How does chronic traumatic encephalopathy correlate with depression induced by traumatic brain injuries?

Interdisciplinary Medical Sciences Capstone

The Florida State University
Abstract

Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disorder that pathologically results in tau proteins similar to those of Alzheimer’s disease when the affected individual has experienced multiple traumatic brain injuries (TBI) over time. As CTE can only be diagnosed post humously, its pathophysiological mechanisms are only basically understood. However, scholars have generally concluded that the pathway of CTE is as follows: 1) multiple TBIs, 2) neuroinflammation, 3) production of a pathological tau protein which typically induces neurodegeneration. Due to traumatic brain injuries sometimes leading to permanent brain damage which can inhibit neuropsychological coping mechanisms, TBIs are sometimes associated with emotional instability which may result in symptoms such as increased aggression and depression. It is hypothesized that there will be a positive correlation between CTE and TBI-induced depression with a biopsychological pathway as follows in chronological order: multiple TBIs, neuroinflammation, neuroprotein production, development of CTE prior to death, cerebral atrophy (through CTE) which hinders psychological coping mechanisms for daily stressors, and the development of depression. To explore the aforementioned possibility, four expert interviews were conducted. Each interviewee was asked 5 questions related to their experience with CTE and TBI patients experiencing depression. The qualitative results exhibited a positive correlation between CTE and TBI-induced depression and supported the proposed pathway but did not solidify the conclusion of causation. Thus, the hypothesis was concluded to be valid based on the qualitative data retrieved from the interviews and the review of literature.

Key Words: Chronic Traumatic Encephalopathy, CTE, Traumatic Brain Injury, TBI, Alzheimer’s Disease, Depression, Neuropathology, Tau Protein, Neurology, Neuroinflammation.
The investigation of a link between chronic traumatic encephalopathy and TBI-induced depression is clinically relevant for the neuropsychiatric well-being of the patient. While depression is generally well understood, its position in the context of patients with TBIs has not been as elucidated academically. The human brain is a complicated organ in its normal state, making its study significantly more difficult when it has been damaged to a state of abnormality as not all regions are as neurologically susceptible to trauma as others. This study is further complicated when discussing multiple TBIs in a lifetime as CTE may consequentially develop from chronic neuroinflammation that produces a lethal tau protein.

It is intuitive to speculate at face-value that long-term brain damage/injuries can result in behavioral disorders as the brain’s emotional complexes may be impaired. However, the psychological and physiological mechanisms are not as clear. Therefore, the goal of this study is to determine whether or not such a correlation exists between TBI-induced depression and chronic traumatic encephalopathy via the proposed pathway from cross-examining the relevant literature to multiple expert interviews to produce a more definitive conclusion.

Review of Literature

Chronic traumatic encephalopathy has been linked to a variety of psychiatric disorders due to its extensive neurodegeneration that include depression, apathy, and suicidal behavior (Antonius et al., 2014; Wortzel, Brenner, Arciniegas, 2013; Mahar, Alosco, McKee, 2017). However, the diagnosis of CTE as well as its causal relationship with these disorders remain difficult to study due to the diagnosis requiring post-humous conditions. It is because of these
difficulties that the topic remains controversial within academia as scholars debate between the possible causal and correlative relationships of CTE and its symptoms; one of the most signature and recognizable symptoms of CTE is not behavioral, but biochemical: patients with CTE have usually developed a tau protein similar to that of Alzheimer’s disease that spatially competes with the brain in its continuous diminishment of volume (Ling, Neal, Revesz, 2017; Shively et al., 2017; Iverson, Keene, Perry, Castellani, 2018). While this tau protein is considered to be useful in its protein sequencing and composition analyses for the purpose of CTE diagnoses, its exact composition is also controversial as the temporal aspects of its growth are not fully understood (Thomsen et al., 2017). Instead, its quantitative development is being studied so that CTE severity can also be concluded. However, it has been found that CTE protein deposits generally increase with an increase in brain injury quantities, establishing CTE’s positive correlation with repetitive brain injuries while also supporting the proposition of interviewing more CTE experts and healthcare professionals regarding the impacts of CTE altogether (McKee & Robinson, 2014; Brody, Benetatos, Bennett, Klemenhagen, Mac Donald, 2015; McAllister & McCrea, 2017).

Depression, on a neurobiological level, also demonstrates physiological complexity that challenges scientists to properly resolve and clarify (Ferrari & Villa, 2017). Similar to CTE, these complications have led to various hypotheses on the origination of depressive episodes and their physiological long-term effects which include an increase in heart disease and a decrease in immune system functions over time. However, the causal link between depression and CTE remains unestablished due to CTE’s post-humous neuropathology/retroactive evaluation and depression’s highly various episodic severity (Yuan & Wang, 2018).
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The severity of depression is also prone to change in the context of traumatic brain injuries (TBI). Its onset, maintenance, and resolution are all currently being researched in the post-TBI context so that clinical and rehabilitative treatments may be further improved to account for the neurotrauma. An example of such would be the recommendation of the participation of meaningful roles and pleasant activities to combat depressive symptoms after a TBI which provides another means for physicians to recommend therapeutic psychiatric treatment (Bombardier et al., 2017). However, depression continues to be clinically relevant due to not only its long-term persistence but also due to its positive correlation with suicidal behavior, an even more serious psychiatric discussion that supports the idea of gathering more expert-based information from the healthcare field to also understand the effects of CTE (Ng, C., How, Ng, Y., 2017).

Regarding treatments for depression, the heterogeneous nature of pathological symptomatic behavior has proven to be a challenge for quantitative methods of more profound depressive screenings (Ferrari & Villa, 2017). The authors discuss various physiological hypothesis regarding depression and its treatments. The issue of a latency period of several hours or weeks from pharmacological methods was discussed as it showed that some patients require urgent treatment effectiveness. Thus, therapeutic methods via verbal communication with a behavioral professional were highlighted to provide such urgent services. However, it has also been demonstrated how a combination of such methods would be the most logical approach as the specific causal factors of depression are still unknown and are currently being studied vigorously. In summation, depression has been described as a heterogeneous disease due diagnostic complexity and a wide variety of contributing factors, such as physiological and behavioral, that complicate the customization of the treatment process.
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Suicide is a grievous topic that tends to evoke tragic discussions and interpretations of disheartening events or memories. Within the discussion of CTE, its relevance is underscored by CTE’s neuropathology as some victims of suicide (usually athletes or military personnel) were later discerned to have the neurodegenerative condition (Abreu, Cromartie, Spradley, 2016; Iverson, 2014; Lehman, Hein, Gersic, 2016). Thus, CTE’s link to depressive and suicidal behavior was formed which triggered an international academic and clinical coalition against its negative physiological effects and diagnostic uncertainties.

An example of CTE-related suicide research is the study of individuals of the German federal state of Hamburg (Matschke et al., 2018); all examinees were victims of suicide that were tested for the Alzheimer’s disease-like tau protein found in CTE. The study concluded that the relevance of age among the victims was severely limited even though each non-control group’s protein was dissimilar to the official tauopathies recognized as CTE due to there being a lack of usable data to causally solidify CTE with victims of suicide. Furthermore, it was found that it may be more utilitarian for further research to focus on intact cognition of individuals at high risk of CTE performing complex acts so that their level of cognitive function may be analyzed in a more depressive/suicidal context. This also demonstrates that investigating more groups similar to the Hamburg individuals from a CTE-oriented perspective would be both necessary and plausible for academic study.

Physiologically, mood regulation protein/neurotransmitter levels have been found to be significant for clinically-oriented studies of treatment options for depressive symptoms induced by TBIs and/or CTE altogether (Bodnar, Morganti, Bachstetter, 2018). TBIs have been described as a public health crisis. Neurologically, an empirical association was found between chronic neuroinflammation and depression among TBI patients. Negative effects of this association were
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found to be an increased risk of depression which would not only affect daily activities but susceptibility to dementia during the aging process. However, the authors repeatedly explained how there was a prominent lack of scholarly evidence to profoundly conclude on the exact role of inflammation. The basis of such conclusions was said to be possibly related to cytokine levels in the brain that may alter mood regulation capabilities of the patients, underscoring the need to research cytokine levels’ impacts on depression. It has also been found that such research may be supplemented by neuroimaging techniques and the use of chemical agents such as sodium selenate (Sundman, Murali Doraiswamy, Morey, 2015; Tan et al., 2016).

Specifically speaking in the military context, personnel may be strongly impacted by the behavioral/functional effects caused by concussive episodes (Beran & Bhaskar, 2018). The authors explain how two patients, both military personnel, were studied after having blast-induced traumatic brain injuries. It was found that TBIs may generally inhibit military personnel activity/operations, especially due to clinical evaluations. However, it was shown how common bed-side clinical studies were not as effective as ones that were carried out by neurological evaluations conducted by computer imaging as the former was discerned to be unreliable, a useful piece of information to know when studying TBIs and CTE. Furthermore, it was stated that a lack of self-reporting by TBI patients was evident as some personnel would fear that it would hinder opportunities related to their careers, signifying social stigmatization of TBI/concussion patients.

In the context of sports, similar repercussions to those of military personnel have been observed with the most unfortunate symptomatic behavior being related to suicide (Abreu et al., 2016). It has been shown by the source how chronic traumatic encephalopathy can be discovered in a victim of suicide such as in the case of Mike Webster, an NFL player. Exposure to repeated
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Traumatic brain injuries is further underscored in the case of CTE as an alarming number of athletes prone to head injuries is being correlated with a national increase in the risk of suicide. The source’s results display that very correlation, which was only previously speculated, establishing a causal relationship overall. The primary means of showing this relationship are through a display of testimonial evidence. As depression remains a causal factor of suicide, it can be retrospectively deduced that depression was also present among the CTE-prone individuals that contributed to the testimony.

With the nature of suicide being highly inflammatory to discuss, it incites the action of various populations and their voices which introduces another complication to its academic study and conceptualization: politics. Due to many CTE patients being former athletes and military personnel (high risk of brain injuries), the resolutions of their own clinical cases are more likely to be politically magnified by the media, further complicating their examinations (Stein, Alvarez, McKee, 2014). This political/academic controversy has led to scholars debating the credibility of various studies due to insinuations of extreme speculation of CTE causation, increasing academic standards of investigation through these confounding/unorthodox pressures (Solomon, 2018). Furthermore, while some physiological mechanisms have been linked to suicidal ideation such as in the case of frontal lobe dysfunction, the physiological connection to CTE has not been sufficiently solidified (Belderbos & Shah, 2003).

With regard to other difficulties in CTE study, a significant level of selection and reporting bias has been identified (Antonius et al., 2014). This has been because of a lack of randomized data, primarily due to the diagnosis being post-humous. Furthermore, it is likely that the families of the autopsied individuals for CTE testing were particularly concerned about neurocognitive impairments with possible neuropathological suspicions. Another contribution of
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this bias was that the majority of personality and behavioral changes reported were done by
family members, next-of-kin, and other acquaintances, making communication with the patients
before death virtually unfeasible. With this in mind, one may speculate that Antonius et al. would
agree with the notion of acquiring more information from various healthcare professionals and
families of CTE victims to corroborate current CTE research findings, thus minimizing bias as
much as possible.

Method
The goal of this study is to qualitatively determine whether or not a correlation exists while
exploring the possibility of causation between TBI-induced depression and chronic traumatic
encephalopathy from cross-examining the relevant literature to multiple expert interviews.

Sample
4 experts on traumatic brain injuries, depression and chronic traumatic encephalopathy were
interviewed: physicians (1 neurologist and 1 neurosurgeon), 1 social worker, and 1
neuroscientist (Ph.D.). Holistically, they represent a diverse pool of professionals who are
experienced in working with patients who are at risk of chronic traumatic encephalopathy. While
still an expert in TBIs and CTE of humans, the neuroscientist had conducted extensive research
on animal models such as rats, showing their significant academic credibility to be interviewed.

Procedures
For clarity, consistency, and efficiency, each of the 4 interviewees was asked the same 5 focus
questions. However, the neuroscientist was interviewed in the context of their research subject
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matter which was via an animal model: rats. Therefore, Question 1 was slightly modified to adapt to the researcher’s medium (“research subjects” instead of “patients”). Each interviewee was given a disclaimer form for the purpose of informed consent which provided authorization for them to be recorded and transcribed verbatim. No follow-up questions were asked, but if an interviewee required clarification of the original question being asked, an explanation was provided. Each interviewee was permitted to elaborate at their own discretion. All interview questions were designed solely by the principal investigator and were produced to efficiently challenge the hypothesis from the foundational information acquired from the review of literature.

Materials

Each interviewee was recorded with a personal recording device and 3 out of the 4 were interviewed via a telephone call. The interview questions were designed solely by the principal investigator and were meant to challenge the hypothesis from the perspective of the review of literature.

Results

After conducting the expert interviews and reviewing the relevant literature, it was concluded that the correlation between chronic traumatic encephalopathy and traumatic-brain-injury-induced depression is clinically undeniable. However, the establishment of causal linkage between CTE and TBI-induced depression was not sufficiently bolstered by the found qualitative data (potential counterarguments). Therefore, conclusions regarding the causation between CTE
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and TBI-induced depression cannot be made. Nonetheless, the hypothesis of a positive correlation via the proposed pathway was validated with the causal factors being sufficiently explored.

**Interview Question 1:** How many patients of traumatic brain injuries have you encountered?

Answers to this question ranged from “dozens” to “hundreds” of patients. Designed to evaluate the level of expertise of the interviewees, each interviewee was concluded to be adequately qualified to be questioned about CTE and TBIs in the context of Question 1.

**Interview Question 2:** Have any of your patients and/or research subjects with TBIs demonstrated symptoms of depression and/or any similar emotional disorder?

The purpose of this question was to establish an academic foundation for TBI-induced depression and to prepare each interviewee for the context of the research question beyond the more basic qualities of TBIs and CTE. All interviewees stated that they had patients/research subjects with TBIs exhibit depressive behaviors and indicated that most cases of such depression were most likely induced by their traumatic brain injuries. General emotional instability was also noted as a common symptomatic demonstration of TBIs.
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**Interview Question 3:** What is your experience with chronic traumatic encephalopathy in comparison to your years of practice/study?

As CTE is closely related to TBIs, all interviewees’ responses were similar to those of Question 1. Nonetheless, the purpose of Question 3 was to demonstrate specialized credibility in CTE and to quantify a range of practice/study among the expert interviewees. All interviewees stated that their understanding of CTE had been cultivated throughout the majority of their clinical/academic careers. Their individual expertise ranged from 10 to 40 years in the field.

**Interview Question 4:** In your expert opinion, do you believe that CTE has a possible positive correlation with TBI-induced depression? How do you know?

Question 4 was designed to directly challenge the hypothesis of a positive correlation without priming the interviewees to excessively speculate on causal factors between TBI-induced depression contributing to CTE. However, the positive correlation was stated to be “absolutely” evident by 2 of the interviewees and similarly corroborated by the remaining 2 experts as the question also required affirmation of evidence through an explanation of the development of CTE. As established by the review of literature, the interviewees articulated the physiological process of CTE being as follows: multiple TBIs, neuroinflammation, development of protein accompanied by cerebral atrophy, impairment of biopsychological function, and eventually patient death. The most informative response was by the neurosurgeon: when questioned on how they knew with confidence that there is a correlation between CTE and TBI-induced depression they stated, “Because I have seen it myself from professional experience. We do not know
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enough yet about CTE to describe the exact reasons for why it happens, but when people are experiencing multiple traumatic brain injuries in a lifetime, their brains are bound to experience long-term damage from that. It used to be drunk driving, but now it’s technological distractions such as texting or car entertainment systems.”

**Interview Question 5:** How would you approach treatment/prevention plans regarding CTE patients exhibiting signs of depression?

Question 5 tended to produce the most complicated responses with each expert interviewee distinguishing themself with their academic and clinical perspectives on the best approach to resolutely hinder the development of CTE/TBI neuropathology. As the sample consists of 2 physicians and 2 experts who are not physicians, clinical opinions naturally differed. Both physicians recognized prevention as being the most effective means to limiting the population of patients who have experienced traumatic brain injuries. The neurosurgeon recommended that “the best way to solve this is by prevention, which is best done through a combination of education and policy.” However, the neuroscientist, similarly to the social worker, recommended “more awareness” as the best solution while supporting the utilization of a “concussion protocol” in sports to combat CTE/TBI damages, especially when potential victims of TBIs are children. The neurologist favored an increase in research-oriented clinical advances as they believed that clinical medicine, not policy, carried the majority of the burden in extinguishing CTE/TBI risk factors such as improved technological advances for “preventive screening.”
Discussion

Conclusions

After conducting the expert interviews and completing the review of literature, it was concluded that while there is an evident correlation between TBI-induced depression and chronic traumatic encephalopathy, the plausibility of causation remains unclear. However, the proposed pathway was found to be both logically and clinically plausible. Thus, the hypothesis of a positive correlation between CTE and TBI-induced depression under the proposed pathway was concluded to be valid. Currently, research is still being conducted by clinicians and neuropathologists to determine the biochemical mechanisms of CTE and their similarities to the tau proteins/plaques found within cerebral tissue of patients with Alzheimer’s disease (Ling, Neal, Revesz, 2017). Behaviorally, most experts agree that it is the long-term damage done to the brain that leads to a loss of executive function to the cerebral cortex and limbic system (Shively et al., 2017). This damage most likely hinders the individual’s ability to cope with stressors and promote positive, non-destructive behaviors. As the degeneration progresses, the patients experiencing CTE become more susceptible to depression and other similar disorders. Therefore, the formally proposed pathway describing the correlation of CTE and TBI-induced depression via potential causal factors was found to be as follows in chronological order: multiple TBIs, neuroinflammation, neuroprotein production, development of CTE prior to death, cerebral atrophy (through CTE) hinders psychological coping mechanisms for daily stressors, development of depression which could lead to patient self-harm, and eventually patient death which may directly result from the physical/anatomical impacts of CTE on the human brain.

The biopsychological logic of the proposed CTE behavioral pathway was constructed from 3 academic phases similar to the elements of a language: 1) analysis of the foundations of the
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review of literature which provided the academic “vocabulary” of the proposal, 2) analysis of qualitative data from expert interviews which provided the “grammar” of the proposal, and 3) fusion and expression of neurophysiological/biopsychological concepts between the review of literature and interviews which formed the overall logic (“language”) of the proposed pathway.

Limitations

Limitations of the proposed biopsychological logic primarily include the possibility of a confounding variable which was acknowledged by 3 of the 4 expert interviewees, serving as a potential counterargument. However, after conducting the interviews, it can be concluded that the counterargument’s perspective is unlikely due to the extensive quantity of clinical evidence in favor of a positive correlation between CTE and TBI-induced depression. Similarly, the rationale of the proposed pathway was discerned to be the most logical as the interviewed experts described the neurobiological and behavioral concepts (i.e. tau proteins, loss of brain volume, loss of executive function etc.) involved in both CTE and TBIs. Furthermore, scholars have admitted the possibility that the depression thought to be induced by TBIs/CTE could be caused by an external factor as many individuals have experienced depression in their lifetimes which was specifically mentioned by both physicians. Thus, the exact evidence of causation requires further academic elucidation through trials distinguishing between patients exhibiting depressive behaviors who have and have not experienced a traumatic brain injury.

Further Research

It is recommended that more research be conducted towards preventive methods against CTE/TBI-related depression towards population subsets that are at the greatest risk of TBIs:
military personnel and athletes who participate in high-impact sports. As both groups are more likely to experience blunt-force trauma to the head, their exposure to physical trauma can be devastating in the long-term. Therefore, research involving the improvement of educative methods of CTE/TBI awareness would promote overall societal change which would be especially helpful in the context of TBIs from car accidents relating to texting and driving and similar driving distractions. Though experts have underscored the necessity of prevention, biochemical and neuropathological research towards understanding the neurochemical pathways involved in the diseases would still be hugely beneficial to the introduction of a cure. Lastly, more behavioral studies indicating psychiatric phenotypes of CTE would accelerate the process of eventually being able to diagnose it before the death of the patient, which would exponentially simplify the means of researching CTE and TBIs altogether.

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Appendix A

Purpose and Risk Document

How does chronic traumatic encephalopathy correlate with depression induced by traumatic brain injuries?

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PURPOSE OF STUDY
1) To determine whether or not there is a correlation between depression and chronic traumatic encephalopathy and to investigate possible causations
2) To explore current clinical knowledge regarding TBI/CTE-related depression

STUDY PROCEDURES
1. You will be asked five questions related to the research question.
2. The researcher, with your permission, will record your responses verbatim.
3. The interview will take approximately 15-20 minutes (more time is available for questioning if interviewee wishes to elaborate).

CONFIDENTIALITY
Findings will be presented in a poster format at a symposium as an educational exercise to satisfy a course requirement for the Interdisciplinary Medical Sciences Bachelor of Science Degree.

This study will not be published or submitted to a journal.

Your responses during the interview will be anonymous. Every effort will be made to preserve your confidentiality.

Participant data will be kept confidential except in cases where the researcher is legally obligated to report specific incidents. These incidents include, but may not be limited to, incidents of abuse and suicide risk.
VOLUNTARY PARTICIPATION

Your participation in this study is voluntary. You are free to withdraw at any time. Please tell the researcher/interviewer if you are uncomfortable with the responses being transcribed or digitally recorded.

Thank you in advance.

QUESTIONS FOR RESEARCHER

If you have any questions related to the purpose, risk, or consent related to this paper, then please do not hesitate to contact the principal investigator.

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