

South Dakota State University

Open PRAIRIE: Open Public Research Access Institutional Repository and Information Exchange

Biology and Microbiology Graduate Students Plan
B Research Projects

Department of Biology and Microbiology


2018

Mild Traumatic Brain Injuries and CTE: A Review Highlighting the Connection Between the Two

LeAndre Kennedy

South Dakota State University, Leandre.Kennedy@jacks.sdstate.edu

Follow this and additional works at: https://openprairie.sdstate.edu/biomicro_plan-b

 Part of the [Biology Commons](#), [Medicine and Health Sciences Commons](#), and the [Microbiology Commons](#)

Recommended Citation

Kennedy, LeAndre, "Mild Traumatic Brain Injuries and CTE: A Review Highlighting the Connection Between the Two" (2018). *Biology and Microbiology Graduate Students Plan B Research Projects*. 4. https://openprairie.sdstate.edu/biomicro_plan-b/4

This Plan B - Open Access is brought to you for free and open access by the Department of Biology and Microbiology at Open PRAIRIE: Open Public Research Access Institutional Repository and Information Exchange. It has been accepted for inclusion in Biology and Microbiology Graduate Students Plan B Research Projects by an authorized administrator of Open PRAIRIE: Open Public Research Access Institutional Repository and Information Exchange. For more information, please contact michael.biondo@sdstate.edu.

Mild Traumatic Brain Injuries and CTE:

A review highlighting the connection between the two

LeAndre Kennedy

Abstract

Chronic Traumatic Encephalopathy (CTE) is a traumatic brain injury based disease that is garnering a lot of attention in the United States. The purpose of this paper is to conduct an extensive review of the information available about the condition. Recently there has been a limited amount of published information and treatment opportunities are rare since the only way of diagnosing has come post mortem. Various literary reviews and experiments were analyzed for appropriate information regarding CTE's pathology and treatments and only peer reviewed published works were allowed in this paper. This resulted in promising information about the disease and the future treatments for the condition were viewed and will be used throughout this article.

TABLE OF CONTENTS

<i>ABSTRACT</i>	2
1. <i>INTRODUCTION</i>	4
<i>A) Pathogenesis</i>	5
1. <i>Tangles of TAU proteins</i>	5
2. <i>Neurotoxic peptides</i>	6
3. <i>PNN destruction</i>	6
<i>B) Symptoms correlated with region of brain damage</i>	
1. <i>Cerebral cortex</i>	8
2. <i>Temp lobes</i>	8
3. <i>Thalamus</i>	10
4. <i>Mammillary bodies</i>	10
5. <i>Brain stem.</i>	11
<i>C) Incidence and Diagnosis</i>	11
<i>D) Treatments and developing treatments of TBI/ CTE</i>	12
2. <i>Conclusion</i>	13
3. <i>Appendix A</i>	15
<i>Appendix B</i>	16
<i>Bibliography</i>	17

Until recent development of advanced imaging technology very little was known about brain injuries. The brain is relatively hidden inside of a skull and there is limited viewing options without expensive imaging techniques (13). With these limitations, understanding of how impact to the head affected the brain was severely hindered, and only showed symptoms could be used to diagnose (7). Traumatic brain injuries (TBI) were considered any significant jolt or blow to the head that results in altered brain function or feeling (2). Many of the complications of severe traumatic brain injuries are well documented and established but the focus of this review is to highlight the mild traumatic brain injury (mTBI) known as the concussion and its correlation to CTE (10). A mild traumatic injury is a blow or jolt to the brain caused by a non-penetrating stimulus. Concussions are mild traumatic injuries that may have varying levels of severity, going from momentary dizziness to a brief loss of consciousness. Rarely are the immediate effects of the concussion long lasting so a mTBI was seen as harmless until recently (7). The correlation of concussions in collision based activities was tied to the onset of the disease

CTE (Chronic Traumatic Encephalopathy) and the medical communities' attitude towards this injury changed (7).

CTE has an increasing impact in the world of neuroscience. CTE is known as a progressive tauopathy neurodegenerative disease (7). Before examining the clinical aspect of the disease this paper will first review a brief history of the condition. The first observed cases of CTE were thought to have come in the early 1900's with boxing (2). In 1928 the term "punch drunk" was coined to describe the unpredictable behavioral, motor and cognitive functions coming from years of repeated nonlethal blows to the head, 10 years later Dr. Millspaugh called it dementia pugilistica and shortly changed to psychopathic deterioration of pugilists (7). In 1949 the name Chronic Traumatic Encephalopathy was used and was cemented by Dr. Critchley (17). Over the next 30 years the scope of potential victims of CTE broadened to include all contact sports and the military with an especially high prevalence in football (Shown in figure 1). All of these sports would include repeated sub lethal blows to the head, often resulting in concussions.

1928: Martland coins term "punch drunk" to describe neurological symptoms in boxers.

1949: The term "chronic traumatic encephalopathy" (CTE) of boxers Introduced by Critchley as an alternate description of punch-drunk.

2005: Omalu describes CTE in an NFL player.

2013: McKee proposes criteria for neuropathological diagnosis of CTE and a staging scheme. This work included 36 NFL players.

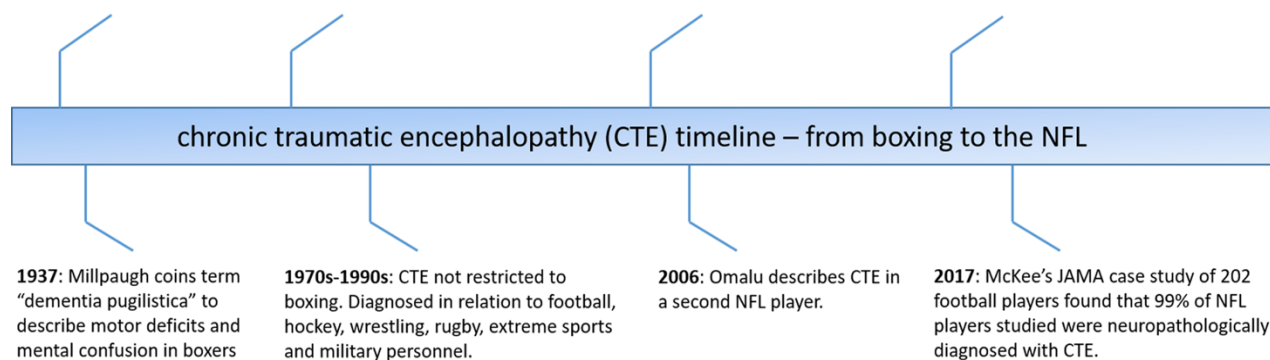


Figure 1: CTE Timeline (7)

Chronic Traumatic Encephalopathy begins to present symptoms 8-10 years after experiencing repeated head injuries, these symptoms are highlighted by headaches, rapid mood swings, impulsivity, increased irritability, aggression, memory loss, varying levels of depression and in some cases gait abnormalities; the most severe symptoms are suicidal thoughts and actions (2). The most recognizable physical symptom of CTE is the atrophy of the following key brain regions: cerebral cortex, temporal lobes, thalamus, mammillary bodies and the brain stem, leading to an abnormally low brain weight which leads to the observed symptoms above (2). CTE shares many signs and symptoms with Alzheimer's disease, ALS and Parkinson's disease which is why for years there was limited ability to distinguish CTE from other neurodegenerative disorders (1). CTE is initiated from repetitive mild traumatic brain injuries. These injuries cause widespread disposition of neurofibrillary tangles composed of hyper phosphorylated tau proteins, instead of the regularly phosphorylated tau. There is also a concentration of neurotoxic peptides beta amyloid and TDP-43 and PNN destruction (9). There has even been a possible gene association with CTE (3). The APOE e4 allele is linked with increased susceptibility (3). Neurodegenerative disorders are clinically distinguishable by the source of the brains degeneration. Neurodegeneration is the single most devastating effect of CTE and brain degeneration is always fatal when untreated. When this occurs, it will result in death unless the patient succumbs to another cause of death before the level of degeneration becomes fatal (9).

CTE Specific Pathologies

TAU: The primary cause of neuronal degeneration in CTE comes at the hand of the neurofibrillary tangles caused by the Tau-protein, a condition commonly seen in Alzheimer's disease and other frontotemporal dementias (1). Neurofibrillary tangles are consisted of aggregated straight or paired helical filaments, twisted ribbons and other forms of overly phosphorylated forms of the microtubule associated protein (MAP) known as tau (16). These lesions are the diagnostic hallmark of the condition, which as of now is hard to find with the currently available forms of imaging (16). It is increasingly evident that tau-mediated neurodegeneration is the result of a toxic gain of function mutation acquired by the tau that come from over phosphorylation of tau in the disease state (16). It is known that tau is key in the organization and stabilization of microtubules used in the central nervous system, which is very important in the structural organization of the brain (6). It is believed that tau may also have additional roles in its interaction with other structures and enzymes such as the actin in the cytoskeleton and tyrosine kinases (6). The build-up of p-tau causes changes in these structures but exactly how this change is caused is not quite understood (1). One of the likely scenarios is that once tau is phosphorylated, it enters an extremely active state where it interacts with the surrounding cellular structures that it normally would not influence (5). These reactions cause proteins in the brain to fold improperly, which triggers apoptosis (6). This error is considered a post translational modification because in the early stages of tau pathology there isn't a change in the genetic properties; there is just an over phosphorylation of a protein triggered by structural damage (6). Other post translational modifications of tau include glycation,

ubiquitination, sumoylation and nitration (1). These are believed to occur at different stages of tau pathology and could be possibly be a way to establish how long CTE has been present in the patient.

The ability for tau to modulate microtubule properties contributes to key structural and key regulatory cellular functions (9). Microtubules play major roles in maintaining neuronal morphology, the process that extend over long distances make the neuron the most asymmetrical of the cells so this morphology is important (16). Microtubules are also key in the transport machinery of neurons which allows the signaling molecules to move into or out of a cell. Under normal cell condition tau is in a constant equilibrium on and off the microtubules, being activated and deactivated when necessary (25). This equilibrium is controlled by the phosphorylation state of tau by kinases (1). In the case of a repetitive traumatic brain injuries the protein tau becomes phosphorylated at an increasingly high rate. The buildup of phosphorylated tau proteins leads to axonal transport defects, synapse loss and neuroinflammation (25). Studies of this protein have shown that the disengagement of tau from microtubules via phosphorylation is a critical step in the tau mediated neurodegeneration (1). There is a threshold of free phosphorylated tau that must be reached before it becomes toxic to the brain, and with traumatic brain injuries the amount of p-Tau increases. When the p-Tau level becomes toxic neurons begin to die and the Tau deposits spread (16).

Other neurotoxic peptides and PNN:

Another symptom of repeated blows to the head is the disruption of the Perineuronal Net (PNN) (14). PNN's represent the highly

organized components of the brains extracellular matrix (5). These nets surround cell bodies, dendrites and axons of particular classes of neurons forming lattice like structures. The roles of PNN's are not completely understood yet, but they do play a beneficial role by stabilizing the extracellular matrix by protecting them from harmful agents (14). These barriers against chemical agents form a physical gate between the neural tissue and ECM. They create a barrier that limits neuronal plasticity and counteracts regeneration of neuronal circuits (6).

The extracellular matrix in the central nervous system contains a highly organized mixture of proteoglycans, tenascin, fibronectin and a scaffolding substance called hyaluronan (6). These materials are dispersed all around the CNS but only particular neurons are enveloped completely by these PNN's. The main component of the PNN is the proteoglycan. The specific proteoglycan varies depending on what type of cell the PNN is protecting (6). It is believed that the disruption of these PNN's helps allow the hyper phosphorylated tau protein to build up in the brain when there is damage to the brain. The repellent properties of the PNN is compromised when there is damage and molecules that may naturally exist in the extracellular space are allowed contact with neurons and may be toxic (14). Along with the direct toxic effects of the tau protein, the damage to the PNN also releases the Amyloid beta peptide. This peptide is a natural occurring peptide in the body but when it is free in the extracellular matrix it initiates an immune response because the peptides are recognized as foreign, causing massive inflammation (15). The charge of the beta amyloid causes them to move towards neurons because that is their natural place as part of the PNN forming what is

called a senile plaque (similar to senile associated brain images) (14). This throws off the ionic balance and conductivity of the neurons, ultimately disrupting brain function. The immune response against these peptides near the neurons results in self damage in an attempt to remove the toxic peptides. When the plasticity limiting properties of PNN's are very important to the way the brain communicates with the rest of the body and other areas of the brain (14). The brain primarily has 3 types of non-specialty neurons; those being inhibitory, excitatory and interneurons. The buildup up of the tau protein and beta amyloid peptide demonstrate a prion like toxic effect on PNN of the GABAergic neuron which is an interneuron (12). PNN show a very limited ability to regenerate on their own, leading to possible movement of neurons if repeated blows to the brain are received. Interneurons connect different areas of the brain, which is necessary for parallel processing used on a daily basis in human life. Overstimulation or under stimulation from a rearranged interneuron caused by traumatic brain injuries could be devastating to the normal processing ability of the brain (2).

One preexisting condition that has been correlated with the onset of CTE is genetic (27). The gene apolipoprotein correlated to tau transcription has two versions, (apopE3) and E4 (apopE4) (27). ApopE4 when combined with traumatic brain injury resulted in a high risk of tau protein based neurodegenerative disorders were 2-4 times more likely than those with the E3 gene. This research was conducted in mice models, and it is believed the human brain follows the same physiological properties (28). In a study with TBI blasts conducted on mice those with the gene ApopE3 had levels of PIP2 phosphate elevated which lead to a reduction in

the PIP2 degrading enzyme synj1. In the mice with the ApopE4 gene the blast induced TBI the PIP2 phosphate levels did not change so there was no down regulation in synj1 (3). Soon after it was discovered that the amount of p-Tau in the E4 type dramatically outgained the amount in the E3 genotype. PIP2 is a signaling lipid that is involved with ion channel homeostasis, exocytosis and endocytosis. It also plays a role in cytoskeletal configuration and cell signaling. The enzyme SYNJ1 is responsible for the degradation of PIP2 (3).

The experiment used to find these results were done by inducing a blast that would cause a non-penetrating TBI (4). The blast measured was blowing up a stick of TNT at a distance of 6 meters from the subject. In the study, it was observed that in the CTE susceptible ApoE4 genotyped subjects reduces PIP2 levels in mouse and in human brains but that reduction doesn't happen early in the life of the mouse (4). Through the first 3 months of the life of the mouse the PIP2 levels post blast, remained constant between the two genotypes. This lead to the hypothesis that continued exposure to blasts causing TBI alters something in the ApoE4 gene that is not in ApoE3(4). Interestingly enough, when the mRNA post blast was compared to the mRNA pre blast in each of the genotypes there was no observed change which lead to the new hypothesis that the true change in the gene expression came from a post transcriptional or post translational alteration. The steps of DNA to protein is a highly regulated process, The DNA (gene) under goes selection via a transcription factor, then undergoes transcription to create mRNA and then the mRNA is translated into a protein. In this experiment there is no alteration prior to transcription meaning that the DNA itself is not altered but there is an epigenetic change (28).

The conclusion gathered from these observations is that when the SYNJ1 enzyme is down regulated after a TBI in the ApoE3 genome subjects, there is no dysregulation of PIP2 levels meaning no free phosphates capable of binding to tau proteins (4). The ApoE4 mice do not down regulate SYNJ1 causing an abundance of phosphates in the cell. This

research concluded with observation that either gene provided subjects that tested positive for hyper phosphorylated tau but the ApoE4 genotype provided a much higher rate of p-Tau, an indicator of CTE (3).

Below is an image of a brain that tested positive for the pathologies explained. The clear neurodegeneration can be seen in the brain (10).

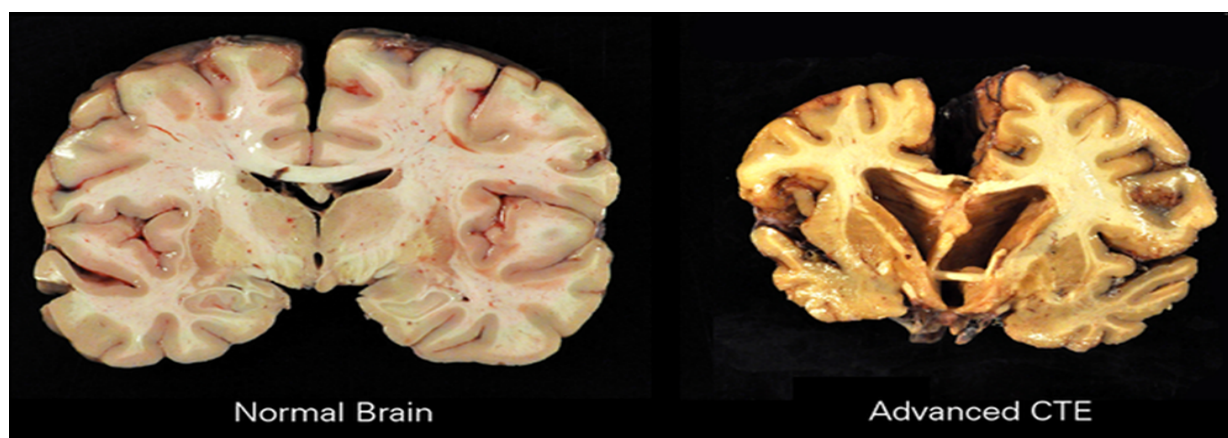


Figure 2: Comparative Imaging of 2 Brains (10)

Cerebral Cortex:

The largest portion of the human brain is the cerebral cortex, and it plays a large role in memory, attention, perception, cognition, awareness, thought, language and consciousness. The reason it is called the cerebral cortex (thinking region) is because essentially all activities that are involved with our consciousness are coordinated here. It is located at the most anterior placement of the brain right behind your skull, effectively encasing the whole brain acting as the outermost “layer” for an idea of the location (10). The outer zone of the cerebral cortex is made up of neural tissue called gray matter. This is where the neuronal cell bodies are. The cerebral cortex is typically folded in order to

increase surface area, allowing more space for more neurons in the limited space of the cranium (20). The different areas of the cerebral cortex are directly correlated with different functions which is why the initial side-effects of a TBI can vary because depending on where the bruising occurs there will be area specific symptoms (24). Initially after a TBI the swelling caused in the aftermath of tissue damage causes pressure to build pushing the cerebral cortex against the skull and interfering with all of the functions previously stated (20). This is why a swollen brain can result in difficulty in all conscious activity, but many of the subconscious activities remain functional (breathing, heart rate) (19). When the neurodegeneration from p-tau accumulation

begins, the cerebral cortex is usually the first place the damage is seen (17).

Temporal Lobe:

Interestingly enough, in many of the TBI cases an area of the cerebral cortex that initially suffers the most damage is the temporal lobe (8). The temporal lobe is responsible for establishing new memories, processing language and object recognition, which are three things a patient who suffers from CTE struggle with (17). There are primarily two different factors in this area specific damage from TBI. One of the hypothesis for this is the natural human reflex. Naturally when a person see's a dangerous stimulus coming directly at them they turn their head away. This is seen constantly in collision sports or near explosions in an attempt to protect the eyes (10). When something potentially dangerous is coming at you, you close your eyes and turn away. With the temporal lobe being located on the sides of the brain right behind where the ears connect to the head, they a prone to direct impact and can sustain a significant amount of bruising (13). The structure of the brain usually makes it so there is an elastic type collision inside the cranium which causes the side opposite of the impact to absorb much of the physical damage from the brain movement towards that side of the skull (20).

A second type of mTBI that has been correlated with concussions that damage the temporal lobe specifically are blast induced TBI (bTBI) (4).

Between 10-20% of soldiers returning from Operation Iraqi Freedom have suffered from at least one of these injuries. The over pressurization due to the shockwave from a blast is the culprit for this type of damage. This type of blast in recent warfare has been the number one cause of mortality for American troops (4). Blast waves specifically have an effect on the organs with fluid filled membranes (e.g. lungs, bowels, brain, etc.). The brain also fits into that category because of the fluid filled ventricles, and all of the vasculature dispersed throughout the brain (8). The temporal lobe specifically is where the hearing and vestibular senses stimuli are relayed to understand the environment (17). These senses respond to a pressure gradient. When the shockwave of a blast is induced there is an extreme increase in pressure that feels like an extreme increase in gravity. This outward pressure increase in pressure causes such intense pressure increases in the brain which then leads to the initial damage to the brain (4). Secondary damage comes from the hearing and vestibular fluid sacs being stimulated so intensely that they are over stimulating the brain, leading to the brain increasing the threshold response which ultimately would lead to the desensitization towards normal stimulus. A result of this over correction would be deafness and difficulty with balancing. Both are common symptoms of patients that have experienced blast shockwaves (4). Since damage to the temporal lobe is often seen with concussions caused by TBI this area is usually the first to result in a build-up of p-tau and the first area of CTE mediated neurodegeneration (1).

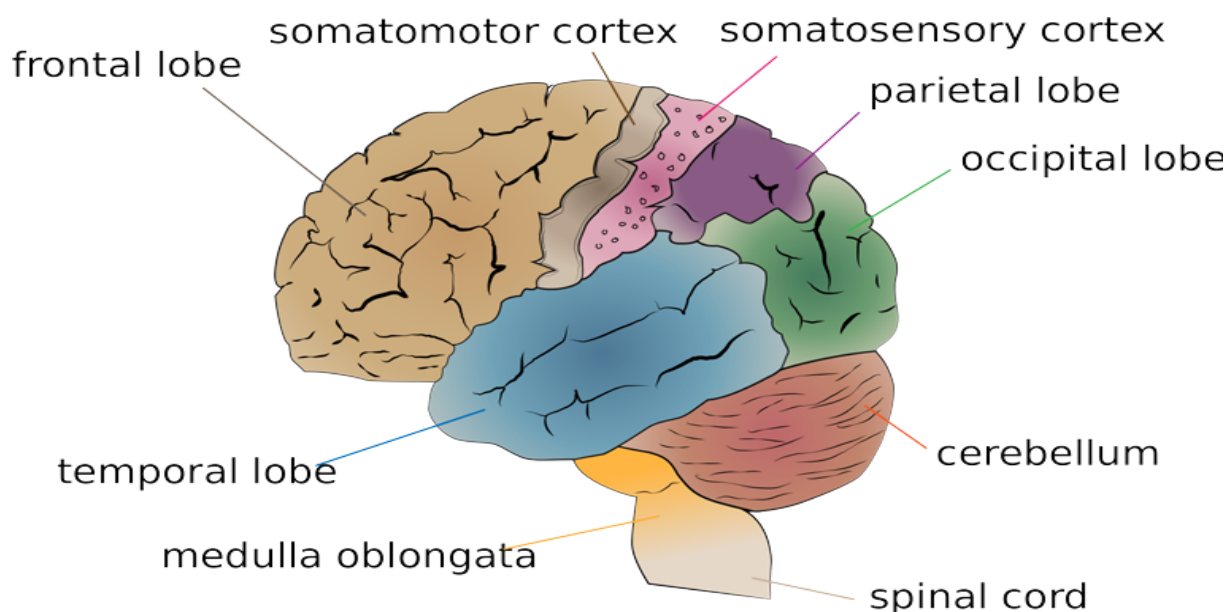


Figure 3. regions of the brain (29)

Limbic System

Thalamus/Hypothalamus: The thalamic region is extremely important in the human brain (21). It is given the task of receiving and relaying all sensory signals to the correct portion of the brain and also regulates consciousness, sleep, alertness and emotions (21). TBI's that cause a change to the environment of the thalamus would lead to a disruption in any of the previously mentioned functions (21). Concussions in particular) rarely cause direct physical damage to the thalamus but the ones that do result in the loss of consciousness which can be permanent resulting in a coma. Secondary effects from inflammation in the non- thalamic regions in the brain lead to increased pressure on the thalamus causing impaired function. The primary side effects from inflammation to the thalamus are delayed reactions and processing of information (21). The thalamus also integrates the limbic system

with the cerebral cortex which allows a person to be aware of their emotions (21). At advanced stages of CTE the p-Tau spreads toward the thalamus and is especially toxic, resulting in unpredictable emotions and difficulty sleeping and waking caused by damage to efferent neurons to the cerebral cortex (9). Damage to the thalamus has been proven difficult to correct because its location is in the middle of the brain. Currently only medications have been used in an attempt to correct the altered neuronal functions (5), anti-inflammatory medications reduce inflammation but the physical damage to the tissue of the brain is usually permanent, due to the inability for the brain to heal itself fully (25).

Mammillary Bodies: The mammillary bodies are a small region of the brain located between the brain stem and the cerebrum (19). This two-lobed structure has been associate with long term memory and in other animals a sense of direction also originates here. When the brain is initially swollen after a TBI there can be a

suppression of long term memory retrieval and in the advanced stages of CTE there is permanent memory loss (10).

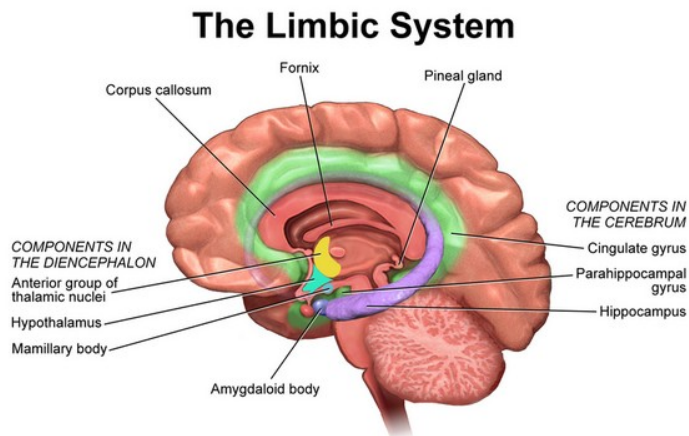


Figure 4. Image of the inner regions of the brain (29).

Brain Stem:

The brain stem contains the centers for all of the autonomic processes such as breathing, cardiac and smooth muscle contractions and the digestive tract (19). Non-penetrating traumatic brain injuries that cause concussions typically do not have enough force to cause physical damage to the brain stem. The brain stem becomes damaged when the spread of hyper phosphorylated tau begins. This interferes with the functioning of the neural cells in the brain stem and leads to death. If a brain stem is damaged there is usually a need for respirator and feeding tube because the autonomic functions are impaired (19).

Incidence and Diagnosis

The incidence of mTBI's are hard to measure because so many go unreported, which is why an effort has been made to treat all head injuries as if they were a concussion (22). It is

known that repeated traumatic injuries are the only known link to CTE the most effective way to stop the disease is to stop head injuries (7). Realistically this is impossible, which is why efforts to find a way to effectively diagnose the disease. If the preventative measures cease and repeated head injuries lead to a confirmed case of CTE then a swift and effective treatment plan must begin immediately (22). First an effective way to diagnose CTE must be developed, and as of November 2017 there may be a promising development here. Until last November every confirmed case of CTE has come post-mortem (18). There have been no FDA approved treatment plans for CTE but possible solutions are in development. Led by Dr. Ben Omalu a special PET scan that highlights the specific tau protein deposits unique to CTE pathology has been developed. Although there has been one case observed, the subject that was observed had a scan that was consistent with what post mortem CTE subjects had shown. After the

subject died the brain was dissected and CTE was confirmed (18).

So far there have been no reported cases of CTE in a person that has not experienced a concussion or other non-penetrating traumatic brain injury. Humans constantly place themselves in situations where TBI is a risk (17). Whether that is from the sports entertainment world or the military, we have shown that we are prone to placing ourselves into these situations. Since there has been published correlation of traumatic brain injuries and neurodegenerative diseases the amount of participants in the collision sports has declined (7). Even though precautions for prevention have been made there has been an increase in the amount of concussions reported. This is likely because of the increased attention to head injuries has led to better recognition and reporting of these injuries. It is widely believed that the actual amount of concussions sustained has lowered but the amount reported has increased. In reality concussions can be caused by many different things (9).

Treatments

When the preventative measures against concussions fail serious complications can occur, possibly leading to CTE. Many pharmacological agents can help against concussion symptoms, which may help prevent CTE. These include anti-inflammatory medications, cell cycle inhibitors, gene therapy and stem cell therapy.

Anti-inflammatory and cell cycle

inhibitors: Drugs of this nature have the ability to slow or even stop the progress of secondary symptoms following a mTBI. This is

especially important in prevention of CTE because the secondary symptoms of TBI's are what lead to CTE (5). An example of a medication that helps combat these secondary effects is minocycline. This drug is a tetracycline that displays neuroprotective and anti-inflammatory functions. It inhibits pro-inflammatory cytokines by suppression of IL-1beta and IL-6 and also inhibits micro gliosis (the process of CNS response to pathogens) which leads to an effective prevention of apoptosis in neuronal tissue. In recent human trials it was shown that minocycline also reduced serum neurofilaments (12). This is especially key in the case of CTE prevention because the culprit in causing CTE is the protein tau which comes from neurofilaments primarily in the cytoskeleton (1).

Microglial proliferation after a mTBI is often observed and glial cells are known as the "quality controlmen" of the brain (23). Microglia operate by removing the debris from damaged regions and induce inflammation in order to supply more blood to the damaged area (12). The problem with inflammation in the brain is that there is an enclosed volume so this causes a pressure build-up which can alter brain function (23). A way to prevent glial proliferation and suppress this response would be by inhibiting the cell cycle in CNS tissue. In comparison to other areas of the body the brain does not have much tolerance for new cell growth after maturity (25). This is to protect the carefully mapped neuronal networks and a traumatic brain injury can cause already mature neurons to undergo cell cycle activation which leads to neuronal apoptosis. The drug flavopiridol effects the cyclic-dependent-kinase (CDK) inhibition which is the kinase signaling that controls mitotic steps in the cell (9). In human trials flavopiridol specifically blocked cell

cycle activation in neurons, astrocytes and microglia. Another inhibitor called roscovitine has demonstrated its ability to inhibit CDK causing a reduction in microglial activation, neuroinflammation and neurodegeneration weeks post injury.

The examples above are options that have shown promising results in clinical trials but more possible anti-inflammatory treatments for the brain are still being developed. For example, erythropoietin is a glycoprotein native to the blood. It also has demonstrated neuroprotective properties by altering a variety of cellular and subcellular processes including suppression of apoptosis, inflammatory and antioxidative stress (9). This medication has not yet made it to human trials but has been very successful in the animal trials of TBI. A debate with many of these anti-inflammatory and cell cycle inhibiting drugs are what the possible long-term effects will be (9). For example, initially the drug class statins proved to be effective in treating the secondary symptoms of a TBI but case studies showed that long term side effects resulted in attention deficits, memory loss and decreased psychomotor speed. Statins are used in medicine for a variety of different reasons and now come with a FDA placed warning for possible cognitive side effects (9).

Biopharmaceuticals: The previously mentioned treatments are considered pharmacological interventions but promising advancements based on preclinical studies have focused on the use of biologics (stem cells, gene therapy).

Neural stem cells and mesenchymal stem cells have shown the ability to restore and

regenerate the damaged area of the brain in mouse models, therefore theoretically this would do the same in humans. The problem is that these stem cells have proven difficult to reach without damaging the brain (5). The number of available neuroblast (stem cells of the brain) also decreases with age placing a high demand for these neuroblast in age related cases of neurodegeneration in comparison to TBI. Another potential effective biological application would be controlling the translation process in gene expression. For example, the inhibitory pathway that leads to RhoA activation comes after a traumatic brain injury (9). This is used to suppress neuronal growth after damage has occurred in an attempt to limit possible spreading of a pathogen. If the activation of this pathway is blocked by dephosphorylating, then there is potential for neuron growth and regeneration. The inhibitor used would be called a ROCK inhibitor and could be an effective adjuvant to biologics for enhancing recovery from TBI (9).

Noninvasive interventions:

Two potential non-invasive therapies have possible benefits for TBI victims, those being physical exercise and transcranial magnetic stimulation (TMS) (30). Both have shown very effective results in pre-clinical studies. These have evoked neuroplasticity changes which ultimately lead to recovery of pre-injury functionality (30).

Conclusion:

CTE has a delayed pathology and this caused the disease to receive less attention than warranted, which delayed action to fund research towards effective treatments and a possible cure (24).

Although the discovery of CTE happened decades ago, the recent correlation with football has made it a lightning rod for conversation. With increased influence from the public, more funding for research backed by the National Football League. As of now there have been no proven cures for CTE, it must also be noted that having a concussion does not guarantee you will have this disease. Multiple concussions have been correlated with onset CTE but there are many people who have experienced multiple concussions with no evidence of the disease (24). The most effective treatment to CTE in the general population has been to limit or eliminate the risks of concussions. In all levels of football targeting a player's head can lead to ejection on top of newer helmets that absorb kinetic energy better than previous years (13). Combat sports have altered their rules to protect heads better, the United States military has spent millions of dollars creating helmets to help with blast shockwaves (4). If preventative measures fail, then concussions must be treated with better urgency; many victims believe they are not a problem but slowly that mindset has begun to change. With the seemingly effective diagnosis protocol developed by Dr. Omalu if CTE is suspected no longer will health care providers wait until after death to observe neural tissue and effective attempts to stop pathogenesis will occur (18). In CTE confirmed live patient's medications can be used in trials to determine what is effective and ideally cure the disease. Better dieting, and supplements have been shown in mouse models to prevent the onset of CTE and also directly help

with concussion recovery and prevention in mouse observations. The fatty acid omega-3 has shown this ability (26). Long term trials are being conducted on whether or not this prevents CTE in humans.

Appendix A

The citations in this review were done with APA format using the scientific numbering method. In the bibliography the sources are placed in alphabetical order, with the numbers showing the order of citation added to this paper.

Appendix B

My external reviewers Dr. Michael J Boxenbaum and Dr. Scott Torness insisted that the content of this paper was sufficient. The only suggestions made to me were to keep a consistent tone/ flow throughout the paper and use citations even if I felt I knew the material without reading it in a journal. I have done my best to incorporate this advice.

Bibliography

1. Ballatore, Carlo, Virginia M. Y. Lee, and John Q. Trojanowski. "Tau-Mediated Neurodegeneration in Alzheimer's Disease and Related Disorders." *Nature Reviews Neuroscience* 8.9 (2007): 663-72. Print.
2. Brenner, Lisa A., et al. "Growing Literature but Limited Evidence: A Systematic Review Regarding Prebiotic and Probiotic Interventions for Those with Traumatic Brain Injury and/or Posttraumatic Stress Disorder." *Brain Behavior and Immunity* 65 (2017): 57-67. Print.
3. Cao, Jiqing, et al. "ApoE4-Associated Phospholipid Dysregulation Contributes to Development of Tau Hyperphosphorylation after Traumatic Brain Injury." *Scientific Reports* 7 (2017): 11372. Print.
4. Chu, Jeffrey J., et al. "Development of a Multimodal Blast Sensor for Measurement of Head Impact and over-Pressurization Exposure." *Annals of Biomedical Engineering* 40.1, Sp. Iss. SI (2012): 203-12. Print.
5. Doherty, Colin P., et al. "Blood-Brain Barrier Dysfunction as a Hallmark Pathology in Chronic Traumatic Encephalopathy." *Journal of Neuropathology & Experimental Neurology* 75.7 (2016): 656-62. Print.
6. Karetko, Magdalena, and Jolanta Skangiel-Kramska. "Diverse Functions of Perineuronal Nets." *Acta Neurobiologiae Experimentalis (Warsaw)* 69.4 (2009): 564-77. Print.
7. Lindsley, C. W. "Chronic Traumatic Encephalopathy (Cte): A Brief Historical Overview and Recent Focus on Nfl Players." *Acs Chemical Neuroscience* 8.8 (2017): 1629-31. Print.
8. Patel, Sarjubhai, and Thomas Rau. *Detection of Traumatic Brain Injury. The University of Montana assignee. Patent US 09605315. 2017.*
9. Pearn, M. L., et al. "Pathophysiology Associated with Traumatic Brain Injury: Current Treatments and Potential Novel Therapeutics." *Cellular and Molecular Neurobiology* 37.4 (2017): 571-85. Print.
10. Perry, D. C., et al. "Association of Traumatic Brain Injury with Subsequent Neurological and Psychiatric Disease: A Meta-Analysis." *Journal of Neurosurgery* 124.2 (2016): 511-26. Print.
11. Salberg, S., et al. "Assessment of a Nutritional Supplement Containing Resveratrol, Prebiotic Fiber, and Omega-3 Fatty Acids for the Prevention and Treatment of Mild Traumatic Brain Injury in Rats." *Neuroscience* 365 (2017): 146-57. Print.
12. Watson, Richard L., Anthony B. Wood, and Gregory J. Archambeau. *Compositions and Methods for Treatment of Tauopathy. Revalerio Corporation assignee. Patent US 09492404. 2016.*
13. Wilde, E. A., et al. "Advanced Neuroimaging Applied to Veterans and Service Personnel with Traumatic Brain Injury: State of the Art and Potential Benefits." *Brain Imaging and Behavior* 9.3 (2015): 367-402. Print.
14. Yang, Sujeong, et al. "Perineuronal Net Digestion with Chondroitinase Restores Memory in Mice with Tau Pathology." *Experimental Neurology* 265 (2015): 48-58. Print.
15. Yang, S., Hilton, S., Alves, J. N., Saksida, L. M., Bussey, T., Matthews, R. T., . . . Fawcett, J. W. (2017). Antibody recognizing 4-sulfated chondroitin sulfate proteoglycans restores memory in tauopathy-induced neurodegeneration. *Neurobiology of Aging*, 59, 197-209. doi:10.1016/j.neurobiolaging.2017.08.002

16. Reilly, P., Winston, C. N., Baron, K. R., Trejo, M., Rockenstein, E. M., Akers, J. C., . . . Yuan, S. H. (2017). Novel human neuronal tau model exhibiting neurofibrillary tangles and transcellular propagation. *Neurobiology of Disease*, 106, 222-234. doi:10.1016/j.nbd.2017.06.005
17. McKee, A. C., Cairns, N. J., Dickson, D. W., Folkerth, R. D., Keene, C. D., Litvan, I., . . . Grp, T. C. (2016). The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathologica*, 131(1), 75-86. doi:10.1007/s00401-015-1515-z
18. Omalu, B., Small, G. W., Bailes, J., Ercoli, L. M., Merrill, D. A., Wong, K.-P., . . . Barrio, J. R. (2018). Postmortem Autopsy-Confirmation of Antemortem F-18 FDDNP-PET Scans in a Football Player With Chronic Traumatic Encephalopathy. *Neurosurgery*, 82(2), 237-246. doi:10.1093/neuros/nyx536
19. Nicholls, J. G., & Paton, J. F. R. (2009). Brainstem: neural networks vital for life. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 364(1529), 2447-2451. <http://doi.org/10.1098/rstb.2009.0064>
20. Messé, A., Rudrauf, D., Benali, H., & Marrelec, G. (2014). Relating Structure and Function in the Human Brain: Relative Contributions of Anatomy, Stationary Dynamics, and Non-stationarities. *PLoS Computational Biology*, 10(3), e1003530. <http://doi.org/10.1371/journal.pcbi.1003530>
21. Rajmohan, V., & Mohandas, E. (2007). The limbic system. *Indian Journal of Psychiatry*, 49(2), 132-139. <http://doi.org/10.4103/0019-5545.33264>
22. Clacy, A., Goode, N., Sharman, R., Lovell, G. P., & Salmon, P. M. (2017). A knock to the system: A new sociotechnical systems approach to sport-related concussion. *Journal of Sports Sciences*, 35(22), 2232-2239. doi:10.1080/02640414.2016.1265140
23. Haslund-Vinding, J., McBean, G., Jaquet, V., & Vilhardt, F. (2017). NADPH oxidases in oxidant production by microglia: activating receptors, pharmacology and association with disease. *British Journal of Pharmacology*, 174(12), 1733-1749. doi:10.1111/bph.13425
24. Hazrati, L.-N., Tartaglia, M. C., Diamandis, P., Davis, K. D., Green, R. E., Wennberg, R., . . . Tator, C. H. (2013). Absence of chronic traumatic encephalopathy in retired football players with multiple concussions and neurological symptomatology. *Frontiers in Human Neuroscience*, 7, 222. doi:10.3389/fnhum.2013.00222
25. Igarashi, M., Takeuchi, K., & Sugiyama, S. (2017). Roles of CSGalNAcT1, a key enzyme in regulation of CS synthesis, in neuronal regeneration and plasticity. *Neurochemistry international*. doi:10.1016/j.neuint.2017.10.001
26. Lewis, M. D. (2016). Concussions, Traumatic Brain Injury, and the Innovative Use of Omega-3s. *Journal of the American College of Nutrition*, 35(5), 469-475.
27. Zhao, N., Liu, C.-C., Qiao, W., & Bu, G. (2018). Apolipoprotein E, Receptors, and Modulation of Alzheimer's Disease. *Biological Psychiatry*, 83(4), 347-357. doi:10.1016/j.biopsych.2017.03.003
28. Koch, G., Di Lorenzo, F., Loizzo, S., Motta, C., Travaglione, S., Baiula, M., . . . Martorana, A. (2017). CSF tau is associated with impaired cortical plasticity, cognitive decline and astrocyte survival only in APOE4-positive Alzheimer's disease. *Scientific Reports*, 7, 13728. doi:10.1038/s41598-017-14204-3

29. Crossman AR, Neary D. *Neuroanatomy*. 2nd. London: Churchill Livingstone; 2000.

30. Maass, A., Lockhart, S. N., Harrison, T. M., Bell, R. K., Mellinger, T., Swinnerton, K., . . . Jagust, W. J. (2018). Entorhinal Tau Pathology, Episodic Memory Decline, and Neurodegeneration in Aging. *Journal of Neuroscience*, 38(3), 530-543. doi:10.1523/jneurosci.2028-17.2017