SAS Honors Program

Capstone Report

Option C

# Neurons to Neighborhoods and Aspects of Aging

Bhavana Kadiyala

RUID: 146008987

May 4th, 2016

## Introduction

Looking back at my undergraduate career at Rutgers University, I have realized how quickly these four, short years have gone by. I began my studies at the university as a Cell Biology and Neuroscience major, as it allowed me to learn about the human body and mind in the most detailed way possible prior to progressing onto my ultimate goal: medical school. However, as I began navigating my way through the many classes offered by the School of Arts and Sciences, I realized that my interests were much more diverse and varied. I began to take psychology classes, economic classes, and cognitive science classes, as they all piqued my interests immensely. I even worked as a research assistant and peer manager for two years in a psychophysiology lab at the Institute of Health, Healthcare, and Aging. Eventually, these classes that I initially began taking shaped the multidisciplinary degree and certificates that I will have in a few weeks: a bachelors degree in Cell Biology and Neuroscience, and certificates in Psychology, Economics, and Cognitive Science.

However, as the ultimate conclusion to my undergraduate career, I chose to work on the Capstone Project for the Honors Program during my senior year. Although a path less traveled by most, I opted to complete Option C of the Capstone Project, for which I took two graduate courses from the neurobiology department at Robert Wood Johnson Medical School. I believed that this would not only prepare me for my future career, but that it would also build on a significant portion of the material that I have learned as a part of my major over the past four years. Much to my surprise, the courses that I opted to take over the last two semesters encompassed not only information from my major, but also from all three of my minors. The experiences that I have gained through this option

of the Capstone Project have been truly interdisciplinary and rewarding. They have left me with both fond academic memories of my undergraduate career and sweet hope for my medical career.

## My First Graduate Course: Neurons to Neighborhoods

### Overview

The first course that I took as part of my Capstone project was Neurons to Neighborhoods - Human Development in Context: Rethinking Nature vs. Nurture. The primary goal of this course was to apply current theories, therapies, and public outreach programs to investigate the importance of infantile and childhood development on subsequent, lifelong physical and mental health. The course specifically approached this developmental investigation from a biopsychosocial and ecological perspective, analyzing how problems regarding any of these aspects during development could lead to severe and long-term physiological, neurological, and psychological consequences. The semester-long seminar finally culminated with an exploration of how exactly these long-term consequences develop, particularly from an epigenetic point of view, and how they can be mitigated or even prevented from developing.

### Lessons Learned

Before we delved into the consequences of developmental complications, we first learned about how exactly infantile development occurred. This part of the course was taught by Dr. Micheal Lewis, a distinguished professor of development and psychiatry at the Child Health Institute of RWJMS. Dr. Lewis began the course by teaching us about the four main models of development: trait model, contextual model, interactional model, and transformational model. The first of the four models, the trait model, states that the

trait of a child during early childhood has the ability to predict the traits of the child later on in life. The logic behind this theory is that traits, whether biologically inherited or learned through experience, entrench themselves into a person very early on. These traits can interact with the environment throughout the person's lifetime, but they are not affected and do not change. In contrast to this theory is the environmental model, which states that childhood development is influenced mostly by the environment. All traits that a child develops are due to how the behaviors influencing that trait were regulated by the environment. Additionally, the theory implies that a change in the environment will automatically lead to a change in the child's behavior. The interactional model came about in order to bridge the stark differences between the two previous models. This model states that both innate characteristics and environmental factors influence development. This model tries to explain that while innate factors do exist, they do interact with the environment and that they are influenced by the environment; at the same time, the environment can influence development, but it also has limitations in the extent to which it can affect one's characteristics. The transformation model, however, counteracts this model. The transformation model states that both the nature part in an individual and the environment of that individual influence each other in a cause-and-effect manner. Specifically, the innate characteristics of an individual influence him to act a certain way with the environment based on his previous experiences. At the same time, the environment responds to the individual based on how that individual received its influence previously. Thus, this theory essentially nullifies the previous models by saying that none of these models can truly explain how, or the extent to which, nature and

nurture purely influence childhood development. Both nature and nurture are intertwined with each other when it comes to influencing development.

After describing the four main theories of development, Dr. Lewis then went on to elaborate on the four main characteristics of children's temperament: difficult, fearful, dull, and predictable. These infantile temperamental characteristics, combined with the environment of the child, form the main stimulus that affects children's developmental trajectory. While difficult and fearful babies are likely to be treated more negatively by their caretakers simply due to their high volatility, dull and predictable babies may be treated more positively simply due to their placidity.

Dr. Geraldine Oades-Sese, another distinguished professor of pediatrics and child psychology at the Child Health Institute that taught the second half of our course, then probed into how this biased, preliminary treatment may form many of the attachment styles of the children, which may be molded and either enhanced or repressed due to their familial, environmental, and situational influences throughout their childhood and adolescence. The four main types of attachment styles in individuals that can develop are: secured, preoccupied, dismissing, and fearful-avoidant. Secured individuals have both low anxiety and low avoidance, which is a fear of partner rejection and a fear of emotionally opening up, respectively. Fearful-avoidant individuals have high avoidance and high avoidance. Preoccupied individuals have high anxiety and low avoidance, while dismissing individuals have low anxiety and high avoidance. These attachment styles can further influence any interpersonal relationships that individuals form throughout their lifetimes. More importantly, the individuals' perspective on relationships may affect the number of and accessibility to close, reliable bonds that they maintain throughout their

life. Consequently, they may employ healthy coping mechanisms, such as using problem-focused coping strategies, if they have healthy attachment styles; on the other hand, they may become dependent on unhealthy coping strategies, such as avoidance-focused or substance-focused coping strategies, if they have unhealthy attachment styles.

However, such negative side effects can be averted and attenuated if children are nurtured to develop a resilient personality. Having even just one, constantly available and responsive adult in their lives may provoke children to become resilient towards psychosocial factors. This may foster their intellectual, emotional, and social development, particularly through adolescence. Resilient individuals have also been shown to lead stable lives with healthy relationships well into adulthood, regardless of any childhood trauma they may have experienced during their early stages of development. Thus, Dr. Lewis and Dr. Oades-Sese have taught me, through their class, that although many developmental quirks can cause serious psychosocial deficits in individuals as they age, the effects can be softened or even eliminated if individuals develop a strong, resilient personality that motivates them to keep persevering.

**Independent Research: *Childhood Trauma and Substance Abuse: A Neuroanatomical Link***

The fundamental principles about development and resilience that both of my professors taught me propelled me to focus my independent research project on childhood trauma and how trauma survivors have a higher susceptibility to engaging in substance abuse. Through my research, I proposed that this mainly occurs due to a combination of permanent neuroendocrine and neurobiological changes that occur during the exposure to trauma. Specifically, the chronic stress response elicited in victims causes

elevated catecholamine and glucocorticoid levels in the body. Together, these hormones have depleting effects on the prefrontal cortex and hippocampus, which in turn decreases victims' decision-making ability as well as declarative and episodic memory. The hormones also have enhancing effects on the amygdala, which increases victims' emotional memory; the emotional memories, however, are often stored without context due to a malfunctioning hippocampus. This, in turn, makes victims prone to seek out rewarding, yet maladaptive, behaviors, such as engaging in substance abuse-related activities.

The process of researching independently for this topic was highly rewarding in and of itself. Not only did I learn a tremendous information about my primary interest in childhood trauma, such as various types of childhood trauma, the prevalence of childhood trauma, and immediate and long-term reactions to trauma, but I also learned a significant amount of information about the neurobiological aspect of childhood trauma. Case in point, I was able to investigate the developmental trajectories, interactional circuits, and response mechanisms of various areas of the brain and hypothalamus-pituitary-adrenal axis. I was then able to learn how all of these pathways played into long-term memory patterns and habits, and how these may be connected to underlying childhood trauma. Understanding that the side effects of both acute and chronic trauma during children's early developmental years may not manifest openly until years, or sometimes decades, later, was the single most valuable link I was able to make between the biological, psychological, and practical approaches to human development. This entire project was the ultimate culmination to my degree in Cell Biology and Neuroscience and certificates in Psychology and Cognitive Science. I was able to conduct research on and write about

an interdisciplinary topic that appeased to the four years of knowledge I have accumulated during my undergraduate career. I have included my final research report at the end of this report, as it reflects, truly and entirely, a combinatorial comprehension of the various fields I have dabbled in over the past eight semesters.

## My Second Graduate Course: Aspects of Aging

### Overview

The research that I conducted for my independent research project piqued my interests in the opposite end of the lifetime spectrum: old age. Conducting such extensive research on childhood and adolescent trauma, as well as taking an entire course directed towards identifying how issues during childhood development can have lasting lifetime consequences, made me ponder about how, or even if, aging processes are affected by childhood and adolescent development. However, a graduate course that was specifically tailored to this topic was not available at the university. Thus, I opted to take a newly offered elective course — Biological, Biomedical, and Social Aspects of Aging — at RWJMS taught by Professor Federico Sesti, an associate professor and researcher who is currently researching oxidative stress mechanisms in aging. This course was completely different from the graduate course I took during the previous semester. While the first course I took was specifically focused on an area of development and its effects, this course approached the general topic of aging from a multitude of perspectives. Each class consisted of one guest lecturer from a selected department at Rutgers University or RWJMS; each lecturer would approach the topic of aging from that department's perspective. Case in point, our lectures consisted of the philosophy, economic, sociology,

psychology, genetic, chemical, neurobiological, oxidative, metabolic, etc. aspects of aging.

**Lessons Learned**

Because of the nature of the course, my experience in this course was quite different from my experience in my first graduate class. While I learned very specific and focused information about one topic during my Neurons to Neighborhoods class, I learned an extensive but very broad amount of information about the general aging process in humans. Every single scientific lecture, however, did point out one, key aspect of human aging: humans were not evolutionarily equipped to live past thirty-five years of age until recent decades. Many of the physiological, psychological, and sociological aspects of aging that humans encounter today are unique to recent times due to the recent advances in medical care, heightened education and health behaviors of individuals of all ages, and increased precautionary health measures and treatment. That being said, much research is currently being conducted to expand the overall lifespan of all humans across the globe. Scientists are currently modeling their beliefs that human lifespan can be extended after organisms in nature that have much longer lifespans than humans, even though their evolutionary trajectory has followed a similar path to that of humans. For example, the Pinus longaeva tree and dahlia anemone have a five thousand-year life span and a potentially unlimited lifespan due to continuous regeneration, respectively. Through the use of C. elegans in the lab, which are a nematode species with a very short lifespan, similar genetic composition to humans, and easily manipulatable genome, researchers have been able to induce and knock out certain genetic mutations and test their effects on phenotype and longevity.

One of the most interesting research studies using C. elegans and longevity that was conducted was caloric restriction. The lecture regarding this research was taught by Dr. David Comoletti, another distinguished professor from the Child Health Institute at RWJMS. Dr. Comoletti introduced to me, for the first time, how restricting the total intake of calories over any length of time would ultimately increase lifespan and decelerate any associated aging processes. However, this does not endorse restricting calories to the point of malnutrition; it simply means that individuals should decrease their calories by anywhere from fifteen to twenty percent of their required caloric intake. Individuals can either reduce their caloric intake daily, or engage in fasting every other day or every few days in order to reap the same benefits. The earlier such a restrictive ritual is adopted, the greater the long-term downstream physiological effects, a few of which include: lower core body temperature, lower insulin levels, lower blood glucose levels, and decreased fat deposits in the body. Most importantly, caloric restriction can result in the reduced production of reactive oxygen species, which are toxic to cells and contribute to an acceleration of aging mechanisms, due to decreased mitochondrial activity; this is because the body's digestive and energy extraction systems are used less as there are less calories to "work on." However, the exact role that caloric restriction plays in conjunction with other long-term healthful practices, such as exercise, healthy diet, emotional stability, etc., is still unknown. There are also not many concrete controlled trials on how such a practice plays into slowing aging-related loss of cognitive and physiological function, or neurodegenerative diseases' onset. Thus, this area of study is still one that is open to much research, but it is one that holds, at least for now, many promising results in terms of health, disease treatment, and overall lifespan.

## Reflections

The combination of material from both of my classes, which encompassed everything from childhood development to aging mechanisms and how these processes are implicated in health, longevity, physiological disease, and mental ailments, has allowed me to truly incorporate everything from my academic background. While learning the material for these courses, I was forced to utilize the knowledge of biological, chemical, and neurological processes that I acquired through the classes I took for my major; the psychological theories and outlooks individuals of different ages and social classes possess that I learned about in my Psychology minor; the economic burden of diseases and aging that I learned about in my Economics minor; and finally, the heuristics people use to make assumptions about their health and age that I learned about in my Cognitive Science minor. Because of these various fields of study, all of which are related but drastically different and specified, that I dabbled in during my undergraduate career at Rutgers University, I felt that designing and executing my own research project as a part of my senior thesis would not do justice to all of the subjects I have taken during the last four years. Thus, I opted to complete Option C of the Capstone Project, which allowed me to take two graduate courses in my field of interest at RWJMS. Both classes that I took were small in size and extremely detailed in material. More importantly, however, they were all-encompassing of a variety of approaches from different fields towards the main topic in class. Consequently, I was forced and, frankly honored, to be able to put all of my academic efforts to good use at the culmination of my undergraduate career.

## Acknowledgements and Gratitude

The knowledge that I have gained during through these two graduate courses will be knowledge that I will be able to use directly in medical school and my medical career. In fact, I have already taken an initiative to employing this knowledge while shadowing an endocrinologist weekly; as I see the doctor's patients, I am able to apply my holistic knowledge of general human mental health, physiological health, and healthful behaviors to analyzing and understanding each patient's unique issues. Moreover, I have already planned to shadow another doctor, this time a geriatrician, later on this summer. My second graduate course about aging has pushed me to further investigate the medical and psychological life of the aging adult population, which is one that is often neglected and overlooked despite the fact that it is singlehandedly the fastest growing age group across the globe.

By allowing me to focus on an array of age groups, specifically on their medical and psychological health, I have been able to explore my interests in the human body and mind to the fullest. I could not have been more thankful to Rutgers University, and more importantly, the School of Arts and Sciences Honors Program, for giving me this opportunity. I am forever indebted to the people that I have met, the professors that I have been taught by, and the deans that have helped me through this process. I would like to sincerely and wholeheartedly thank each and every one of these wonderful people. The knowledge, confidence, and memories that I walk away with at the conclusion of my undergraduate career are something that I will remember and cherish forever.

# Childhood Trauma and Substance Abuse: A Neuroanatomical Link

## Childhood Trauma

### The Definition of Trauma

A trauma is any event that brings about "physical, emotional, or psychological distress" in an individual (Kaneshiro, 2010). Consequently, the labeling of a particular event as traumatic depends on the consequences of the event and the individuals affected by those consequences. Individuals with more potent coping mechanisms, greater internal resilience, and readily available recovery resources may be more cushioned from the negative effects of an event than those without those particular assets. Therefore, these individuals may not identify an event to be as traumatic as those that are not as well cushioned.

### The Definition and Prevalence of Childhood Trauma

Whether or not children label particular events from their childhood as traumatic depends on, similar to the process of general trauma labeling, their interpretation of the event and its aftermath. Any traumatic events, as labeled by the affected children, experienced between the ages of zero to twelve fall into the category of childhood trauma.

In a 2011 survey conducted by the Center for Disease Control in the states Arkansas, Louisiana, New Mexico, Tennessee, and Washington, 59.4% of 26,229 adults reported having at least one traumatic childhood experience (Bynum et al., 2010). That same year, the Substance Abuse and Mental Health Services Administration estimated that approximately one out of every four children will experience a traumatic event before the age of four ("Childhood Trauma," 2012). Childhood trauma has been found to

be much more prevalent than previously calculated. Hence, all children, regardless of age, gender, ethnicity, financial background etc., run the risk of experiencing childhood trauma, of which there are many types.

### Types and Overall Effects of Childhood Trauma

Commonly experienced types of childhood trauma include: natural disasters, terrorism, community violence, refugee trauma, domestic violence, physical abuse, sexual abuse, medical trauma, neglect, death or loss of loved ones, and traumatic grief ("Types of Traumatic Stress," n.d.). All of these traumas can range, on a continuum, from acute to chronic occurrence. While both types of occurrences have severe, short-term effects, chronic traumas are much more prone to having permanent, long-term effects on the affected children. Not only do chronic traumas cause temporary changes in cognition, affect, behavior, and physiology, but they also cause some of the permanent changes in the neuroendocrine and neurophysiology systems found in childhood abuse victims (Perry, 2003). These neurological changes make the children more susceptible as adolescents and adults to the development of a slew of psychological disorders, of which substance abuse is the most overt and detrimental.

## General Stress Response to Trauma in Children

### Physiological Changes

Children do not react to trauma in the same way as adults, simply because they are physically, mentally, and psychologically underdeveloped. Unlike adults, children neither have a typical, full-blown "fight or flight" response stage, nor do they calm down as quickly when the threat is removed. Thus, when exposed to trauma, children engage in

an altered type of stress response called the alarmed response (Perry, 2003). This response has two phases: the hyperarousal phase and the dissociative phase (Perry, 2003).

The first stage is the hyperarousal phase, or the "fight or flight" response stage. This acute response is controlled mainly by the sympathetic nervous system, which produces physiological changes in order to prepare the body for self-protection through either offensive or defensive methods. Except for the generation of glucose, which is used as a fuel source, all other digestive processes are temporarily shut down. Heart rate, blood pressure, and respiration all also increase in order to provide the brain and limbs with ample blood and energy. Because these changes occur for a "protective" purpose, children in this phase of the stress response are hyperaware of all external cues and negligent of any internal physiological, emotional, or psychological signs; their full focus is put on trying to escape the stressful trauma environment.

However, if children are prevented from escaping the trauma situation, they enter the second phase of the alarm response, which is the dissociative phase (Perry, 2003). This phase is controlled by the parasympathetic nervous system, which returns physiological processes to their resting conditions. Digestive functions are resumed, and blood pressure, heart rate, and respiration levels drop. Not only do children become aware of their physiological, psychological, and emotional status during this stage, but they also begin to employ coping strategies in order to deal with the imminent threat. These strategies include "avoidant and psychological fleeing mechanisms," such as fantasizing, time suspension, or in extreme cases, a loss of contact with reality resembling psychosis (Perry, 2003).

## The Neuroendocrine Changes That Cause the Physiological Changes

The principal source of the physiological changes during the alarm response are catecholamines, which are produced by the sympathetic nervous system and adrenomedullary system, and glucocorticoids, which are produced by the hypothalamic-pituitary-adrenal (HPA) axis (Kolk, 1994).

**Catecholamines.** The two most important catecholamines regarding an alarm reaction to trauma are norepinephrine and epinephrine; the former is produced by the sympathetic nervous system, while the latter is produced by the adrenomedullary system. Both are excitatory in effect, which in this case is useful for readying the body for dealing with trauma. Researchers have found an "association between norepinephrine and active escape, avoidance, or attack, and an association between epinephrine and passive, immobile fear" (Dimsdale & Moss, 1980; Goldstein, 2003).

A third catecholamine, dopamine, is also produced in response to stress. However, dopamine does not cause any direct physiological effects by itself. Instead, it mediates the production of the other catecholamines. Additionally, it aids norepinephrine and epinephrine in interacting with the pituitary gland in the HPA axis in a positive feedback loop that increases the production of cortisol.

**Glucocorticoids.** Cortisol is the most important glucocorticoid involved in the alarm response. It is essential for controlling the body's metabolic and immune systems in order to prepare the body for the alarm response. Case in point, the hormone causes an increase in gluconeogenesis and glycogenolysis, both of which create glucose for the body to use as energy. It also weakens the immune system, which helps the body focus its energy on defense rather than repair and maintenance. The production of this

glucocorticoid begins in the hypothalamus, which is the first structure involved in the HPA chain. The hypothalamus releases corticotropin releasing factor (CRF), which in turn signals the pituitary gland to release adrenocorticotropic hormone (ACTH). This hormone then signals the adrenal cortex to release cortisol.

**Cortisol's Negative Feedback Loop.** Cortisol itself is involved in a negative feedback loop with the HPA axis. As the concentration of cortisol in the blood stream increases, it negatively feeds back to both the pituitary gland and the hypothalamus in order to hinder the further production of ACTH and CRF, respectively. This causes a lower concentration of cortisol to be made as the concentration of cortisol in the body increases. In normal individuals, the excessive production of cortisol, as well as that of norepinephrine and epinephrine, will cease when the trauma ends. This will help the body terminate its stress response and resume its normal, vital functions.

## The Long-Term Effects of Chronic Childhood Trauma

When children experience the same acute, traumatic event repeatedly; multiple types of trauma; or one, chronically present traumatic event, the cortisol levels in their bodies become permanently altered. This occurs due to the constantly aroused physiological state they are in, as the repeated exposure to trauma causes a series of "overlapping" stress responses. Consistently elevated catecholamine and glucocorticoid levels serve to weaken the children's immune systems, slow or stunt their psychological development, and, most importantly, permanently alter their neurobiology. The most obvious and drastic of these alterations can be seen on the hippocampus, amygdala, and prefrontal cortex (PFC). The first two are a part of the limbic system and vital to the

formation of memories; the last is a part of the frontal lobe and is involved with higher order thinking.

**Elevated Hormone Levels**

**Elevated Catecholamine Levels.** When faced with chronic trauma, children's bodies repeatedly enter the alarm response stage. Thus, as numerous studies have confirmed, the sympathetic nervous system remains chronically overactive (Heim et al., 2000; Sherin & Nemeroff, 2011; Wortsman & Frank, 1984). Ergo, norepinephrine and epinephrine levels remain elevated in the children. Because these hormones regularly activate a similar set of neural pathways, they help those pathways develop stronger connections. Ultimately, this leads to a permanent sensitization of those "neural response pathways associated with their traumatic experiences" (Perry, Pollard, Blaicley, Baker, & Vigilante, 1995).

**Elevated Glucocorticoid Levels.** Having higher levels of catecholamines present in the body also means that the HPA axis is regularly activated via a positive feedback loop. This leads to an overproduction of cortisol by the HPA axis, which is incapable of regulating itself as sustained stress responses can actually override the negative feedback loop of cortisol.

However, individuals that are chronically stressed have been found to produce less cortisol in response to stress, have lower stress baseline cortisol levels in the body, and a greater amount of cortisol receptors in all cells in comparison to non-stressed individuals (Elzinga et al., 2003; Heim et al., 2000; Kolk, 1994; McFarlane, Yehuda, Barton, & Wittert, 2010; Sherin & Nemeroff, 2011; Yehuda, McFarlane, & Shalev, 1998). Because less cortisol is produced in reaction to a stressor, the overall cortisol

levels never reach the threshold needed to fully stop further production of CRF and ACTH.

**Effects of Elevated Stress Hormones.** The elevated levels of glucocorticoids, which are further enhanced by high levels of catecholamines, cause some of the physiological symptoms seen in and risks faced by childhood trauma victims. These include: greater vulnerability to sickness and "stress hyperglycemia" (Eigler, Sacca, & Sherwin, 1979); increased risk of developing post-traumatic stress disorder (PTSD); exaggerated acute stress responses; chronically higher heart rate; and increased auditory startle responses (Nisembaum, Zigmond, Sved, & Abercrombie, 1991; Pike et al., 1997; Sherin & Nemeroff, 2011; Yehuda, McFarlane, & Shalev, 1998).

## The Effects of Elevated Glucocorticoid Levels on the Hippocampus

**Hippocampal Structure and Function.** The hippocampus is a horseshoe shaped structure located in the medial temporal lobe, spanning both hemispheres of the brain. It is a structure vital to the storing of long-term memories, particularly declarative and episodic memories. A distinctive attribute of the hippocampus is its ability to create "relational representations" between memories, or more specifically, "the binding of arbitrary relations between the elements of experience into durable representations of past experiences and the flexible expression of these representations…for the search, reconstruction, and recombination of the information contained within them" (Rubin, Watson, Duff, & Cohen, 2014). In other words, the hippocampus stores the spatial, temporal, and relational information of memories as well as their content (Kolk, 1994; Rubin et al., 2014).

**Development of the Hippocampus.** The main, memory-related functions of the hippocampus do not emerge until approximately eighteen to twenty-four months after birth (Gomez & Edgin, 2015; Kolk, 1994; Kolk & Saporta, 1991; Woon & Hedges, 2008). Until this age, the hippocampus exists and is functioning in the brain. However, key features, such as the process of long-term potentiation and contextual memory, are not fully developed. This is one of the key explanations for infantile amnesia, or the lack of memories during early infancy, prior to the development of the hippocampus. Despite the fact that the hippocampus begins to fully function around thirty six months of age, children continue to see growth and development in this area until adolescence (Gomez & Edgin, 2015; Woon & Hedges, 2008). Peak volume of the hippocampus has been found to occur around nine to eleven years of age (Uematsu et al., 2012). Thus, children's hippocampal development is highly dependent on and impressionable by the events that occur during childhood.

**Glucocorticoids and Hippocampal Development.** Hippocampal growth, the majority of which occurs during childhood, is stunted in children faced with trauma. The elevated glucocorticoid levels in the body have been found to decreased dendrite branching, dendrite spines, and neurogenesis in the hippocampus (Fuchs & Gould, 2000; Kolk & Saporta, 1991; Sherin & Nemeroff, 2011; Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002;). Not only does this lead to a decrease in hippocampal volume, but it also dampens the long-term potentiation of neural pathways that are often used (Bonne et al., 2001; Divarci & Pare; Sherin & Nemeroff, 2011). Consequently, commonly activated neural pathways and contextual memories are not stored properly. This is especially

detrimental to childhood trauma victims, as they are unable to remember the source or context of many of their traumatizing experiences.

## The Effects of Elevated Glucocorticoid Levels on the Amygdala

**Amygdal Structure and Function.** The amygdala is the main emotional and emotional memory center of the brain. Also located in the medial temporal lobe, it has two halves like the hippocampus, each located in one hemisphere of the brain. However, each half of the amygdala performs differential functions; this contrasts with the hippocampus, in which both halves perform the same functions. Researchers have found that the right amygdala specializes in recognizing and forming negative emotions, whereas the left amygdala recognizes and forms both negative and positive emotions (Launteaume et al., 2006). Thus, a loss of function to one half of the amygdala prevents it from being fully compensated for by the other half of the amygdala.

**Development of the Amygdala.** Like the hippocampus, the amygdala also continues to develop during childhood. Both structures reach their peak volume when children are between nine to twelve years of age (Uematsu et al., 2012). However, whereas the hippocampus is not fully functional until around thirty-six months of age, the amygdala is much more developed at birth. In fact, researchers have found that "the distribution of opiate receptors" and "the pattern of serotonergic innervation" of the amygdala of a newborn macaque monkey, which is highly similar to humans in terms of development, and adult macaque monkey were almost identical after one month (Schumann, Bauman, & Amaral, 2011). Thus, the amygdala plays a greater role in children's perception, memory, and actions during childhood than the hippocampus.

**Glucocorticoids and Amygdala Development.** Elevated glucocorticoid levels, which have a detrimental effect on hippocampal development, have a different effect on the amygdala. Dendritic branching actually expands in the amygdala under high glucocorticoid levels (Divarci & Pare, 2007; Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002). This means that there is a higher receptor affinity for the higher levels of glucocorticoids, which means that overall, the excitability of the neurons in the amygdala increases. Moreover, amygdala neurons become increasingly sensitive to excitation while becoming decreasingly sensitive to inhibitory effects such as GABA neurons, which decrease the function of the amygdala (Divarci & Pare, 2007). Elevated glucocorticoid levels have also been found to enhance long-term potentiation in the amygdala; in other words, emotional memories are encoded much more strongly and efficiently under stress (Sherin & Nemeroff, 2011; Shin et al., 2005). Emotional memory is further enhanced by the interaction between norepinephrine and cortisol, such as during the initial trauma response; during this interaction, children's negative emotion response to the trauma increases (Kukolja et al., 2008). All of these effects coupled together explain why childhood trauma survivors have extremely emotional reactions to any trauma-related signs. Furthermore, a lack of context for the emotional memories heightens the victims' sense of fear and anxiety. This puts victims at a higher risk of developing depression, PTSD, or substance-abuse disorders at a later age.

## The Effects of Elevated Glucocorticoid Levels on the Prefrontal Cortex

**Prefrontal Cortex Structure and Function.** The prefrontal cortex (PFC) is the part of the cerebral cortex that covers the frontal lobe. Its main purpose is to control executive functions, such as higher-level thinking, planning, decision-making, regulation

of behavior, and most importantly, learning. It is, as the general public would describe, the "rational" part of a human being. Because of its inherent function, the PFC plays a large role in moderating the body's response to stress. Not only does it activate the autonomic nervous system and HPA axis in reaction to a stressful situation, but it also regulates the strength of these stress responses (Sherin & Nemeroff, 2011; Sinha, 2008). The PFC has the power to override any feedback loops or signals produced by the sympathetic nervous system, adrenomedullary system, or HPA axis. It also "learns" how to deal with certain types of stressors, and implements the same types of responses when faced with similar situations. However, it is also vulnerable to negative side effects when those same systems are chronically activated.

**Development of the Prefrontal Cortex**. The PFC is not fully mature at birth. The majority of its development, especially regarding its executive functions, occurs postnatally and through adulthood. It is, perhaps, the brain area that is singularly most affected by experience. Environmental, emotional, psychological, and social stimuli that children are repeatedly exposed to during the critical periods of development in childhood become permanently embedded in the brain; this is the source for much of the learning that occurs in children during their childhood. When the neural pathways activated in response to these frequently exposed stimuli become strengthened, the once-temporary reactions develop into permanent personality traits (Perry et al., 1995). This can lead to a lifelong change in how children identify, react to, and recover from traumatic experiences.

**Glucocorticoids and Prefrontal Cortex Development.** Chronic childhood trauma or stress hinders the development of the PFC. Normally, the PFC has a high level

of glucocorticoid receptors. When chronic trauma or stress causes chronically elevated glucocorticoid levels, these receptors become over-sensitized to the presence of glucocorticoids. Researchers have found that "chronic [glucocorticoid presence] results in a dramatic dendritic reorganization of PFC neurons similar to that seen in the hippocampus" (Sinha, 2008). Individuals who have been exposed to chronic trauma, especially during their childhood, have been found to have a smaller PFC volume; moreover, researchers have discovered that chronic stress promotes the growth of white matter but not the growth of gray matter in both the PFC and hippocampus (Chetty et al., 2014; Sherin & Nemeroff, 2011). This, in turn, hinders the connectivity of the PFC and hippocampus with not only each other, but also the amygdala and HPA axis during the mediation of stress responses.

## Chronic Childhood Trauma and Substance Abuse

Researchers have found time and time again that the risk of engaging in substance abuse is heightened in individuals that face chronic trauma or stress. The perpetuated cycle of substance use, which was previously thought to be mostly due to physiological and psychological aftereffects, has now been found to be one that is also intertwined with neurobiological factors. The collective effects of decreased behavioral control caused by an under-active PFC; loss of clear, context-dependent memory due a smaller hippocampus; and increased emotional response due to a hyper-sensitized amygdala found in childhood trauma victims make them especially vulnerable to succumbing to substance abuse.

## The Definition of Substance Abuse

According to the World Health Organization, substance abuse is "the harmful or hazardous use of psychoactive substances" ("Substance abuse," n.d.). Traditionally, alcohol, nicotine, and marijuana are the most commonly abused substances. Other commonly abused substances include: cocaine, opioids, amphetamines, and prescription and over-the-counter drugs.

Substance abuse can occur at any age. All types of substance abuse have three main stages: 1) an acute drug effects stage, 2) a transition to addiction stage, and 3) an end-stage addiction (Kalivas & Volknow, 2005). The first stage occurs when individuals begin use of the substance; this is when their bodies and minds adapt to the rewarding drug effects. Over time, repeated administration of the drug leads to resistance. Therefore, individuals use an increasing amount of drugs to reach the same effects they felt initially; this is the second stage, in which the increasing frequency and amount of administered drugs paves the way for addiction. The ever-present use and effects of the drugs ultimately create an addiction that is beyond pure biological addiction. After using drugs for an extended period of time, they feel a psychological and behavioral addiction to the substance. This leads to the end-stage addiction, when the user can no longer quit due to the physiological, psychological, and emotional withdrawal symptoms that come from halting drug use. This type of severe addiction also increases the risk for a relapse even after treatment.

## The Neurobiological Basis Between Childhood Trauma and Substance Abuse

**The Effects Stress on Dopamine.** Dopamine is a neurotransmitter that is mainly involved in motivation and reward pathways. Although it is not directly involved in the

alarm response stage, dopamine helps mediate the alarm response by positively stimulating the HPA axis and autonomic nervous system to produce glucocorticoids and catecholamines, respectively (Rasheed & Alghasham, 2012; Sinha, 2008). Therefore, chronic levels of stress have been found to hyperactivate dopaminergic neurons, causing dopamine to accumulate in areas that contain a large number of dopaminergic neurons. Specifically, this occurs in the amygdala and hippocampus (Belujon & Grace, 2011; Rasheed & Alghasham, 2012; Sinha, 2008).

**Dopamine and the Prefrontal Cortex.** Although dopamine does not necessarily accumulate in the PFC, there are many dopaminergic pathways that connect to the PFC from various areas of the brain (Sinha, 2008). Stress causes the overall dopaminergic systems in the brain to become overactive; therefore, more dopamine is secreted in the PFC. Stress also causes the PFC to lose some of its effectivity in the decision-making and learning processes. Thus, the hyperactivity of the motivational and reward-seeking hormone in the PFC causes chronically stressed individuals to consciously seek out and engage in behaviors that are rewarding.

**Dopamine and the Hippocampus.** Through the hippocampus, dopamine causes individuals to remember the reward-seeking behaviors they seek and engage in. This occurs because the hippocampus is one of the locations in which dopamine accumulates. Because the hippocampus encodes long-term, context-dependent memories, the accumulation of dopamine in this area when under chronic stress causes the hippocampus to specifically strengthen the neural pathways elicited by rewarding actions. It is true that chronic stress causes a decrease in hippocampal volume and its process of long-term potentiation. However, when the remaining functionality of this structure is flooded by

dopamine, it behaves in a biased manner, emphasizing the remembrance of behaviors and their context related to rewards (Belujon & Grace, 2011).

**Dopamine and the Amygdala.** This reward-seeking behavior is especially heightened by the amygdala, which is another location in which dopamine accumulates during chronic trauma. Unlike the PFC and hippocampus, chronically elevated levels of catecholamines and glucocorticoids actually have an enhancing effect on amygdala function. This means that the amygdala is especially responsive to any type of emotion. When this increased responsiveness is influenced by dopamine, the amygdala becomes selectively more responsive to the emotional effects associated with dopamine-activated emotional memories (Kalivas & Volknow, 2005).

**The Combined Effect.** The total effect of accumulated dopamine on the weak prefrontal cortex, smaller hippocampus, and hyper-sensitized amygdala is that rewarding behaviors are sought out, acted upon, and remembered strongly. This is the initial cycle that causes individuals to begin engaging in addictive, maladaptive behaviors. First, they consciously make a decision to engage in rewarding behavior. The behaviors they engage in then cause a strong, positive emotional response, which is remembered by the amygdala. The episodic content, spatial context, and temporal context of the rewarding action is strongly encoding by the hippocampus. Because of all of these positive effects and associations, the individuals seek out the same behavior repeatedly.

This is repeated behavior seeking is, essentially, the perpetuated cycle of substance abuse. Victims of childhood trauma are especially prone to substance abuse, as the negative effects of their traumas manifest themselves at a very young age. This means that the tendency to find and use drugs as a method of "escape" from their trauma and its

aftereffects also begin very early. In fact, more than seventy percent of adolescents that are treated for drug abuse have reported being victims of childhood trauma ("Making the Connection," n.d.). Children that develop PTSD, lack proper coping strategies, expose themselves to trauma cues, or have less internal resilience are much more likely to develop substance abuse ("Understanding Links," n.d.). This occurs because these children seek a physical outlet for relieving their traumatic symptoms, as opposed to seeking an emotional or psychological outlet. Ultimately, this causes an increased internalization of the negative emotions associated with the trauma instead of engaging in activities associated with emotional catharsis.

The chronic substance abuse further exacerbates the negative, neurobiological symptoms associated with chronic trauma. Case in point, the PFC, hippocampus, and amygdala become partial to functioning in the presence of drugs. Thus, when the users attempt to quit their drug usage, one of the main withdrawal symptoms is the change in cognitive, emotional, and memory functions. The brain, which has encoded the rewarding sentiments associated with drug use, craves the drug use in order to function as before. The amygdala will no longer be able to encode the positive emotions associated with drug use, and the hippocampus will not be able to encode the context of those positive feelings; thus, the user is much more likely to relapse into drug use simply to satisfy these mental needs. The substance abuse, which began due to the neurobiological side effects of childhood trauma, will be continued due to those same neurobiological side effects.

## Conclusion

Childhood trauma is a relatively common phenomenon that all children are at risk of experiencing. Chronic childhood trauma, to which children have repeated stress

responses, cause sustained, higher levels of catecholamines (norepinephrine, epinephrine, and dopamine) and glucocorticoids (cortisol) in the body. While these elevated hormonal levels have detrimental effects on the development and function of the prefrontal cortex and hippocampus, they actually have enhancing effects on the development and function of the amygdala. The combination of all of these effects cause children to turn towards reward-seeking behavior. Thus, childhood trauma victims have a higher risk of succumbing to substance abuse, particularly during their adolescence.

References

Belujon, P., & Grace, A. A. (2011). Hippocampus, amygdala and stress: Interacting systems that affect susceptibility to addiction. *Annals of the New York Academy of Sciences, 1216*, 114-121.

Bonne, O., Brandes, D., Gilboa, A., Gomori, J. M., Shenton, M. E., Pitman, R. K., & Shalev, A. Y. (2001). Longitudinal MRI Study of Hippocampal Volume in Trauma Survivors With PTSD. *American Journal of Psychiatry, 158*, 1248-1251.

Bynum, L., Griffin, T., Ridings, D. L., Wynkoop, K. S., Anda, R. F., Edwards, V. J., . . . Croft, J. B. (2010). Adverse Childhood Experiences Reported by Adults. Retrieved January 18, 2016, from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5949a1.htm

Chetty, S., Friedman, A. R., Taravosh-Lahn, K., Kirby, E. D., Mirescu, C., Guo, F., . . . Kaufer, D. (2014). Stress and glucocorticoids promote oligodendrogenesis in the adult hippocampus. *Molecular Psychiatry, 19*, 1275-1283.

Childhood Trauma and Its Effect on Healthy Development. (2012, July). Retrieved January 18, 2016, from http://www.promoteprevent.org/sites/www.promoteprevent.org/files/resources/childhood trauma_brief_in_final.pdf

Dimsdale, J. E., & Moss, J. (1980). Plasma Catecholamines in Stress and Exercise. *The Journal of the American Medical Association, 243*(4), 340-342.

Duvarci, S., & Pare, D. (2007). Glucocorticoids Enhance the Excitability of Principal Basolateral Amygdala Neurons. *The Journal of Neuroscience, 27*(16), 4481-4491.

Eigler, N., Sacca, L., & Sherwin, R. S. (1979). Synergistic Interactions of Physiologic Increments of Glucagon, Epinephrine, and Cortisol in the Dog. *Journal of Clinical Investigation, 63*(1), 114-123.

Elzinga, B. M., Schmahi, C. G., Vermetten, E., Dyck, R. V., & Bremner, J. D. (2003). Higher Cortisol Levels Following Exposure to Traumatic Reminders in Abuse-Related PTSD. *Neuropharmacology, 28*, 1656-1665.

Fuchs, E., & Gould, E. (2000). In vivo neurogenesis in the adult brain: Regulation and functional implications. *European Journal of Neuroscience, 12*, 2211-2214.

Goldstein, D. S. (2003). Catecholamines and Stress. *Endocrine Regulations, 37*, 69-80.

Gomez, R. L., & Edgin, J. O. (2015). The extended trajectory of hippocampal development: Implications for early memory development and disorder. *Developmental Cognitive Neuroscience*.

Heim, C., Newport, J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., . . . Nemeroff, C. B. (2000). Pituitary-Adrenal and Autonomic Responses to Stress in Women After Sexual and Physical Abuse in Childhood. *The Journal of the American Medical Association, 284*(5), 592-597.

Kalivas, P. W., & Volkow, N. D. (2005). The Neural Basis of Addiction: A Pathology of Motivation and Choice. *The American Journal of Psychiatry, 162*(8), 1403-1413.

Kaneshiro, N. K. (2010, April 26). Traumatic Events. Retrieved January 18, 2016, from https://www.nlm.nih.gov/medlineplus/ency/article/001924.htm

Kolk, B. V., & Saporta, J. (1991). The Biological Response to Psychic Trauma: Mechanisms and Treatment of Intrusions and Numbing. *Anxiety Research, 4*, 199-212.

Kolk, B. V. (1994). The body keeps the score: Memory and the evolving psychobiology of posttraumatic stress. *Harvard Review of Psychiatry, 1*(5), 253-265.

Kukolja, J., Schlapfer, T. E., Keysers, C., Klingmuller, D., Maier, W., Fink, G. R., & Hurlemann, R. (2008). Modeling a Negative Response Bias in the Human Amygdala by Noradrenergic–Glucocorticoid Interactions. *The Journal of Neuroscience, 28*(48), 12868-12876.

Launteaume, L., Khalfa, S., Regis, J., Marquis, P., Chauvel, P., & Bartolomei, F. (2006). Emotion Induction After Direct Intracerebral Stimulations of Human Amygdala. *Cerebral Cortex, 17*(6), 1307-1313.

Making the Connection: Trauma and Substance Abuse. (n.d.). Retrieved January 18, 2016, from http://www.nctsnet.org/nctsn_assets/pdfs/Linking_Trauma_and_Substance_Abuse_Complete_4-18-07.pdf

McFarlane, A., Yehuda, R., Barton, C. A., & Wittert, G. A. (2010). Cortisol response to acute trauma and risk of posttraumatic stress disorder. *Psychoneuroendocrinology, 36*(5), 720-727.

Nisenbaum, L. K., Zigmond, M. J., Sved, A. F., & Abercrombie, E. D. (1991). Prior exposure to chronic stress results in enhanced synthesis and release of hippocampal norepinephrine in response to a novel stressor. *The Journal of Neuroscience, 11*(5), 1478-1484.

Perry, B. D., Pollard, R. A., Blaicley, T. L., Baker, W. L., & Vigilante, D. (1995). Childhood Trauma, the Neurobiology of Adaptation, and "Use-dependent" Development of the Brain: How "States" Become "Traits" *Infant Mental Health*

*Journal, 16*(4).

Perry, B. D. (2003). Effects of Traumatic Events on Children: An Introduction. Retrieved January 18, 2016, from http://www.mentalhealthconnection.org/pdfs/perry-handout-effects-of-trauma.pdf

Pike, J. L., Smith, T. L., Hauger, R. L., Nicassio, P. M., Patterson, T. L., McClintick, J., . . . Irwin, M. R. (1997). Chronic Life Stress Alters Sympathetic, Neuroendocrine, and Immune Responsivity to an Acute Psychological Stressor in Humans. *Psychosomatic Medicine, 59*(4), 447-457.

Rasheed, N., & Alghasham, A. (2012). Central Dopaminergic System and Its Implications in Stress-Mediated Neurological Disorders and Gastric Ulcers: Short Review. *Advances in Pharmacological Sciences*.

Rubin, R. D., Watson, P. D., Duff, M. C., & Cohen, N. J. (2014). The role of the hippocampus in flexible cognition and social behavior. *Frontiers in Human Neuroscience*.

Schumann, C. S., Bauman, M. D., & Amaral, D. G. (2011). Abnormal structure or function of the amygdala is a common component of neurodevelopmental disorders. *Neuropsychologia, 49*(4), 745-759.

Sherin, J. E., & Nemeroff, C. B. (2011). Post-traumatic stress disorder: The neurobiological impact of psychological trauma. *Dialogues in Clinical Neuroscience, 13*(3), 263-278.

Shin, L. M., Wright, C. I., Cannistraro, P. A., Wedig, M. M., McMullin, K., Martis, B., . . . Rauch, S. L. (2005). A Functional Magnetic Resonance Imaging Study of Amygdala and Medial Prefrontal Cortex Responses to Overtly Presented Fearful

Faces in Posttraumatic Stress Disorder. *Arch Gen Psychiatry, 62*(3), 273-281.

Sinha, R. (2008). Chronic Stress, Drug Use, and Vulnerability to Addiction. *Annals of the New York Academy of Sciences,* 105-130.

Substance abuse. (n.d.). Retrieved January 18, 2016, from http://www.who.int/topics/substance_abuse/en/

Types of Traumatic Stress. (n.d.). Retrieved January 18, 2016, from http://www.nctsn.org/trauma-types

Uematsu, A., Matsui, M., Tanaka, C., Takahashi, T., Noguchi, K., Suzuki, M., & Nishijo, H. (2012). Developmental Trajectories of Amygdala and Hippocampus from Infancy to Early Adulthood in Healthy Individuals. *Public Library of Science One, 7*(10).

Understanding Links Between Adolescent Trauma and Substance Abuse. (n.d.). Retrieved January 18, 2016, from http://www.nctsnet.org/nctsn_assets/pdfs/Linking_Trauma_and_Substance_Abuse_Complete_4-18-07.pdf

Vyas, A., Mitra, R., Shankaranarayana Rao, B. S., & Chattarji, S. (2002). Chronic Stress Induces Contrasting Patterns of Dendritic Remodeling in Hippocampal and Amygdaloid Neurons. *The Journal of Neuroscience, 22*(15), 6810-6818.

Woon, F. L., & Hedges, D. W. (2008). Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: A meta-analysis. *Hippocampus, 18*(8), 729-736.

Wortsman, J., & Frank, S. (1984). Adrenomedullary response to maximal stress in humans. *The American Journal of Medicine, 77*(5), 779-784.

Yehuda, R., McFarlane, A. C., & Shalev, A. Y. (1998). Predicting the Development of Posttraumatic Stress Disorder from the Acute Response to a Traumatic Event. *Biological Psychiatry, 44*, 1305-1313.