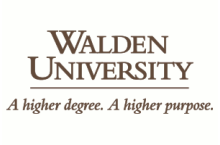

2020

Traumatic Early Life Stress in the Developing Hippocampus: A Meta-Analysis of MRI Studies

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This is to certify that the doctoral dissertation by

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has been found to be complete and satisfactory in all respects,
and that any and all revisions required by
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Walden University
2020

Abstract

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by

Sharon Lee Johnson

MPhil, Walden University, 2019

M.Ed., Youngstown State University, 1994

BA, Kent State University, 1979

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

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Abstract

Advancements in neuroimaging techniques afford researchers the opportunity to examine the actual brains of living persons, which exponentially contributes to new insights regarding brain and behavior phenomena. However, empirical studies investigating stress and the hippocampus attend primarily to adult populations - less on children and adolescents. Covariates such as the type of trauma, the duration and severity of the abuse, genetic predispositions, gender, poverty, and age often present as confounding factors that muddle the attempts to establish linkages between interpersonal, environmental, and neurobiological correlates. Although researchers primarily agree that traumatic early life stress (TELS) has some impact on early brain development, there is a lack of consensus around specific causes and the strength of influence. Tenets from Charcot's trauma theory and Selye's general adaptation syndrome organized the development of a meta-analysis which carefully examined the relationship between TELS and aberrant hippocampal development. Study selection was based on PRISMA standards, which provide a template of a 27-item qualitative checklist for the writing and reviewing of research using secondary data sources. Criteria for inclusion resulted in 22 studies identified for preliminary analysis and 9 for the final report. The analysis revealed a vast range in individual study effect sizes (d = 0.000 to -1.892). The cumulative analysis of p values ranged from p = .005 (random effects) to p < .001 (fixed effects) indicated a relationship between TELS and hippocampal development existed and underscored the necessity for researchers to shift more attention and resources to how covariates influence effect size differences.

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Dedication

When I received my bachelor's degree many years ago, my father, in his confusion about the letters following my name, told everyone he knew that I was now a doctor. I vowed back then to make him honest. The effort and outcome of this dissertation are due to the unquestionable love and deep sense of pride I always felt when I looked into my father's eyes – Warren Lee Poole, Sr.

Acknowledgments

I am deeply grateful for the endless support of my mother, Catherine, who modeled incredible tenacity and perseverance, and for my children, each of my ten siblings, and my dearest friend whose constant cheers and check-ins gave me the strength to keep going.

And to my dissertation committee members, Dr. Patricia Costello, whose constancy and presence served as an anchor, and Dr. Scott Wowra, whose gentle nudging helped me to see the light at the end of the tunnel finally.

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Chapter 1: Introduction to the Study

Abnormal hippocampal change is frequently associated with severe episodic or chronic stress in the neuroscientific literature. How stress affects the developing brain is obscured by several factors and conditions, such as the type of stressor, the duration of the stressor, the severity of the stressor, age, genetic predispositions, gender, economic deprivation, the timing of the insult, and many other variables not yet uncovered by researchers. Although deemed as one of the most frequently studied parts of the brain, research relative to hippocampal dysfunction tends to concentrate on related diseases and disorders like Alzheimer's and dementia, borderline personality disorder (BPD), posttraumatic stress disorder (PTSD), or major depressive disorder (MDD; Karl et al., 2006; Nunes et al., 2009; O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015; Hollands, Bartolotti, & Lazarov, 2016). Furthermore, there are very few meta-analytic studies that investigate traumatic stress and hippocampal morphology. The few meta-analytical studies which published results on hippocampal dysfunction and traumatic stress analyzed data gleaned from adult or mixed-aged populations. Meta-analytical research dedicated to studying the relationship between hippocampal development and traumatic early life stress (TELS) in primary studies with participants under the age of 30 at the time of the investigation, may be rare.

This research comprises the results of a quantitative meta-analysis that assessed the magnitude, strength, and direction of the relationship between TELS and hippocampal structural and volumetric change as measured by magnetic resonance imaging (MRI) in the developing brain. I selected the hippocampus for study because of

its crucial role in social adaptation, memory, and learning and because of its association with various types of psychiatric disorders and disease. The parameters of inclusion are early life experiences of traumatic stress in developing brains, as verified through MRI brain scans. Early life experiences, as defined in this research, include those that occurred from birth through late adolescence. Traumatic stress includes chronic or episodic exposure to any or all the experiences of severe neglect, poverty, physical abuse, sexual abuse, and psychological trauma including verbal abuse that results in the experience of an intense sense of powerlessness, fear, anxiety, deprivation, isolation, or physical and emotional pain (Herman, 1992). The developing brain defines the evolution of the brain's structural change and function that occurred from conception until young adulthood (Casey, Tottenham, Liston, & Durston, 2005). The use of MRI was fundamental to the analysis of this research as the foci included hippocampal structural and volumetric changes that are effectively measured through this type of instrumentation.

In the remainder of this section, I offer the rationale for conducting this research project. Included in the Background section of this chapter is a discussion on TELS and a brief overview of historical and recent trends in neuropsychological research regarding TELS and its impact on the brain. The purpose of the study and the theoretical basis that informs the research process are addressed. The rationale for the choice of the methodology is reviewed. Also included is an overview of the variables, covariates, and how these factors connect to the theoretical precepts. Chapter 1 concludes with a summary of the scope, delimitations, limitations, and contributions that can be made as a result of the analysis.

Background

Although some stress is considered normal, and even necessary, for adequate brain development (Fonzo, 2013; Selye, 1950), exposure to traumatic stress in childhood can result in adverse morphological changes in the brains of adult populations (Andersen et al., 2008; Carrion, Weems, & Reiss, 2007; Edmiston et al., 2011; Hanson et al., 2010). However, evidence substantiating the strength or influence of traumatic stress on developing brains, and the way covariates influence this problem, lacks consensus.

Traumatic stress is characterized by a real or perceived sense of life-threatening danger. Herman's (1992) definition of trauma distinguished the psychological perception of traumatic stress by feelings of powerlessness and helplessness. Exposure to TELS has been linked to cognitive problems, language delays, and behavioral problems in children (Bassuk et al., 2014; Behen et al., 2009; Carrion et al., 2001). Traumatic stress is also a cofactor in many psychiatric disturbances, such as depression, PTSD, bipolar disorder, and anxiety (Baykara et al., 2012; Kemp & Felmingham, 2008). Additionally, traumatic stress is often the root cause of antisocial behavior, aggression, delinquency, and drug abuse (Raineki, Cortés, Belnoue, & Sullivan, 2012; Siever, 2008).

This meta-analysis measured the effect size of 22 matched studies to analyze the magnitude, strength, and direction of the relationship between TELS and aberrant morphological changes in the hippocampus. The hippocampus was selected because it coordinates or co-facilitates many vital functions, including the regulation of declarative memory, spatial relationships, and response inhibitions. Declarative memory organizes and stores facts and details of events. Spatial relationships help to determine where we

are, how we got there, and where we need to go. The inhibitory response functions interpret and regulate afferent and efferent connections to the limbic system, thereby contributing to regulating mood and emotion (Hanson & Chung, 2012; Jackowski et al., 2011; Van der Kolk, 1994). Disruptions in these areas can create long-term consequences that extend over a lifetime.

One of the goals of this study was to contribute new information to the knowledge base regarding the relationship between TELS and biological adaptations in the hippocampus. During the analysis of data, several covariates, such as type and duration of trauma, gender, and age, were identified as significant confounding variables that warrant further investigation. Expanding the scientific knowledge of the relationship between all variables can further development of clinical interventions that sustain brain and psychological health. According to Perry (2009), when clinical interventions are explicitly linked to the area where dysregulation originated, in this instance, to the injured area of the hippocampus, treatment would be in alignment with the stages of neuronal development, and interventions would become more precisely attuned.

Problem Statement

TELS is a crucial factor in the modification and reprogramming of the developing brain. However, there has been little effort to establish the precise degree of influence TELS has on early hippocampal development. Furthermore, many covariates such as the type of stressor, the duration and the severity of the stressor, genetic predispositions, gender, economic deprivation, racism and discrimination, and timing of the insult (Baker et al., 2013; Kaur, 2014; Nemeroff, 2016) serve as a continuous source of debate, and

firm conclusions cannot ascertain. The lack of consensus amongst early childhood trauma researchers seems to be a systemic problem that may also inhibit the progress of standardized investigative procedures and protocols in this particular branch of research.

As stated earlier, some stress is considered normal, and even necessary, for adequate brain development (Fonzo, 2013; Selye, 1950). Chronic exposure to traumatic stress in childhood, however, exacerbates certain risks to neuroanatomical development. Researchers lack agreement regarding the risk factors and the critical periods of sensitivity that may contribute to these aberrant changes. For example, out of a sample of 33 empirical studies published between 2001 and 2017 that examined hippocampal development and TELS in participants of all ages, one study focused on the factor of timing relative to hippocampal vulnerability (Andersen et al., 2008; also see Hambrick, Brawner, & Perry, 2019). In another study, researchers considered individual differences in developing brains as a key in the identification of risk (Koolschijn, van IJzendoorn, Bakermans-Kranenburg, & Crone, 2013). A different study concluded that environmental factors, such as poverty or illness of a primary caretaker, had more of an impact on how the brain developed (Ritchie et al., 2012). These conclusions may all have validity, but the literature lacks conclusive evidence and consensus to make any of the conclusions absolute. What is now required, more than 30 years into brain and trauma research, is a clear and definitive statement describing the exact magnitude, strength, and direction of the relationship between traumatic stress in early life and adverse brain development. Conditions and factors that produce this vulnerability also need to be precisely identified.

Although the hippocampus is one of the most frequently studied parts of the brain, meta-analytical research, an approach that can significantly enhance investigative efforts, are rare. One of the complications in brain and trauma studies is that participant pool per study may be small. A sound meta-analysis can collect and analyze data from numerous small studies and produce data that a single study cannot provide.

For this research study, the independent variable (IV) is TELS, and the dependent variables (DVs) are hippocampal volume and structure. Inclusion criteria require participants under the age of 30 who have had a clinical assessment to substantiate exposure to TELS and an MRI scan to determine the extent of hippocampal change. Meta-analytical research specific to hippocampal morphology tends to focus on related disorders and diseases like BPD, PTSD or MDD (O'Doherty et al., 2015; Nunes et al., 2009; Karl et al., 2006;). Moreover, most meta-analytic studies, as is the case with primary research studies, tend to draw data from middle and older adult populations.

A search on Google Scholar using keywords representing the research variables (e.g.., meta-analysis + traumatic early life stress + hippocampus + MRI), and published between 2012 and 2017, produced approximately 11,000 results. A careful review of search results produced only 19 meta-analytical research studies like the current study but lacked the specificity for inclusion criteria. This meta-analysis could represent a first of its kind using the variables outlined for inclusion. Findings from this research can significantly contribute to the body of empirical evidence relevant to brain and trauma.

Purpose of Study

This meta-analysis was designed to quantitatively explicate the effects of TELS on the hippocampus of the developing brain. The parameters of this research included the following definitions: traumatic experiences include sexual abuse, physical abuse, exposure to family violence, emotional neglect, physical neglect, poverty, abandonment, and psychological abuse. Racism, sexism, and other forms of discrimination, as well as exposure to community violence, bullying, and terrorism as traumatic experiences, may not be isolated stressors in this research, but are considered and categorized as forms of emotional and psychological abuse. Early life, in this research, is defined as the period of life experiences that occur between the ages of 0 and late adolescence.

Summarizing, this study examined the relationship between TELS (IV) and hippocampal volume and structure (DVs) as measured through MRI scans in developing brains. The hippocampus is an essential part of brain functioning as it contributes to memory and spatial relations. The results of this investigation can support ongoing efforts to enhance assessment and treatment protocols for the affected population. Future investigative efforts to deepen understanding of the complicated relationship between TELS and hippocampal change, and the effects of age, gender, and other covariates is essential.

Research Question and Hypotheses

This study examined the relationship between TELS (IV) and hippocampal development, particularly hippocampal structure and volume (DVs) in the developing brain.

RQ: To what extent does the exposure to TELS impact the structure and volumetric measures of the hippocampus in the developing brain?

$H_{0:}$ There is no relationship between TELs and aberrant morphological changes in the hippocampus of the developing brain.

H_1: There is a relationship between TELs and aberrant morphological changes in the hippocampus of the developing brain.

In each of the final selected studies, all criteria for selection were met: a licensed clinical professional assessed the nature of the stressor or type of traumatic experience in participants who were under the age of 30. MRI measures of controls and demographically matched comparison group participants were also documented in the empirical research.

Theoretical Framework: Trauma Theory and Selye's Adaptation Theories

The seminal works of Charcot (1881) and Selye (1950) served as the theoretical foundation to inform the research methodology in this study. Their theories are discussed briefly here and more in-depth in the Literature Review of this study.

The concept of traumatic stress as an etiological variable of psychiatric and physical illness is linked primarily to the 19th-century French neurologist, Jean-Martin Charcot. In his work with sexually traumatized women, Charcot began to develop a theory that would link traumatic experiences to psychiatric disorders (Kumar, Aslinia, Yale, & Mazza, 2011). Before Charcot's research, physicians generally regarded psychological symptoms to be indicative of a physiological disorder. For example, hysteria, physicians who diagnosed in women believed the symptoms to originate in the

uterus. So, to cure hysteria, the patient would undergo a hysterectomy. Charcot would argue that the origin of many disorders such as psychiatric and physical disorders such as paralysis, amnesia, sensory loss, or convulsions, could be linked to psychological trauma (Ringel, 2012; Kumar et al., 2011). Charcot's students, like Sigmund Freud and Pierre Janet (Ringel, 2012), would further the development of trauma theory.

Selye's (1950, 1976) theories of general adaptation syndrome (GAS) and local adaptation syndrome (LAS) provided the catalyst that moved research on traumatic stress from the psychological to the neurobiological arena. Selye suggested that living organisms had the innate ability to adapt themselves to changes in their surroundings. He argued that adaptation was an evolutionary process necessitated by the organism's will to survive (Selye, 1952).

Contemporary neuroscientists, including Bessel Van der Kolk (2003); Michael De Bellis (2002); Susan Andersen (2008); Douglas Bremner (2005); Bruce Perry (2009); Martin Teicher (2012); and Thomas Frodl (2010) have presented strong evidence that suggests traumatic stress, particularly in early life, can produce adverse neurobiological responses. Their research observations, also gathered from brain scan imaging technology, underscore the enormous capacity traumatic stress has in altering the actual physical shape and volume of the human brain. That these alterations are potentially adaptive, maladaptive, reversible, or permanent are issues that demand continued examination. The theoretical constructs of trauma theory and GAS, combined with neuroscientific clinical findings from contemporary researchers, served to inform the way I conducted this current analysis.

Nature of Study

The independent variable is TELS, and the dependent variables include hippocampal volume and structure. For review, stressors include any or all the following: sexual abuse, physical abuse, exposure to family violence, exposure to and the experience of severe neglect, including emotional and physical neglect, poverty, abandonment, and psychological trauma, including verbal abuse. Hippocampal volume is relative to mass, and the hippocampal structure is defined by boundary. Mass and boundary were measured through an MRI scan of developing brains. The effect size was analyzed against MRI measures of demographically matched comparison group participants with no exposure to TELS. Some of the major covariates identified in this body of research include age at the time of insult, stages of development, gender, genetic propensities, the timing of insult, severity, duration of abuse, and poverty. These confounding variables will be addressed in detail in subsequent chapters.

The clinical studies identified for the final analysis had varying numbers of participants ranging from *n*12 (Veer, 2015) to *n*63 (Morey, 2016). I conducted a cumulative meta-analytical technique which assigned weights to the standard deviations of each study. Assigning weights to specific variables balances the evidence so that no one individual study can over-shadow another. Cumulative meta-analytic approaches are further addressed in Research Design and Rationale.

Definition of Terms

Abandonment includes the failure to provide reasonable support and/or to maintain regular contact with a child. Abandonment can be physical, psychological, or both (Child Welfare Information Gateway, 2016).

Developing brain defines the evolution of brain structural change and function that occurs from conception until young adulthood (Casey, Tottenham, Liston, & Durston, 2005).

Domestic/Family violence includes actual or threatened physical, sexual, or emotional abuse among adults in an intimate partnership or directed at former spouses or partners of children who witness or are exposed to domestic violence. Many states constitute the witnessing of domestic violence within the neighborhood as a form of child abuse (Evans, Davies, & DiLillo, 2008).

Early childhood trauma refers to exposure to traumatic experiences between birth and age 6 (The National Child Traumatic Stress Network, 2017).

Early life experiences are defined as life experiences occurring from the ages of 0 to late adolescence (Hambrick, Brawner, & Perry, 2019).

Hippocampal structure is defined by its shape and borders. The hippocampus borders the amygdala, the temporal horn of the lateral ventricle, and the pulvinar, the largest nucleus of the thalamus. The hippocampus is segmented into three major components, which include the dorsal hippocampus, ventral hippocampus, and the intermediate hippocampus. (Lenroot & Giedd, 2006)

Hippocampal volume is determined by its mass or density. Calculations are made using complicated MRI and tracing procedures which segment the area and distinguishes grey matter and white matter and the possible presence (or lack) of other fluids (Hayman, Fuller, Pfleger, Meyers, & Jackson, 1998; Keller & Roberts, 2009; Obenaus, Yong-Hing, Tong, & Sarty, 2001; Wu et al., 2018).

Neglect is defined by the inability or unwillingness of a parent or caregiver to provide for age-appropriate basic needs, including food, clothing, shelter, and medical attention. Neglect can also manifest as educational neglect, exposing a child to dangerous living situations, abandonment, leaving the child in the care or custody of persons who are incapacitated. Emotional neglect is the lack of adequate nurturing and affection and includes withholding love, rejecting a child, and ignoring a child's emotional needs (Child Welfare Information Gateway, 2016).

Neuroanatomy is a branch of neurology focused on the anatomical structures of the nervous system (APA, 2017).

Neurobiology is the scientific study of the biological processes of the nervous system (APA, 2017)).

Neurology focuses on the anatomy, physiology, and organic diseases of the nervous system in both research and diagnosis of diseases (APA, 2017)).

Neuroscience focuses on the development, structure, function, chemistry, and pathology of the nervous system (APA, 2017).

Neuroanatomical hand tracing is an imaging technique that utilizes computerized tracing devices that capture the boundaries of tissue and visually reproduces the connections of neuronal branches (Köbbert et al., 2000).

Neuroimaging instruments include computed tomography, diffusion tensor imaging, functional MRI, positron emission tomography, MRI, magnetic resonance spectrometry (Laviña, 2016; Rinne-Albers, Van Der Wee, Lamers-Winkelman, & Vermeiren, 2013).

Physical abuse is the intentional and excessive infliction of physical pain that results in psychological damage or physical injury, and in extreme cases, death (Child Welfare Information Gateway, 2016).

Posttraumatic stress disorder (PTSD) is an anxiety disorder rooted in traumatic events such as combat, natural disaster, crime, or accidents. It may impact personal relationships and health (APA, 2017).

Sexual abuse includes an array of sexual behaviors such as exposure to or victimization in pornography, physical bodily contact that includes actual penetration to fondling, abusive language of a sexual nature, genital exposure. These acts can occur between same-age children or a child and an older person (Child Welfare Information Gateway, 2016).

Toxic stress is the accumulation of stressors that trigger prolonged activation of the stress response systems, which poses risks of damage to or disruptions in the development of brain architecture and other organ systems, thereby increasing the risks for stress-related disease and cognitive impairment (Franke, 2014).

Traumatic early life stress, as defined in this study, refers to traumatic experiences occurring between birth through late adolescence. Traumatic stress includes any of the following: sexual abuse, physical abuse, exposure to family violence, exposure to and the experience of severe neglect including emotional and physical neglect, poverty, abandonment, and psychological trauma, including verbal abuse. These experiences result in an intense sense of powerlessness, fear, anxiety, deprivation, isolation, physical and emotional pain, and a pervasive absence, either real or perceived, in safety, security, and belonging needs (Herman, 1992).

Traumatic grief occurs when a child's ability to experience the typical process of bereavement is compromised, rendering the child either frozen or stuck in the grief process, resulting in severe psychological and emotional impairment (The National Child Traumatic Stress Network, 2017).

Assumptions

The impetus for this research project is rooted in the assumption that the safety, health, and well-being of any child are significantly enhanced through empirical knowledge. Most researchers concur that the developmental and neurobiological responses to trauma and stress in the human body are poorly understood; therefore, continued effort to grasp the complexity of TELS is crucial to the welfare of the victims.

For this analysis, I assumed that the empirical studies selected for review were employing the highest ethical standards while conducting research with human subjects while utilizing the most effective scientific protocols, with results recorded in entirety. I also assumed that the statistical protocols used to measure data from each selected study

were followed to increase reliability and validity. I assumed that all participants included in the selected empirical studies were free from severe psychiatric disturbances and the use of medications or intoxicants that could impact results during scanning. I understood that brain differences in the participants could be influenced by neurobiological diathesis. Additionally, it is reasonable to assume that the timing, chronicity, and experience of reported trauma may differ significantly between groups, thereby contributing to variations in how data is viewed and recorded. Lastly, I assumed that any between-study variances would have a minimal effect on the final statistical results.

Scope and Delimitations

This research only focused on the relationship between TELS and hippocampal structure and volume. Various parts of the limbic system, like the amygdala, are also referenced if they are an integral part of the limbic system.

I analyzed data from 9 empirical studies that assessed the relationship between early traumatic stress and hippocampal structural and volumetric changes in participants under the age of 30. Jackson & Turner (2017) demonstrated that a sound meta-analysis requires five or more studies to achieve statistical power to detect effects when using a random-effects approach.

Although it could have been possible to study other areas of the brain, such as the amygdala or prefrontal cortex, I chose to focus on the hippocampus because of the significance of social, emotional, and cognitive functioning concerning health and well-being. By understanding the relationship between TELS and hippocampal change, future

investigative efforts to elucidate the covariates of age, stages of development, and specific stressors can be justified.

The studies under analysis were published between 2001 and 2017. All were focused on hippocampal development and TELS. All but one study included both control and demographically aged-matched comparison groups. All studies used both clinical assessment instruments and MRI scans to evaluate the relationship between the IV and DV variables.

Many research studies on TELS and brain development recruited participants within the same study whose ages spanned across the human lifetime. It is outside of the scope of this research to include all age groups. The age span of this study, childhood to early adulthood years, reflects changes that could occur while the hippocampus is still in physiological development. Isolating morphological changes that occur during the developmental stages may help resolve certain debates. One such debate, for example, is focused on whether smaller hippocampal volume is a causative factor increasing pathological risks versus chronic stress as the cause of smaller hippocampal volume, which then increases the risks for pathology (Gianaros et al., 2007; Lindgren, Bergdahl, & Nyberg, 2016). Certain factors, such as the age at the time of insult versus the age at the time of the study, as well as the type, duration, and severity of the stressor(s), could pose as confounding variables relative to morphology in brain development. I did not address these variables in detail but referenced any unusual or significant findings and the possibilities associated with interpretations of data.

This research project only included studies that utilized MRI technology to measure hippocampal volume and structure in documented cases involving TELS. Data collected from other types of brain scan devices do not align with the purpose of this research. For example, fMRI assesses the relationship between behavior and biochemical activity in the brain during testing. Other types of brain imaging technology, including diffusion tensor imaging, positron emission tomography, and computed tomography, measure different functions of the brain.

Finally, it is recognized that many factors can influence brain development and subsequent personality, behavioral, social, and emotional response mechanisms. However, it is beyond the scope of this research to account for all the individual, cultural-social, gender, and genetic differences that serve as confounding factors. There will be references made to covariates that frequently appear in association with relative effect size. Otherwise, the primary focus of the meta-analysis is to identify the magnitude, strength, and direction of the effect size between the IV and DVs under study.

Limitations

Ensuring homogeneity in selected research studies has been the most difficult challenge of this study. For example, the variation in ages of participants and the numbers of participants studied may pose as mitigating factors. In the initial review process for this meta-analysis, the numeric range of participants varied from 15 to 427 participants with an age range of 5 weeks to 87 years. Huge variances in sample size and age differences can influence the interpretation of data significantly. As stated previously, the literature search for inclusion targeted an age range from 3 to 28 years of age.

The types of clinical assessment tools used in research studies vary. However, all the tools are similar in assessing types of abuse and age at the time of the original trauma. These variations may significantly influence the way the clinical assessment data is interpreted, and gradients of stress are measured. Efforts have been made to ensure that common questions to assess types of trauma appear throughout the 22 studies in this research, and the presence of emotional, physical, or psychological trauma is clearly documented. For this study, allowances have been made to accept the clinical assessment protocols as valid if references to stress or maltreatment are identified in the assessment questionnaire or interview. Any significant differences amongst the selected studies under review will be referenced.

The use of MRI technology is critical to the analysis of this project because the measures of hippocampal structure and volume correlated with levels of traumatic stress are the primary variables under investigation. The studies reviewed were from 2001 to 2017 and reflect the rapidity of growth in the MRI technology employed over these years. Different magnification properties of MRI instruments, as well as neuroanatomical hand tracing techniques used to assess brain size, will reflect the structural and volumetric changes, if any, in the hippocampus. One project may use a 1.5 Tesla machine, and another may use a 3 Tesla machine, although it has been reported that these instruments function similarly when scanning for structure and volumetric measures (Wood, Bassett, Foerster, Spry, & Tong, 2012a). Accurate interpretations of any brain scan are highly dependent on the capacity of magnification properties of the machine as well as the skill of the technician in decoding the images. It is beyond the scope of this review, and the

current level of my technological expertise, to analyze or predict how the differences in technology may influence the interpretation of data.

Significance of Study

Trauma theorists fundamentally agree that consequences of adverse childhood factors are significantly influenced by personality, gender, genetics, family dynamics, social-cultural factors, poverty, and other variables that determine vulnerability, resiliency, or resistance (Butterworth, Cherbuin, Sachdev, & Anstey, 2012; Everaerd et al., 2012; Garmezy & Streitman, 1974). What remains uncertain is the processes involved that produce the disproportionately high rates of severe mental health conditions diagnosed yearly in some young people but not in others. According to the Citizens Commission on Human Rights (CCHR, 2017), there are over 8 million children between the ages of birth and 17 years of age who are prescribed various types of psychotropic medications. With 74 million children under the age of 18 in the United States (United States Census, 2018), this means that 10.81% of the child population is suffering from a diagnosable mental illness. In 2017, the Centers for Disease Control and Prevention (CDC) identified suicide as the second leading cause of death for persons aged 10–24.

The economic burden linked to the experiences of TELS is enormous. According to the CDC, the costs incurred through every new child protective cases in any given year can exceed 124 billion dollars when expenses for case management, criminal justice fees, disease, and health care expenditures, foster care or institutional care, and special education are considered (as cited in Fang, Brown, Florence, & Mercy, 2012). Peterson,

Florence, and Klevens (2018) estimated the economic burden of child maltreatment in the United States to be at 2 trillion dollars.

The insight gathered from this study could be shared with policymakers, program administrators, grant funders, and other entities who legislate and fund efforts to protect and treat this vulnerable population. The research can also support efforts to support the development of new and innovative clinical approaches to early identification, intervention, and treatment of the numerous consequences produced by TELS.

Summary

The hippocampus is one of the most frequently studied parts of the brain, yet meta-analytical research specific to hippocampal morphology is scarce, particularly with populations under the age of 30. Most scientific research dedicated to the study of stress and its interaction with the brain has been focused on the aftermath of psychiatric disease and disorders in adult populations. This meta-analysis seeks to elucidate the effects of TELS on the hippocampus of the developing brain. TELS includes sexual abuse, physical abuse, exposure to family violence, emotional neglect, physical neglect, poverty, abandonment, and psychological abuse. The research question is: to what extent does the exposure to TELS impact the shape or the volumetric measures of the hippocampus in developing brains?

The data used in the preliminary analysis was taken from 22 research studies that were published between 2001 and 2017. Nine of these studies were selected for the final analysis. All nine empirical studies were focused on hippocampal development and TELS; all but one study used both control and demographically aged-matched

comparison groups. All studies used clinical assessment instruments and an MRI scan to evaluate the relationship between TELS and hippocampal volume and structural changes.

The number of control group participants totaled *n*294; comparison group participants totaled *n*474. The number of male participants in the final studies totaled *n*129; the numbers of non-White participants represented less than 7% of the total population of *N*=768 participants. Knowledge gleaned from this current research can also support the continued efforts to improve clinical interventions for the prevention, early identification, and treatment of psychiatric disorders and behavioral problems stemming from TELS.

Chapter 2: Literature Review

Introduction to Literature Review

Recent neuroscientific studies have consistently linked TELS to specific abnormalities in the developing brain (Anderson, 2012, 2008; Carrion, 2007, 2001; De Bellis, 2006, 2002). How stress affects the brain is obfuscated by several factors and conditions, such as the type of stressor, the duration of the stressor, the severity of the stressor, age, genetic predispositions, gender, economic deprivation, and the timing of the insult. The current meta-analysis examined the degree of influence TELS has in relationship to aberrant development in the hippocampal region of the developing brain. The analysis included 22 MRI-supported studies published between 2001 and 2017 with participants representing early childhood through young adulthood, and who have been assessed as TELS survivors. Nine of these studies were chosen for closer analysis and comprised the focus of this project. Current and historical research from peer-reviewed publications is presented in this section to support the justification of continued research in TELS and its impact on hippocampal development.

The Literature Review begins with a highlight of the search strategies used to gather data followed by a discussion of trauma theory and general adaptation theory, which are the theoretical foundations guiding this meta-analysis. The subsequent section links these seminal theories to the research hypothesis by assimilating the data from current research to provide a contemporary overview of the brain's response to traumatic stress.

The main body of the Literature Review is divided into several subsections, including the anatomy and function of the hippocampus; a discussion on how TELS influences its development; and how these variables relate to psychopathology and disease. A basic understanding of the role of MRI is also included. I present a brief discussion on the various types of MRI instruments utilized in the studies selected for analysis, as well as the various types of clinical assessment tools used to determine the type and severity of TELS experiences measured in the control group. The concluding section summarizes the key findings of the Literature Review and identifies the studies used for data analysis.

Literature Search Strategy

I conducted a comprehensive literature search through Academic Search Complete, Biomedical Informatics Research Network, Research Gate, ERIC, EBSCO, Collaborative Research in Computational Neuroscience – Data Sharing; ProQuest, Science Direct, Google Scholar, PsycINFO, CINHAHL, IUCAT, NIH/NIM MEDLINE, PubMed, Pdf Search Engine and a variety of library sources including Walden University, Kent State University, and the University of Michigan.

Keywords and search terms included the following: *aberrant brain development, child brain development, childhood trauma, child maltreatment, complex traumatology, domestic violence, early childhood stress, family violence, human brain development, MRI, domestic abuse, early deprivation, early life stress, exposure to violence, family violence, general adaptation theory, hippocampus, hippocampal anatomy, hippocampal functions, hippocampal volume, hippocampal structure, magnetic resonance imagery,*

neurosequential model of therapeutics, neuroanatomy, neurobiology, neuroplasticity, neurophysiology, neuropsychiatric, posttraumatic stress, poverty and hippocampal development, psychopathology and stress, racism and hippocampal development, stress and the brain, trauma theory, and *traumatic stress*.

Theoretical Framework

The focus of this research, which addresses the correlations between TELS and hippocampal development, requires a synthesis of two major theories in neurology and neurobiology. Trauma theory, a construct first introduced by 19th-century French neurologist Charcot (New Sydenham Society, 1877), and Selye's (1950, 1976) theories of GAS and LAS serve as demarcations for this project.

Trauma Theory

Trauma theory represents a multi-faceted organic phenomenon with its evolution branching to and from many different individual and sociocultural perspectives. The term *trauma theory* did not appear in psychological literature until the 1990s (Radstone, 2007). Charcot's work with traumatized women is seminal in the development of contemporary theories into the complicated relationship between trauma and mental health. Psychiatric disorders during Charcot's time were believed to be rooted in physiological disease or illness. For example, hysteria, which was a common diagnosis for women, was diagnosed as a symptom of a diseased uterus. Therefore, the intervention for hysteria was to administer a complete hysterectomy. Most of the women in the Salpêtrière Hospital, whom Charcot observed, had histories of various forms of severe violence, including rape and sexual abuse (Kumar et al., 2011; Ringel, 2012). Charcot argued that the origin of

symptoms in his patients, such as paralysis, amnesia, sensory loss, or convulsions, was not physiological but psychological. Equally important, especially in the contemporary field of neuroscience, Charcot's pioneering research in cerebral localization began the examination into the connections between specific sites in the brain and corresponding nervous system functions (Kumar et al., 2011; Charcot, 1881)

Two of Charcot's students, Pierre Janet (Hart & Horst, 1989) and Sigmund Freud (Webster, 2014), incorporated Charcot's beliefs regarding psychological trauma into the developments of their theories. Janet was among the first to identify the capacity traumatic memory carried for inducing intense emotional reactions, which are symptoms we now address as PTSD reactions. Janet also expanded the theory of disassociation—the experience of physical and emotional detachment—as a reaction to protect oneself against trauma (Hart & Horst, 1989).

Freud, in conjunction with his beliefs about repressed memory, developed the theory of reenactment (e.g., the compulsion to repeat trauma; Levy, 1998). Freud believed that the individual's compulsion to recreate or relive the traumatic experience continually was an unconscious attempt to resolve the cycle of experience that the original infliction had disrupted (Frankel, 1998; Hart & Horst, 1989; Van der Kolk, 2000). Whereas disassociation can be viewed as an avoidant behavior and reenactment as an attempt to resolve conflict, both processes represented the individual's attempts to manage the overwhelming residue wrought from the traumatic experience. Charcot, Janet, and Freud agreed that it was the individual's unconscious attempt to manage the

trauma that resulted in the subsequent development of psychiatric disorders such as hysteria or war neurosis, which I discuss in the subsequent paragraphs.

During the first and second world wars, trauma research made a subtle shift towards connecting the psychological experiences to the physiological casualties of combat. “Shell-shock” and “war neurosis” (Crocq and Crocq, 2000) became the foci of observational research, and the battlefield or veteran’s hospital became laboratories. Studies conducted by Sandor Ferenczi, Abram Kardiner, and Herbert Spiegel began to shed light on what Kardiner coined as *physioneurosis*, a term used to explain the extreme states of physiological arousal (Van der Kolk, 2000), indicative of the direction research was moving towards in connecting trauma with body processes.

Ferenczi, who served as a medical officer in the Austro-Hungarian army during the First World War, referred to shell-shock as a mental “concussion” rooted in the experience of an unbearable sense of helplessness (Frankel, 1998). Decades later, Herman (1992) would echo Ferenczi’s remarks, stating that “Psychological trauma is an affliction of the powerless” (p. 33). Ferenczi believed that *mental* concussion could lead to paralysis (Peláez, 2009). Ferenczi also came to believe that trauma could produce physiological symptoms such as tremors and gait disturbances, which he felt represented an unconscious effort of the soldier to prevent returning to dangerous situations (Frankel, 1998).

Kardiner and Spiegel, who treated soldiers during the First and Second World Wars, noted that their patients would become easily agitated or startled by any abruptness or change, such as a slap on the back or a misstep, or by sudden tactile stimuli such as a

change in temperature (Van der Kolk, 2000). Kardiner conducted his independent research during his employ at the United States Veteran's Hospital #81 (Bronx, NY) during World War I and would later record his findings in *The Traumatic Neuroses of War* in 1941, which served as "a guide for the study, treatment, and post-war care of those neurotic disturbances which are incidental to war" (Kardiner, p. vi). Kardiner's monograph essentially became the model for the diagnosis and treatment of what we now identify as symptoms of PTSD. Spiegel served as a battalion surgeon in North Africa during WWII from 1942 to 1946 and would become the first psychiatrist to use hypnosis to treat war trauma (Carey, 2010). Spiegel and Kardiner would collaborate to produce *War Stress and Neurotic Illness* in 1947, an update of Kardiner's first writings on war neurosis.

As an interesting side-note, most of the early trauma theorists were psychoanalysts with diverse backgrounds and training. All had been strongly influenced by Freud's work, although many deviated from his fundamental teachings. Ferenczi, for example, was one such close friend and confident of Freud's. However, as it followed suit with most psychoanalysts of the day who deviated from fundamental Freudian ideology, the relationship between the two became strained following Freud's strong disapproval of some of the concepts in Ferenczi's paper, *Confusion of Tongues Between Adults and the Child* (Szecsödy, 2007). Kardiner was an anthropologist and later completed his education in psychiatric medicine. After fulfilling his psychiatric residency requirements, Kardiner traveled to Vienna to study and receive an analysis directly from Freud (Farber, 1981). Spiegel, even as a young psychoanalyst, would openly rebel against

the Freudian orthodoxy, adhering firmly to his belief that the patient had the innate capacity to heal himself (Connery, 2009).

Contemporary Paradigms

Although there exists a complicated psychological component in the processes of adaptation, the primary focus of this research is on the neurobiological aftermath rather than psychiatric or socially maladaptive consequences. As a researcher, I felt it was important to understand the seminal roots of trauma theory for the reader to develop a more balanced perspective of the neurobiological consequences of trauma. These early theories are the catalytic agents to current neurobiological research that seeks to unravel how neuropsychiatric disease differentially affects the biochemical functions and structure of various parts of the brain (O'Neill et al., 2013; Wisse et al., 2012; Bremner, 2002).

The synergistic relationship between theory and research is organic and innately expansive; hence, the theoretical paradigms regarding what constitutes traumatic experience follow suit. Contemporary discourse on trauma theory draws perspective not only from history, but includes politics, culture, race, gender, religion, family, group, and individual experiences (Caruth, 1996; Herman, 1992; also, Onwuachi-Willig, 2016; Radstone, 2007; Becker-Blease & Freyd, 2005). This more inclusive approach to understanding the various ways trauma can manifest necessitates the development of research strategies that will measure the impact of experiences like domestic and family violence, community violence, sexism, poverty, bullying, terrorism, discrimination, and racism. Combining scientific, psychological, and sociological perspectives to include

experiences from the individual and the collective has proven immensely valuable to the field of trauma research.

General Adaptation Syndrome and Local Adaptation Syndrome

Selye's (1950, 1976) theories of GAS and LAS served as catalytic agents, moving research on traumatic stress from the psychological to the neurobiological arena. Selye (1950) believed that stress was the most medically and sociologically important subject in humanity. Selye was an 18-year-old medical student at the German University (Prague) in 1925 when his natural, unbiased curiosity raised questions in his mind as to how so many different diseases tended to share the same symptoms. It would be another decade before his curiosity spurred him to more closely examine the relationships between morphological changes in the organ tissues of his animal subjects and the human-induced antigens that the laboratory animals were inoculated with and reacted to. Selye then began developing a theory around what appeared to be a natural response for living organisms to adapt to stress biologically. He argued that adaptation was an evolutionary process necessitated by the organism's will to survive and mostly dependent upon genetic factors. "This was the first time that we used the word stress in its present connotation, as a state of non-specific tension in living matter, which manifests itself by tangible morphological changes in various organs" (Selye, 1950a, p. 20). Selye believed that although specific actions from different agents (*e.g.*, infections, intoxications, trauma, heat, cold) were all distinct, the commonality was that they placed the body under stress. From this perspective, Selye concluded that the body's response to stress was a stereotypical one, "which is superimposed upon all specific effects" (Selye, 1950, p.

234). Selye eventually dropped the term *neuroendocrine* after realizing that other organs of the body, including the cardiovascular, pulmonary, and renal systems, were also involved in several stages of the stress response (Szabo, Tache, & Somogyi, 2012). However, he would prove relentless in his debate against the idea that morphological changes varied and positively correlated to the type or degree of induced stress. Selye maintained that "non-specificity" was the main characteristic of any stressor relative to the physical body's reaction. It would take another 40 years for Selye to concede that stress reactions could differ significantly and be also significantly influenced by the individual's perceptions and emotional reactions (Szabo et al., 2012). Selye was also convinced that normal stress was a natural and necessary component of human existence, observing that "total elimination of stress—that is, cessation of demands made upon any part of the body, including the cardiovascular, respiratory and nervous systems—would be equivalent to death" (Selye, 1976, p. 56).

Selye would study the effects of stress for well over half a century, with his primary participants being laboratory rats. After 15,000 articles and 32 published books, his contribution to the theory of general adaptation syndrome would remain his most recognized achievement (Szabo, Tache, & Somogyi, 2012). GAS responses are characterized by three phases: alarm, resistance, and exhaustion (Selye, 1976). Summarizing Selye's teachings, alarm signals the body that there is a perception of threat or danger; resistance invokes the release of hormones to prepare the body for defense or flight. Exhaustion occurs when the body has been subjected to intense or chronic periods of stress. This stage is where most internal physical damage can occur. Selye coined the

term “systemic stress”, which includes stressors that affect the entire body (Selye, 1976). LAS, on the other hand, affects a particular part of the body and can produce symptoms that are primarily localized, as in a sense organ or muscle group (Selye, 1976).

Theories regarding the nature of stress and its correlations with health and diseases have become much more numerous and complex because of Selye’s works. The notion that the neurobiological system of the human body has the capacity to develop unique responses at multiple levels to the experience of stress is now widely accepted.

Contemporary Researchers

Understanding how brain regions are impacted, linking the time of insult and the level of vulnerability of the developing region, understanding genetic biomarkers related to stress, along with other potential mediating factors, is paramount to the advancement of research aimed at decoding the links between TELS and brain development and in the development of appropriate therapeutic interventions. Throughout the study and within the final analysis, the following contemporary researchers will be referenced. They have made significant contributions to the field of traumatic stress and brain dysfunction, and their findings will help to lend structure to the analysis of this project.

Van der Kolk (*Biography*, n.d.) established one of the first clinical research centers in the U.S. dedicated to the study and treatment of trauma. His research specializes in how trauma impacts different stages of development and incorporates emerging findings from neuroscience and attachment disorder research to develop empirically-driven treatments for TELS adults and children.

Teicher (*Martin Teicher,* n.d.) established the Developmental Biopsychiatry Research Program at McClean Hospital in 1988. His research focus is on identifying the sensitive periods when the brain regions are most vulnerable to TELS. He also evaluates innovative treatments, including sensory enrichment and mindfulness practices, to treat depression, ADHD, and learning disorders in children.

Andersen's (*Susan L. Andersen*, n.d.) work focuses on specific parts of the brain, including the prefrontal cortex, amygdala, and hippocampus to assess the underlying mechanisms of change during childhood (McLean Hospital. (n.d.). *Susan L. Andersen, Ph.D.* Retrieved from http://www.mcleanhospital.org/biography/susan-andersen).

Carrion (*Victor Carrion – Professor,* n.d.) studies the relationship between stress and brain development using a variety of methods, including neuroimaging, psychophysiology, neuroendocrinology, and phenomenology. He also assesses the potential of treatment effects on stress-related conditions in children and adolescents who have experienced TELS.

Bremner's (*J. Douglas Bremner*, n.d.) research focused on the study of the neural correlates and neurobiology of posttraumatic stress disorder (PTSD) and depression related to child maltreatment and combat, utilizing both neuroimaging and neurobiological techniques. His current research focus examines the relationship between physical and behavioral health and the interchange between body and brain.

Perry's (*Bruce Perry, M.D.*, n.d.) work is dedicated to the research of innovative treatment strategies for children exposed to TELS. He is an internationally-recognized authority on children in crisis, and his conceptual model, the neurosequential model of

therapeutics, has been utilized in various clinical settings as a guidepost for the development of treatment protocols and applications.

Frodl's (*Thomas Frodl,* n.d.) work focuses on identifying the genetic biomarkers related to the pathophysiology of disease, vulnerability, and resilience using innovating neuroimaging techniques combined with data from blood markers gleaned from clinical trials. He has applied his expertise to explore the effects of stress-related blood markers on brain function and structure.

De Bellis (*Michael D. De Bellis,* n.d.) has been the lead investigator on a number of research projects related to the effects of child maltreatment and developmental traumatology for the National Institutes of Health, the University of Pittsburgh, Duke University, and New York University Medical Center. His work is focused on neurobiological dysfunction, mental illness, and mood disorders in traumatized children.

Several of the empirical clinical studies selected for this project include studies conducted by Anderson (2012, 2008), Carrion (2007, 2001), De Bellis (2006, 2002), and Teicher (2012). I will continue to reference the contemporary works of Drs. Bessel Van der Kolk, Martin Teicher, Susan Andersen, Victor Carrion, Douglas Bremner, Bruce Perry, Thomas Frodl, Michael De Bellis, and other forerunners in the field of traumatic stress and neurobiology.

Summary of Theoretical Foundations

Trauma theory represents a multi-faceted organic phenomenon, its evolution branching to and from many different individual and sociocultural perspectives. The seminal works of Jean-Martin Charcot, Pierre Janet, and Sigmund Freud during the latter

part of the 19th-century and throughout the first half of the 20th-century produced a proliferation of thoughts and ideologies that have significantly influenced the development of contemporary thought regarding the complex relationship between trauma and mental health. Observations of the mental and psychological aftermath of war by Sandor Ferenczi, Abram Kardiner, and Herbert Spiegel began to shed light on the concept of *physioneurosis*, a term used to explain the extreme states of physiological arousal, indicative of the direction science was moving towards in connecting trauma with body processes. It would be Selye's theories of GAS and LAS that would catapult scientific research on traumatic stress from the psychological to the neurobiological arena

Contemporary discourse on trauma theory draws perspective from history, politics, culture, race, gender, religion, family, group, and individual experiences. This more inclusive approach to understanding the various ways trauma can manifest necessitates research that will measure the impact of experiences like domestic and family violence, community violence, sexism, poverty, bullying, terrorism, discrimination, and racism. Brown (1996) articulated that the relationship between theory and research was a dialectic transaction, whereas the progressive development in one facilitates the progressive development in the other. The ongoing investigations into the nature of the relationship between the experiences of trauma and the human mind and body certainly exemplify this type of interchange.

Integrating Neuroscience and Psychology

The Hippocampus: Anatomy and Function

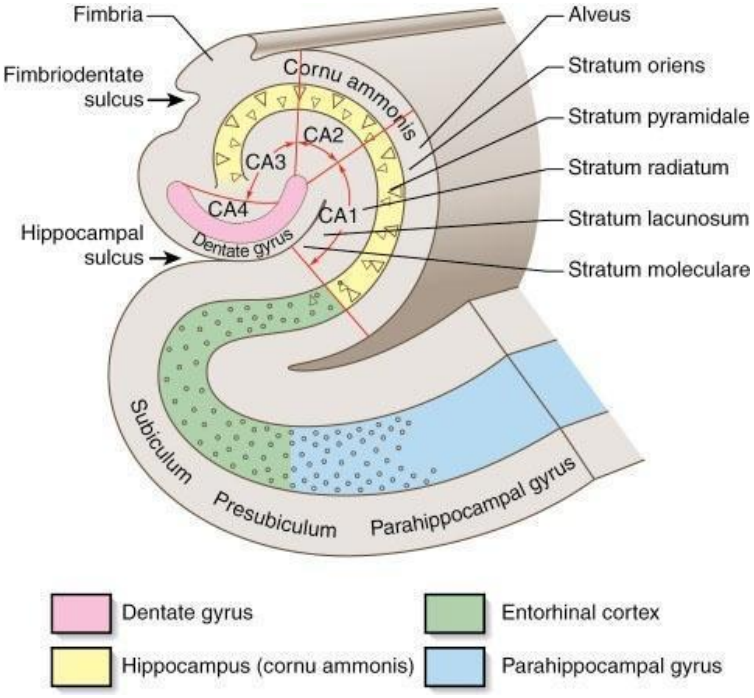


Figure 1. Hippocampal regions showing fields.

(Retrieved from https://medicine.academic.ru/3923y#. Open-source image)

The hippocampus is a tiny seahorse-shaped organ located in the medial temporal lobe. Along with the amygdala, the hippocampus forms the central apex of the limbic system. Its actual form is comprised of two interlocking cortex sheets. A visual cross-section of this area would reveal a clearly defined laminar structure lined with rows of pyramidal cells that form a tunnel "s-shape" loop. The tunnel-shaped loop originates adjacent to the entorhinal cortex of the medial temporal lobe, which serves as an information hub connecting the hippocampus with the neocortex. Information pathways within the hippocampus generally flow unidirectionally (Hayman et al., 1998; O'Keefe &

Nadel, 1978). These pathways are defined regionally as CA1, CA2, CA3, dentate gyrus (DG), and CA4. (CA stands for *cornu ammonis* which means "*curved like a ram's horn").*

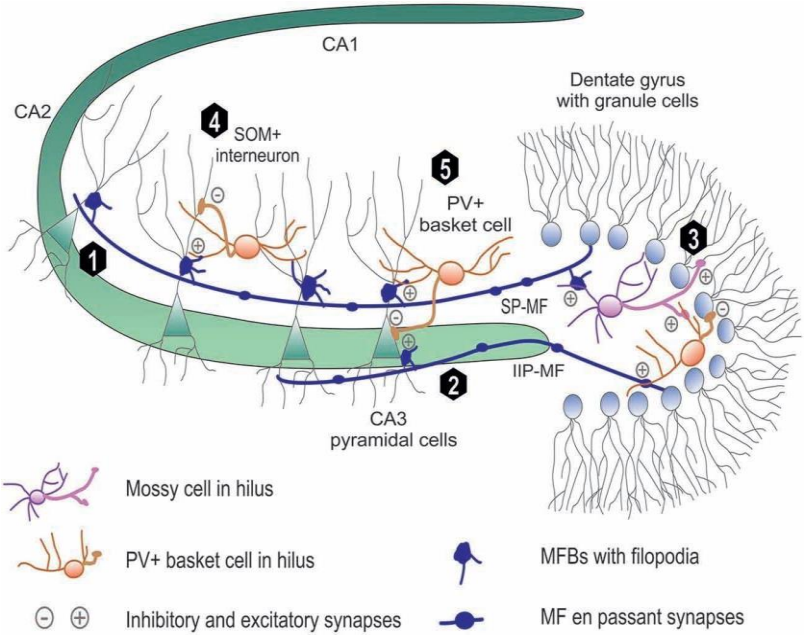


Figure 2. Diagram of the mossy fiber projections of the dentate gyrus (DG) (Reprinted from "Extracellular proteolysis in the structural and functional plasticity of mossy fiber synapses in the hippocampus," by G. Wiera and J. Mozrzymas, p. 3. Copyright 2015)

CA1 is responsible for the formation of new memories and the retention of stimuli (Ramaswamy, 2014). CA2 is not as well understood, although altered formations have been linked to autism and Alzheimer's. CA2 functioning is also associated with synaptic plasticity (Caruana, Alexander, & Dudek, 2012). CA3 is a content addressable memory station and partners with the DG to detect mismatches, particularly when a familiar object is placed within a new spatial relationship (Hasselmo, 2005). CA3 is responsible for

storing, assimilating, and rearranging information about patterns and associations of projection topology (Myers & Scharfman, 2009; Wiera & Mozrzymas, 2015). Additionally, CA3 may be one of the most severely impacted subfields in relationship to TELS (Teicher, Anderson, & Polcari, 2012). CA4 is different from the other subfields as it looks like a field of fine mossy fibers that appear and seem to function as antennae. This subfield, often referred to as the hilar region, assists in stimulating excitatory synaptic activity when working in conjunction with the DG (O'Keefe & Nadel, 1978). It also appears to facilitate the actions to promote synaptic plasticity in consort with the other subfields, including the DG (Wiera & Mozrzymas, 2015). The DG, incidentally, is one of the few regions in the brain that has the capacity to generate the production of new neurons, which are functionally integrated throughout the adult life span (Jonas & Lisman, 2014).

The hippocampal structure is defined by its shape and borders. Its actual location in the temporal lobe borders the amygdala, the temporal horn of the lateral ventricle, and the pulvinar, the largest nucleus of the thalamus. Its segmented parts include the dorsal hippocampus (DH); ventral hippocampus (VH); and the intermediate hippocampus (Lenroot & Giedd, 2006). These parts serve very distinct functions. For example, the dorsal hippocampus influences spatial memory, verbal memory, and the ability to conceptualize information. Its activity forms a pathway into the medial septal nucleus and supramammillary nucleus (SuM). The septal area in humans gives us the ability to express prosocial behaviors by creating positive feelings towards others and includes feelings such as trust, empathy, and bonding (Morelli, Rameson, & Lieberman, 2014).

The SuM controls the theta wave functions of the hippocampus, which are crucial to learning, motivation, intuition, and memory (Pan & McNaughton, 2004).

Hippocampal volume is determined by thickness and density, as measured on imaging planes. Ranges of hippocampal volumes extend from 1.73 to 5.68 ml. MRI scans composite both gray and white matter density to determine the volume (Keller & Roberts, 2009; Krogsrud et al., 2014; Shen, Moffat, Resnick, & Davatzikos, 2002). Calculations are made using complicated MRI procedures that segment the area and distinguish grey matter and white matter and the possible presence (or lack) of other fluids (Obenaus et al., 2001; Wu et al., 2018). Reductions in volume have been associated with a number of psychiatric disorders, including schizophrenia, depression, autism, Alzheimer's, and memory loss (Hickie et al., 2005; Wible, 2013).

The development of the hippocampus extends into early adulthood, and its integrity is critical to intact memory function. MRI studies show that the most significant changes occur prenatally (Graham et al., 2014) and that hippocampal volume rapidly spikes around age 2, with gradually decelerating volume increases until mid-adolescence; followed by tapering down well into late adolescence (Nagel et al., 2004; Wisse et al., 2012b).

There are serious matters of debate within the field of traumatic stress research regarding the way data is interpreted. For example, Woons and Hedges (2008) suggested that changes in hippocampal volume may not be apparent until a disorder develops in adulthood, which would impact the reliability and validity of MRI scan interpretations on young populations. Another point of dispute is between the views of aberrant

hippocampal structural and volumetric indices as biological precursors for the development of pathology rather than the result of traumatic stress (Gilbertson et al., 2002; Lindgren et al., 2016). These questions are crucial and warrant further investigation as the field advances in understanding the correlations between TELS, brain development, and psychopathology.

Gender as a determinant of the hippocampal volume is an area alive with debate (Gross et al., 2012; Samplin, Ikuta, Malhotra, Szeszko, & Derosse, 2013; Woon & Hedges, 2011). This issue is discussed in more detail later in the sub-section marked "Covariates and Debates."

Hippocampal Dysfunction

The hippocampus enables long-term memory and is also associated with spatial navigation (Gross et al., 2012; Martin H Teicher, Anderson, & Polcari, 2012). Any loss or damage to this area can lead to significant memory loss and can also inhibit the ability to form new memories, which in turn, compromises the ability to learn new skills. Participants with hippocampal lesions often function poorly on tests that involve recall implying that the hippocampus (Oomen et al., 2010).

The hippocampus is responsible for regulating cortisol levels in humans, but under conditions of chronic stress, its functioning is severely compromised (Mello et al., 2009; Carrion et al., 2007). Cortisol imbalances are linked to depression, anxiety, insomnia, and obesity. This tiny area also contains very high levels of glucocorticoid receptors (Jackowski et al., 2011; Carrion, Weems, & Reiss, 2007), which makes it more vulnerable to long-term and toxic stress than any other part of the brain.

Individuals who suffer aberrant morphology during specific periods of brain development are at higher risk of later developing psychopathology, including anxiety, depression, posttraumatic stress disorder (PTSD), substance abuse, and psychosis (Bremner, 2006; Carrion et al., 2009). Perry (2009) stated that effective therapy must link to the innervating neural system, the area in the brain where the original point of disruption began. The development of effective therapeutic models is dependent upon the depth of insight gleaned from neurobiological research on traumatic stress and brain morphology.

TELS is associated with disruptions in cognitive processes (Bonne et al., 2001; DePrince, Weinzierl, & Combs, 2009); in language, visuospatial and attention processing (Bellis, n.d.; Chugani et al., 2001; McCrory, De Brito, & Viding, 2010; Behen et al., 2009); in the psychopathology of PTSD, anxiety, and depression (Carrion et al., 2009) and a causal factor in high risk-taking behaviors alcohol and drug abuse (Shonkoff et al., 2012). Risks of delays are consistently identified in every developmental domain, including behavior, emotion, cognition, speech, social, physical, and neurological (Spilsbury et al., 2008; Wolfe et al., 2003). Altered brain development is also linked to other psychological disturbances as well as linguistic, cognitive and social-emotional skill development (Hanson et al., 2014; Lupien, McEwen, Gunnar, & Heim, 2009), which can be deemed as supportive evidence for the existence of a high correlation between TELS and brain morphology.

Glucocorticoid (GC) levels in the brain were linked to early-stage, reversible dendritic remodeling along the primary channels of the hippocampal area, the CA1, and

CA3 pyramidal granule neurons. These hippocampal subfields are responsible for the formation of new episodic memory (Sousa et al., 2000; Swaab, 2005; Uno et al., 1989). Animal studies have demonstrated that a damaged hippocampus can impair the ability to recall learned responses to behavioral cues and contributes to hyperactivity (Carrion et al., 2007; Jin et al., 2013; Lin et al., 2013).

Deciphering the relationship between TELS and hippocampal development is vital because the vast range of symptoms appearing in children and young adults indicates thought-related disorders, such as traumatic recall, and difficulties in emotional regulation, which severely impacts social functioning. Neuropsychological and psycho-social problems more than likely go unrecognized when complicated by depression, substance abuse, and memory problems (American Academy of Child and Adolescent Psychiatry, 1998; Carrion and Steiner, 2000a).

Primary Variables, Covariates, and Debates

This study examined the relationship between TELS (IV) and hippocampal structure and volume (DVs). Hippocampal volume and structure were measured through MRI scans in developing brains. The effect size was analyzed against MRI measures of a demographically matched comparison group of participants who experienced no TELS.

Specific indicators of TELS that emerged in this study included child maltreatment, sexual abuse, physical abuse, physical neglect, emotional abuse, emotional neglect, abandonment, institutionalization, chronic illness of the primary caretaker, and low socioeconomic status or poverty. Significant covariates that emerged during the analysis of the data included age, gender, genetic predisposition, duration of abuse, and

poverty. Other confounding variables included relationship to the perpetrator, severity of abuse, multiplicity, the timing of abuse, and frequency.

Types of Traumatic Stressors

Child Maltreatment

In this research study, "child maltreatment" is a generalized term that defined numerous forms of abuse and neglect. Researchers sometimes opted to generalize the variable rather than identify the numerous trauma types that control group participants may have identified during the clinical assessment process. For example, Edmiston's (2011) control group reported physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse. This researcher generalized the data under child maltreatment to focus more on gender-specific influences rather than specific trauma types.

In addition to the specific trauma types identified in this section, Gerson & Rappaport (2013) cited exposure to family or domestic violence. Other trauma experts added that TELS could result from racism and discrimination (Sanders-Phillips, 2009), and environmental stressors such as overcrowding, noise pollution, and natural disasters (Sanders-Phillips, 2009; Weithorn, 2012).

Sexual Abuse

Douglas Bremner (see Bremner et al., 1995) was among the first researchers to measure differences in hippocampal volume. Later, Bremner conducted an MRI study with adult survivors of childhood sexual abuse and found a significant reduction in the left hippocampal volume of the adult survivors' group (Bremner et al.,1997). He

replicated the study in 2003 with women survivors of childhood sexual abuse, this time adding positron emission tomography (PET scans), and again, findings revealed smaller hippocampal volumes in women who suffered PTSD relative to childhood sexual abuse (Bremner, Vythilingam, & Vermetten, 2003). However, Teicher, Anderson, & Polcari, 2012, used a similar research design with young adults (ages 18-22) with histories of sexual abuse and found no significant variance when compared with healthy age-matched controls. Teicher et al., 2012, suggested that the discrepancies could be attributed to the possibility that PTSD effects were gradual, substance-induced (alcohol, for example), or that smaller hippocampal volumes were a risk factor of PTSD rather than a consequence.

Andersen (2008) identified sexual abuse as a significant variable in association with decreases in hippocampal volume in young adult women. In Andersen's study, hippocampal volume was reduced in association with childhood sexual abuse experienced at ages 3–5 years and ages 11–13 years - a finding that also supports the construct of age as a significant covariate.

Physical Neglect/Physical Abuse

Researchers classify traumatic stressors to include physical abuse and physical neglect (Hambrick et al., 2019; McEwen & Morrison, 2013). Hanson et al., 2014, found that children who suffered physical abuse had smaller right hippocampi relative to comparison children. Relative to physical neglect, Hanson stated that smaller left hippocampi were found in children from low SES. Hanson concluded that for children exposed to any form of TELS, higher levels of cumulative stress were associated with smaller volumes in the hippocampus.

Abandonment/Orphanage/Institutionalization

Maternal or familial separation leading to adoption, (Gross, Flubacher, Tinnes, Heyer, Schelle, Herpfer, et al., 2012; McEwen & Morrison, 2013) presented in many studies as a primary stressor. Mehta's et al., 2009, post-institutionalized (PI) adoptees had significantly reduced brain volumes compared with the control group. In another study of PI adoptees, Tottenham et al., 2010, using a one-way ANOVA, showed differences between control and comparison groups for the amygdala change but not for the hippocampal change. Later, researchers would again present data noting large differences in structural brain development between PI children and non-adopted controls (Hodel et al., 2014; Hanson et al., 2014). In the Hodel study, PI children had smaller left hippocampal volumes than non-adopted children.

Emotional Neglect/Emotional Abuse

Edmiston's (2011) results concluded that emotional maltreatment inversely correlated with hippocampal development. According to Edmiston, emotional maltreatment seemed to have a more substantial influence on negative self-concept and depressive symptoms. In this study, physical abuse was reported by sixteen subjects, physical neglect by eighteen subjects, emotional abuse by twenty-three, emotional neglect by thirty-four, and sexual abuse by six. It is important to note that many of the studies under analysis coupled emotional neglect and emotional abuse with the term "child maltreatment". However, in future research endeavors, these particular stressors should be isolated and more closely examined.

Chronic Illness of Primary Caretaker

In an animal study conducted by Karten, Olariu, & Cameron, 2005, rat pups separated for three hours per day from their mothers experienced a decrease in the production of new dentate granule cells (GCs) in adulthood. GCs integrate information from the different mossy fibers and generate new patterns of neuronal activity. They are the only neuronal type generated in the adult hippocampus. Hence, the conclusion of this study suggests that TELS can permanently damage the hippocampus-dependent learning and memory processes and increase susceptibility to depression. Human studies indicate that moderate to severe exposure to psycho-social adversities which include debilitation or mental illness of the primary caretaker (Walsh, Dalgleish, Lombardo, Dunn, Van Harmelan, Ban, et al., 2014), or parental death or chronic physical illness (Petchtel, Pia; Pizzagalli, 2011) can place a child at high risk for aberrant hippocampal (and whole brain) development.

Poverty/Low SES

Poverty and abandonment were consistently linked to adverse hippocampal development, notably smaller overall volumetric measures and smaller left hippocampal size (Butterworth et al., 2012; Duval et al., 2017; Hanson et al., 2014; Hodel et al., 2015; Lawson et al., 2017; Piccolo & Noble, 2017; Tottenham et al., 2010). Yu et al., 2017, and Hanson et al., 2014, reported differences in reductions in both left and right hippocampi in children with low SES. It is important to note that Luby et al., 2013, and Wang et al., 2016, found that caregiving behavior and self-esteem can mediate the impact of stress-

related to poverty. Those kinds of findings lend support to further research into how specific conditions or experiences can promote resilience in vulnerable children.

Covariates

Gender and Age

Gender may play a role in plasticity. McEwen & Milner (2007) determined that estradiol was responsible for spine density and synaptogenesis in the CA1 region. Estradiol is a female sex hormone produced in the ovaries. Gender may also play a vital role in the risk of developing psychopathology when coupled with TELS. Everaerd, Gerritsen, Rijpkema, Frodl, Franke & Fernandez, et al. (2012) reported that gender modulated the effects of the 5-HTTLPR genotype relative to childhood maltreatment and hippocampal morphology. 5-HTTLPR is a serotonin transporter-linked polymorphic region that has been associated with depression. The Everaerd study concluded that females who suffered severe forms of childhood maltreatment had much smaller hippocampi than males, even those males who may have been carriers of the gene. Frodl, Reinhold, Koutsouleris, Reiser, & Meisenzahl, 2010, also supported the notion of gender functioning as a primary variable in the relationship between decreases in hippocampal volume as detected in patients with MDD.

In one of Carrion's studies (2001), smaller hippocampal volumes (an average of 8.5% smaller) were detected in groups who had been screened for PTSD, but the average did not prove significant when contrasted with total brain volume. However, he did discover that the clinical group demonstrated attenuation of frontal lobe asymmetry and

smaller total brain and cerebral volumes when compared with the control group. In a subsequent study, however, Carrion (2007) linked hippocampal reductions when controlling for pubertal maturation and gender over time (a 12 to 18-month interval). Chen, Hamilton, and Gotlib (2010) also confirmed reduced left hippocampal volume in high-risk girls with a family history of depression. However, Tupler and De Bellis (2006) argued that the age of trauma onset and level of psychopathology were the primary causes of risk for psychiatric disorders regardless of age or gender. De Bellis had conducted three separate pediatric tests and determined that volumetric measures could not be detected in children under the age of 12 (De Bellis et al., 2002).

Age changes in volume and structure are reportedly more apparent and visible during adolescence (Korgaonkar et al., 2013; Mehta et al., 2009; Morey et al., 2016; Rao et al., 2010a) and not in children under the age of 12 (De Bellis et al., 2002). Korgaonkar (2013) noted a significant difference in cortical thickness and volume in TELS adolescent participants in his study when compared with older participants. He proposed that these differences may reflect the levels of vulnerability in adolescent brains during this phase of neurodevelopment. Cortical thickness is associated with intelligence, while cortical volume is related to the reduced thickness, which has been associated with diseases like Alzheimer's, schizophrenia, and dementia. Kogaonkar also concluded that relief from traumatic stress or effective management of symptoms consequential of traumatic stress could help the volume levels to return to more balanced states.

Everaerd (2016) could not detect volumetric changes in late adolescence. However, many other studies did report that volume and structure were more apparent

and visible during adolescence (Korgaonkar et al., 2013; Mehta et al., 2009; Morey, Haswell, Hooper, & Bellis, 2016; Rao et al., 2010). This is an area that will require continued research.

Duration

Chronic stress results from the experience of emotional or psychological pressure endured over extended periods of time. Bagley and Moghaddam (1997) found that prolonged stress, coupled with increased levels of glucocorticoids, have proved disruptive to hippocampal neurogenesis. In cases of extreme and chronic stress, volumetric declines were noted with increased risk for metabolic injury and cellular death in the cornu ammonis (CA) regions of the hippocampus (Czeh and Lucassen, 2007; Harlan et al., 2006; Sousa and Almeida, 2002). Wang and his colleagues reached a similar conclusion - that extended exposure to stress suppresses neurogenesis and dendritic branching in these particular subfields - when they confirmed an association between PTSD and selective volume loss in the CA3/dentate gyrus subfields of the hippocampus (Wang et al., 2010). Additionally, Frodl et al., 2010 and De Kloet, 2003, concluded that excess glutamatergic transmission into the hippocampus could worsen cellular damage or even contribute to cellular death. Glutamate is a potent excitatory neurotransmitter that has been associated with hyperalgesia, anxiety, restlessness, and poor concentration (Liou, 2011).

Perry (2009) explained that when the stress response is repetitive and extremely prolonged, the neural networks undergo a “use-dependent” molecular change (p. 244), which alters the baseline activity and reactivity of the individual’s stress response system. In effect, the brain becomes re-wired, signaling a persistent state of danger to the

traumatized individual. Additionally, chronic stress can severely compromise the functioning of memory and mood, limiting the ability to discriminate between conditions that may be dangerous versus safe (Shin et al., 2006). The sense of ever-present danger and the inability to perceive danger are symptoms of PTSD.

Cardiovascular disease, asthma, fibromyalgia, obesity, diabetes, eczema, and even cancer, have been linked to chronic stress (Cohen, Janicki-Deverts, & Miller, 2007; Frodl & O'Keane, 2013). Chronic or excessive stress strains or inhibits the return to homeostasis and negatively impacts the neuroendocrine, immune, cardiovascular, and neurological functions of the body/mind producing a state of allostatic load (McEwen, Gray, & Nasca, 2015). Neurobiological studies have also linked chronic and traumatic stress to telomere erosion, which contributes to cellular aging and disease (Shalev et al., 2012).

Chronic stress has also been associated with executive function deficiencies in rats and primates as well as humans (Hanson et al., 2012; Holmes & Wellman, 2009; Sánchez, Hearn, Do, Rilling, & Herndon, 1998). Executive function skills govern impulse control, emotional regulation, thinking, memory, self-monitoring, planning and prioritizing, task initiation, and organization. Animal studies involving hippocampal functioning found correlations between memory, hippocampal morphology, and inhibited neurogenesis when exposed to ongoing stress (O'Mahony et al., 2009). An exciting and potentially powerful outcome of the O'Mahoney study was that these adverse outcomes were reversible with treatment, demonstrating the brain's capacity for plasticity. Insights

such as the one just described serving as an impetus in the quest to unravel the complex questions related to the brain's response to chronic and traumatic stress.

Genetic Predisposition

Perry (2006) explained that traumatic experiences could contribute to the abnormal organization of vital neural systems in the developing brain. Both Perry and Andersen concurred that the nature, timing, genetic predisposition, and duration of the stressor(s) are cofactors that deserve a much more rigorous investigation.

Data from human studies suggest the possibility of a linear relationship between PTSD, depression symptoms, and TELS relative to hippocampal functioning. A renegade degenerate gene expression known as S-allele (serotonin-transporter-linked polymorphic region) has been extensively associated with neuropsychiatric disorders since its discovery in the early 1990s (Everaerd et al., 2012; Heim, Shugart, Craighead, & Nemeroff, 2010). Children who carry S-allele have smaller hippocampal volumes when coupled with a history of emotional maltreatment in Frodl's (2010) study, in contrast to children who only had one risk factor, be it environmental (stress) or genetic. Additionally, Frodl discovered that the left prefrontal cortex in carriers who also experienced chronic stress was smaller than children with environmental risks only. Frodl (2010) suggested that the presence or lack of volumetric changes in children was more linked to an interaction between genetic susceptibility with chronic or cumulative stress as a covariate. His research concluded that childhood stress and brain abnormalities were independent and interactive. Rao (2010) determined that smaller hippocampal volume in high-risk adolescents could serve as a point of vulnerability, particularly increasing risks

for the depression when early life stress intersects genetics. Molendijk et al., 2012, found genetic polymorphisms that produce low or abnormal hippocampal volume can then create higher risks for the later development of brain diseases.

The Chen study (Chen, Hamilton, & Gotlib, 2010) examined the relationship between genetic propensity for depressive episodes in girls who had mothers with chronic depression. The researchers used voxel-based morphometric analysis findings which found significantly less gray matter density in clusters in the bilateral hippocampus and volumetric reduction in the left hippocampus.

Other Covariates

Additionally, the severity of effects from abuse appeared in direct proportion to age and duration. Timing (relative to age & stage development) appears to be the most crucial factor when coupled with the variables of gender and type of abuse (Andersen et al., 2008; Korgaonkar et al., 2013.). Other confounding variables that were identified in the studies were multiplicity, the severity of abuse, and relationship to the perpetrator (Andersen et al., 2008; Mehta 2009; Edmiston 2011; Hanson 2014; Everaerd 2016). Mehta (2009) and Morey (2016) reported significant differences between TELS groups and comparisons when influenced by severe deprivation or abuse. Paquola and colleagues (2017) reached a different conclusion when they examined the MRI scans of 14 to 28-year-old participants. Although the researchers found significantly stunted structural growth in the right hippocampus of participants who were exposed to child maltreatment, an MRI scan revealed that hippocampal and amygdala volume increased linearly with age

and were not moderated by symptoms of severity. Their findings negated definitive associations between child maltreatment and psychopathology (Paquola et al., 2017).

Magnetic Resonance Imaging

The use of high-resolution MRI technology to measure and understand brain structure and activity began almost 50 years ago (at the time of this publication) and has dramatically enhanced the ability to accurately measure brain morphometry (Arbabshirani, Plis, Sui, & Calhoun, 2016). Douglas Bremner was among the first researchers to measure differences in hippocampal volume using an MRI. His analysis of combat-related PTSD patients relative to a comparison group with no PTSD symptoms revealed a smaller right hippocampal volume in those who had suffered PTSD (Bremner et al., 1995). These findings stimulated interest amongst other researchers to utilize brain scan technology to support their works.

I selected only MRI studies and chose not to include similar studies that used other types of instrumentations, such as PET scans, electroencephalogram (EEG), and functional magnetic resonance (fMRI), because these instruments image the human anatomy for very different reasons. PET scans are used to evaluate organ and tissue functions and to screen for the early onset of disease. EEG and fMRI tests are used to measure brain activity (the EEG tracks brain waves, and the fMRI measures blood flow). The MRI, on the other hand, creates powerful magnetic fields and radio frequencies to produce highly detailed images of the body's organs. This instrument serves as the primary measure for assessing volumetric and structural changes in the brain. Hand-

tracing, to confirm the boundaries of poorly developed brain regions, is often used in conjunction with MRI.

Clinical Assessment Tools Utilized in Studies

All studies selected for this analysis utilized a clinical assessment, utilized standardized clinical assessment forms, clinical interviews with trained professionals, or both, to assess exposure to TELS. Efforts have been made to ensure that similarity in the use of protocols and assessment tools remained as consistent as feasible throughout the studies analyzed in this project. Table 1 in the Research Methods chapter lists identified project studies and the various criteria, including the age-range of participants, clinical assessment tools or measures, and magnification properties of the MRI scanning instruments used.

Summary of Literature Review

The Literature Review molds the seminal works of trauma theory, a construct first introduced by Charcot, and Selye's theory of general adaptation into the foundational compass for the analysis of data in this project. These theories will be supported by contemporary research on stress and neuroanatomical adaptation to link together the key variables: TELS, aberrant hippocampal development in developing brains, as documented in scans taken from MRI instrumentation.

How stress affects the brain is complicated by several factors and conditions, such as the type of stressor, the duration of the stressor, the severity of the stressor, age, genetic predisposition, gender, economic deprivation, the timing of the insult and many other variables not yet uncovered by researchers. While it is challenging to identify and isolate

the numerous confounding factors that are complicit with chronic stress, researchers in the fields of sociology, psychology, neuropsychology, and neuroscience must persevere to bring these variables to the surface; develop standardization in research protocols; which promotes the knowledge and understanding necessary to effect positive change.

Chapter 3: Research Method

In this investigation, I examined the relationship between TELS and hippocampal volume and structure. The research question stated, “To what extent does TELS exposure impact the structure and volumetric measures of the hippocampus in the developing brain?”

Chapter 3 presents an overview of the research design and rationale for the selection of meta-analysis as the preferred methodology. Chapter 3 identifies variables of interest and the criteria used for the selection of the studies for this meta-analysis. The primary studies selected for final analysis are also listed along with the types of clinical assessment strategies, population demographics, and the specific type of MRI instrument used to image the brains of study participants. The data analysis plan includes any known threats to validity. Ethical considerations and a summary of the research protocols conclude the chapter.

Research Design and Rationale

Meta-analysis is a quantitative research methodology that integrates the results of similar empirical studies to obtain a more comprehensive understanding of the effect size and moderating variables (Sanchez-Meca & Marin-Martinez, 2010). Meta-analysis affords more opportunities and numerous exploratory pathways to help develop more awareness about populations by accumulating results across studies than by single study analysis. This approach also assists in understanding the interplay of effect size and covariates (Glass, McGaw, & Smith, 1981).

This meta-analytic study examined the impact of TELS (IV) on hippocampal volume and structure (DV). Clinical neuroimaging studies of MRI hippocampal changes and TELS are generally comprised of relatively small sample sizes, challenging the ability to generalize conclusions to larger populations. Synthesizing the data gleaned from the selected clinical studies has produced a more reliable estimate of effect size regarding the controls and the related variables. For data analysis, I applied fixed, random, and cumulative meta-analytical methods to assess effect size utilizing Hedges' *g*, Cohen's *d*, and correlation values. These statistical approaches are discussed in detail later in this chapter.

Methodology

Population

According to the 2017 statistics presented by the U.S. Department of Health and Human Services, TELS is the experience of 3.5 million children whose caretakers are investigated by child welfare institutions; the 10 million children who witness domestic violence; and the 2.5 million children who live in homeless shelters. Globally, the World Health Organization (2017) reported that 1 in 4 adults had experienced abuse as a child.

The total number of TELS participants included in the primary data analysis equaled 294; comparison group participants totaled 474. The mean age of all groups was μ14.77 years, with a range of μ10 years to μ27 years. The number of male participants in the final studies totaled 129; the numbers of non-White participants represented less than 7% of the total population of 768 participants. The ROI included only the hippocampal region scanned through MRI of both control (TELS) and comparison (no TELS) groups.

Sampling and Selection Procedures for Empirical Research

Over 200 studies were reviewed for this meta-analysis, and four primary criteria were identified for study inclusion. First, the study had documented evidence that participants were assessed for the presence or absence of TELS by a qualified professional through the method of an interview or clinical assessment tool. Secondly, all participants were under the age of 30 at the time the study was conducted. Third, evidence of MRI hippocampal scans for controls and comparisons was included in all studies. Furthermore, demographically matched comparison groups were included in the study. Only one study did not have a comparison group but was included for consideration as all other criteria were represented. The combined number of participants in the comparison groups sufficiently represents the numbers in the controls.

The focus of this research in each empirical study that was selected had to include TELS as the IV, defined by the exposure to and the experience of severe neglect, physical abuse, sexual abuse, and psychological trauma, including verbal abuse that produces intense fear, deprivation, isolation, and physical and emotional pain. The ROI was limited to or included in the hippocampus (DV).

Databases and Data Collection

Electronic databases used for data collection included Biomedical Informatics Research Network (BIRN), Medline, PubMed, Academic Search Premier, ProQuest, Science Direct, PsycLIT, and PsycINFO.

Selected Empirical Studies

A systematic review of the literature resulted in over 200 studies relevant to the topic of TELS and hippocampal development, of which only 22 met the criteria for inclusion. Studies were coded and selected using the model provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher, 2015). PRISMA standards provide a template of a 27-item qualitative checklist for the writing and reviewing of research using secondary data sources. The checklist helps to ensure integrity and transparency in the reporting of meta-analysis and systematic reviews (Liberati et al., 2009).

Study Coding

A code sheet (*Figure 3*) specific to this research listed 17 items to determine if the study matched the protocols required for analysis screening process assessed the following:

- Establish relevance—if the study was a "primary" study rather than a meta-analysis or review and if the study was published or unpublished.
- Verify registration—whether the study was peer-reviewed or met other inclusion protocols if unpublished.
- Establish authenticity—whether the primary researchers were clearly identified.
- Match inclusion criteria—whether the study met the age requirements for inclusion (3 years to 28 years).

- Determine if the study included a comparison group, a clinical assessment protocol, and an MRI protocol in which the data acquisition was documented.

The coding review also assessed the methodology to establish whether statistical data specific to the hippocampus was appropriated and whether TELS variables were identified. Finally, the final selected studies met inclusion criteria if statistical data to support or reject the null hypothesis was defined and if any covariables were identified in the research body.

Figure 3.

Code sheet for study selection based on PRISMA

Section and topic	Item No	Checklist item Notations
Search Criteria		
Title:		
Primary Study	1a	Include
Meta-Analysis	1b	Automatically Exclude
or Review	1c	Assess for Appropriateness
Unpublished		
Registration	2a	Peer-Reviewed
	2b	Not Peer Reviewed but meets inclusion protocols (if unpublished)
Authors:		
Contact	3a	Provide name, institutional affiliation, the e-mail address of all protocol authors; provide the physical mailing address of the corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Age Range	4a	Include 3 years to 28 years
Assessment:		
Comparison Group	5a	Include if all other protocols are present*
Clinical Assessment	5b	Provides a type of clinical assessment tool or type of evaluation
MRI protocol	5c	Identifies MRI data acquisition
Purpose of Study		
Hippocampus	6	Data on hippocampus clearly identified in the study
TELS	7	Traumatic early life stress variable(s) clearly identified
METHODS		
Statistical Analysis	8	Methodology clearly identified
Hippocampal Change	9	Data on the absence or presence of hippocampal changes are noted
Results	10	Statistical data to support or reject the null hypothesis is highlighted
Discussion	12	Relevant variables are identified

Inclusion criteria for data analysis required documentation that the participants were assessed for the presence or absence of TELS through the method of an interview or clinical assessment tool. Secondly, all participants had to be under the age of 30 at the time the study was conducted. Third, the selected project used MRI technology to

measure hippocampal change. Finally, the project had to include a demographically matched comparison group. Each of the 22 selected research studies used in either primary or post hoc analysis focused on hippocampal development as the primary DV. After a review of statistical analysis applications in each selected study, only 9 of the 22 met all criteria for inclusion. The remaining 13 studies were included in later discussions as references. Table 4 provides details of all selected studies that were reviewed for preliminary analysis. Any study followed with an asterisk (*) was included in the final analysis.

Figure 4. *List of Selected Studies for Preliminary Analysis*

Study Name	#TELS Group	TELS Male subgroup	# Non-TELS Comparison	Mean Age	Variables Measured	Clinical assessment tool	MRI acquisition
Andersen 2008	21	0	16	19	Childhood sexual abuse, hippocampal volume, female	BDI, CTQ	1.5 T magnetic resonance scanner
Carrion 2001*	24	14	24	11	PTSD, childhood trauma Hippocampus volume	CAPS-CA	1.5 T scanner
Carrion 2007	15	6	0	10	CM, PTSD, baseline cortisol at baseline levels, hippocampal volume	Clinical evaluation for PTSD	1.5-T GE-Signa scanner
Chen 2010*	23	0	32	13	MDD, female, genetics, hippocampal volume	Structured Clinical Interview for DSM-IV	1.5-T GE scanner
De Bellis 2002*	28	14	66	12	maltreatment-related posttraumatic stress disorder (PTSD)	CBCL, CDI	GE 1.5 Tesla
Edmiston 2011	42	21	0	15	Relationships among GM volume, subtypes of exposure to CM and gender	CTQ	3 Tesla Siemens Trio
Everaerd 2012	192	79	165	24	gender, childhood adversity, 5-HTTLPR genotype	LTE	3 Tesla Siemens Trio
Everaerd 2016	253	110	129	22	deprivation, abuse, hippocampal volume, gender	LTE	1.5 T & 3 T scanners
Hanson 2014	128	67	41	12	Hippocampal volume institutionalized orphaned or abandoned children, physical abuse, early neglect, low SES	LTE	3T General Electric SIGNA MRI scanner
Hoedel 2014	110	37	62	13	Hippocampal volume, institutionalized orphaned or abandoned children	Axis I disorder based on caregiver interviews with a trained clinician	Siemens 3 T Trio MRI scanner
Korgaonkar 2013*	18	11	118	12	tels, age, hippocampal structure and volume	ELSQ	1.5 Tesla Siemens

Note. ACE = Adverse Childhood Experiences; BDI = Beck Depression Inventory; CAMEEI = Cambridge Early Experiences Interview; CAPA, CAPS-CA-5 = Child & Adolescent Psychiatric Assessment; CBCL = Children's Behavior Checklist; CDI = Children's Depression Inventory; CTQ = Childhood Trauma Questionnaire; ELSQ = Early Life Stress Questionnaire; HDRS = Hamilton Depression Rating Scale; K-SADS-PL = Kiddie-Sads-Present & Lifetime Version; MSSSS = MacArthur Scale of Subjective Social Status; PSS = Perceived Stress Scale; PAPA = Preschool Age Psychiatric Assessment; SCARED = Screen for Child Anxiety Related Emotional Disorders; LTE = The List of Threatening Experiences. **denotes final selected study*

Figure 4 continued. *List of Selected Studies for Preliminary Analysis*

Study Name	#TELS Group	TELS Male subgroup	# Non-TELS Comparison	Mean Age	Variables Measured	Clinical assessment tool	MRI acquisition
Mehta 2009*	14	6	11	16	hippocampal volume, early severe deprivation orphaned/separated	Structured Clinical Interview	1.5T GE Excite Scanner
Morey 2016*	63	30	57	10	hippocampal volume, maltreatment, PTSD	CTQ	3 Tesla GE scanner
Piccola 2017	143	77	0	16	Self-perceived stress, SES, hippocampal structure and volume	PSS-10	3-dimensional T1-weighted scan
Rao 2010*	51	23	32	15	early-life adversity, morphologic changes in the hippocampus, and vulnerability to depressive disorder	K-SADS-PL, BDI, HDRS	(GE) 1.5 Tesla scanner
Teicher 2012	193	73	0	22	Childhood maltreatment and hippocampal volume	ACE, CTQ	T1-weighted MRI datasets acquired on a Trio Scanner (3-T; Siemens)
Tottenham 2010	34	8	28	9	Hippocampal volume and Institutional Child Rearing (orphanages), relative care-giving	CBCL, SCARED	GE 1.5 Tesla Unit and a 3 Tesla Unit 3 (Signa System, General Electric Medical Systems
Tupler 2006*	61	31	122	12	Hippocampal volume and early age trauma/adversity	CBCL, CDI	GE 1.5-Tesla Signa system
Veer 2015*	12	0	12	27	Hippocampal Volume and shape; in PTSD Childhood Trauma	K-SADS-PL	Philips 3.0-T Achieva MRI scanner
Walsh 2014	27	10	31	18	Hippocampal volume and early age trauma/adversity	CAMEEI	3-T Siemens Tim Trio
Whittle 2017	166	85	0	16	Hippocampal volume and childhood maltreatment	CTQ	3 Tesla GE scanner
Yu 2017	31	13		10	SES and Hippocampal volume	MSSSS	3 Tesla Siemens Verio scanner

Note. ACE = Adverse Childhood Experiences; BDI = Beck Depression Inventory; CAMEEI = Cambridge Early Experiences Interview; CAPA, CAPS-CA-5 = Child & Adolescent Psychiatric Assessment; CBCL = Children's Behavior Checklist; CDI = Children's Depression Inventory; CTQ = Childhood Trauma Questionnaire; ELSQ = Early Life Stress Questionnaire; HDRS = Hamilton Depression Rating Scale; K-SADS-PL = Kiddie-Sads-Present & Lifetime Version; MSSSS = MacArthur Scale of Subjective Social Status; PSS = Perceived Stress Scale; PAPA = Preschool Age Psychiatric Assessment; SCARED = Screen for Child Anxiety Related Emotional Disorders; LTE = The List of Threatening Experiences. **denotes final selected study*

Instrumentation and Operationalizing of Constructs

TELS is defined as the exposure to and the experience of severe neglect, physical abuse, sexual abuse and psychological trauma including verbal abuse that produces intense fear, deprivation, isolation, physical and emotional pain and/or a pervasive absence, either real or perceived, in safety, security and belonging needs (Herman, 1992). Events may be experienced through family, community, school, medical intervention, or some other caretaking system, such as daycare. TELS can be experienced through single episodic experiences such as rape, witnessing a murder, and natural disasters. TELS is also indicative of a repetitive cycle or a series of events, with a duration of days, weeks, or months and that could continue throughout childhood into early adulthood. The hippocampal structure is defined by its shape and borders. Hippocampal volume is determined by the thickness and density as measured on imaging planes.

Data Analysis Plan

There were several characteristics within studies that required adjustment to standardize the variables and improve the accuracy of data analysis. The first was some studies separated their participants who experienced “severe” abuse as defined by type, frequency, or duration from those who never experienced abuse or had a mild experience with a frequency of one or two episodes (see (Chen, Hamilton, & Gotlib, 2010; Everaerd et al., 2012; Korgaonkar et al., 2013). Those projects whose participants reported less than severe abuse (mild or limited occurrences) were listed with healthy controls who were at low risk for aberrant hippocampal morphology. Secondly, some studies reported statistical changes in hippocampal volume or structure in various subgroups, such as in

the Hanson study (Hanson et al., 2014), which examined emotional neglect, physical abuse, or abandonment, to contrast the influence of covariates on hippocampal change. In these instances, summaries of results were collapsed to produce averages for reporting values relative to hippocampal changes. Thirdly, some studies segmented results for left and right hippocampal volume or structure (Carrion et al., 2007; Chen et al., 2010; De Bellis et al., 2002). Those numbers were combined to produce a single number for the hippocampal whole. Carrion (2007) conducted a follow-up MRI of the same participants in 12- and 18-month intervals. In this matter, those counts are recorded as separate studies as there was significant variation at points in the timeline.

Data pertaining to any other part of the brain, such as the amygdala or prefrontal cortex, are generally excluded, and information relative to the hippocampus has been isolated. Statistical data were only analyzed for those participants with completed neuroimaging.

Comprehensive Meta-Analysis software v3

I used Comprehensive Meta-Analysis v3 (CMA) software for this analysis. The CMA software development began in 1993 and is spearheaded by a well-known professor and author Michael Bornstein (Borenstein, 2009). Borenstein is one of the foremost authorities in the field of meta-analysis and has written numerous publications and books on the subject. CMA takes the summary data from each study, regardless of format, and computes both effect size and variance. CMA can make comparisons of two or more groups and subgroups, estimates of means, proportions, rates of one group at one point in time; generic point estimates; and generic point estimates with a log scale. Means

can be recorded in various ways: dichotomous (number of events), continuous (means), correlation, rates, and survival. The grid used in CMA is very similar to Microsoft Excel: columns are created to list study names, sub-group data, and effect size data – the program can accept data from 100 different formats. In this research analysis, I am using comparison data of two groups; and continuous data, which focuses on means. I also identified my studies as unmatched groups so that I can record and calculate post-data only for two independent groups. CMA can recalculate data from studies that presented statistics in varying formats. For instance, some studies included means and standard deviations; others presented p-values; a few recorded t-values; and others used beta formats produced from multiple regression techniques. Using CMA, I was able to develop a customized spreadsheet and input data as initially recorded. The program computed the effect size for each grouping, which allowed for the results to be combined into a single analysis.

CMA also can create forest plots. A forest plot graphically reflects the effect size of each study as well as the combined effect. The forest plot helps to determine several factors, including the consistency of the effect size, and how the number of studies analyzed influenced that consistency.

Research Question and Hypotheses Restated

This study examined the correlation between TELS (IV) and hippocampal structure and volume (DVs). The nature of the stressor or type of traumatic experience was assessed through clinical assessment. Hippocampal volume and structure were measured through an MRI scan of developing brains. The effect size was analyzed

against MRI measures of demographically matched comparison group participants who were not exposed to TELS.

RQ: To what extent does the exposure to TELS impact the structure and volumetric measures of the hippocampus in the developing brain?

$H_{0:}$ There is no relationship between TELs and aberrant morphological changes in the hippocampus of the developing brain.

H_1: There is a relationship between TELs and aberrant morphological changes in the hippocampus of the developing brain.

Data Interpretation Strategy

An exploratory analysis was the first phase of the analysis to determine the frequency of associations linked to hippocampal volume changes and structural changes. *Statistical power,* according to Cohen (1988), refers to the probability that the effect or relationship between the variables under analysis exists. Cohn and Becker (2003) demonstrated that fixed-effects meta-analysis increases the statistical power by reducing the standard error of the weighted average effect size. They also demonstrated similar results through the use of random-effects meta-analysis, although the observation of this approach revealed that increasing the number of studies does not necessarily increase the precision of statistical power. Using the CMA program, I was able to ascertain data using random, fixed, and cumulative meta-analysis, which are discussed below.

Fixed and random effects methods. Fixed and random effects approaches were applied to determine individual study and cumulative effect sizes. Using a fixed-effect model, the researcher assumes that each study in the meta-analysis shares a common or

true effect size. In other words, all characteristics that could influence the effect size are the same in all studies; thus, the effect size remains the same and is labeled "fixed." In order to obtain the most precise estimate of the population effect (to minimize the variance), the researcher computes a weighted mean, where the weight assigned to each study is the inverse of that study's variance.

Whereas a fixed-effects model has a goal of estimating one "true" effect size, a random-effects model is used to estimate the *mean of a distribution of effects*. The mean effect of distribution was calculated through a weighting schema based on within-study variance plus t2, which represents a constant for the between-study variance. As a constant, t2 allows the relative weights assigned to each study to have a more balanced or equally relative influence. The methodology suggested by Borenstein (2009) is to first compute Q, which will represent the total variance and the degrees of freedom (df), which represents the expected variance if the studies have the same true effects. The difference, Q *minus* df, will reflect the excess variance. This value was then transformed and placed on the same scale as a within-study variance. The result produced a statistic called Tau-squared ($\tau 2$).

I used both random and fixed analysis to compare any differences that the two methods may produce. According to Borenstein (2009), estimates using the two models will generally produce different numbers (provided that t2, which represents between-study variance, is not zero). Borenstein stated that the reason that calculations report different effect sizes is because the mean of studies is weighted differently, depending on the model of choice.

Each of the nine studies included in the pilot study reported unique findings that no other study presented. The Mehta study, for example, had only 14 TELS and 11 controls and consistently proved an outlier in this research. However, a more in-depth analysis of this study yields extremely relevant information on how the IV and DV interact, proving a connection which warrants further attention. Therefore, a cumulative meta-analytic method was added to the analysis process. Through the use of a cumulative meta-analysis (this approach is explained in the following chapter), weights are assigned based on standard deviations to balance the effects of individual studies. This technique affords the best possible opportunity to examine the variations in effect sizes between studies with careful regard for how individual covariates and other factors may influence the outcome. When I applied the cumulative meta-analytic model, the final output for individual studies ranged from small to large in effect sizes, as measured by Hedges' *g* and Cohen's *d*. The results from all approaches are presented graphically in Chapter 4.

Cumulative meta-analysis. A cumulative meta-analysis is a statistical procedure that can examine data in several different ways. One way, for example, is to add one study at a time to estimate changes. For example, study results can be pooled sequentially, starting from earlier studies and concluding with more recent ones (Allen & Seaman, 2005). By combining studies chronologically, consistency in results is determined to the point where no further experiments are necessary because results will remain constant. Another approach using cumulative meta is to assess how the evidence shifts because of the influence of other factors such as combined effects or sample size, for example. For this analytic approach, I chose to assess the cumulative standard

difference in means because this variable appeared to be more of a determining factor for effect size between the selected studies.

Using the CMA program, weights were assigned to each of the final selected studies as a way to balance or distribute the evidence so that outliers, like the Mehta study, would not overshadow other studies. Hedges' g and Cohen's *d* statistical equations were used in determining the effect size. Cohen (1988) suggested that d = 0.2 can be equated to a "small" effect size, 0.5 can represent a "medium" effect size, and 0.8 a "large" effect size. Another way to conceptualize *d* according to Cohen was through standard deviations: .2 = 1/5 of a standard deviation, .5 = ½ of a standard deviation, and .8 = 8/10 of a standard deviation unit. Cohen further postulated that if the two groups' means do not differ by 0.2 standard deviations or more, the difference is trivial, even if it is statistically significant. Durlak (2009) advised that concepts of "large" vs. "small" effect do not translate into levels of significance in this research. Durlak added that small differences could have a significant impact when extended to the broader context.

Threats to Validity

Despite the proliferation of research publications describing hippocampal structure and volume, definitions in how these parts demarcate vary greatly. The differences may be due to variations in interpretations of boundaries or an MRI scan and neuroanatomical tracing techniques. These differences could impact interpretations of results when measurements are compared.

The effect sizes in the individual selected studies are influenced by inherent differences: different sample sizes, different age groups, gender, and other

demographics. Additionally, projects varied in the type of clinical assessment instruments used. The use of different clinical assessment tools could influence the way the traumatic experiences are interpreted, and gradients of stress are measured. These variances could make the results appear inflated, weak, or inconsistent.

The validity and accuracy of the results are dependent on the quality of the integrated studies. If one study is significantly biased, the entire meta-analysis will carry that bias. Other issues, such as the use of studies that only report positive results, can reduce the effectiveness of any research. This is particularly true for meta-analytical research.

Ethics: I guarantee the quality and integrity of her research, and that the composition of this document is free from plagiarism. I have utilized the data from approved and published primary empirical research studies, which resolved the issue of potential harm to individual participants. All publications were void of any type of identifying information, and I do not have access to such, nor to the codes utilize, to record pertinent demographic information. I strive to remain impartial in my analysis of data and declares that she has no competing interests.

Summary of Research Methods

This meta-analysis examined the conditions and degree of influence TELS has to aberrant development in the hippocampal region. The analysis includes 22 studies that were published between 2001 and 2017 and included participants between the ages of 3 and 28 years, who had been identified as TELS survivors.

Meta-analysis has become a preferred approach in psychological research because of the preciseness given in providing the magnitude, strength, and direction of the effects and the rigor those effects reflect within a specific domain. Because there is an emphasis on effect size, rather than statistical significance which, this approach stretches the scope for future directions in research; most importantly, data from a meta-analysis can support the development of innovative therapies that are appropriately matched to the source of dysfunction. Instead of identifying and treating symptoms, practitioners can incorporate information that identifies neurobiological variables and employ a more comprehensive approach to treatment planning.

The results of this project can be utilized to promote additional research efforts that would further isolate and investigate the influence of covariates that significantly increase the risk of adverse morphological change in developing brains. Such knowledge could support the continued development of effective clinical interventions for the prevention, early identification, and treatment of psychiatric disorders and behavioral problems stemming from TELS.

Chapter 4: Results

Introduction

This study examined the relationship between TELS (IV) and hippocampal volume and structure (DVs) as measured through MRI scans in developing brains (childhood through early adulthood). I analyzed the results of both the standard deviations and effect sizes of the control and comparison groups of nine out of 22 selected empirical studies that met all the criteria outlined in the selection process. The studies not included in the primary data analysis were analyzed using various post hoc procedures to determine patterns or relationships between co-variants not previously identified in the primary objects of this study. The research question and hypotheses are:

Research Question 1: To what extent does the exposure to TELS impact the structure and volumetric measures of the hippocampus in the developing brain?

$H_{0:}$ There is no relationship between TELS and aberrant morphological changes in the hippocampus of the developing brain.

H_1: There is a relationship between TELs and aberrant morphological changes in the hippocampus of the developing brain.

In restating the variables under analysis, TELS included any or all the following: sexual abuse, physical abuse, exposure to family violence, exposure to and the experience of severe neglect, including emotional and physical neglect, poverty, abandonment, and psychological trauma including verbal abuse. Hippocampal volume and structure were measured through an MRI scan of developing brains (childhood through early adulthood). The null hypothesis states that there is no relationship between TELS and

hippocampal development. The alternative hypothesis concludes there is a relationship between TELs and aberrant morphological changes in the hippocampus of the developing brain

Chapter 4 describes the data-analysis processes for determining the effect size as determined by Hedges' *g* and Cohen's *d* using cumulative meta-analysis. The ROI is limited to the hippocampal structure and volume. CMA V3 (Borenstein, 2009) software program was used for statistical analysis, and the functions of CMA are detailed in this section. Effect size computations for individual studies varied significantly with a total cumulative effect size ranging from small to moderate range (*d*= -0.296 to -0.413). Covariates frequently associated in studies with moderate to large effect sizes are identified and discussed later on in this chapter.

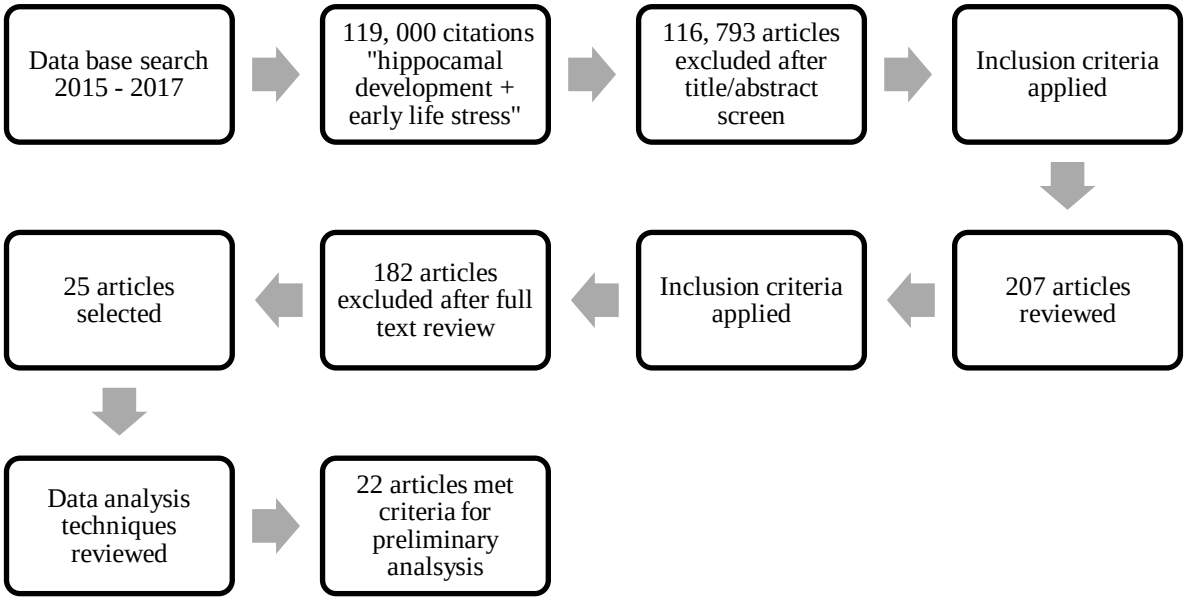
Data Collection

Inclusion and Exclusion Characteristics

Over 200 studies were reviewed for this meta-analysis; 22 studies were selected for analysis, and nine met the inclusion criteria for primary data analysis. Many of the reviewed studies were excluded (see Appendix A) because of extreme age variations; for example, groups with mixed-age populations, ranging in ages from 5 weeks old to 87 years old. Other studies focused on symptoms and diseases in participants who had been assessed for psychiatric disturbances.

Figure 5

Study selection process



Selected Studies

The table below lists the names of studies that met the final criteria for inclusion. After analysis of data, only nine studies met the criteria for inclusion for data analysis. Those studies are listed below. Out of the 22 final selected studies, nine were used in the final analysis, and others not used in the final analysis were used in post hoc analysis of left and right hippocampal profiles. Jackson & Turner (2017) argued that a meta-analysis requires at least five or more studies to achieve the power to detect effects consistently.

Table 1

Final Selected Studies

Study Name	#TELS Group	TELS Male Subgroup	#Non-TELS Comparison	Mean Age	Variables Measured
Carrion 2001	24	14	24	11	PTSD, childhood trauma Hippocampus volume
Chen 2010	23	0	32	13	MDD, female, genetics, hippocampal volume
De Bellis 2002	28	14	66	12	maltreatment-related posttraumatic stress disorder (PTSD)
Korgaonkar 2013	18	11	118	12	TELS, age, hippocampal structure and volume
Mehta 2009	14	6	11	16	hippocampal volume, early severe deprivation amongst orphaned/ separated
Morey 2016	63	30	57	10	hippocampal volume, maltreatment, PTSD
Rao 2010	51	23	32	15	early-life adversity, morphologic changes in the hippocampus, and vulnerability to depressive disorder
Tupler 2006	61	31	122	12	Hippocampal volume and early age trauma/adversity
Veer 2015	12	0	12	27	Hippocampal Volume and shape; in PTSD Childhood Trauma

Descriptive Statistics

Heterogeneity. Heterogeneity was determined using statistical procedures outlined by Hedges and associates (1985, 1998) wherein the presence of heterogeneity was recognized if variance (t2) was greater than zero or where within-study variance (w2) was significant. The weight of each study was calculated by the inverse of its variance, the difference reflecting the within-studies variance plus the between-studies variance or tau-squared. *Figures* 6 and 7 display the basics statistics for each of the selected studies used in the final analysis.

Figure 6

Independent groups (means, SDs)

Study name	TELS Mean	TELS Std-Dev	TELS Sample size	CONTROL Mean	CONTROL Std-Dev	CONTROL Sample size
Carrion 2001	7.200	1.300	24	7.800	1.000	24
Chen 2010	5813.220	337.690	23	5914.550	307.130	32
De Bellis 2002	7.950	1.240	28	8.190	1.200	66
Korgaonkar 2013	8387.000	565.000	18	8557.000	867.000	118
Mehta 2009	4.720	0.410	14	5.630	0.560	11
Morey 2016*	7710.420	737.320	63	7758.100	672.510	57
Tupler 2006	8.200	1.120	61	8.200	1.040	122
Veer 2015	10293.120	703.130	12	10623.510	519.050	12

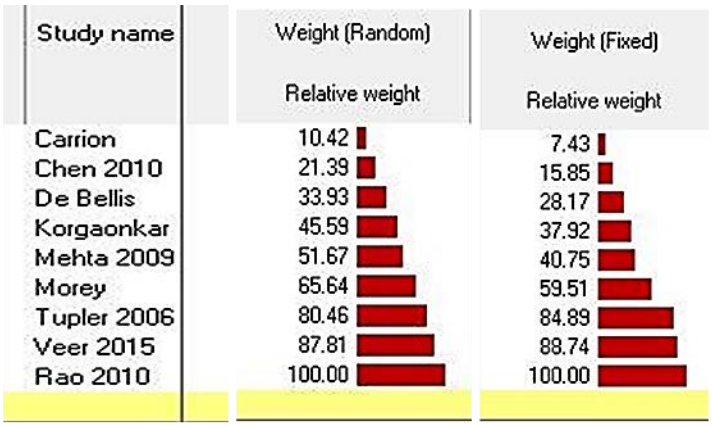
Figure 7
Independent groups (Sample size, p)

	TELS Sample	Control	Independent group P-value	Tails
Rao 2010	51	32	0.000	2

Relative weight. CMA calculated relative weights for the standard deviations in each study by adjusting the combined beta weights to sum 100. Through cumulative meta-analysis, the results are much more balanced through the use of relative weight and chronological summations, so that larger studies do not overshadow smaller ones.

Figure 8

Chart indicating relative weights of each study, fixed and random.



Effect size computations. The effect size was corrected for bias using Hedges' *g* and results recorded. In the computation, d is Cohen's standardized mean difference, J is the correction for bias, g is Hedges' standardized mean difference, and $N = n1 + n2$ for the total sample size. The program computed the standardized mean difference (*d*) and multiplied d by the correction factor (J) to compute *g*.

Data for left, right, and combined hippocampal volumetric measures were analyzed separately and as a total volume mass. Statistics from studies were entered using the means, standard deviation, and sample sizes of both TELS and control groups.

Cumulative meta-analysis data summary. Using a cumulative meta-analytical methodology, the effect size for all studies ranged from Hedges' *g* (- 0.295; -0.408) and Cohen's *d* (-0.296; -0.414) using fixed and random methods, respectively, reflecting a small to moderate according to Cohen's (1988) measurements for effect size. Effect sizes for individual studies range from Hedges *g* = 0.00 (95% CI [-31, .31]) to Hedges *g* = 1.89 (95% CI [=2.84, =.94]).

Rejection of the null hypothesis. Whereas the results of using either random or fixed methods reflected variances of significance in effect size measures within studies and as a cumulative measure, the cumulative analysis of *p* values ranged from *p* = .005 (random effects) to *p* < .001 (fixed effects). Lower *p* values are often interpreted as strength in the relationship between variables. Statistical significance in this meta-analysis suggests that it is unlikely that the null hypothesis is true.

Figure 9

Effect size using Hedges' g.

Model	Study name	Statistics for each study						
		Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Carrion	-0.509	0.289	0.083	-1.075	0.057	-1.763	0.078
	Chen 2010	-0.312	0.271	0.074	-0.843	0.219	-1.151	0.250
	De Bellis	-0.196	0.224	0.050	-0.636	0.243	-0.876	0.381
	Korgaonkar	-0.203	0.252	0.063	-0.696	0.291	-0.804	0.421
	Mehta 2009	-1.830	0.468	0.219	-2.746	-0.913	-3.912	0.000
	Morey	-0.067	0.182	0.033	-0.423	0.289	-0.369	0.712
	Tupler 2006	0.000	0.156	0.024	-0.306	0.306	0.000	1.000
	Veer 2015	-0.516	0.401	0.161	-1.302	0.270	-1.287	0.198
	Rao 2010	-0.915	0.234	0.055	-1.374	-0.455	-3.901	0.000
Fixed		-0.295	0.079	0.006	-0.449	-0.141	-3.752	0.000
Random		-0.408	0.145	0.021	-0.692	-0.125	-2.823	0.005

Figure 10

Standard difference in means Cohen's d.

Model	Study name	Statistics for each study						
		Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Carrion	-0.517	0.293	0.086	-1.093	0.058	-1.763	0.078
	Chen 2010	-0.316	0.275	0.076	-0.856	0.223	-1.151	0.250
	De Bellis	-0.198	0.226	0.051	-0.641	0.245	-0.876	0.381
	Korgaonkar	-0.204	0.253	0.064	-0.700	0.293	-0.804	0.421
	Mehta 2009	-1.892	0.484	0.234	-2.840	-0.944	-3.912	0.000
	Morey	-0.067	0.183	0.033	-0.426	0.291	-0.369	0.712
	Tupler 2006	0.000	0.157	0.025	-0.307	0.307	0.000	1.000
	Veer 2015	-0.535	0.415	0.173	-1.349	0.280	-1.287	0.198
	Rao 2010	-0.923	0.237	0.056	-1.387	-0.459	-3.901	0.000
Fixed		-0.296	0.079	0.006	-0.452	-0.140	-3.728	0.000
Random		-0.414	0.147	0.022	-0.702	-0.125	-2.814	0.005

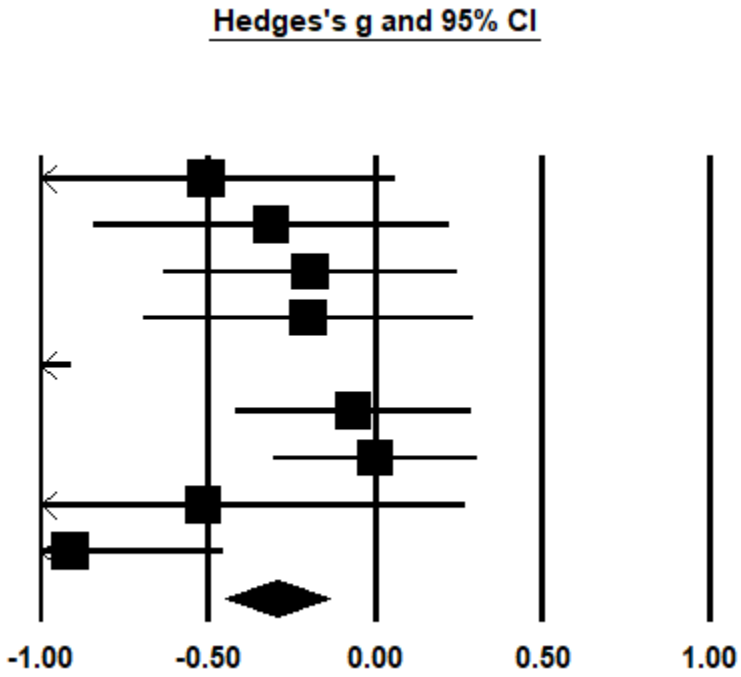
Figure 11

Correlation and 95% CI.

Model	Study name	Statistics for each study					-1.00
		Correlation	Lower limit	Upper limit	Z-Value	p-Value	
	Carrion	-0.250	-0.489	0.023	-1.801	0.072	
	Chen 2010	-0.154	-0.395	0.107	-1.160	0.246	
	De Bellis	-0.090	-0.284	0.111	-0.879	0.380	
	Korgaonkar	-0.069	-0.232	0.099	-0.805	0.421	
	Mehta 2009	-0.685	-0.828	-0.458	-4.786	0.000	
	Morey	-0.034	-0.209	0.144	-0.369	0.712	
	Tupler 2006	0.000	-0.144	0.144	0.000	1.000	
	Veer 2015	-0.258	-0.577	0.128	-1.317	0.188	
	Rao 2010	-0.410	-0.566	-0.226	-4.145	0.000	
Fixed		-0.147	-0.215	-0.078	-4.159	0.000	
Random		-0.205	-0.338	-0.064	-2.833	0.005	

Figure 12

Forest plot Hedges' g and 95% CI.



Publication Bias

Publication bias was examined using both Classic fail-safe N and Orwin's fail-safe N, computed by CMA. Publication bias requires examination in meta-analytic studies primarily because (a) not all studies are published; (b) studies that report relatively large treatment effects are more likely to be submitted and accepted which inherently contributes to bias; (c) and therefore, results from selected studies are more likely to overestimate the true effect size or treatment effects (Borenstein, 2009). The inclusion criteria would also automatically determine the type of studies that would be analyzed in this research.

Even with the rigorous measures used to identify appropriate studies, it is more than likely that studies were missed and that at the time of analysis, new studies were published. Failure to include missing studies results in obviously less data, wider confidence intervals, and less powerful tests, according to Borenstein (2009) although, he added that missing studies have no systemic impact on effect size unless they are systemically different from the ones chosen.

The degree of publication bias is represented below from calculations made with Egger's Regression Intercept and Classic fail-safe N, all computed by CMA. These statistics are presented below, along with a rationale for its use.

Egger's test of the intercept. Egger's test was used to estimate the asymmetry of data. Hence, two-tailed p-values above 0.03822 could be related to possible bias. P-values less than 0.05 implicates publication bias. Egger suggested that bias is assessed using precision, which is the inverse of the standard error, to predict the standardized

effect size (Rothstein, Sutton, & Borenstein, 2005). The size of the effect is reflected by the slope of the regression line, while bias is reflected by the intercept. In this particular equation, the size of the treatment effect is reflected by the slope of the regression line (B1), while bias is reflected by the intercept (B0). Hence, the intercept (B0) is -4.12927, 95% confidence interval (-7.33944, -0.91909), with $t = 3.04163$, $df = 7$. The 1-tailed p-value is 0.00940, and the 2-tailed p-value is 0.01880.

Table 2

Egger's test of the intercept

Intercept	-4.12927
Standard error	1.35758
95% lower limit (2-tailed)	-7.33944
95% upper limit (2-tailed)	-0.91909
t-value	3.04163
df	7.00000
P-value (1-tailed)	0.00940
P-value (t-tailed)	0.01880

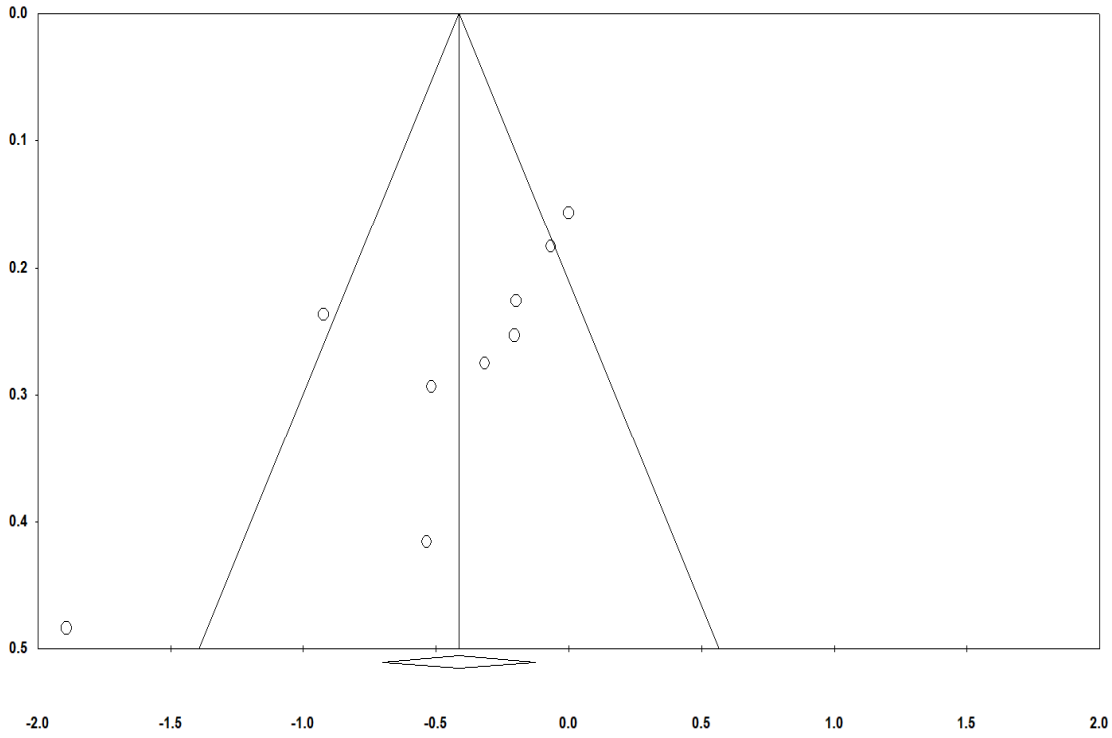
Rosenthal's fail-safe N. Rosenthal's fail-safe N calculates how many missing studies would be required before the p-value of the effect-size would become non-significant. This approach focuses on statistical significance rather than the number of missing studies required to produce a non-significant effect. There is also a belief that the mean effect size of all missing studies is zero. This assumption counterbalances the possibility of a mean effect is positive or negative. Additionally, classical fail-safe N is a useful method to combine all the p-values across studies that are based on a test of combined significance to determine if the estimate is small or true; large or false (Rosenthal, 1979). In the results presented below for fail-safe N, the number of studies required to bring the p-value to greater than alpha is 43. The p-value for observed studies computed at zero, rejecting the null hypothesis.

Table 3

Rosenthal's fail-safe N

Z-value for observed studies	-4.68735
P-value for observed studies	0.00000
Alpha	0.05000
Tails	2.00000
Z for alpha	1.95996
Number of observed studies	9.00000
*Number of missing studies to bring p-value to > alpha	43.00000

Figure 13
Funnel plot of standard error by standard difference of means



The funnel plot (figure 13) reflects the relationship between the standard error or precision on the vertical axis and the effect size on the horizontal axis. According to Borenstein (2009), larger studies will appear toward the top of the graph and cluster near the mean effect size while smaller studies hover toward the bottom of the graph and will disperse across a range of values. Sterne and Egger explained that although an effect size larger in small studies because of bias, it is also possible that the effect size is actually larger because of the use of different protocols or different populations (Sterne & Egger, 2001).

Post Hoc Analysis of Left and Right Hippocampal Changes

The left and right hippocampi have distinct roles and can be impacted differently according to functional and structural neuroimaging findings. The left side of the hippocampus encodes the verbal memory, and the right hippocampus encodes visual-spatial memories (Schmidt & Schachter, 2008). In the final post hoc analysis of this study, I examined differences in reported changes between left and right hippocampal regions in six of the pilot studies.

Figure 14

Left hippocampal changes

Model	Study name	Comparison	Statistics for each study						
			Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Chen 2010	Left Hipp	-0.312	0.271	0.074	-0.844	0.219	-1.151	0.250
	DeBellis	Left Hipp	-0.234	0.224	0.050	-0.674	0.206	-1.043	0.297
	Morey 2016	Left Hipp	-0.088	0.182	0.033	-0.444	0.268	-0.485	0.628
	Mehta 2009	Left Hipp	-1.000	0.414	0.172	-1.812	-0.188	-2.412	0.016
	Tupler 2006	Left Hipp	0.010	0.156	0.024	-0.297	0.316	0.061	0.951
	Veer 2015	Left Hipp	-0.220	0.395	0.156	-0.995	0.555	-0.555	0.579
Fixed			-0.157	0.092	0.009	-0.338	0.024	-1.701	0.089
Random			-0.175	0.104	0.011	-0.379	0.028	-1.686	0.092

Figure 15

Right hippocampal changes

Model	Study name	Comparison	Statistics for each study						
			Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Chen 2010	Right Hipp	0.018	0.269	0.073	-0.510	0.546	0.067	0.947
	DeBellis	Right Hipp	-0.110	0.224	0.050	-0.549	0.329	-0.492	0.622
	Morey 2016	Right Hipp	-0.039	0.182	0.033	-0.395	0.317	-0.214	0.831
	Mehta 2009	Right Hipp	-0.809	0.406	0.165	-1.604	-0.013	-1.991	0.046
	Tupler 2006	Right Hipp	-0.018	0.156	0.024	-0.324	0.288	-0.115	0.909
	Veer 2015	Right Hipp	-0.324	0.397	0.158	-1.102	0.454	-0.817	0.414
Fixed			-0.092	0.092	0.009	-0.273	0.089	-0.999	0.318
Random			-0.092	0.092	0.009	-0.273	0.089	-0.999	0.318

Except for the Mehta study, which determined statistical significance for both left and right hippocampal change, the CMA post hoc of remaining individual studies did not reflect statistical significance between left and right hippocampi. However, when comparing *p* values of left and right regions, it is data does reflect differences.

Several variables that researchers can identify as determinants to left and right functioning included duration, age, and severity of abuse. For example, using MRI in animal studies, Rahman (2016) concluded that volume loss in the right hippocampus was visible after long periods of chronic stress. By contrast, volume loss in the left hippocampus could be detected as early as three days and progressively following a ten-day chronic stress paradigm. Rahman reported that chronic stress could contribute to spatial memory impairment, the rates of deterioration varying over time (Rahman, Callaghan, Kerskens, Chattarji, & O'Mara, 2016).

Poverty and abandonment were consistently linked to adverse hippocampal development, notably smaller overall volumetric measures and smaller left hippocampal size (Butterworth et al., 2012; Duval et al., 2017; Hanson et al., 2014; Hodel et al., 2015; Lawson et al., 2017; Piccolo & Noble, 2017; Tottenham et al., 2010; Yu et al., 2017).

Summary of Results

In this chapter, the data collection and preliminary analysis were discussed, showing the process of study selection from empirical studies on TELS and hippocampal development over two years. Over 200 studies were reviewed for this meta-analysis; 22 met inclusion criteria for preliminary analysis. Of those 22, only nine empirical studies, conducted between 2001 and 2016, met the rigorous criteria for inclusion. The

researchers of the nine empirical studies used MRI scans to compare TELS participants with Non-TELS comparisons. They also administered a clinical assessment measure to determine intensity, type, and duration of abuse. The mean age of all groups was μ14.77 years, with a range of μ10 years to μ27 years. The total number of TELS participants equaled 294, and comparison group participants totaled 474. The number of male participants in the final studies totaled 129, and the numbers of non-White participants represented less than 7% of the total population of 768 participants. The ROI included the hippocampal region of both control (TELS) and comparison (Non-TELS) groups.

The purpose of this project was to examine the relationship between TELS and hippocampal volume and structure. The research question stated: "To what extent does TELS exposure impact the structure and volumetric measures of the hippocampus in the developing brain?" Analyses of data from fixed and random effects methods, in addition to cumulative meta-analysis computations, indicated associations between TELS and hippocampal volume and structure exist, thereby rejecting the null hypothesis.

Chapter 5 includes a summary of key findings, how results match with those of previous research efforts, and recommendations for future explorations into the complicated relationship between TELS and hippocampal development. Implications for social change are included, along with suggestions for continued research in the field of TELS and neuroanatomical development.

Chapter 5: Discussion

Introduction

This meta-analysis examined the influence of TELS on the hippocampus of the developing brain. Trauma is defined as sexual abuse, physical abuse, exposure to family violence, emotional neglect, physical neglect, poverty, abandonment, and psychological abuse. Early life experiences refer to limited childhood life experiences that occur between the ages of 0 and late adolescence.

In this study, I examined the relationship between TELS (IV) and hippocampal volume and structure (DVs) as measured through an MRI scan in developing brains using a meta-analytical approach, extracting data from 22 empirical studies, nine were selected for final analysis using the CMA program. The hippocampus was selected as the ROI as it is crucial in the functioning of memory and spatial relations. Determining the magnitude, strength, and direction of the correlation between TELS and hippocampal change supports the need for continued research in this arena. Additionally, the results could support the ongoing development of appropriate clinical assessment and treatment protocols.

In the selected studies, hippocampal volume and structure were measured through an MRI scan of developing brains. The effect size was analyzed against the MRI measures of demographically matched comparison group participants who were not exposed to TELS.

The morphology of the human brain, including size and shape, is crucial in understanding neurological diseases and dysfunction. Since the 1990s, the popularization

of high-resolution neuroimaging techniques has enabled researchers to focus on the subdivisions of the brain and the relationship between abnormal brain development and traumatic stress. For this research project, the hippocampus was selected for study because of its crucial role in social adaptation, memory, and learning, and because of its association with various types of psychiatric disorders and diseases. The null hypothesis assumes there was no correlation between TELS (IV) and aberrant morphological changes in the hippocampus of the developing brain. The alternative hypothesis suggests there is a relationship between TELs and aberrant morphological changes in the hippocampus of the developing brain. Analysis of nine pilot studies determined statistical significance, particularly when results were combined utilizing the cumulative meta-analytical approach, between TELS (IV) and hippocampal structure and volume (DVs), thereby rejecting the null hypothesis.

Covariates that were identified will be elaborated upon in this chapter to help the reader understand all the mitigating factors involved in this research, how these variables intersect with key findings, and why continued research into these issues is evident.

Chapter 5 summarizes the results of the research pilot studies. Implications for social change are included, along with suggestions for continued research in the field of TELS and neuroanatomical development.

Interpretation of Findings

Summary of Research Design

The studies under analysis were published between 2001 and 2016. The ROI included only the hippocampal region scanned through MRI of both control (TELS) and

comparison (No TELS) groups. All but one study included both control and demographically aged-matched comparison groups. All studies used both clinical assessment instruments and MRI scans to evaluate the relationship between the IV and DV variables. The total number of TELS participants included in the primary data analysis equaled 294; comparison group participants totaled 474. The number of male participants in the final studies totaled 129, and the numbers of non-White participants represented less than 7% of the total population of 768 participants. The mean age of all groups was μ14.77 years, with a range of μ10 years to μ27 years.

The purpose of this research was to determine if a relationship based on effect size could be established between the TELS and comparison groups, whereas effect size reflects the magnitude, strength, and direction. Cohen (1988) gave a guideline of 0.2 to reflect a small effect size, a medium effect size by 0.5, and a large effect size by 0.8. Analysis of data using fixed, random, and cumulative meta-analysis varied in the reports of effect size when applying Hedges' *g*, Cohen's *d*, and correlation values. Studies under analysis demonstrated significant variability with a negative slant reflecting the direction of the mean of the TELS group away from the mean of the comparison group. The data analysis also reflected effect sizes ranging from small to large in individual studies. The cumulative analysis of *p* values ranged from $p = .005$ (random effects) to $p < .001$ (fixed effects). The null hypothesis is unsubstantiated.

The most frequently reported stressors were typically generalized as child maltreatment. The term, *child maltreatment,* could encompass all forms of abuse including witnessing violence, sexual abuse, and separation and loss (Carrion et al., 2001;

Carrion et al., 2007; De Bellis et al., 2002; Everaerd et al., 2012, 2016; Korgaonkar et al., 2013; Morey, Haswell, Hooper, & Bellis, 2016; Piccolo & Noble, 2017). Sexual abuse presented as one of most severe forms of stress and was highly correlated with age at the time of onset and other factors like the relationship to caretaker and duration (Andersen et al., 2008; Carrion, Weems, & Reiss, 2007; De Bellis et al., 2002; Edmiston et al., 2011; Teicher, Anderson, & Polcari, 2012). Although sexual and physical abuse highly correlated with increased risk of depression (Hambrick et al., 2019; McEwen & Morrison, 2013), emotional maltreatment seemed to have a more substantial influence on negative self-concept and depressive symptoms (Edmiston et al., 2011). Researchers (Hanson et al., 2014; Hodel et al., 2014; Tottenham et al., 2010; Mehta et al., 2009,) also identified abandonment, which includes acts of separation from the birth family resulting in adoption, institutionalization, or foster care placement as a high-risk factor in abnormal hippocampal development. In fact, debilitation or mental illness of the primary caretaker (Chen, Hamilton, & Gotlib, 2010; Karten, Olariu, & Cameron, 2005; Walsh, Dalgleish, Lombardo, Dunn, Van Harmelan, Ban, et al., 2014), or parental death or chronic physical illness (Petchtel, Pia; Pizzagalli, 2011) can place a child at very high risk for aberrant brain development. Yu et al., 2017, and Hanson et al., 2014, reported differences in reductions in both left and right hippocampi in children with low SES.

Covariates frequently identified during analysis included gender (Everaerd, Gerritsen, Rijpkema, Frodl, Franke & Fernandez, et al., 2012); age (Korgaonkar et al., 2013; Mehta et al., 2009; Morey et al., 2016; Rao et al., 2010a; Andersen et al., 2008); adolescence as a sensitive period in the structural development of the hippocampus

(Morey, Haswell, Hooper, & De Bellis, 2016; Korgaonkar et al., 2013; Everaerd et al., 2012; Rao et al., 2010), genetic predisposition (Rao, 2010; Frodl, 2010; Everaerd et al., 2012), and duration of abuse (Perry, 2009; De Bellis et al., 2002).

Additionally, the severity of abuse and timing (relative to age & stage development) appears to be crucial factors when coupled with the variables of gender and type of abuse (Andersen et al., 2008; Korgaonkar et al., 2013.). Other confounding variables that were identified in the studies were multiplicity and relationship to the perpetrator (Andersen et al., 2008; Mehta 2009; Edmiston 2011; Hanson 2014; Everaerd 2016).

The final data analysis summary supports evidence that volume and structural hippocampal change correlates with age and the severity of abuse. How the hippocampal volume is influenced by covariables, such as gender and genetics, demands further investigation. Furthermore, some researchers believe that hippocampal volume cannot be detected before adolescence and others believed that the measure could not be adequately detected until early adulthood (De Bellis, 2002; Everaerd, 2016; also see Korgaonkar et al., 2013; Mehta et al., 2009; Morey, Haswell, Hooper, & Bellis, 2016; Rao et al., 2010). This particular variable requires further research.

The hippocampal structure appears to be significantly influenced by age and low SES, although the influence of the latter variable is not as evident. Further investigation into the relationship between low SES and hippocampal volume is warranted.

Table 4

Most frequently identified trauma types and covariates

Most frequently studied trauma type	Study	Area frequently associated with trauma
Child Maltreatment	Carrion 2007; De Bellis 2002; Edmiston 2011; Everaerd 2012; Everaerd 2016; Hanson 2014; Morey 2016; Piccola 2017; Rao 2010; Teicher 2012; Tupler 2006; Veer 2015; Walsh, 2014	hippocampal volume
Abandonment/Orphanage Institutionalization	Hanson 2014; Hoedel 2014; Mehta 2009; Tottenham 2010	hippocampal volume
Emotional Neglect	Edmiston 2011	hippocampal volume
Emotional Abuse	Edmiston 2011	hippocampal volume
Physical Abuse	Edmiston 2011; Hanson 2014	hippocampal volume
Physical Neglect	Edmiston 2011, Hanson 2014	hippocampal volume
Sexual Abuse	Edmiston 2011; Andersen 2008; Carrion 2007; Teicher 2012; De Bellis 2002	hippocampal volume
Chronic Illness of Primary Caretaker	Chen 2010	hippocampal volume
Low SES[4]	Yu 2017; Hanson 2014	hippocampal volume hippocampal structure
Covariate: Age of Onset	Andersen 2008; Carrion 2007; De Bellis 2002; Walsh 2014; Whittle 2017	hippocampal structure and hippocampal volume
Covariate: Age Adolescent	Korgaonkar 2013	hippocampal structure
Covariate: Gender	Everaerd 2012; de Bellis 2002; Edmiston 2011; Whittle 2017	hippocampal volume
Covariate: Genetic Propensity	Chen 2010; Everaerd 2012	hippocampal volume
Covariate: Duration of Abuse	Andersen 2008	hippocampal volume

Theoretical Synergy Revisited

The concept of traumatic stress as an etiological variable of psychiatric and physical illness is primarily rooted in the early works of 19th-century French neurologist, Charcot and Selye's (1950, 1976) theories of GAS and LAS. These early theories are the catalytic agents to current efforts of neurobiological researchers who seek to unravel how neuropsychiatric disease differentially affects the biochemical functions and structure of various parts of the brain (Bremner, 2002; O'Neill et al., 2013; Wisse et al., 2012). Charcot's ideologies developed the concepts we now refer to as trauma theory, in which Charcot suggested that many psychological disturbances had links to physiological trauma. Selye's (1950, 1976) theories of GAS and LAS provided the catalyst that moved research on traumatic stress from the psychological to the neurobiological arena. Selye (1950, 1976) proposed that living organisms had the innate ability to adapt to changes in their surroundings.

Several of the empirical studies selected for the final analysis included studies conducted by contemporary neuroscientists Anderson (2008), Carrion (2007), and Teicher (2012). The results of this research support their earlier findings.

Limitations of the Study

Study Sample

In a data search that spanned over two years, over 200 studies were identified for review, yet only 22 met the inclusion criteria for preliminary analysis. From this pool, nine empirical studies, conducted between 2001 and 2016, met the rigorous criteria for

final analysis. It has been stated earlier in this discourse that statistical power for meta-analytical studies can substantiate with five empirical studies (Jackson & Turner, 2017).

Lack of Consensus in Definition

Definitions of hippocampal structure and volume were not clearly defined, and what definitions existed seem to vary on the exactness of terminology. Interpretations may be due to variations in interpretations of boundaries or an MRI scan and neuroanatomical tracing techniques. These differences could impact reliability when measurements are compared.

Publication Bias

Interpreting results is dependent on the quality of the integrated studies. If one study is significantly biased, the entire meta-analysis will carry that bias. Other issues, such as the use of studies that only report positive results, can reduce the effectiveness of any research.

Standardization

Although research is demonstrating that TELS impacts the actual structure, volume, and subsequent functions of the brain, the published results seem to lack cohesiveness or standardized investigative procedures, which may prevent a clear consensus of results.

Recommendations

The following recommendations are made based on the experience of gathering information and conducting data analysis:

1. Further research is required to identify the processes that link levels of vulnerability to age and timing of insult;
2. Further investigation is also necessary to understand how gender and genetic biomarkers relate to or create vulnerability;
3. More research is needed to investigate the links between low SES and hippocampal functioning;
4. The contributions made through trauma-brain research can progress significantly with the development of a unified language and coding system that clearly and systematically defines traumatic stress and its biomarkers;
5. Additionally, the field will significantly benefit in developing standardized research protocols.

Implications

As accurate, evidence-based research is made available, this information must then be quickly dispersed to the individuals, organizations, and systems that can affect positive social change through early identification, intervention, and treatment. Policymakers, educators, pediatricians, and those who serve this vulnerable population need current information to expand their knowledge-base and enhance awareness of the neurobiological implications of exposure to trauma and its impact on the brain.

Developing a deeper understanding of the relationship between all variables can further the development of clinical interventions that sustain brain and psychological health or possibly even reverse the damage. As referenced earlier, Perry (2009) argued that when clinical interventions are explicitly linked to the area where dysregulation

originated, in this instance, to the injured area of the hippocampus, treatment would be in alignment with the stages of neuronal development and interventions would become more precisely attuned.

Conclusions

Social and Psychological Significance

Each time a child experiences a severe occurrence of physical, emotional, or psychological trauma, the risks of long-term adverse consequences increase exponentially. Current statistics regarding early trauma state that over 38% of children in the United States will witness or experience a traumatic event (Centers for Disease Control and Prevention [CDC], 2019). Also, children exposed to five or more significant adverse experiences in the first three years of life face a 76% likelihood of having one or more delays in their language, emotional, or brain development (Vervoort-Schel et al., 2018). These consequences include cognitive, psychiatric, and sociological disabilities, which may compromise the individual's ability to thrive and live happily.

I designed this research study to determine if an effect size between TELS and hippocampal development identified. These efforts aim to make a meaningful contribution to the current knowledge base of this complicated subject. During the analysis of data, it became increasingly apparent that the type and severity of stressor, in combination with factors such as age and duration, significantly contribute to the potential damage in the developing brain. Other questions arose from the exploration into this area. For example, how does the individual's perception of stress influence the experience and subsequent reactions? Which variables enhance resiliency and protection

during brain development? Also, how do the relevant experiences of social isolation produced by acts of discrimination or exclusion impact brain development? More information regarding genetic propensity and risks due to the influence of gender, or at least learned gender roles, is also required.

This chapter provided a summary and interpretation of the results of this meta-analysis. From a neurobiological perspective, understanding the pathways that could lead to biological and psychological dysregulation could further future efforts in the development of early intervention and treatment protocols for young children and adolescents who are deemed high-risk. Demonstrating that an effect size is evident between TELS and hippocampal morphology supports the need for continued efforts to decode the complicated interactions between the brain and trauma. The results of this study can contribute to the knowledge base regarding the psychological and neurobiological factors that create the highest risks for aberrant hippocampal development.

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Appendix: Excluded Studies

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