF and its involvement in sculpting the function and structure of synapses. *Neuropharmacology*, *76 Pt C*, 628–38. doi:10.1016/j.neuropharm.2013.05.029

Zatorre, R. J. (2013). Predispositions and plasticity in music and speech learning: neural correlates and implications. *Science (New York, N.Y.)*, *342*(6158), 585–9. doi:10.1126/science.1238414

Zatorre, R. J., Belin, P., & Penhune, V. B. (2002). Structure and function of auditory cortex: music and speech. *Trends in Cognitive Sciences*, *6*(1), 37–46. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11849614

Zatorre, R. J., Fields, R. D., & Johansen-Berg, H. (2012). Plasticity in gray and white: neuroimaging changes in brain structure during learning. *Nature Neuroscience*, *15*(4), 528–36. doi:10.1038/nn.3045

Zucker, R. S., & Regehr, W. G. (2002). Short-term synaptic plasticity. *Annual Review of Physiology*, *64*, 355–405. doi:10.1146/annurev.physiol.64.092501.114547

The thesis of Brocke Addison is approved by:

_____	_____
Dr. Alan Evans	Date
_____	_____
Dr. Barry Bedell	Date
_____	_____
Dr. Tim Kennedy	Date

The thesis of Brocke Addison is approved by:

_____	_____
Dr. Alan Evans	Date
_____	_____
Dr. Barry Bedell	Date
_____	_____
Dr. Tim Kennedy	Date