Chronic Traumatic Encephalopathy (CTE) is a progressive degenerative disease of the brain known to occur in individuals who have sustained repeated brain injuries such as concussions. The condition was historically associated with boxers, but recent studies identifying CTE in retired football players have attracted widespread interest. CTE has also been recognized in participants in other contact sports, military veterans, and domestic abuse survivors. The physical pathology and the social and psychiatric implications of the disorder are under increased investigation.

Clinical Presentation

- Investigators have described CTE as “a composite syndrome of mood disorders and neuropsychiatric and cognitive impairment.”
- Visible symptoms of CTE typically arise between the ages of 35 and 60.
- CTE is often divided into three common clinical presentations or “subtypes.”
  - Subtype 1
    - Occurs at an earlier age of onset (average: 34.5 years).
    - Is characterized predominately by mood and behavioral abnormalities. These can include:
      - Paranoid thoughts, social phobias, exaggerated responses to stress, highly inconsistent (labile) mood, hyperactivity, disinhibition, major depression, insomnia, suicidality.
    - Many patients within this group eventually display cognitive symptoms, as well.
    - Patients in this group are often more explosive, out of control, physically and verbally violent, and depressed than those in the second subtype.
  - Subtype 2
    - Presents at a later age (average 58.5 years).
    - Is characterized by cognitive deficiencies including:

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4 Omalu et al. (2011).
• Dementia, disorientation, memory loss, speech impairment, difficulty processing information and making decisions, especially in relation to work performance and management of finances.
  ▪ Symptoms may eventually extend to speech and gait abnormalities, including Parkinsons-like tremors, decreased facial expression, and rigidity.  
  ▪ Significantly fewer subjects in this subtype demonstrate behavioral and mood changes during the course of their illness.
    ○ A third group displays symptoms combining those of the previous two subtypes.

Pathology

- CTE develops subsequent to repeated mild traumatic brain injuries (mTBIs) such as concussions.
  ○ In a concussion, rapid acceleration, deceleration, or rotation (whipping around) of the head can cause the brain to collide with the inside of the skull. Such movements may cause the brain to elongate, stretching individual components such as neurons, glial cells, and blood vessels and damaging them.
- Because not all cases of CTE occur in individuals who have experienced concussions, researchers believe that “subconcussive” blows may also play a role in development of the disorder.
- Though similar, symptoms of CTE are nevertheless distinct from those of concussion itself.
  ○ Clinical symptoms of CTE typically appear years or even decades after the last brain trauma, whereas the effects of concussion are perceptible almost immediately.
  ○ CTE symptoms are more acute than those that characterize a concussion.
- On autopsy, the brains of individuals suffering from CTE reveal distinct signs of damage and change.
  ○ Gross Pathology
    ▪ Investigators have observed visible damage to brain tissue, including atrophy to the frontal and temporal lobes, thinning of the corpus callosum, enlargement of the cavum septum pellucidum, and cerebellar scarring.
  ○ Neuropathology

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8 Stern et al (2013).
13 McKee et al (2014); Andrew E. Budson, Paul R. Solomon (2016). “Contact Sports That Have Been Associated With Multiple Concussions” in Memory Loss, Alzheimer’s Disease, and Dementia (Second Edition).
On microscopic examination, investigators have noted a range of injuries to CTE brains, including microhemorrhages and damage to the axons of nerve cells. A high rate of death among nerve cells is also observed.\textsuperscript{14}

Investigators also observe accumulation of an abnormal form of tau protein (p-tau), which can cause major interference with the function of the neurons.\textsuperscript{15}

- In advance cases, p-tau accumulation has been seen to spread through much of the brain.\textsuperscript{16}
- The deposits of p-tau observed in the brains of CTE patients are biochemically the same as the “plaques and tangles” found in the brains of patients with Alzheimer’s Disease, suggesting similarities between the conditions.\textsuperscript{17}
- It has been suggested that recurrent brain injury may activate pathologic mechanisms that are similar in both diseases.\textsuperscript{18}

- head trauma and degenerative disease cluster around boxing

**History**

- The earliest references to CTE-type disorders occur in the context of professional boxing, a sport in which participants were frequently said to be “punch-drunk,” or “slug-nutty” after repeated knock-outs.
  - Once begun, the condition worsened over time, even if the individual had long given up the sport.
- Though well-known to the lay public, it was not until 1928 that the disorder received clinical attention.\textsuperscript{19}


\textsuperscript{15} “Understanding Questions about Chronic Traumatic Encephalopathy (CTE)” Cdc.gov/Headsup.

\textsuperscript{16} Ibid.

\textsuperscript{17} It has been suggested that brain injury may activate a chronic neuroinflammatory response common to both conditions. Moretti L, Cristofori I, Weaver SM, Chau A, Portelli JN, Grafman J. Cognitive decline in older adults with a history of traumatic brain injury. *Lancet Neurol*. 2012;11(12):1103.

\textsuperscript{18} McKee et al (2014). o Nevertheless, significant differences exist between CTE and Alzheimer’s Disease. The first and most central symptoms of Alzheimer’s involve memory problems, while the initial symptoms of CTE generally include problems with judgment, reasoning, problem solving, impulse control, and aggression. In addition, symptoms of CTE tend to present earlier (in one’s 40s) than those of AD (in one’s 60s).https://www.bu.edu/cte/about/frequently-asked-questions/

In 1928, New Jersey Pathologist Harrison Martland examined 23 cases of retired fighters said to be “goofy,” and introduced the term “punch drunk syndrome” to describe the condition. Martland outlined a symptom complex characterized by unsteadiness of gait, mental confusion, and slowing of muscular movements among the fighters. These symptoms were sometimes paired with slowness of speech, tremors of the hands, and nodding of the head. Martland noted that a correlation existed between the number of fights (especially lost fights) and the severity of the condition. Martland’s findings reinforced a new and growing hypothesis that multiple head traumas were associated with distinct neurodegenerative problems.

Numerous studies followed Martland’s description, as did new terms to describe the condition. These included:

- “Traumatic Encephalopathy” (1934)
- “Dementia Pugilistica” (1937)
- “Chronic Traumatic Encephalopathy of Pugilists” (1940)

In this instance, investigators estimated that the disorder was present among 60% of boxers who fought professionally for more than 5 years.

Because CTE can only be diagnosed on autopsy, early studies were often based on the physical findings of one or two brains at a time, augmented by descriptions of other cases. In the second half of the 20th century, the existence of larger samples began to yield more information.

- In 1968, a postmortem examination of 15 brains (including those of 6 boxers) conducted by EE Payne, revealed scattered but extensive damage throughout the brains of the boxers.
- All possessed enlarged ventricles, scarring in the grey matter, and degeneration in the white matter.
- A 1973 case series conducted by Corsellis et al replicated and expanded the findings.

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21 Turner (2016).
24 Investigators noted that the condition occurred most often in “second rate fighters who are used for training purposes and are knocked out several times a day.” Bowman & Blau (1940).
25 Ibid.
• The group noted extensive damage to neurons as well as an abundance neurofibrillary tangles.
• Cerebral atrophy was marked, as was enlargement of the lateral and third ventricles.
• The authors concluded: “There is now a solid foundation for the view that some experienced boxers develop a clinical disorder, the greater part of which has a neuropathological basis.”
  o At the same time, reports of a “punch drunk state” among football players attracted clinical attention to this sport, as well.28
  o In 2005, a postmortem study of the brain of former NFL player Mike Webster demonstrated pathology similar to that of professional boxers.29
    ▪ Omalu et al noted that it was the first documented case of CTE in a retired professional NFL player.
    ▪ They identified it as a “sentinel case” drawing attention to unrecognized disease likely to be of high prevalence within the sport.
  o In 2008, the U.S. Department of Veterans Affairs, Boston University, and the Concussion Legacy Foundation together established the VA-BU-CLF Brain Bank to enhance the study of mild traumatic brain injury and CTE.
    ▪ Using this resource, McKee et al published the largest case series to date, analyzing the tissue of 85 individuals with confirmed CTE.30
    ▪ Of 580 brains, over 320 have been diagnosed with CTE.31

Risk

Attention to CTE has thus far been focused on a handful of groups known to be at elevated risk due to frequency of mild head trauma.

- Contact sports
  o The annual incidence of sports-related concussion in the United States is 1.6 to 3.8 million.32
  o Studies have estimated that likelihood of an athlete in a contact sport experiencing a concussion is as high as 20% per season.33

- Professional Football
  o Much attention has been brought to CTE due to increasing reports of dementia among American National Football League (NFL) players with a history of multiple concussions.

30 McKee et al (2013).
33 Ibid.
Multiple studies have of retired NFL players have noted significant cognitive deficits.\(^{34}\)

- One study of retired professional football players in 2005 found that those who experienced three or more concussions had a threefold increase in diagnosed depression and a fivefold increase in diagnosed mild cognitive impairment.\(^{35}\)
- One study published in 2012 found that retired NFL players died from neurodegenerative diseases at three times the rate of the general population.\(^{36}\)

In 2012, more than 4,500 former players brought a class action lawsuit against the NFL for willfully deceiving them about the effects of concussions and collisions endured on the field.

- In response to the filing, the NFL commissioned an actuarial report to evaluate the prevalence of neurodegenerative disorders such as Alzheimer’s, ALS, and dementia among players.
  - The report concluded that 33% of the plaintiffs (and 28% of players generally) would develop such a disease.
  - Those who developed CTE would do so at notably younger ages than the general population.\(^{37}\)
- The NFL settled the suit in 2013 for $765 million.
  - Concerns that the sum would be inadequate to cover the affected players prompted a federal judge to reopen it.
  - A new settlement in 2015 removed the $765 million cap on damages.
  - The ultimate cost to the NFL is estimated to be more than $1 billion.
- As evident of widespread CTE among players and former players continues to mount, fears persist that the settlement will be inadequate to cover the costs of managing the disorder.
  - In 2017, investigators published a study analyzing the brains of 202 deceased football players, and diagnosed CTE in 87% of them.
  - Among individuals who had played for the National Football League, 99% brains exhibited CTE.\(^{38}\)

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- Young Athletes
  - The NFL’s “concussion crisis” has sparked growing concern and increased research into the vulnerability of children and adolescents to developing CTE.
  - CTE has been diagnosed at autopsy in individuals as young as 17, and in contact sport athletes who only played sports through high school or college.\(^{39}\)
    - In football alone, an estimated 10% of college players and 20% of high school players in the United States sustain brain injuries each season.\(^{40}\)
    - One study noted concussions among 35% of high school football athletes.\(^{41}\)
    - Concussions among girls participating in high school soccer rank second only to boys’ high school football.\(^{42}\)
  - Participation in youth football may be dropping as a result of widespread concerns.\(^{43}\)
    - The annual number of news reports about tackle football and brain injuries markedly increased from 2009 to 2016.
    - Participation in tackle football decreased 4.93% during the same period, even while overall participation in high school athletics increased for other sports.
    - Investigators conjecture that the drop may have prevented as many as 14,436 concussions in 2016.

- Deployed Military Personnel
  - Active-duty military personnel and veterans are at high risk of moderate to and severe brain injury, a risk not limited to those who were engaged in active combat.\(^{44}\)
    - In 2008, the *New England Journal of Medicine* reported that 15% to 20% of Army infantry soldiers deployed for 1 year in Iraq had experienced 1 or more TBIs.\(^{45}\)
      - 5% reported injuries with loss of consciousness and 10% reported injuries with altered consciousness.\(^{46}\)

\(^{39}\) Harvard Medical School Psychiatry Neuroimaging Laboratory, “Chronic Traumatic Encephalopathy,” http://pnl.bwh.harvard.edu/education/what-is/chronic-traumatic-encephalopathy/
\(^{42}\) Marar et al (2012).
\(^{46}\) Ibid.
The mechanisms of injury (in order of frequency) included explosions, falls, motor vehicle accidents, and wounds from fragments, shrapnel, and bullets.  

- A 2018 study of veterans receiving care through the VA found that veterans who had experienced traumatic brain injury developed dementia twice as often as those who did not.

- **Domestic Abuse Survivors**
  - Victims of domestic abuse are known to experience blows likely to result in traumatic brain injury, and are among the populations currently being examined for increased prevalence of CTE.
    - Domestic attackers most often inflict trauma to the head, neck, and face, and may do so repeatedly over a period of years, a circumstance strongly associated with the development of CTE.
    - Approximately half of those who experience domestic violence report strangulation injuries, often to the point of losing consciousness.
      - In addition to cutting off the supply of oxygen or blood flow to the brain, strangulation injuries can lead to strokes and blood clots, constituting a severe form of TBI.
        - The neurologic effects of strangulation injury include altered mental status, seizures, stroke-like symptoms, and incontinence.
      - In one shelter sample, 68% of abused women seeking emergency support had experienced choking or attempted strangulation.

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47 Ibid.
• One study of attempted strangulation found that 34% of victims reported being strangled three to five times, with 23% reporting more than five attempted strangulation episodes.\textsuperscript{54}
  
  o Literature reviews suggest that the rate of injury and neuropsychological impairment experienced by victims of domestic violence correlates with that associated with CTE.
  
  ▪ Survivors of domestic assault often display debilitating psychological changes similar to those found in CTE, including paranoia, sleeplessness, agitation, depression, slurred speech, headaches, pain, vertigo and other physical symptoms associated with brain injury.
  
  ▪ In a 2002 study, survivors of domestic assault exhibited poorer performance than nonabused controls on measures of working memory, sustained auditory attention, and response inhibition.\textsuperscript{55}
  
- A dose response relationship exists between domestic violence and symptoms of CTE.
  
  o That is, the longer women experience domestic abuse, the more poorly they tend to perform on measures of memory, learning, and cognitive flexibility.
  
  o Longer exposure to intimate violence also correlates with higher levels of depression, anxiety, worry, and symptoms of post-traumatic stress.\textsuperscript{56}

**Recommended Analysis:**


