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The Chicken or the Egg: A Proposed Longitudinal Study on Post-Traumatic Stress Disorder and Memory Impairment

Hominy Tara McMahon
Bard College, hm1795@bard.edu

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The Chicken or the Egg:
A Proposed Longitudinal Study on Post-Traumatic Stress Disorder and Memory Impairment

Senior Project Submitted to
The Division of Science, Math, and Computing
of Bard College

By
Hominy McMahon

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# Abstract

## Introduction

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Abstract

Background: After experiencing trauma, some people go on to develop PTSD while others do not. Resilience and response to treatment also differ depending on the individual. To date, little research has been done to narrow down the reasons for these differences. Therefore, the main goal of this proposed 3-year longitudinal study of PTSD is to better understand the temporal relationship between the development of PTSD and structural changes in the hippocampus. Since PTSD is a costly disorder and disproportionately affects those serving in the military, this study may help determine better prevention tactics and treatment plans for those entering the military in active combat as well as the general population.

Method: Structural MRI scans of 300 randomly chosen active-combat soldiers at baseline, 1yr, 2yr, and 3yr periods will be used in conjunction with clinical assessments on PTSD and symptom severity carried out by a group of 30 licensed clinicians.

Predicted Results: My first hypothesis is that participants with greater PTSD symptom severity and a PTSD diagnosis will experience a greater difference in hippocampal volume. My second hypothesis is that smaller baseline hippocampal size will predict higher symptom severity and PTSD diagnosis.

Conclusions: Should our results support these hypotheses, this will have implications for the treatment of PTSD as well as provide more clarity to its development and effects on important brain structures related to memory and cognitive impairment. It may become a lot easier with studies like this one to get closer to understanding how and why PTSD develops.
As any person knows, life is full of stressful situations. Stress can arise from external conflicts, such as losing a credit card, slipping on black ice, or stubbing your toe as, well as internal conflicts, like the emotional turmoil of being left on read or the embarrassment of waving back to somebody who was not waving at you. Stress is a normal part of life and not necessarily a bad thing, however. Balance is the key to any functioning system. Depending on the frequency and severity, a buildup of stressful situations can affect the mental, emotional, and physical state of an individual and lead to potential long-term health issues.

The Brain and Stress

Certain regions of the body play major roles in how people respond and react to stress. The Hypothalamic-Pituitary-Adrenal (HPA) axis functions as the body’s stress response and is responsible for acclimating the body to handle stressful situations (de Souza-Talarico et al., 2011). For example, spotting a snake in the grass is a stressful event which would trigger an individual’s stress response. During this process, the HPA axis releases glucocorticoids (GCs) such as cortisol from the adrenal gland to spread to other areas of the brain and body. These glucocorticoids contains lots of receptors in the pituitary gland, hypothalamus, and hippocampus (Starkman et al., 1992). Cortisol plays a lot of important roles in the body. It acts as a messenger and is crucial for the body’s return to homeostasis as it crosses the blood-brain-barrier and binds to the pituitary gland and hypothalamus to initiate a negative feedback loop in order to regulate cortisol levels in the body.

This negative feedback loop —hence its name — communicates to the body that the stressor has been dealt with and that the response can shut off. Due to cortisol’s ability to cross
the blood-brain-barrier, it can make its way directly to the nuclei of cells and activate receptor genes, meaning that heightened or diminished levels of cortisol in the body can have lasting effects on genes which influence an individual’s physical, emotional, and mental presentation. Imbalanced cortisol levels can lead to potentially lifelong effects such as greater risk for developing certain types of disorders and illnesses such as Cushings disease (Kim et al, 2016).

**Acute versus Chronic Stress**

The positive and negative effects of stress on the body depend on factors such as extremity, frequency, and duration of the stress response. Short-term stress, also referred to as “acute” stress, is stress which is dealt with for a short period of time. Whether it be a daily life stressor like running late for work or preparing for a presentation, the duration to which this stress affects and remains in the body is not prolonged and eventually homeostasis is once again reached. With a normally functioning HPA axis, recovery follows a typical trajectory. Stress may build up in anticipation but after the stressor disappears and there is no longer something to anticipate or worry about, the stress levels of the individual should return to normal. Other examples of acute stress include anticipation for an upcoming exam, a fight with a loved one, or public speaking. In most cases, these are temporary conflicts which can be reconciled.

Chronic stress, or long-term stress, is stress which is persistent and remains constant past a typical duration of time. Someone dealing with chronic stress may experience physical symptoms such as headaches, fatigue, or emotional and mental symptoms of anxiety, depression, and general irritation. The effects of prolonged or chronic stress can even persist for so long that the initial stressor isn’t obvious or recognizable. Our bodies react to stressful situations in many ways which can go unnoticed or untreated. In the case of trauma, even a single stressful event
can impact an individual for months, years, or a lifetime. By the time another stressor or traumatic event is realized, there may already be significant differences in one’s way of functioning and experiencing the world.

Imbalanced levels of cortisol in the body, which may be caused by a dysfunctional HPA axis, is a factor which has become associated with cognitive functioning variability. An overreactive stress response can lead to continuing production of cortisol. Heightened levels of cortisol in the body and hippocampus due to allostatic load or chronic stress create an environment which hosts neurotoxicity (de Souza-Talarico et al., 2011). Neurotoxicity is when the normal activity of the nervous system is disrupted or altered due to cell atrophy or death, leading to the halting of neurogenesis and plasticity. These processes are crucial for the brain’s resilience from damage and creating new neurons to replace those that are lost. Serious consequences of neurotoxicity are not entirely irreversible, but time is of the essence. Studies have shown that damage to the brain caused by neurotoxicity can be reversed with therapy and other recovery methods (Feder et al., 2009). Resilience to stress can also be built up with different strategies such as increased social contact, cognitive reappraisal, and physical exercise.

A common assumption, which was quite prevalent in early research on stress disorders, was that higher levels of cortisol were to blame for relevant physical and cognitive abnormalities.

Up until recently, a large majority of non-human and human studies supported this narrative that stress disorders were associated with excessive levels of cortisol. Some theories have suggested that different types of trauma, such as bodily harm versus social harm, can display different patterns of HPA axis activity, leading to different outcomes for cortisol production. Evidence from a meta-analysis in 2007 revealed a trend of chronic stress accompanied by a lower production of cortisol in the mornings and increased levels of cortisol
throughout the rest of the day (Miller et al., 2007). Overall, individuals dealing with chronic stress still had high levels of hormone secretion, but the appearance of a flatter diurnal slope (Miller et al., 2007). Serious stress-related conditions such as chronic fatigue syndrome, Addison’s disease, and Post-Traumatic Stress Disorder have all been linked to lower than average rates of cortisol in the body (Miller et al., 2007).

**PTSD**

Post-Traumatic Stress Disorder (PTSD) is a disorder which can be diagnosed when a person has experienced a traumatic event and has subsequent difficulty functioning in daily life. PTSD is characterized by symptoms such as flashbacks, intrusive thoughts, and severe anxiety related to the trauma endured. Even proximity to something similar or reminiscent of an individual’s trauma can evoke a stress response in the body. An individual with PTSD may even appear to close friends and families as a changed person, feeling that the world and their relationships aren’t “safe” spaces anymore. Based on prevalence estimates analyzed in 2017 and from the Census Bureau in 2018, between two to six percent of people in the United States will develop PTSD and that percentage more than doubles for military veterans (Davis et al., 2022).

The type of trauma experienced can also influence the severity and duration of PTSD. Due to their increased chance of exposure to combat trauma, military personnel, especially those in active combat, are at an elevated risk for developing PTSD (Hoge et al., 2004).

Even within the military, differences in PTSD incidence and prevalence may result from location and duration of deployment, training, and rank (Wittchen et al., 2012). Active combat brings the risk of experiencing physical, emotional, and mental trauma with the threat of death or serious injury, knowledge that one may have to inflict harm on others, and likely rough living conditions. A study following 1,599 soldiers a year after deployment to Afghanistan in 2012
found that 49.2% of them experienced at least one traumatic event with 13% experiencing as many as three events (Wittchen et al., 2012). Approximately 2.9% of the soldiers, 46 of the 1,599 deployed, developed PTSD, though only half of them sought treatment. As expected, prevalence of PTSD was highest within combat units. The results of this study reflect a grim reality: only one in every two soldiers diagnosed with PTSD may actively seek help for their disorder.

Reasons to avoid seeking treatment for symptoms could be based in a number of factors such as cultural beliefs, societal expectations, convenience, isolation and more. A study conducted by Hoge et al. in 2004 with the objective of assessing soldiers’ mental health and informing treatment policy found that soldiers who reached criteria for PTSD after deployment reported stigmatization and other barriers as preventing them from accessing and receiving mental health services. Even though this study was conducted almost two decades ago, the rate of soldiers seeking treatment almost eight years later reflects a continuing problem with mental health engagement in the military (Wittchen et al., 2012).

Differences in PTSD prevalence, cause, and treatment also differ across gender lines. Women veterans report the highest rates of lifetime and past-year PTSD compared to male veterans and civilians of both genders. They were also the most likely group to report instances of childhood abuse, sexual assault, and domestic violence (Lehavot et al., 2018). Women also have far less representation in the military than men, making up a miniscule 17.3% of all active-duty soldiers in 2021 (Department of Defense Releases Annual Demographics Report — Upward Trend in Number of Women Serving Continues, 2022). Although they make up a minority of soldiers and report more instances of PTSD, women veterans are also more likely to seek treatment for their symptoms (Wittchen et al., 2012). It’s possible that studies recruiting
veterans may report lower numbers of PTSD acquisition among women as a result of treatment effects, especially if veteran studies are conducted years after retirement from the military.

It is also the case that much of the research which has been focused on military personnel has recruited majority male soldiers and veterans for studies. One pilot study with the aim of controlling for comorbidity with PTSD and hippocampal damage conducted in 2003 recruited only eight veterans – all of which were male – (Hedges et al., 2003).

**Consequences of PTSD**

The consequences of PTSD extend beyond the more visible short-term health issues it creates. Other health issues which develop from chronic stress often have long-term effects on wellbeing, personal relationships, and even susceptibility for other disorders and illnesses such as depression and anxiety (Smith et al., 2016). In their personal lives, those with PTSD may find it challenging to foster current relationships or even develop new ones (Renaud, 2008). Re-experiencing trauma can feel alienating and create distance between oneself and others. It is a common experience of trauma survivors to feel like changed people, experiencing difficulty fitting back into the shoes of who their loved ones knew them to be (Signs of PTSD in Military Service Members, 2023).

Even when they are recognized, these mental and emotional hurdles can be extremely difficult to overcome, as every case of PTSD will require its own treatment plan. It can also be very challenging as an individual struggling with PTSD to understand the symptoms they may be experiencing due to probable overlap with other disorders. Many of the symptoms of PTSD coincide with those of depression, such as a loss of interest in things once previously enjoyed, difficulty concentrating, and difficulty sleeping. The symptoms themselves also act as
impediments to recovery. Someone diagnosed with PTSD may deal with comorbidity such as depression and anxiety, leading to low self-esteem, anxious attachments to the people around them, or isolation tendencies (Renaud, 2008).

While the personal cost of having PTSD is incalculable, the cost of treatment and maintenance is a heavy reminder. In 2018, the cost of treating PTSD in the United States alone was $232.2 billion dollars. Further, the average cost for individuals with PTSD was $18,640 and $25,684 respectively for civilian and military populations (Davis et al., 2022). Even though there are far more civilians diagnosed with PTSD than those in the military, the prevalence of PTSD is much higher among the military population. This is a testament to the prevalence of PTSD in specific at-risk communities. In addition to these direct costs, there are also many indirect costs associated with PTSD. These include unemployment, productivity loss at work, caregiving, and premature mortality (Davis et al., 2022). Those with PTSD are also more likely to develop substance abuse disorders such as alcoholism to cope with their symptoms (Hedges et al., 2003).

These current cost and diagnoses estimates are also very likely an underestimation of the actual scope and cost of PTSD. There is growing concern that due to recent traumatic world events such as mounting effects of climate change and COVID-19, the prevalence of PTSD may increase. There has already been a documented influx of diagnoses for other disorders such as anxiety and depression in concurrence with the timeline of COVID-19 and policies of social isolation. In a study from 2022, researchers Hornstein and Eisenberger found that feelings of disconnection from others as well as levels of daily threat caused by COVID-19 impaired underlying mechanisms of extinguishing fear. Loneliness and social isolation are thought to augment the way in which individuals identify and react to threatening or fearful environments,
with social isolation even being noted as a risk factor for developing trauma (Hornstein & Eisenberger, 2022).

Understanding these possible risk factors for PTSD development as well as the disorder’s impact on long-term health is imperative for determining the best methods for prevention and treatment. PTSD doesn’t only affect the emotional, societal, and economic wellbeing of those diagnosed with it. The impact of excessive stress on the brain can also lead to serious long-term health issues.

**Structural Changes to the Brain in PTSD**

A large amount of literature looking into PTSD has focused on its relationship to structural changes which occur in the brains of those diagnosed and their implications for impairment to cognitive functioning. Specifically, several studies have noted a relationship between reductions in certain brain regions like the hippocampus and PTSD (Bonne et al., 2001; Chao et al., 2014; Acheson et al., 2012). The hippocampus is known for the role it plays in regulating the encoding, maintenance, and retrieval of short-term, long-term, explicit, and declarative memory. Any damage or reduction to this region can result in memory deficits and hinder general functioning (Acheson et al., 2012).

It is chronic PTSD which is often associated with detriment to cognitive function such as memory impairment. PTSD is defined as “chronic” when it lasts for longer than 3 months. In a longitudinal study looking at hippocampal volume and PTSD, participants were scanned for structural damage to the hippocampus one week and six months after experiencing a traumatic event (Bonne et al., 2001). No significant differences were found, suggesting that a longer duration of PTSD is necessary to observe any actual structural changes in the brain (Bonne et al.,
In another study looking at current and chronic PTSD, researchers utilized a much larger range for PTSD duration from six to thirty-six years. They found a significant difference in right hippocampal volume and PTSD duration. However, the recruited participants were not excluded from the study on the basis of comorbidities such as depression or taking medication, meaning that any observed atrophy of the right hippocampus could be attributed to those factors as well (Chao et al., 2014).

Since stress has physical effects on the body, it has been hypothesized that prolonged stress can lead to visible differences in size and functionality of certain parts of the brain, emphasizing the importance of a functioning stress response system (de Souza-Talarico et al., 2011). Some of the crucial brain structures involved in the HPA axis stress response are the hippocampus, the amygdala, and the hypothalamus, all of which belong to the central nervous system.

The central nervous system is made up of grey matter and white matter. Grey matter makes up the outer layer of the brain and plays a crucial role in our daily functioning. It also extends down through the inside of the spinal cord while white matter surrounds the outside of the spinal cord. Grey matter gets its name and color from the large concentration of neuronal bodies that make it up. It also contains the majority of neuron somas, or the cell bodies that house the nuclei of these cells. Large concentrations of grey matter are known as cortexes, the largest two being the cerebral and cerebellar cortices. Grey matter communicates and processes large amounts of information throughout the body with axon signaling found in white matter. It is crucial for movement, memory, and emotions. Damage to the grey matter in the brain due to neurotoxicity and other factors can lead to decreased cognitive as well as motor function (Mercadante & Tadi, 2022).
The Hippocampus

The hippocampus is a pivotal brain structure for memory encoding, storage, and retrieval, marking any individual with PTSD at risk for serious memory impairment. The hippocampus is made up of grey matter tissue, almost like a folding up of the cerebral cortex itself. There are three main parts of the hippocampus structure: the dentate gyrus, the hippocampus proper, and the subiculum. The subiculum acts as a bridge that connects the dentate gyrus and hippocampus proper.

Figure 1. The diagram displays the different regions of the hippocampus. More current studies on the relationship between PTSD and hippocampal size have started to shift towards focusing on specific subregions.

While I have not proposed to do so in the current study, many current studies on PTSD and hippocampal damage have narrowed their focus to specific subregions rather than the entire hippocampus to try and pinpoint areas of interest.
The hippocampus can also be stimulated by activity in nearby regions also associated with memory such as the amygdala and hypothalamus. As reviewed by Fogwe et al., the hypothalamus, as mentioned previously, instigates the stress response in the body. From a survival standpoint, the hippocampus helps an individual to remember what is safe, what is dangerous, and encode that information into long-term memory for later use (Fogwe et al., 2022).

In the case of PTSD, an individual who has experienced a traumatic event may be reminded of their trauma and face trouble functioning in daily life as a result. Just like stress, memory functions as a bit of a double-edged sword. Encountering stimuli reminiscent of their trauma can force those with PTSD to relive it through flashbacks. Their hippocampus and amygdala can begin to code various stimuli as threatening even when no danger is present. Conversely, they may also find themselves forgetting large pockets of time surrounding their trauma. When the body undergoes chronic stress as a result of PTSD or otherwise, the resulting neurotoxicity can lead to hippocampal impairment as a result of the loss of neuronal cells and synapses (Fogwe et al., 2022).

Hippocampal impairment is present in disorders such as Alzheimer's disease and Dementia. Individuals with Alzheimer's struggle with decision-making, lose track of dates and time, find it difficult to maintain conversations as well as frequently misplace items. (Memory, Forgetfulness, and Aging: What’s Normal and What’s Not, 2020). It's also well-known that those with Dementia can have difficulty recognizing family members or remembering details about their own life.
**Vulnerability vs. Acquisition**

While the hippocampus has been associated with PTSD, the exact relationship between the two is a source of contention for researchers. There is plenty of evidence to suggest that hippocampal volume is inversely related to PTSD duration (Chao et al., 2014; Acheson et al., 2012). What is unknown is whether this relationship is due to pre-existing conditions or a direct result of mechanisms underlying PTSD itself. Some researchers posit that an accumulation of trauma exposure can create a neurotoxic environment in the brain (Kolassa & Elbert, 2007). A neurotoxic environment of chronic exposure to glucocorticoids such as cortisol and excessive glutamate leads to cell atrophy or death, inhibition of neurogenesis, and potentially, reduced hippocampal volume. In their study from 2001, Bonne et al. presented an image of the differences between the hippocampi of a participant with PTSD versus a control. The term “normal” was used to refer to the brain of the individual without PTSD, however a more correct and appropriate description would be “typical”.

![Image](image.png)

**Figure 2.** This image presents the coronal plane of participants with a “typical” hippocampal structure and size compared to a participant with PTSD. The hippocampi of the individual with PTSD can be seen to have a different overall shape and size than that of the “typical” individual’s.
In their study from 2014, Chao et al. looked at 55 combat veterans with current and chronic PTSD to study neurotoxic effects over time, finding a significant correlation between PTSD duration and reduced right hippocampal volume. These results remained even after accounting for comorbidities such as early life trauma, current major depression, psychotropic medication, and history of substance abuse. Even though this study provides support for the relationship between decreased hippocampal volume and PTSD duration, it fails to determine whether or not these results are due to cell atrophy and neurotoxicity or genetic predisposition for PTSD, such as a smaller hippocampus at birth. It is possible that the participants with smaller hippocampal volume already had these structural differences which would put them at risk for developing persistent PTSD.

This is the foundational question behind what is known as the Vulnerability versus Acquisition theory. Examined by Acheson et al., the vulnerability hypothesis posits that pre-existing conditions — whether that be smaller brain size, gene expressions such as polymorphisms, or something else entirely — increase an individual’s risk for developing PTSD after trauma exposure, even affecting the symptom severity and duration of the disorder experienced (2012). In contrast, the acquisition hypothesis is rooted in the idea that harmful mechanisms related to severe stress such as neurotoxicity are responsible for changes to an individual’s brain structure.

Since it isn’t ethical to expose human participants to trauma in order to study both a baseline and post-exposure scan of the brain, many researchers interested in PTSD have utilized non-human animal subjects instead. In a study from 2015, a team of researchers set out to study changes to brain extracellular norepinephrine (NE) and free corticosterone (CORT) levels in mouse model PTSD and their relationship to retention of fear memory and hyperarousal. Kao et
al. found that one day after exposure to foot shock (FS) trauma, NE and CORT levels in the medial prefrontal cortex (mPFC) predicted arousal, while NE and CORT levels in the hippocampus predicted contextual fear (CF). In most cases, NE and CORT levels also predicted long-term FS outcomes with strong time- and structure-dependency, although levels from the first day were not informative likely due to underlying mechanisms of plasticity. Even though these results specifically relate to PTSD in mice, they offer potential avenues for instilling preventative measures against PTSD. If cortisol and norepinephrine levels in humans could be used to reliably predict distinct PTSD outcomes such as severity and likely duration, it would be easier to create a system which allocates resources to those in immediate need.

Non-human animal research doesn’t require the same levels of ethical application as research with human participants and, therefore, trauma can actually be induced. Some common physical and social methods for inducing trauma, specifically with rodents, include early separation from mothers, single-prolonged stress, restraint stress, housing instability, social instability, social defeat, and controlled shocks over long periods of time (Borghans & Homberg, 2015). Researchers can even implant probes to measure corticosterone levels throughout longitudinal studies rather than being limited to specific internals of time. Even though there are obvious differences between the brains of rodents and humans, non-human animal research allows for inferences as to the underlying mechanisms which would be unethical to measure directly in humans.

Most of the human research on stress-related structural changes to the brain to date has focused on trauma-exposed individuals who have already experienced a traumatic event or been diagnosed with PTSD. One of the caveats to this approach is that it is impossible to determine whether or not an observed structural difference, such as a smaller hippocampus, was
pre-existing. Outside of risk factors and predictors, it is impossible to know which individuals will develop PTSD, especially if researchers aren’t focusing on a specific population known to be at risk for developing the disorder. Locating participants quickly after they’ve experienced traumatic events is one method which has been used, though there is evidence to suggest that changes to the brain induced by trauma can take as little as two days to take effect (Yawen et al., 2013). A study from 2013 aimed at identifying predictors for PTSD development, specifically chronic PTSD, found that decreased fractional anisotropy (FA) within two days of trauma exposure reliably predicted greater future Clinician-Administered PTSD Scale (CAPS) scores (Yawen et al., 2013). The impact of trauma-related stress on the brain could be taking effect in an incredibly small window of time. The study suggests that methods of gathering participants post-trauma exposure may be inefficient for gathering a holistic view of trauma’s effects on the brain. It should be noted that the participants in this study were recruited from the Emergency Department of Ren Ji Hospital after involvement in traffic accidents in which their lives were likely at risk (Yawen et al., 2013). Whether or not changes to white matter in the brain would result after exposure to less severe trauma would require further research and also be more difficult to carry out in terms of recruitment.

**Current Proposal**

In order to better understand the effects of PTSD on brain structure differences, it is imperative to collect data from participants before and after trauma exposure. My proposal will respect the ethical protocols in place by recruiting active duty soldiers in combat units as they are a population well-known to be at-risk for trauma exposure and PTSD. They would not be exposed to any level of trauma or risk outside of what they would be normally expected to experience in their career path.
All participants will complete three structural MRI scans over the course of three years, the first of which will be carried out shortly after the participant is designated for deployment to active combat to serve as a baseline scan. Based on my current understanding of pre-disposition and acquisition stances, I’m hypothesizing that participants who experience more severe symptoms of PTSD will also experience a significant reduction of hippocampal volume. I am also hypothesizing that hippocampal size at baseline will predict the severity of symptoms experienced.

Method

Participants

For the purposes of running a longitudinal study and considering the likelihood of attrition and the sensitivity of the disorder of focus, this study will recruit approximately 300 active duty soldiers from the base of Fort Drum. This base is located in Jefferson County, New York, and relatively close to Carthage Area Hospital which contains an MRI scanner and would not be an unreasonable distance to transport soldiers to and from their scanning appointments. Fort Drum contains 15,000 active duty soldiers, 3,700 civilian personnel, and 15,000 family members living either on post or in the local area. The actual selection of the soldiers for the study would be carried out randomly by the military personnel in charge of that fort to avoid any potential bias. Since this study would be interested in differences between a subject’s initial and final scores for both PTSD symptomology and hippocampal volume, participants who do not develop PTSD over the course of the study can be used as controls against those who do develop
PTSD. The same logic applies for any exploratory analyses focused on differences within gender or other demographic variables.

The assessment of any pre-existing conditions that could have an effect on brain structure and development such as depression, anxiety, schizophrenia, bipolar, and alcoholism would require exclusion from the study and would be carried out by a group of approximately 10 licensed clinicians. The assessments would include a demographic questionnaire (see Appendix G), the BDI (Beck Depression Inventory) (see Appendix H), a structured interview based on the DSM-V for all relevant criteria of previously mentioned disorders and illnesses such as anxiety, depression, and Bipolar Disorder (see Appendix F), as well as the CAPS-5 (Clinician-Administered PTSD Scale) for PTSD symptom severity (see Appendix E). The CAPS-5 will be used to assess the PTSD symptom severity of the participants, splitting them up into three levels of “Low (0-10)”, “Medium (10-20)”, and “High (20-40)”. These scores are based on the newest version of the CAPS-5 which has a score of up to 40 points that encompasses both severity and frequency of symptoms. The CAPS-5 will also be used to diagnose participants for PTSD. A diagnosis of pre-existing PTSD at baseline would also be grounds for exclusion from the study. Since this study’s aim is to deliberate between pre- and post-PTSD, it is imperative that participants have not experienced levels of stress which could already have an impact on their brain composition.

Exclusion criteria for this study would also include those diagnosed with claustrophobia and any internally-deposited ferrous metals such as pacemakers or chips. These criteria are included for the personal safety of participants in the study as ferrous metals can be shifted or moved towards an MRI scanner due to its use of magnetization. MRI scanners don’t typically have great enough static field strengths to cause any long-term health effects such as raised blood
pressure in response to the magnetohydrodynamic forces, but there have been fatalities as a result of ferrous metals. In the event of being shot or in proximity to an explosion, shrapnel is also a relevant concern for military soldiers in an MRI scanner. If participants do have shrapnel located in their bodies throughout the course of the study they can still be interviewed and assessed for PTSD symptoms. Combat exposure which leads to embedding of shrapnel or other metal material will also likely decrease the overall number of eligible participants over the course of the study.

Participants would also be warned about potential factors of the MRI scanning procedure which could induce stress or anxiety such as loud noises during the imaging process and potential side effects of nausea, vertigo, and headaches. Since the primary focus of this study is PTSD, it is highly likely that some participants may experience heightened anxiety from loud noises or have difficulty staying still while inside the scanner. Movement inside the scanner may result in artifacts which would render some of the data incapable of analysis.

Participants would be informed of the procedure, including MRI scanning and structured interviews, but would not be given unnecessary information on the purpose of the study to avoid potential harmful situations. If the participants were aware that PTSD was the focus of interest, they may either unconsciously direct themselves towards or avoid traumatic exposure events. Avoiding these effects would also be conducive to the goal of the study itself in better understanding risks for and effects of PTSD.

**Procedure**

The participants would be subjected to structural MRI scanning once a year over a period of three years including a baseline measurement before deployment. This is to ensure that any
potential structural changes as a result of developed PTSD or otherwise can be observed and considered accordingly. Participants will be assessed by a team of 30 licensed clinicians on their mental state, state of PTSD diagnosis, and PTSD symptom severity on the same days as their scanning appointments as to not take up too much of their time and avoid further issues of travel and availability. Due to the large amount of participants, though, this will likely dwindle due to attrition. Also, factoring in the hospital’s own schedule for use of the MRI machine, scanning sessions will be split up among multiple days. As a hospital, they are expected to prioritize the patients currently receiving care over use for research studies.

The structural MRI scans will take place over the course of three years with participants undergoing four total scanning sessions. The scans themselves would be T1-weighted, three dimensional MRI scans with coronal, axial, and sagittal orientations in order to capture different angles (Acer et al., 2011).

![Figure 3](image.png)

**Figure 3.** This image depicts structural MRI scans of the coronal, axial, and sagittal planes from Acer et al.’s study in 2011.

Images in each of these planes will be necessary to acquire a view of the entire hippocampus. Contiguous slices will also be used to ensure smooth transitions between images.
MR images will be acquired on a 1.5 T Philips MRI system. The use of a 1.5T MRI scanner rather than a 3T which has been known to capture clearer images is due to location constraints with Fort Drum (Isaacs et al., 2020). The nearest hospital to the base, Carthage Area Hospital, only has a Philips 1.5T MRI scanner. Using Bonne et al.’s 2001 study for reference, the intracranial cavity will be measured by using TE=30 and 80 msec, TR=3000 msec, field of view=24 cm, acquisition matrix=56×256, and 192 phase-encoding steps, resulting in two double-echo images at 54 different levels with 3-mm slice thickness (contiguous slices). 124 coronal slices of 1.5-mm thickness (TE=5 msec, TR=35 msec, 45° angle, field of view=24cm, acquisition matrix=256×256, 192 phase-encoding steps) will be used to evaluate the volume of the hippocampus. The volume measured will combine both the left and right hemispheres rather than measuring both separately for comparison (see Appendix B).

Sessions would have to be scheduled when all of the participants are back from duty and have the time to come in for scanning. Since they would all likely be staying at the same fort and have similar schedules, I don’t believe this would be a huge issue. It would also be preferable to scan and interview all of the participants either the same day or within days of each other as this is time-sensitive. Realistically, with such a large sample size and the time needed to scan and then interview each participant, this process will not be possible to perform in a single day. Furthermore, the hospital granting us use of their MRI would no doubt prioritize it’s use for their own services.

The scans will focus on capturing the overall volume of the participants’ hippocampi in cubic centimeters as the measured variable. Some studies have split the hippocampus in the left and right hemispheres to document differences between them. However, for the scope of this study, the main point of interest is any change to the structure of the entire hippocampus.
While the main hypotheses and focus of the study will be on potential changes to the hippocampal region, any changes to either the dorsolateral prefrontal cortex or the amygdala may provide insight into other relationships with PTSD long-term effects of stress in exploratory analyses. Greater dorsolateral prefrontal cortex thickness has been linked to resiliency and recovery from PTSD (Lyoo et al., 2011). A thicker cortex was found to predict greater response to treatment and therapy, and may be helpful for determining the best recovery plans for those dealing with PTSD.

After scans are obtained, they will be assessed by both a team of hired neuroanatomy specialists and the analysis software NeuroQuant to verify accuracy across both parties. With a sample size of 300 soldiers and approximately hour-long sessions required to assess each of them, a team of 30 neuroanatomists will be recruited for the study. Since men have typically larger hippocampi than women, this will be controlled for in the analyses by correcting for total brain volume or intracranial volume (Lee et al., 2020; Tan et al., 2016).

**Predicted Results**

The predicted results of this study reflect the hypotheses previously stated as no actual data has been collected for this proposal. Therefore, the graphs below depict expectations based on the background research which was done for this proposal. The first hypothesis was that participants who have been diagnosed with PTSD and have high symptom severity will show the greatest difference in hippocampal size. The second hypothesis was that smaller baseline hippocampal volume will predict higher symptom severity levels and development of PTSD. If both of these hypotheses are supported by the data, it would mean that people with naturally
smaller hippocampi may be at greater risk for developing PTSD. In such cases, it would be crucial to treat the PTSD as soon as possible to minimize further reductions to the hippocampus.

**Primary Analyses**

![Graph showing difference in hippocampal volume by symptom severity and diagnosis](image)

<table>
<thead>
<tr>
<th>ANOVA - Difference in Hippocampal Volume</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Severity</td>
<td>0.4128</td>
<td>2</td>
<td>0.20642</td>
<td>50.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>0.0620</td>
<td>1</td>
<td>0.06204</td>
<td>15.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Symptom Severity × Diagnosis</td>
<td>0.0937</td>
<td>2</td>
<td>0.04684</td>
<td>11.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Residuals</td>
<td>1.2050</td>
<td>294</td>
<td>0.00410</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4.** This graph and table display the predicted results of the first hypothesis. Participants who have been both diagnosed with PTSD and scored “High” in their symptom severity score show the greatest difference in overall hippocampal volume. The overlapping of error bars between the PTSD and No-PTSD groups in the “Low” and “Medium” symptom severity categories show that, while there is
greater variability for difference in hippocampal volume within the PTSD group, there is no statistical difference between them. This is due to the significant interaction between symptom severity and diagnosis, \( p < .001 \).

The first hypothesis (as shown above) was analyzed using a 3x2 ANOVA with the following independent variables: symptom severity (Low, Medium, High), and diagnosis (PTSD and No-PTSD), as well as difference in hippocampal volume (Baseline scan compared against Year 3 scan) as the dependent variable. As predicted, participants with in both the PTSD and “High” symptom severity cell have the greatest difference in hippocampal volume.

There is a significant interaction between diagnosis and symptom severity as there was no significant difference in hippocampal change within the “Low” and “Medium” groups and significant difference in hippocampal volume difference within the “High” symptom severity groups (PTSD vs No-PTSD).

This interaction was predicted due to the small percentage of active-duty soldiers expected to actually develop PTSD by the end of the study. While both groups of participants in the PTSD and No-PTSD groups with “High” symptom severity will experience the most severe symptoms, it is possible that there may be differences between them which cannot be measured. For example, those in the “High” symptom severity category are designated to that category when they garner a score on the CAPS-5 scale between 20 and 40. The experience between an individual whose score is 20 and an individual whose score is 40 could be very different, yet both would be lumped together in the same category.
Figure 5. This figure compares predicted differences in overall hippocampal volume (Final scan minus Baseline scan) and participant’s relative symptom severity scores. I predict that participants who scored “High” on symptom severity levels at the time of the final scan would have a significantly greater difference in hippocampal size than both the “Medium” and “Low” levels, $p < .001$.

These predicted results would support my hypothesis that participants experiencing more severe PTSD symptoms will experience an overall decrease in hippocampal size. The error bars for “High” symptom severity are greater because out of those who are exposed to trauma and deal with greater symptoms, only a small portion are likely to actually develop PTSD. Differences in hippocampal size, while not impossible, would likely not be as large in either reduction or growth in the “Low” symptom severity group, since the processes which facilitate hippocampal reduction would not be great enough to cause visible damage.

The variability among those in the “High” and “Medium” symptom severity groups will be greater than those in the “Low” symptom severity group since, with greater symptom severity,
it’s possible the underlying mechanisms responsible for reductions in hippocampal size may be activated. Further, participants in the “Medium” and “Low” groups aren’t expected to have as much variability as the “High” symptom severity. This is shown in the error bars in Figure 4 as it’s unlikely for participants outside of the “High” symptom severity group to actually go on to develop PTSD. This is based on the data previously mentioned, suggesting that only a small percentage of active duty soldiers — roughly 2.9% — actually go on to develop PTSD (Wittchen et al., 2012).

Figure 6. This figure displays the predicted measurements of hippocampal volume from the baseline, 1st year, 2nd year, and 3rd year scans. Participants in the “High” symptom severity group had significantly smaller hippocampal volume at baseline than participants in both the “Low” and “Medium” symptom severity groups.
A 4x3 Repeated Measures ANOVA with independent variables of scanning session, or Time, (Baseline, Year 1, Year 2, Year 3) and symptom severity (Low, Medium, High) with hippocampal volume as the dependent variable was used to analyze the relationship between symptom severity and time. I predicted that those in the “High” symptom severity group would have significantly smaller hippocampal size at baseline and experience the greatest decrease in hippocampal size. Also, due to the documented relationship between PTSD duration and hippocampal atrophy, the size of the hippocampus is expected to begin decreasing approximately three months after initial trauma exposure. These predicted data are based on an assumption of initial trauma exposure happening within the first year after deployment and at least three months before the Year 1 scanning session.

Figure 7. This graph depicts the predicted relationship between symptom severity and baseline hippocampal volume. There is no significant difference between the baseline hippocampal volume between the “Low” and “Medium” symptom severity groups, shown by the overlapping error bars.
Conversely, participants who scored “High” on symptom severity are predicted to have significantly smaller hippocampal volume at baseline than those in the “Medium” and “Low” severity groups as shown by the error bars.

These predicted findings suggest that initial smaller hippocampal size could be an indicator for susceptibility for developing more severe symptoms of PTSD. The data would lend support to the vulnerability hypothesis, as it suggests that correlations between small hippocampal size and PTSD may be due to the fact that those individuals already had smaller hippocampi before trauma exposure. This doesn’t discredit the acquisition hypothesis but suggests that, instead, both may provide insight into the seemingly contradictory findings between them. It may very well be the case that those with smaller pre-exposure hippocampi are more likely to develop PTSD but that severe reductions in size are also a product of the underlying mechanisms attributed to stress and PTSD itself. Even if an individual had a smaller hippocampal size to begin with, a baseline scan may reveal further reductions over time with PTSD.
Exploratory Analyses

**Figure 8.** This graph depicts an independent t-test looking at the relationship between gender and difference in hippocampal volume. I predicted that even though women in the military are more likely to develop PTSD, they would not have a significantly greater difference in hippocampal volume compared to men. This is shown in the overlapping of the error bars between the male and female gender categories.

The predicted results in this graph display one of the exploratory analyses related to gender and differences in hippocampal volume. I predicted that there would be no significant difference between women and men when it comes to differences in hippocampal size. This is due in large part to the likelihood of treatment effects. Even though women in the military are more likely to develop PTSD, their greater likelihood of seeking treatment for their symptoms may result in treatment effects. In a future study focusing its primarily analyses on gender differences in relation to PTSD, it would be worthwhile to track treatment seeking and factor that
in as a potential covariate or confounding variable. The combination of greater prevalence in PTSD development coupled with greater prevalence for seeking treatment opens up a lot of different avenues for potential future research aimed at PTSD among women in the military.

**Discussion**

**Limitations**

Despite the large aims of this study, there were several areas which I did not manage to tackle sufficiently in this proposal. Since this study was designed to address the large task of discerning between predisposition and neurotoxic effects in relation to PTSD, there are many limitations to its structure and likely execution. Even though longitudinal designs can get us closer to causality in the case of PTSD, it is impossible to rule out all other factors. Those who develop more severe symptoms or even PTSD may seek treatment or decline to participate for the entirety of the study as a result of their condition. Treatment effects, whether that be the use of medication or therapeutic measures, may interfere with otherwise collected data which would have provided deeper insight into the relationships of interest.

Working with participants from the military will also be a challenge as any data collection must take deployment and general schedules into account. The level of collaboration required between researchers, administration at Fort Drum, and the Department of Defense will likely be time-consuming, expensive, and necessitate intricate planning. The cost of a study like this including compensation for participants, payment for use of Carthage Area Hospital’s MRI machine, cost of transportation including vehicles and drivers, payment for licensed clinicians, neuroanatomists, and the analysis software NeuroQuant would be extremely expensive. Payment
for neuroanatomists, licensed clinicians, and participants alone is already close to $200,000 (See Appendix I).

There is also a large body of research on the differences in PTSD prevalence and severity across different demographic variables such as gender and socioeconomic status. While women have anatomically smaller hippocampi, they are also much more likely to be diagnosed with PTSD. Women veterans report the highest rates of Post-Traumatic Stress Disorder among civilians and veterans, though their likeliness to seek treatment for PTSD over male soldiers may result in treatment effects that skew the actual amount of women soldiers capable of being diagnosed with PTSD at any given time (Lehavot et. al, 2018). In order to make more meaningful comparisons across gender lines, researchers should also take care to measure whether or not participants have been seeking care and utilizing resources to cope with their PTSD symptoms.

Furthermore, actual rates of PTSD prevalence in a group of 300 deployed soldiers resulted in a very small amount of participants who would likely develop PTSD. In a sample size of 300 soldiers, that amount would only be approximately eight or nine soldiers. With such a small sample size in that cell, it would be hard to generalize a lot of results, especially to a greater civilian population with already lower rates of PTSD prevalence. Meaningful comparisons across gender within the PTSD cell would also not be possible as the respective groups would only contain about three or four participants each. Small sample sizes also create a much larger amount of variability.

If this study were to be conducted at multiple different military forts, more meaningful comparisons could be made between PTSD and control groups. Additionally, this type of experiment could be carried out in multiple military bases at the same time and within different
specific units such as the Air Force or the Navy Seals which may provide more information on effects of location, duration of service, and rank on PTSD acquisition rates, symptom severity, and duration of the disorder.

Another area I’d wished to cover more in this proposal is differences in hippocampal atrophy between the left and right hemispheres as well as specific subregions. In their article, Acheson et. al mention several meta-analyses conducted in the early 2000’s confirming bi-lateral hippocampal reductions between participants with PTSD and trauma-exposed controls (2012). If I had more time to work on this proposal before submission, I would have liked to factor in bi-lateral hippocampal differences to my analyses.

**Future Directions**

The goal of this proposal study was to provide more clarity to the controversy surrounding PTSD and observed changes to the hippocampus. Despite what is known about excessive stress and its affect on the social, emotional, and physical health, its true impact on long-term structural differences in the brain is still debated. The vulnerability and acquisition hypotheses posit seemingly contradictory foundations for these observed differences. The vulnerability hypothesis suggests that differences in hippocampal size pre-date PTSD development and are therefore not a result of the disorder itself. The acquisition hypothesis, on the other hand, suggests that PTSD creates an incredibly neurotoxic environment which leads to hippocampal damage and reduction as time goes on. Based on these theories and the background literature, I predicted that a smaller baseline hippocampus would be associated with higher PTSD symptom severity and diagnosis. I also predicted that participants with both high PTSD symptom severity and a PTSD diagnosis would experience the greatest difference in hippocampal volume
over the course of the study. These predictions were based on my belief that these two hypotheses do not actually conflict with each other at all, and that both can be used to establish more effective methods of determining risk, preventing damage, and fostering resilience.

Regardless of whether or not collected data would resemble these predicted results and support the hypotheses presented, the unique difficulties in understanding and treating Post-Traumatic Stress Disorder require a lot more research than what can be covered in a single study. The design of this study is aimed at filling in the gaps of previous literature on the temporal relationship between PTSD and long-term changes to brain structure. Future studies should adopt a similar approach to this one and fill in the gaps which my own proposed study presents.

If the data were to reflect and support my hypotheses, then it would be both beneficial and essential to invest time, resources, and money into implementing policies for determining risk for PTSD before entry into military positions with greater-than-average exposure to potential trauma. For example, if smaller hippocampal size is a risk for developing PTSD after exposure to trauma, the military should administer entry scans and avoid deploying soldiers with greater susceptibility for developing PTSD from open combat. They could be relegated to managerial positions, medical units, or some other position which would decrease their chances of exposure to combat.

There are also important distinctions to make across gender lines in the military when it comes to PTSD. As discussed previously, women in the military, when compared to men in the military and civilians of both genders, are the most likely group to develop PTSD (Wittchen et al., 2012). However, the PTSD accounted by these women is more often attributed to interpersonal conflict rather than combat exposure which most male soldiers attribute with their
PTSD. The methods for preventing PTSD mentioned earlier would not necessarily apply or be as effective for women in the military compared to men. If interpersonal conflict among other soldiers is a possible leading factor for PTSD, then preventative systems aimed at women would have to tackle larger issues of sexual harrassment, rape, and gender-based discrimination in the military organization as a whole which is no small feat.

The true aim of this study was to spread awareness to the long-term brain damage of the hippocampus which has become associated with PTSD as well as inform the next steps in developing the most efficient method for dealing with the potential long-term effects of PTSD. I can only hope with this proposal to inspire further research and designs centered around grasping the temporal relationship of PTSD and changes to the brain.
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### Appendices

#### Appendix A

Diagrams of Relevant Brain Regions
Figure A1. Diagram of the Hippocampus

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Figure A2. Diagram showing a method of segmentation for the Hippocampus and Amygdala on MRI Scan (Schumman et. al, 2004)
Figure A3. Diagram of a “typical” coronal brain scan compared to an individual with PTSD (Bonne et al., 2001)

Figure A4. Diagram of coronal, axial, and sagittal planes used to analyze volumetric changes in the brain (Acer et al., 2011)

Appendix B

Consent Form

Informed Consent
Principal Investigator
Hominy McMahon
Psychology Program
Bard College

Project Title
The Chicken or the Egg: A Proposed Longitudinal Study on Post-Traumatic Stress Disorder and Memory Impairment

Introduction
You are being asked to be a volunteer in an experiment conducted by members of the Psychology Program at Bard College. Please read the following information carefully prior to proceeding to the experiment.

Purpose
The purpose of this experiment is to better understand the relationship between Post-Traumatic Stress Disorder and changes in brain structure.

Study Procedure
If you decide to participate, you will be asked to partake in four sessions of MRI scanning and interviewing. Before your participation, you will be provided with information about the specific hypothesis in this study. The duration of your participation will be approximately an hour and half once per year over the course of three years. Participation in this study is completely voluntary and you are free to stop at any time without penalty.

Risks and Discomforts
There is minimal potential risk and discomfort from participating in this study. You will be required to notify researchers of any ferrous materials on your body which cannot be removed such as shrapnel or pacemakers.

Benefits
You are not likely to benefit directly from participating in this study. However, what we learn from this experiment will contribute to what we know about how PTSD develops and will inform efficient care and protective services for those experiencing symptoms of diagnosis in the future. Since there will be a baseline scan at the beginning of the study, this can be used later as viable evidence for any medical conditions that take place over the course of the study which may be helpful in seeking treatment.

Compensation
Participants will be compensated for their time with a payment of $5 dollars per hour. They may also be compensated with particular benefits from the military.

Exclusion/Inclusion Criteria
Individuals must be over the age of 18 to participate in this study and be an active duty soldier at Fort Drum. Participants must not have any history of drug abuse or mental and emotional disorders which could have an impact on brain structure and size. Participants must also be comfortable with the use of an MRI machine, meaning that those with claustrophobia are highly discouraged from taking part in this study.

Confidentiality
Once you have completed the experiment, your data will be automatically assigned a participant ID code. There will be no way to directly link your name with your data. In addition, study data will be kept on password-protected folders and only study personnel will have access to these files. No personally identifying information will be collected electronically or appear when the results of the study are presented or published.

Questions
If you have any questions about your rights as a research participant, you may contact the Principal Investigator, Hominy McMahon at hm1795@bard.edu or the chair of the Bard College IRB, irb@bard.edu

By clicking the box below, you affirm that you have read and understood the context of the consent form.

Appendix C

Pre-registration (AsPredicted template) for submission to OSF

Data collection
Have any data been collected for this study already? Note: 'Yes' is a discouraged answer for this preregistration form.

- No, no data have been collected for this study yet.

Hypothesis

*What's the main question being asked or hypothesis being tested in this study?*

We hypothesize that a decrease in hippocampal volume will predict worse PTSD symptom severity and more prevalence of PTSD. Since the temporal relationship between these factors is what is being studied, it is possible that worse PTSD symptom severity will also predict smaller hippocampal volume.
**Dependent variable**

*Describe the key dependent variable(s) specifying how they will be measured.*

The dependent variables are PTSD symptom severity, PTSD diagnosis, left and right hippocampal volume, and amygdala volume. PTSD symptom severity will be measured using the CAPS-5 with levels of Low (0 - 10), Medium (10 - 20), and High (20 - 40). PTSD Diagnosis will also be measured using the CAPS-5. Left and right hippocampal, and amygdala volumes will be measured in cubic centimeters and assessed by hired neuroanatomists alongside the analysis software NeuroQuant.

Based on a similar study conducted in 2011 by Bonne et al., MR images will be acquired on a 2-T Elscint GYREX “Prestige” MRI system. The intracranial cavity was measured by using TE=30 and 80 msec, TR=3000 msec, field of view=24 cm, acquisition matrix=56×256, and 192 phase-encoding steps, resulting in two double-echo images at 54 different levels with 3-mm slice thickness (contiguous slices). They used 124 coronal slices of 1.5-mm thickness (TE=5 msec, TR=35 msec, 45° angle, field of view=24 cm, acquisition matrix=256×256, 192 phase-encoding steps) to evaluate the volume of the hippocampus.

**Conditions**

*How many and which conditions will participants be assigned to?*

Since this is a longitudinal study, there are no experimental conditions. However, those experiencing high PTSD symptom severity or diagnosis will be matched with other participants who are not diagnosed or experiencing symptoms for the comparative analyses.

**Analyses**

*Specify exactly which analyses you will conduct to examine the main question/hypothesis.*

Analyses will include:

- 3 x 2 Factorial ANOVA: PTSD Symptom Severity (Low, Medium, High) x Diagnosis (PTSD, No-PTSD) with the difference in hippocampal volume as the dependent variable.
- One-Way ANOVA using symptom severity (Low, Medium, High) with the difference in hippocampal volume as the dependent variable.

- Repeated 4x3 ANOVA: Scanning Session (Time) (Baseline, Year 1, Year 2, Year 3) x Symptom severity (Low, Medium, High)

One-Way ANOVA using symptom severity (Low, Medium, High) with baseline hippocampal volume as the dependent variable.

- Independent t-test comparing Diagnosis (PTSD and No-PTSD) with difference in hippocampal volume as the dependent variable.

**Outliers and Exclusions**

*Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.*

Since this is an observational study, there will be many factors that cannot be controlled in the scope of this project. Exclusion criteria will include any pre-existing disorders that could have an impact on brain development (depression, anxiety, etc.) as determined through a DSM-5 structured interview. Exclusion criteria for this study would also include those diagnosed with claustrophobia and any internally-deposited ferrous metals such as pacemakers or chips. These criteria are included for the personal safety of participants in the study as ferrous metals can be shifted or moved toward an MRI scanner due to its use of magnetization.

**Sample Size**

*How many observations will be collected or what will determine sample size? No need to justify decision, but be precise about exactly how the number will be determined.*

The sample size will be approximately 300 active duty soldiers recruited from the Fort Drum military base. In order to account for attrition over a three-year-long study, a large number of participants is necessary. Also, since it is impossible to determine who will be exposed to trauma, we can expect a smaller number of those with PTSD diagnoses or high symptom severity.

**Other**
Anything else you would like to pre-register? (e.g., secondary analyses, variables collected for exploratory purposes, unusual analyses planned?)

Secondary analyses will include looking at gender differences (ANOVA, t-test), relationships with amygdala volume, and potentially other demographic factors.

Name

Give a title for this AsPredicted pre-registration. Suggestion: use the name of the project, followed by study description.

The Chicken or the Egg: A Proposed Longitudinal Study on Post-Traumatic Stress Disorder and Memory Impairment

The main goal of this proposed 3-year longitudinal study of PTSD is to better understand the temporal relationship between the development of PTSD and structural changes in the hippocampus. Structural MRI scans of 300 randomly chosen active-combat soldiers at baseline, 1yr, 2yr, and 3yr periods will be used in conjunction with clinical assessments on PTSD and symptom severity carried out by a group of licensed clinicians.

Finally

For record keeping purposes, please tell us the type of study you are pre-registering.

- Class project or assignment

Appendix D

NIH Human Participant Protection Certificate
Appendix E

Sample of Questions from the CAPS-5 Measurement

Sample Item

In the past month, have you had any unwanted memories of (EVENT) while you were awake, so not counting dreams?

How does it happen that you start remembering (EVENT)?
[If not clear:] (Are these unwanted memories, or are you thinking about [EVENT] on purpose?)

How much do these memories bother you?
Are you able to put them out of your mind and think about something else?
How often have you had these memories in the past month?

Appendix F

Sample of PTSD Diagnostic from the DSM-5 Structured Interview
### Posttraumatic Stress Disorder

**Lifetime Trauma History**

I'd now like to ask about some things that may have happened to you that may have been extremely upsetting. People often find that talking about these experiences can be helpful. I'll start by asking if these experiences apply to you, and if so, I'll ask you to briefly describe what happened and how you felt at the time.

**Screen for each type of trauma (based on DSM-5 text and PTSD criterion A using the questions below):**

- Have you ever been in a life-threatening situation like a major disaster or fire, combat, or a serious car or workplace-related accident? [ ]
- What about being physically or sexually assaulted or abused, or threatened with physical or sexual assault? [ ]
- How about seeing another person being physically or sexually assaulted or abused, or threatened with physical or sexual assault? [ ]
- Have you ever seen another person killed or dead, or badly hurt? [ ]
- How about learning that one of these things happened to someone you are close to? [ ]

**If unknown:** Have you ever been the victim of a serious crime? [ ]

**If no events endorsed:** What would you say has been the most stressful or traumatic experience you have had over your life? [ ]

**If no events acknowledged, continue with **H1** (Attention-Deficit/Hyperactivity Disorder), page 86.**

**If any events acknowledged:** In G10-G12 below, review and inquire in detail for up to three past events (e.g., select three worst events: select trauma of interest plus two other worst events).

### Past Lifetime Event #1

<table>
<thead>
<tr>
<th>G10</th>
<th>Description of traumatic event:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indicate type of traumatic event (check all that apply):</td>
</tr>
<tr>
<td></td>
<td>__ Death, actual</td>
</tr>
<tr>
<td></td>
<td>__ Death, threatened</td>
</tr>
<tr>
<td></td>
<td>__ Serious injury, actual</td>
</tr>
<tr>
<td></td>
<td>__ Serious injury, threatened</td>
</tr>
<tr>
<td></td>
<td>__ Sexual violence, actual</td>
</tr>
<tr>
<td></td>
<td>__ Sexual violence, threatened</td>
</tr>
<tr>
<td></td>
<td>Indicate mode of exposure to traumatic event:</td>
</tr>
<tr>
<td></td>
<td>__ Directly experienced</td>
</tr>
<tr>
<td></td>
<td>__ Witnessed happening to others in person</td>
</tr>
<tr>
<td></td>
<td>__ Learning about event in close family member or friend</td>
</tr>
<tr>
<td></td>
<td>__ Repeated or extreme exposure to aversive details of traumatic events (e.g., police officers repeatedly exposed to details of child abuse)</td>
</tr>
</tbody>
</table>

**Age at time of event:** [ ]

**Indicate single event vs. prolonged/repeated exposure by circling appropriate number:**

- 1—Single event
- 2—Prolonged or repeated exposure to same trauma (e.g., witnessing repeated episodes of parental domestic violence over years)

---

**Appendix G**
Demographic Questionnaire

1. **What is your age? ____**

2. **What is your gender?**
   1. Cisgender Male
   2. Cisgender Female
   3. Transgender Male
   4. Transgender Female
   5. Nonbinary
   6. Not Listed *(Please specify if you choose)* __________

3. **What is your sexual orientation?**
   1. Heterosexual
   2. Bisexual
   3. Gay
   4. Lesbian
   5. Asexual
   6. Not Listed *(Please specify if you choose)* __________

4. **What is your ethnicity?**
   1. Hispanic or Latino
   2. Non-Hispanic or Latino
   3. Not Listed *(Please specify)* __________

5. **What is your race? (Please select all that apply)**
   1. Asian
   2. Black
   3. Native American/Alaskan, American Indian, Native/Indigenous
   4. Pacific Islander/Native Hawaiian
   5. Middle Eastern, North African (Non-White)
   6. White
   7. Latinx/Hispanic (Non-White)
   8. Not Listed *(Please specify)* _________________

6. **What is the highest grade in school, year in college, or post-college degree work you have completed?**
   1. 8th grade or less
   2. Some high school
   3. High school graduate or GED
4. Some college or 2 year degree College graduate (4 year degree)
5. Graduate degree

Appendix H

Sample of Questions from the Beck Depression Inventory

1. I do not feel sad.
   0 I do not feel sad.
   1 I feel sad
   2 I am sad all the time and I can't snap out of it.
   3 I am so sad and unhappy that I can't stand it.

2. I am not particularly discouraged about the future.
   0 I am not particularly discouraged about the future.
   1 I feel discouraged about the future.
   2 I feel I have nothing to look forward to.
   3 I feel the future is hopeless and that things cannot improve.

3. I do not feel like a failure.
   0 I do not feel like a failure.
   1 I feel I have failed more than the average person.
   2 As I look back on my life, all I can see is a lot of failures.
   3 I feel I am a complete failure as a person.

4. I get as much satisfaction out of things as I used to.
   0 I get as much satisfaction out of things as I used to.
   1 I don't enjoy things the way I used to.
   2 I don't get real satisfaction out of anything anymore.
   3 I am dissatisfied or bored with everything.

5. I don't feel particularly guilty
   0 I don't feel particularly guilty
   1 I feel guilty a good part of the time.
   2 I feel quite guilty most of the time.
   3 I feel guilty all of the time.

6. I don't feel I am being punished.
   0 I don't feel I am being punished.
   1 I feel I may be punished.
   2 I expect to be punished.
   3 I feel I am being punished.

Appendix I
### Spreadsheet for Senior Project Expenses

<table>
<thead>
<tr>
<th></th>
<th>Cost per hour</th>
<th>Hours (Scanning vs. Analyzing)</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroanatomist</td>
<td>30</td>
<td>$80</td>
<td>$19,200</td>
</tr>
<tr>
<td>Participants</td>
<td>300</td>
<td>$66</td>
<td>$158,400</td>
</tr>
<tr>
<td>Licensed Clinici</td>
<td>30</td>
<td>$90</td>
<td>$16,200</td>
</tr>
</tbody>
</table>

$183,800 Total Cost

**Based on:**

- NYS Minimum’s: $13.20
  - [https://www.bls.gov/oes/current/oes291217.htm](https://www.bls.gov/oes/current/oes291217.htm)

**FLAT PAY OPTION**

<table>
<thead>
<tr>
<th>Participants</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hour proportion</td>
<td>500.00%</td>
</tr>
<tr>
<td>Pay PER PARTICIPANT</td>
<td>$66.00</td>
</tr>
</tbody>
</table>

FSE for best T-1 weighted images w/ ETL of 4: 3.2 minutes → 960 min → 16 hours → 4, 4, 4

75 participants each 4 hours, 19 participants each hour

More scans per participant? Could be up to an hour for each participant

With 30 minutes approx. for SCID-5 interview and 50 min. Approx. for the CAPS-5 (add basic demographic questionnaire)

<table>
<thead>
<tr>
<th>SCID-5 and CAF Scanner</th>
<th>2 hr total x 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hr 20 min</td>
<td>30 min</td>
</tr>
</tbody>
</table>

Total time per participant: 1 hr 30 minutes approx (separate scanner time from interview time)