Risk of Dementia Following Traumatic Brain Injury: A Review of the Literature

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PATE REHABILITATION

Media Presence

Study: CTE, other brain diseases can start earlier if tackle football played before age 12

A.J. Perez, USA TODAY Sports Published 12:00 p.m. ET April 30, 2018 | Updated 2:20 p.m. ET May 1, 2018

CTE found in 99% of studied brains from deceased NFL players

By Daniella Emanuel, CNN
Updated 3:26 PM ET, Wed July 26, 2017

Media Presence

Brain Injury May Increase Risk of Alzheimer's Disease

People who have a history of traumatic brain injury (TBI) may be at risk for developing dementia or Alzheimer's disease earlier than those who didn't have a TBI.

Contact sports associated with Lewy body disease, Parkinson's disease symptoms, dementia

July 25, 2018, Boston University School of Medicine

Dementia

What is dementia?

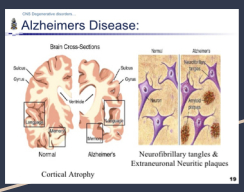
Dementia is a general term for a decline in mental ability that interferes with daily life.

- It is not a disease
- It is a general term describing a group of symptoms

Major neurocognitive disorder DSM-5 Criteria

- Evidence of cognitive decline in one or more of the following:
  - Complex attention
  - Executive Function
  - Learning and Memory
  - Language
  - Perceptual-motor function
  - Social cognition

Alzheimer's Disease (AD)



A diagnosis for individuals who have experienced cognitive decline related to onset and progression of Alzheimer's Dementia (a neurological disorder related to the inclusion of beta amyloid plaques and neurofibrillary tangles in cholinergic neurons).

DSM-5 Diagnostic Criteria

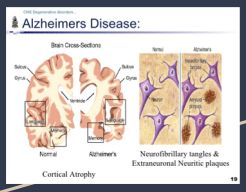
A. Diagnostic criteria for major or minor neurocognitive disorder
B. Insidious onset and gradual decline of cognitive function in one or more areas
C. Diagnostic criteria for Alzheimer's dementia are fulfilled by:

(1)Presence of genetic mutation based on family hx or genetic testing

(2) Steady cognitive decline without periods of stability

(3) No indicators of other psych, neurological, or medical problems responsible for cognitive decline

Clinical Presentation of AD



Prevalence rate = 6-10% of 70yo+ *

Symptoms are progressive

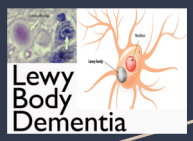
Impair daily functioning

More severe than what is expected by normal age-related decline

- Forgetting recently learned information
- Asking the same questions again and again
- Difficulty creating and following a plan
- Trouble managing money
- Difficulty completing familiar tasks in familiar settings
- Confusion-losing track of date or where they are
- Difficulty with conversation - word finding or calling things the wrong name.
- Withdrawal from work/social activities
- Change in mood - confused, suspicious, depressed, fearful

* Prince et al., 2013. Brookmeyer et al., 2011

Dementia with Lewy Bodies (DLB)



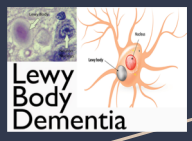
Diagnostic Criteria:

Meet Neurocognitive D/O criteria from DSM-V

Plus two of the following core symptoms:

- Fluctuating and unpredictable alertness and cognitive function
- Repeated visual hallucinations
- Parkinsonian symptoms
- REM sleep behavior disorder (act out their dreams during sleep)

Symptoms of DLB



Prevalence

<1 to 5 per 100,000 *

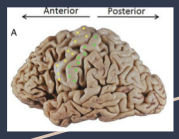
4.2 % of all dementia cases in the community **

Common symptoms include:

- Cognitive problems (similar to Alzheimer's disease)
- Visual Hallucinations
- Movement disorders
- Poor regulation of body functions (blood pressure, pulse, sweating, dizziness, falls, bowel issues)
- Sleep difficulties
- Fluctuating attention
- Depression
- Loss of motivation

* Zaccai et al., 2005
** Jones & O'Brien, 2014

Frontotemporal Dementia (FTD)



FTD is a group of conditions in which nerve cell damage leads to loss of function in these brain regions, which variably cause deterioration in behavior and personality, language disturbances, or alterations in muscle or motor functions.

Prevalence ranges from 2-31 per 100,000 (15 is thought to be best estimate) *

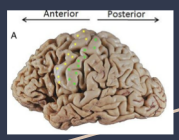
10-20% of all dementia cases

Three Variants

1. Behavioral variant - changes in personality and interpersonal relationships
2. Primary Progressive Aphasia - language skills
3. Motor variant - changes in muscle or motor function without language or behavior problems

* Onyike & Diehl-Schmind, 2013; Knoppman & Roberts 2011

Symptoms of FTLD



Pathological studies show compromise to the frontal and temporal regions of the brain, in contrast to global atrophy in AD

Diagnostic Criteria *

- Progressive decline in behavior or cognition
  - Disinhibition
  - Apathy
  - Empathy
  - Perseveration/compulsive/ritualistic behavior
  - Hyperorality
  - Executive functions (decision making, idea generation) with spared memory
- Age of onset often younger than other dementias

* Rascovsky et al., 2011

	Alzheimer's Disease	Lewy-Body Dementia	Frontotemporal Dementia	Chronic Traumatic Encephalopathy
CLINICAL PRESENTATION	Progressive cognitive decline, learning and memory impairments characterized by poor recall and recognition, anomia and decreased semantic fluency.	Fluctuations in attention, visuospatial deficits more pronounced than memory deficits, extra-pyramidal features (i.e., Parkinsonism), hypophonia, bradykinesia, visual hallucinations, REM, neuroleptic sensitivity, cognitive symptoms before motor	Dramatic personality changes characterized by a loss of personal and social awareness, poor judgement, and innapropriate behaviors. Or loss of language with spared cognitive abilities (PPA variant).	Proposed clinical criteria: Persistent cognitive, behavioral, and mood disturbances following head trauma.
NEUROPATHOLOGY	Global cerebral atrophy, neurofibrilary tangles, beta amyloid plaques	Hypometabolism in frontal and non-dominant temporal lobe (PET/SPECT imaging)	Cause unknown. Hypometabolism in frontal lobes (PET/SPECT), atrophy in frontal lobes	Deposits of hyperphosphorylated tau in cells around blood vessels (seen post-mortem)
PREVALENCE	6-10% of those age 70 years or older. 60-80% of all dementia cases.	3.5 per 100,000. 6% of all dementia cases.	15 per 100,000. 10-10% of all dementia cases	Not yet known. Less than 300 known cases
ONSET	Typically after age 50. <65=early onset. >65 late onset.	Typically 60-70s	Late 50's.	Not well understood
COURSE	Gradually progressive decline. 10-12 year course.	Rapid progressive decline. 6 year course.	Progressive decline. 8 - 11 year course.	Not well understood

Table 1: Review of common causes of dementia, prevalence rates, typical age of onset, and symptoms

What is CTE?

Chronic Traumatic Encephalopathy

- A neurodegenerative disease
- Has been linked to repetitive head trauma
- Characterized postmortem by deposits of hyperphosphorylated tau in cells around blood vessels
- Dementia pugilistica (1928)
- Neuropsychiatric symptoms may accompany CTE but no clinical criteria established, unlike other dementias
  - Persistence of cognitive, behavioral, mood disturbances following head trauma

Limitations of CTE research

1. The majority of CTE researchers have examined donated brains from subjects who have already exhibited abnormal symptoms (e.g., NFL players who have committed suicide).
2. Many studies have not accounted for drug abuse, particularly opiate abuse, which is associated with CTE pathology (i.e., hyperphosphorylated tau) in up to 44% of brains (Solomon et al., 2014).
3. CTE is a rare condition, with less than 300 confirmed cases of CTE.
4. No prospective longitudinal studies of confirmed CTE to date.
5. Of note, only a handful of females (N=18) have ever been confirmed to have CTE.

TBI

TBI Severity

Glasgow Coma Scale, Loss of Consciousness, Imaging Findings, and Post-Traumatic Amnesia

Table 1. Mayo TBI Severity Classification System

A. Classify as Moderate-Severe (Definite) TBI if one or more of the following criteria apply:
1. Death due to this TBI
2. Loss of consciousness of 30 minutes or more
3. Post-traumatic anterograde amnesia of 24 hours or more
4. Worst Glasgow Coma Scale full score in first 24 hours <13 (unless invalidated upon review, e.g., attributable to intoxication, sedation, systemic shock)
5. One or more of the following present:
   - Intracerebral hematoma
   - Subdural hematoma
   - Epidural hematoma
   - Cerebral contusion
   - Hemorrhagic contusion
   - Penetrating TBI (dura penetrated)
   - Subarachnoid hemorrhage
   - Brain Stem Injury

B. If none of Criteria A apply, classify as Mild (Probable) TBI if one or more of the following criteria apply:
1. Loss of consciousness of momentary to less than 30 minutes
2. Post-traumatic anterograde amnesia of momentary to less than 24 hours
3. Depressed, basilar or linear skull fracture (dura intact)

C. If none of Criteria A or B apply, classify as Symptomatic (Possible) TBI if one or more of the following symptoms are present:
- Blurred vision
- Confusion (mental state changes)
- Dazed
- Dizziness
- Focal neurologic symptoms
- Headache
- Nausea

TBI, traumatic brain injury.

Recovery after Moderate-Severe TBI

Clinical consensus is that cognitive recovery following TBI improves rapidly within the first 6 months after injury (Christensen et al., 2008).

Recovery curves are not uniform by domain (Wong et al., 2001) and are moderated by several factors.

Age at injury is associated with cognitive improvement at 1-year post moderate to severe injury (Green et al., 2008). Those who have a younger age of injury have better cognitive improvement.

Severity measures, such as LOC, PTA, and GCS can all influence cognitive recovery (Chu et al., 2007 & Spikman et al., 1999).

Challenges: Attrition in longitudinal studies, practice effects, high variability among samples, and high variability among injury characteristics.

Long-term outcomes of TBI

What do we know about "long-term" (i.e., ≥ 5 years post-injury) recovery?

E.g., A 26-year-old male sustains a moderate-severe TBI, and at 1-year post-injury he returns back to work and living independently. He has mild to moderate cognitive impairments on several measures of neuropsychological testing but is using compensatory strategies to improve his daily functioning…….

What can we say about his outcome ≥ 5 years from now?

Long-term recovery after TBI

Cognitive Recovery

Limited objective testing data more than 5-years post-injury

Ruttan et al., 2008: Meta-analysis revealed that cognitive impairments persist > 4.5 years after injury

Brown et al., 2011: Cognitive and emotional complaints are more likely to be reported than physical complaints **decades after injury**. **Moderate-severe TBI** survivors were significantly more likely to report memory, emotional, and physical problems.

Functional Recovery

Brown et al., 2011: Majority of responders function at a high-level without need for assistance. No injury-severity differences in educational or vocational attainment, marital status, income, personal relations, or quality of life were found. Time since injury was positively correlated with chances of complaints.

Marquez de la Plata et al., 2008 - functional decline 5-years post-injury was more likely in older (i.e., > 26 years old) subjects. Older TBI survivors may be more likely to suffer progressive decline than younger survivors.

Dementia Risk Following TBI

Dementia Risk following a single-TBI

28 studies finding an association between TBI and dementia

Gedye et al., 1989; Mayeux et al., 1993; O'Meara et al 1997; Schofield et al., 1997; Nametz et al., 1998; Guo et al., 2000; Plassman et al. 2000; Luukinen et al., 2005; Isoniemi et al., 2006 Bazarian et al., 2009; Wang et al., 2012; Lee et al., 2013; Barnes et al., 2014; Gardner et al., 2014; Gilbert et al., 2014; Nordstrom et al., 2014; Mendez et al., 2015; Li et al., 2016; Deutsch et al., 2016; Perry et al., 2016; LoBue et al., 2016; Lobue et al., 2017, LoBue et al., 2017; , Li et al., 2017; Raj et al., 2017; Weiner et al., 2017 LoBue et al., 2018; Schaffert et al., 2018; Nordstrom et al., 2018, Gardner et al., 2018; Barnes et al., 2018

9 studies not finding an association between TBI and dementia

Fratiglioni, et al., 1993; Launer et al., 1999; Mehta et al., 1999; Lindsay et al., 2002; Rapoport et al., 2008; Helmes et al., 2011; Dams-O'Conner et al., 2013; Xu et al., 2015; Crane et al., 2016; Cations et al., 2018

Centers for Disease Control & Prevention:

"A TBI can also cause epilepsy and increase the risk for conditions such as Alzheimer's disease, Parkinson's disease, and other brain disorders."

https://www.cdc.gov/traumaticbraininjury/outcomes.html

Alzheimer's Association:

"Over the past 30 years, research has linked moderate and severe traumatic brain injury to a greater risk of developing Alzheimer's disease or another type of dementia years after the original head injury."

"Not everyone who experiences a head injury develops dementia. There's no evidence that a single mild traumatic brain injury increases dementia risk. More research is needed to confirm the possible link between brain injury and dementia and to understand why moderate, severe and repeated mild traumatic brain injuries may increase risk."

https://www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/traumatic-brain-injury

Institute of Medicine Committee:

"there is sufficient evidence of an association between moderate and severe TBI and dementia … limited/suggestive evidence of an association between mild TBI (with loss of consciousness) and dementia … [and] inadequate/insufficient evidence to determine whether an association exists between mild TBI (without loss of consciousness) and dementia." (p214).

Institute of Medicine Committee on Gulf War and Health. Long-Term Consequences of Traumatic Brain Injury. Vol. 7. Washington, DC: National Academies Press; 2009. Gulf War and Health

Moderating/Mediating Factors

Factors that influence dementia risk: Age at injury

Table 2. Association Between TBI and Risk of Dementia Stratified by Age and TBI Severity[a]

Patient Group	No. of Patients	HR (95% CI)	*P* Value
Aged 55-64 y (reference NTT)	40 444		
Mild TBI	4670	1.11 (0.80-1.53)	.55
Moderate to severe TBI	10 027	1.72 (1.40-2.10)	<.001
Aged 65-74 y (reference NTT)	27 991		
Mild TBI	2810	1.25 (1.04-1.51)	.02
Moderate to severe TBI	8808	1.46 (1.30-1.64)	<.001
Aged 75-84 y (reference NTT)	29 113		
Mild TBI	2800	1.21 (1.08-1.36)	<.005
Moderate to severe TBI	12 803	1.27 (1.19-1.36)	<.001
Aged ≥85 y (reference NTT)	15 314		
Mild TBI	1443	1.25 (1.09-1.44)	<.005
Moderate to severe TBI	8438	1.14 (1.06-1.24)	<.005

mTBI in those ≥ 65 years old was associated with increased dementia risk.

Older age at injury is associated with greater dementia risk.

Gardner et al., 2014. *JAMA Neurology*

Factors that influence dementia risk: Severity

Table 3. Association Between TBI and Risk of Dementia Stratified by Age and TBI Severity, Excluding Patients Not Seen Alive Within 1 Year of the End of Follow-up[a]

Patient Group	No. of Patients	HR (95% CI)	*P* Value
Aged 55-64 y (reference NTT)	10 281		
Mild TBI	1226	1.08 (0.77-1.49)	.66
Moderate to severe TBI	2769	1.65 (1.35-2.02)	<.001
Aged 65-74 y (reference NTT)	8607		
Mild TBI	850	1.22 (1.02-1.47)	.03
Moderate to severe TBI	2750	1.50 (1.33-1.68)	<.001
Aged 75-84 y (reference NTT)	10 025		
Mild TBI	938	1.26 (1.13-1.42)	<.001
Moderate to severe TBI	4347	1.38 (1.29-1.47)	<.001
Aged ≥85 y (reference NTT)	4218		
Mild TBI	422	1.25 (1.09-1.44)	<.005
Moderate to severe TBI	2278	1.31 (1.21-1.41)	<.001

More severe injuries are associated with higher dementia risk.

Gardner et al., 2014. *JAMA Neurology*

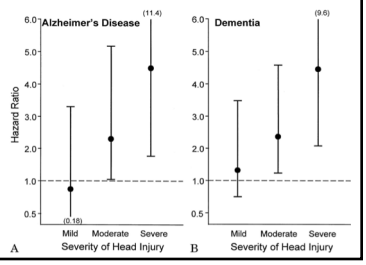
Factors that influence dementia risk: Severity

Plassman et al., 2000, *Neurology*
- Only long-term prospective study to date

Dementia and AD risk was doubled after moderate head injury.

Dementia and AD risk was quadrupled after severe head injury.

Mild TBI had a non-significant association with Dementia and AD risk.



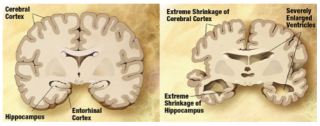
Factors that influence dementia risk: Frequency

Does repetitive TBI increase dementia risk more than a single moderate-severe TBI?

In Gardner et al., 2014, more than 1 TBI doubled the risk of dementia (56% increase) compared to a single TBI (26% increase) although they did not comment on severity of the injuries.

A more recent meta-analysis revealed no increased risk of neurologic or psychiatric disorder following multiple vs. single TBI (Perry et al., 2016)

Chronic and repetitive TBI may be more associated with certain neurodegenerative conditions, such as CTE (Smith et al., 2013) versus AD, although this difference has not been thoroughly researched.



Factors that influence dementia risk: *APOE ε4* alleles

Findings suggesting genetics moderates TBI and dementia risk are mixed.
The protein apolipoprotein with the allele ε4 (APOE ε4) is one of the most established risk factors for AD.

APOE ε4 interacts

Mayeux et al., 1993 found the opposite, APOE ε4+ and TBI had 10x risk compared to APOE ε4- and TBI.

Isoniemi et al., 2006 – some individuals with APOE ε4 may have worse long-term cognitive outcome.

APOE ε4 interacts in opposite direction

Guo et al., 2000 found that those with APOE ε4+ and TBI had a lower risk of subsequent AD than those without APOE ε4- and TBI.

No association

O'Meara et al., 1997 found TBI w/LOC was a risk factor for AD, and APOE ε4 had no effect on this relationship.

LoBue et al., 2017 and Schaffert et al., 2018 observed TBI w/LOC hastens age of AD onset, but LoBue et al., 2017 observed no interaction between APOE ε4, TBI, and Age of Onset.

What does the research suggest?

1) Moderate to severe TBI likely increases risk.

2) Older age of injury may increase dementia risk.

3) More severe injuries increase dementia risk.

4) There may be genetic factors at play, but findings are mixed regarding APOE e4 alleles.

5) Dementia risk following repetitive injuries requires further investigation.

- How does TBI increase dementia risk?

Mechanisms of TBI increasing dementia risk

Neurometabolic Cascade?

Recall that dementias have multiple causes with different underlying neuropathology:

- AD (amyloid-beta + hyperphosphorylated tau)
- DLB (alpha-synuclein)
- FTLD (hyperphosphorylated tau or TDP-43)
- CTE (hyperphosphorylated tau or TDP-43)
- Vascular (white matter lesions or infarcts)
- PD (alpha-synuclein)

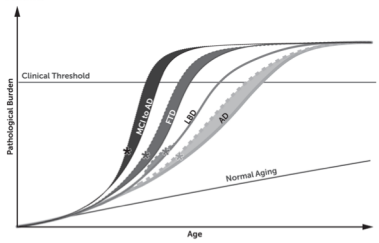
Dementia risk after TBI has varied between disease, suggesting that TBI may have different effects across neurodegenerative conditions.

The consensus is that TBI is likely a risk factor for AD in some individuals, perhaps interacting with tau or amyloid-beta. The risk is not as established in other neuropathologies.

The risk of TBI appears to be stronger for FTLD and AD, leading to earlier onset of symptoms in some individuals, possibly from increased neuropathological burden.

The association between TBI and LBD is less established.

FIGURE 1. A Potential Role for Traumatic Brain Injury (TBI) in Developing Neurodegenerative Dementias[a]



[a] Asterisk indicates sustaining a history of TBI. AD=Alzheimer's disease; FTD=frontotemporal dementia; LBD=Lewy body dementia; MCI to AD=developing mild cognitive impairment and progressing to Alzheimer's disease.

Proposed model adopted from LoBue et al., 2018, *J Neuropsychiatry Clin Neurosci 2018; 30:7–13; doi: 10.1176/appi.neuropsych.17070145*

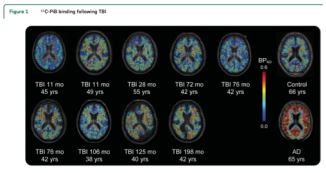
Neurometabolic Cascade?

Autopsy and imaging findings

Johnson et al., 2012 - increased AD pathology found in those years after moderate-severe TBI compared to controls.

Tomaiuolo et al., 2012 - continual white matter degeneration in those with moderate-severe TBI 8-years post-injury

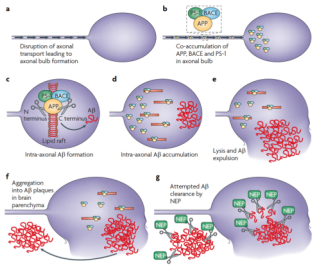
Scott et al., 2016 - amyloid deposits and white matter inflammation were found in TBI that appear similar to those with AD, although several distinctions were found.



Axonal injury is a hallmark pathology of TBI.

Axonal disruption can lead to intracellular beta-amyloid accumulation.

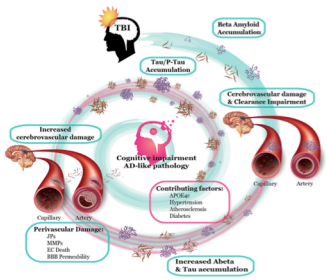
After cell-death, beta-amyloid is released into surrounding tissue, where it could form the beta-amyloid plaques seen in Alzheimer's disease.



Johnson, V. E., Stewart, W., & Smith, D. H. (2010). Traumatic brain injury and amyloid- pathology: A link to Alzheimer's disease? *Nature Reviews Neuroscience*, 11, 361–370.

Multifactorial model:

Tau and beta-amyloid accumulation following TBI may interact with cerebrovascular and genetic factors.



Ramos-Cejudo et al., 2018, Traumatic Brain Injury and Alzheimer's Disease: The Cerebrovascular Link. *EBioMedicine.*

Static Effect?

TBI increases dementia risk by lowering cognitive and neuronal reserve.

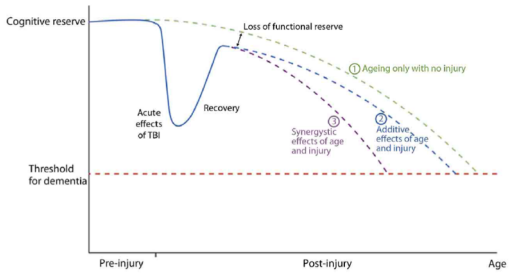
Cognitive reserve:

Higher cognitive abilities at baseline may result in later onset or lower risk of dementia.

Neuronal reserve:

Higher brain volumes or greater resistance to neuropathology may delay onset or reduce risk of dementia.

TBI may simply result in a static, one-time lowering of cognitive or neuronal reserve, thus hastening age of onset and increasing risk of developing dementia.



Bigler et al., 2013, Traumatic brain injury, neuroimaging, and neurodegeneration. *Frontiers in Human Neuroscience*

If static effects are the only mechanisms…

Wouldn't we expect the same dementia risk across all conditions?

ANCOVA Results and Effect Size (adjusted for group sample size):

	TBI- N	TBI+ N	TBI- M (SD)	TBI+ M (SD)	M-diff.	F (p-value)	d
AD	882	84	68.98 (10.2)	66.16 (10.4)	2.82	4.1 (.043)*	0.28
AD+LBD	332	37	67.82 (9.2)	63.08 (9.8)	4.74	6.8 (.009)*	0.51
LBD	210	16	69.94 (8.4)	71.25 (11.2)	-1.31	0.59 (.556)	-0.15
FTLD	298	30	63.11 (9.4)	59.03 (7.3)	4.08	4.6 (.033)	0.44

Age of dementia onset in autopsy-confirmed conditions. Schaffert et al., 2018 (*in preparation*), unpublished data.

Limitations of the literature

TBI has not been well characterized.

Most studies rely on self-report of TBI.

Variability exists among dementia criteria and TBI criteria.

Vast majority of studies rely on clinical diagnoses of dementia, and accuracy of these diagnoses can vary depending on the neurodegenerative condition.

What's next?

Future directions in research

1. Determining mechanisms of how TBI may increase dementia risk in some individuals.
2. Longitudinal, prospective studies are needed. Several are currently underway (e.g., Professional Fighters Brain Health Study).
   - Studies that well-characterize injury related factors along with dementia symptoms and disease course are needed.
3. Although media exposure is beneficial in terms of promoting brain health, objectivity continues to be needed within this field of research.

   E.g., Most individuals who sustain a TBI do not develop CTE or dementia.

Questions?

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References available upon request