Psychiatric phenotypes in chronic traumatic encephalopathy

Short title: **Psychiatric phenotypes in CTE**

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Highlights

- CTE is progressive neurodegenerative disorder including psychiatric symptoms
- Symptoms include depression and suicidality, and have not been fully characterized
- These may be related to pathology in particular brain regions affected in early disease stages
- Postmortem studies in these sites will lead to insight regarding CTE and psychiatric symptoms
- *In vivo* studies may aid in detection and prevalence determination, and resolve clinical challenges

Abstract

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disorder involving cognitive, motor, and psychiatrically-relevant symptoms resulting from repetitive head impacts. Psychiatric phenotypes of CTE, including depression and suicidality, present particular challenges for CTE research, given that the diagnosis requires postmortem neuropathological examination. The pathognomonic lesion of CTE is the

perivascular accumulation of hyperphosphorylated tau (ptau) protein at the depths of cortical sulci. These lesions are found in the earliest disease stages, and with advancing pathological severity, ptau deposition occurs in widespread brain regions in a four-stage scheme of severity. We review the psychiatric phenotypes of individuals neuropathologically diagnosed with CTE, and suggest that earlier CTE stages hold particular interest for psychiatric CTE research. In the early CTE stages, there is ptau pathology in frontal cortex and axonal loss in the frontal white matter, followed by progressive ptau neurofibrillary degeneration in the amygdala and hippocampus. Neuropathological changes in the frontal and medial temporal lobes may underlie psychiatric phenotypes. Additional insight into the association between CTE pathology and psychiatric sequelae may come from advancements in *in vivo* methods of CTE detection. Further epidemiological, clinical, and postmortem studies are needed to validate the nature of psychiatric sequelae in CTE.

Key words: Chronic traumatic encephalopathy, depression, suicide, neuropathology, head trauma, neurofibrillary tangles

1. INTRODUCTION

Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease caused by exposure to repetitive head impacts (RHI), such as those sustained in contact sports (Bieniek et al., 2015; McKee et al., 2016; McKee et al., 2013). The characteristic neuropathology of CTE involves accumulation of hyperphosphorylated tau (ptau) protein as neurofibrillary tangles, disordered neurites, and astrocytic inclusions around small blood vessels at the base of sulci (McKee et al., 2016; McKee et al., 2013). CTE can only be definitively diagnosed using defined neuropathological criteria (McKee et al., 2016), and to date all neuropathologically-confirmed cases of CTE have had a history of exposure to RHI (Bieniek et al., 2015; McKee et al., 2013). CTE was historically found primarily in boxers, but is now well-documented in American football players, other contact sport athletes (e.g., rugby, soccer, ice hockey, wrestling), and military veterans (Bieniek et al., 2015; Geddes et al., 1999; Goldstein et al., 2012; Ling et al., 2017; McKee et al., 2014; McKee et al., 2013; Omalu et al., 2010a). Notably, many CTE cases with exposure to RHI do not have a history of concussion (Stein et al., 2015), and CTE neuropathology does not appear to be a consequence of a single traumatic brain injury (TBI) (Bieniek et al., 2015), emphasizing the role of subconcussive RHI in the pathogenesis of this disease (Bailes et al., 2013; Stein et al., 2015).

The clinical features of CTE include a constellation of impairments in cognition (e.g., executive dysfunction, episodic memory impairment), behavior (e.g., aggression), and mood (e.g., depression) (Stern et al., 2013). Although cognitive decline and eventual dementia is typical in the setting of neurodegeneration, the onset, course, and nature of behavior and mood changes observed in CTE are atypical for any other neurodegenerative disease (McKee et al., 2016; McKee et al., 2013; Stern et al., 2013). The psychiatrically relevant symptoms of CTE can be severe, and include a subset of individuals with neuropathologically-confirmed CTE who have died by suicide (Bieniek et al., 2015; McKee et al., 2013).

CTE cannot currently be diagnosed during life, primarily due to the lack of *in vivo* biomarkers to detect the presence of pathology and the lack of validated clinical criteria for diagnosis. Mood and behavioral symptoms are common clinical features in subjects with autopsy-confirmed CTE, and are a critical

component to proposed clinical diagnostic criteria for traumatic encephalopathy syndrome (TES) (Montenigro et al., 2014). However, critical challenges remain in the clinical domain of psychiatric CTE research, as well as in understanding the pathological substrates underlying the psychiatric manifestations of CTE, including their particular presentation, prevalence, putative etiology, and clinical confounds. The objective of this manuscript is to review the relevant literature concerning the psychiatric phenotypes associated with CTE and the long-term clinical consequences of RHI exposure. Challenges in the investigation of psychiatric symptoms, the autopsy bias inherent in establishing prevalence of psychiatric phenotypes, the preliminary relationship between psychiatric symptoms and CTE stages, and the potential etiological mechanisms underlying psychiatric phenotypes in CTE are presented in this review. Future studies are outlined that may help to resolve current uncertainties regarding CTE, including potential studies associating CTE pathology with particular psychiatric symptoms, epidemiological studies investigating symptom prevalence, and longitudinal clinical studies informing the identification, prevalence, and etiology of these symptoms.

2. CLINICAL MANIFESTATIONS OF CTE

CTE clinically presents with a diverse combination of symptoms, including disruptions in cognitive, mood, behavioral, and (in some instances) motor function. Based on retrospective next of kin interviews of autopsy-confirmed cases, CTE clinically manifests as two variants: 1) early in life (30s) impairments in behavior or mood, such as depression, aggression, explosivity, apathy, impulsivity, followed by later onset of cognitive impairment; and 2) later in life (late 50s to early 60s) cognitive impairments in executive function, episodic memory, and attention that led to dementia (Stern et al., 2013). Motor disturbances in former American football players appear to be less common (relative to boxers) and tend to occur later in the disease course (Stern et al., 2013). Clinical symptoms in CTE often begin several years after exposure to RHI has ended (McKee et al., 2009; Stein et al., 2015). In addition, certain factors likely alter the course of CTE symptoms; a recent study found higher cognitive reserve delayed the onset of cognitive and behavioral/mood symptoms by more than 10 years in a sample of former professional football players with autopsy confirmed CTE (Alosco et al., 2016).

The proposed clinical research diagnostic criteria for CTE, known as Traumatic Encephalopathy Syndrome (TES) are based on clinical symptoms of autopsy-confirmed cases of CTE (Montenigro et al., 2014). These criteria include a history of RHI, lack of confounding comorbid neurological condition, duration of symptoms greater than 12 months, at least one core clinical symptom (cognitive, behavioral, or mood dysfunction), and at least two supportive symptoms (Montenigro et al., 2014). The supportive features include delayed onset, progressive decline in function, motor dysfunction, headache, impulsivity-related behavioral changes, apathy, and psychiatrically-relevant symptoms (anxiety, paranoia, and suicidality). The core mood component refers specifically to depression-related symptoms. The criteria for TES distinguish it from post-concussion syndrome, in which symptoms appear acutely after concussive impact injury but are usually not progressive, an important distinction given that there is overlap in some symptoms of post-concussion syndrome and TES (Montenigro et al., 2014).

The collective psychiatrically relevant (e.g. mood and behavior) features of CTE also help distinguish it from other neurodegenerative diseases. Clinical features of CTE bear some similarities to frontotemporal dementia, although the cardinal disinhibited and inappropriate social behaviors of frontotemporal dementia are not common in CTE (Stern et al., 2013)). In the following section, the psychiatric phenotypes associated with CTE are discussed in detail.

2.1 PSYCHIATRIC SYMPTOMATOLOGY IN CTE

2.1.1 Depressive symptoms in CTE

Depressive symptoms are often identified in CTE cases. Most of the recent histopathologically validated individual case studies have been in former football players (Montenigro et al., 2014). The first pathologically verified case reports of CTE in former professional football players reported dysthymia in one case (Omalu et al., 2005) and mood lability, as well as a diagnosis of severe major depressive disorder in the second (Omalu et al., 2006). A subsequent case study of a former NFL player with CTE reported progressive affective symptoms including mood lability and continual depressed mood, but also included insomnia, a vegetative symptom of depression (Omalu et al., 2010b). Similarly, a case study of a 25 year-old former college-level football player found a wide range of major depressive symptoms, including anhedonia, feelings of worthlessness, apathy, and vegetative symptoms (decreased appetite and hypersomnia) (Mez et al., 2016).

Subsequent larger-cohort studies of histologically validated CTE have provided substantial verification of the frequent association between depression and CTE, although typically with less specificity in reporting individual depressive symptoms (Mez et al., 2017). An assessment of 17 athletes with CTE noted major depression as common amongst the cases reviewed, with mood lability as well as vegetative symptoms including insomnia and psychomotor alterations as frequent as depressive symptoms (Omalu et al., 2011a). An assessment of 36 athlete CTE cases found that of the 33 symptomatic cases, 85% experienced some mood disturbance, with 27% experiencing mood disturbance as the initial clinical presentation, although the particular affective symptoms were unspecified (Stern et al., 2013). In a larger-sample study of 202 pathologically verified and unverified CTE cases, depressive symptoms were commonly noted, including depressed mood or mood lability, hopelessness, suicidal ideation, and neurovegetative symptoms such as insomnia, fatigue, and apathy (Montenigro et al., 2014). Most recently, in a case series of pathologically confirmed CTE in 177 American football players, depressive symptoms were reported in 64 of 111 (59%) (Mez et al., 2017).

Overall, these studies offer repeated support of an association between CTE and depressive symptoms. These symptoms include not only depressed mood, but also hopelessness, suicidal ideation, and vegetative symptoms. As a result of these findings, depressive symptoms have been proposed as core clinical criteria in the identification of putative CTE cases (Jordan, 2013; Montenigro et al., 2014; Reams et al., 2016). These include depressed mood and hopelessness in particular (Montenigro et al., 2014), although future clinical studies may refine the association of particular depressive symptoms individually with CTE.

2.1.2 Suicidality in CTE

In addition to the depressive symptoms associated with CTE, suicidal ideation has been identified in CTE case studies (Mez et al., 2016; Omalu et al., 2006; Omalu et al., 2010b). This has been supported by larger-scale studies, which have repeatedly identified suicidal ideation in a substantial proportion of CTE cases to date, representing 26-33% of cases in some cohorts, compared to 3.7% in the general adult American population (Crosby et al., 2011; McKee et al., 2013; Mez et al., 2017; Montenigro et al., 2014; Omalu et

al., 2011a; Stern et al., 2013). As such, suicidality has been proposed as a supportive feature for diagnosis of TES (Montenigro et al., 2014).

Behaviorally, a high proportion of pathologically-validated CTE cases have died by suicide, ranging from 10- 29% between cohorts (Bieniek et al., 2015; McKee et al., 2013; Mez et al., 2017; Omalu et al., 2011a; Stern et al., 2013). However, the ascertainment bias in using a brain donation cohort for pathological verification of CTE makes precise determination of the risk of death by suicide in CTE difficult (McKee et al., 2013).

As former NFL players likely represent a high-risk cohort for developing CTE, given that CTE has been identified in 99% of former NFL players examined in published postmortem series, this population may offer one possibility for estimating suicidal prevalence in CTE. This would avoid the ascertainment bias of postmortem studies, although this estimate might still differ from other CTE populations. A complete epidemiological examination of the prevalence of suicidality in former NFL players has yet to be performed. A recent study examined mortality in a subset (537 decedents) of former professional football players and did not observe an increased mortality rate of intentional self-harm (Lehman et al., 2016), leading to speculation that risk of death by suicide is not increased in CTE in contrast to increased risk of depression (Iverson, 2016). However, the Lehman *et al.* study analyzed only a specific subgroup of the total cohort (identifying only 12 suicides), determined comparative risk of suicide relative to healthy years at risk (despite this cohort having reduced overall mortality), and did not compare suicide risk between football positions involving contact (e.g. linemen) and those without contact (e.g. kicker/punter) (Baron et al., 2012; Lehman et al., 2012; Lehman et al., 2016). This suggests that a more rigorous investigation into suicide risk across the entire cohort is warranted.

2.1.3 Other psychiatric phenotypes in CTE

To date, associations between CTE and affective psychiatric phenotypes other than depression have been found less often. Anxiety has been identified in some studies (McKee et al., 2009; Mez et al., 2016; Montenigro et al., 2014; Stern et al., 2013), including 55 of 111 American football players (51%) (Mez et al., 2017). Anxiety has also been identified in cases showing clinical features of CTE without pathological verification (Montenigro et al., 2014; Spillane, 1962). Manic-like symptoms have been found in studies of cases clinically similar to CTE without histological verification (Jordan et al., 1997; Montenigro et al., 2014). Manic-like symptoms were reported in only 8% (9 of 111) American football players with confirmed CTE (Mez et al., 2017), suggesting that depressive symptoms are typically unipolar in CTE.

Non-affective changes to behavior or personality, including increased aggression, explosivity, and impulsivity are common in CTE (McKee et al., 2013; Mez et al., 2017; Stern et al., 2013). Impulsivity was present in majority of CTE cases in the Mez *et al.* case series (82%), which may be particularly psychiatrically relevant, given the association between impulsivity and suicidal behavior (Dougherty et al., 2004; Mez et al., 2017; Zouk et al., 2006). Behavioral changes are also a core clinical feature in TES (Montenigro et al., 2014). Notably, it has been observed that the behavioral symptoms of CTE co-occur with mood symptoms in a subtype of CTE cases with an earlier clinical presentation, whereas the subtype in which cognitive symptoms occur first often has a later age of symptom onset (Stern et al., 2013). Paranoia has also been observed in confirmed or probable CTE cases (Johnson, 1969; McKee et al., 2013; Montenigro et al., 2014; Omalu et al., 2011a; Omalu et al., 2006; Omalu et al., 2010b; Stern et al., 2013). In the Mez *et al.* case series, paranoia was present in 34% of confirmed CTE cases (Mez et al., 2017).

3. NEUROPATHOLOGY OF CTE, AND MECHANISTIC CANDIDATES FOR NEUROPSYCHIATRIC SEQUELAE

Neuropathologically, CTE is characterized by neurofibrillary tangles (NFTs), dystrophic neurites and astrocytes that are immunoreactive for ptau around small blood vessels and at the depths of cortical sulci. As the disease advances, ptau immunoreactive NFTs, neurites, and astrocytes are distributed throughout the cerebral cortex, medial temporal lobe, diencephalon, basal ganglia, and brainstem (Armstrong et al., 2016; McKee et al., 2016; McKee et al., 2013). The pattern and regional distribution of NFTs is unique in CTE, and can be readily distinguished from Alzheimer's disease and other tauopathies (McKee et al., 2016).

Four stages of CTE have been identified neuropathologically (McKee et al., 2013). Stage I is characterized by isolated perivascular foci of NFTs located at the depths of cortical sulci. Axonal loss, astrocytosis, and microglial neuroinflammation are present in the white matter in stage I; these abnormalities increase as the disease advances. Stage II CTE is characterized by multiple perivascular foci of NFTs; ptau in the amygdala and hippocampus is minimal. NFTs are found in enlarged and confluent perivascular cortical foci, the hippocampus and amygdala in stage III disease. In stage IV disease there are widespread NFTs throughout the cortex, medial temporal lobe, diencephalon, brainstem and cerebellum (McKee et al., 2013). It is unclear how the neuropathology influences neuropsychiatric symptoms in CTE. However, recent studies suggest that putative targets for etiological studies regarding CTE-related psychiatric sequelae might emerge from a focus on specific stages of pathology and affected brain regions. In order to identify candidate brain structures that might influence psychiatric endophenotypes in CTE, a review of the literature on CTE stage, symptom emergence, and the brain regions affected at each stage was performed.

3.1 CTE psychiatric endophenotypes by stage

Clinically, few studies have associated individual neurocognitive or psychiatrically-relevant symptoms with particular CTE stages. However, the stages of CTE correlate not only with level of exposure to football and years since retirement, but also with symptomatology (McKee et al., 2013).

The initial symptoms of CTE may include either cognitive dysfunction or behavioral and mood changes, with the latter being more common than the former in one study (Stern et al., 2013). Headache and attention deficits are the most common stage I symptoms, followed by memory dysfunction, with depression, explosivity, and aggression also observed (McKee et al., 2013) (see **Table 1**).

Depression and suicidality are common symptoms at stage II, persisting relatively consistently to stage IV, and aggression and explosivity increasing through stages II-IV. Suicidality as a symptom was observed in stage I in one study and was consistently present in roughly a quarter of stage II-IV cases (McKee et al., 2013). Cognitive and memory dysfunction are also common in stage II, becoming more common and severe in subsequent stages. Similarly, common stage III symptoms also include behavioral issues (aggression, explosivity), with mild dementia emerging as a symptom.

Stage IV includes the previously mentioned symptoms, with severe dementia and aggressivity and explosivity, and paranoia progressing from rare to common in this stage (McKee et al., 2013).

Thus, of CTE-associated neuropsychiatric phenotypes suggested to date, depression and suicidality are commonly referred to, emerging at earlier stages, with paranoia identified in approximately one third of

CTE patients . Future studies will hopefully solidify associations between particular symptoms and pathological staging.

3.2 Candidate brain regions contributing to psychiatric endophenotypes in CTE

One of the challenges in CTE research is the widespread nature of the associated neuropathology, progressing across multiple brain regions. However, presence of CTE-related NFTs in certain brain regions may specifically associate with psychiatric endophenotypes of CTE (see **Table 2**). This is particularly plausible for the frontal cortex, hippocampus, amygdala, and brainstem given their repeated involvement in studies using other populations (Bassi et al., 2015; Choi et al., 2015; Mahar et al., 2014; Mahar et al., 2017; Maheu et al., 2013; Schneider et al., 2015; Torres-Platas et al., 2014; Tripp et al., 2012; Turecki, 2014), and the presence of CTE-related neuropathology in these regions (McKee et al., 2016; McKee et al., 2013).

Behavioral changes such as aggression and explosivity may be related to pathology in the frontal cortex, which is often damaged in early CTE and involved in behavioral regulation (Brower and Price, 2001; McKee et al., 2013; Stern et al., 2013). The frontal cortex has also been implicated in depression, suicide, and other psychiatric conditions (Frey et al., 2007; Goswami et al., 2013; Johnston-Wilson et al., 2000; Schneider et al., 2015; Sequeira et al., 2009; Taylor et al., 2014). Other studies have suggested that the cingulate is associated with depression and suicide (Torres-Platas et al., 2014; Tripp et al., 2012) and monoamine-related structures, including raphe nuclei and the locus coeruleus, are related to depression and suicide (Arango et al., 1996; Chandley et al., 2014; Mahar et al., 2014).

The hippocampus, especially the anterior hippocampus, has been associated with depression and suicide (Mahar et al., 2014; Mahar et al., 2017; Sequeira et al., 2009). Deficits in numbers of granule cell neurons in the hippocampal dentate gyrus have been found in depression and suicide, though this decrease is reversed or absent with antidepressant treatment (Boldrini et al., 2014; Mahar et al., 2017). The hippocampus is a region of interest for suicidal etiology (Turecki, 2014), and hippocampal volume was reported to be decreased in post-traumatic stress disorder (PTSD), depression, and schizophrenia (Campbell et al., 2004; Chan et al., 2016; Haukvik et al., 2013; van Rooij et al., 2015). Amygdalar dysfunction has also been associated with depression (Bassi et al., 2015; Guilloux et al., 2012), amygdalar neuroplasticity with suicide (Maheu et al., 2013), and amygdalar activity and volume with impulsivity and aggression (Kerr et al., 2015; Matthies et al., 2012).

Pathology in some or all of these structures may be responsible for the psychiatric phenotypes seen in CTE. For medial temporal lobe structures, this might be particularly relevant for relevant phenotypes seen at intermediate or late stages (McKee et al., 2013). The hippocampus may be an especially important target for future neuropsychiatric CTE research in former athletes, as extent of football exposure is inversely related to hippocampal volume, and players with concussion history also had decreased hippocampal volume relative to players without concussive history (McKee et al., 2013; Singh et al., 2014; Strain et al., 2015).

Football exposure prior to the age of 12 in former professional players was associated with differences in corpus callosum microstructure, and white matter alterations in former players have been associated with depressive symptoms (Stamm et al., 2015; Strain et al., 2013), which is in agreement with other studies suggesting that white matter alterations may underlie depression or depressive symptoms (Choi et al.,

2015; Riva-Posse et al., 2014). These findings suggest that white matter structures as another focus for studies associating CTE neuropathology with neuropsychiatric sequelae.

Finally, to a lesser extent, depression has also been associated with regions such as the basal ganglia and locus coeruleus (Bernard et al., 2011; Husain et al., 1991; McKee et al., 2013). However, a focused investigation associating particular sites of CTE neuropathology to particular psychiatric endophenotypes has yet to be performed. Such an investigation could prove valuable not only for the etiology of CTE, but could reveal or strengthen associations between particular brain regions and psychopathology in other clinical populations or in the general public. Previous investigations have involved postmortem neuropathological studies and assessment of antecedent psychiatric sequelae however, evaluation of living individuals exposed to RHI and TBI might also be valuable in informing future CTE research.

4. INSIGHT FROM STUDIES OF RHI/TBI AND PSYCHIATRIC SEQUELAE

Although most published reports on CTE have used post-mortem analyses, our current understanding of CTE has also been informed by studies of living subjects with RHI, given that RHI is believed to etiologically underlie CTE. These studies are especially valuable in providing insight into symptom prevalence and progression in CTE, and identification of candidate affected brain regions and biomarkers. RHI in former high school and college football players (who may sustain over 1000 head impacts per season (Bailes et al., 2013)) has been associated with depression, apathy, and cognitive and behavioral dysfunction, with a cumulative head impact index (CHII) revealing a dose-dependent relationship between number of impacts and subsequent symptom development (Montenigro et al., 2016) and predicting subsequent peripheral expression of tau (Alosco et al., 2017b). Though preliminary, this index suggests that there appears to be a certain threshold of number of head impacts that is sufficient to increase risk for depression later in life, which may be as few as approximately 1800 impacts (Montenigro et al., 2016). Retired NFL players also show increased prevalence of depression and depressive symptom severity (particularly with repeated concussive TBI), including higher depressive scores on 18 of 21 Beck Depression Inventory II items and a trend towards increased suicidal cognition (Didehbani et al., 2013; Guskiewicz et al., 2007; Hart et al., 2013; Kerr et al., 2012). The breadth of symptoms present in participants of these studies (including the presence of both mental and somatic depressive symptoms in depressed former NFL players that suffered repeated concussions) also suggest that RHI-induced depression may show similar symptom variety to depression induced otherwise (Didehbani et al., 2013; Guskiewicz et al., 2007). However, focused examinations of how the individual symptoms of depression in CTE, RHI, and TBI differ in appearance from depression without head injury have not been performed. It is possible that individual depressive symptoms (e.g. anhedonia, hopelessness, or depressed mood) might occur in the absence of other canonical depressive symptoms in these conditions (as suggested for apathy (Jorge and Arciniegas, 2014)), or occur more frequently in association with symptoms not typically considered depressive. Examples of the latter may include impulsivity, which is found in CTE and after repeated concussive TBI, and is also associated with suicidality (Alosco et al., 2017a; Mann et al., 1999; McKee et al., 2013; Montenigro et al., 2014), or pseudobulbar affect (spontaneous laughing/crying episodes) (Jorge and Arciniegas, 2014). The manifestation of specific depressive symptoms may depend on the particular brain regions and neuronal connections affected by CTE neuropathology. However, overall RHI studies examining psychiatric sequelae support the occurrence and breadth of depressive and other psychiatric phenotypes observed in CTE, and preliminarily indicate the extent of exposure necessary for psychiatric phenotypes to develop.

Neuroimaging studies also show brain changes following exposure to RHI. White matter abnormalities have been observed in former NFL players (Hart et al., 2013), former NFL players who started playing before age 12 show greater changes in white matter fractional anisotropy compared to players who started playing after age 12 (Stamm et al., 2015), and white matter fractional anisotropy negatively correlates with depressive symptoms in former NFL players (Strain et al., 2013). Playing in more than 120 NFL games was associated with decreased left hippocampal volume (Strain et al., 2015). Together, these studies, reveal structural alterations following RHI and support specific brain regions as targets for future CTE studies, including the hippocampus and white matter structures.

TBI has previously been associated with depression and suicidality (Fralick et al., 2016; Jorge and Arciniegas, 2014), and studies investigating the treatment of depression or other psychiatrically relevant symptoms after TBI, may be potentially informative for prospective treatments for CTE. However, these studies have been sparse in comparison to those examining depression treatment efficacy in the general population (Fann et al., 2009; Warden et al., 2006).

Traditional depressive treatments have been examined in the context of post-TBI depressive symptoms and demonstrated treatment efficacy. Selective serotonin reuptake inhibitors (SSRIs) may be effective in treating post-TBI depression, particularly for citalopram and sertraline, although the latter may not be advisable due to adverse treatment effects potentially related to post-injury symptoms (Fann et al., 2009; Lee et al., 2005; Wheaton et al., 2011). Methylphenidate has also been shown to ameliorate depressive symptoms (Lee et al., 2005; Wheaton et al., 2011). Non-pharmacological treatments for post-TBI depression have also been examined in some preliminary studies, including electroconvulsive therapy, transcranial magnetic stimulation, and biofeedback; however, these studies require validation due to small sample sizes and methodological constraints such as lack of proper control groups (Fann et al., 2009; Kant et al., 1999; Martino et al., 2008; May et al., 2013; Surmeli et al., 2017). Conversely, results of cognitive behavioral therapy in studies of these cohorts are mixed, but tend to show encouraging results in improving depressive symptoms (Anson and Ponsford, 2006; Bombardier et al., 2017; Fann et al., 2009; Gurr and Coetzer, 2005; Ownsworth, 2005; Tiersky et al., 2005). Overall, some traditional treatments for depression have also shown efficacy in treating depression following TBI, although which treatments might be selectively efficacious in brain trauma-related depression remains to be thoroughly determined. There is some evidence that β-blockers such as propranolol may be effective at reducing aggression after TBI (Fleminger et al., 2006; Warden et al., 2006), and a recent meta-analysis suggests that dopaminergic agents such as methylphenidate may be effective in addressing post-TBI combative behavior (i.e. agitation, irritability, and aggression) (Wheaton et al., 2011). However, overall support for particular pharmacological treatments and behavioral alterations following TBI is limited (Fleminger et al., 2006; Warden et al., 2006).

Overall, *in vivo* RHI studies support the association between CTE and psychiatric sequelae and are useful in determining the time course of symptom development. TBI depression studies generally show similar symptom breadth to depression without head trauma and respond to typical antidepressant treatments. These findings may also guide not only future CTE studies investigating sites of brain pathology in relation to psychiatric phenotypes, but also provide a framework for future *in vivo* CTE studies, a burgeoning and informative field of research .

5. CLINICAL CHALLENGES OF NEUROPSYCHIATRIC SEQUELAE IN CTE, AND POTENTIAL RESOLUTION THROUGH FUTURE *IN VIVO* CTE STUDIES

In considering the psychiatric phenotypes of CTE, it is critical to acknowledge that CTE represents particular clinical challenges. Symptoms can vary widely between individuals and at different CTE stages and occur across diverse modalities (McKee et al., 2013; Montenigro et al., 2014). Similarly, the sensitivity and specificity of clinical symptoms to CTE neuropathology are unknown. Other medical conditions and psychosocial confounds can create difficulty in distinguishing CTE-related psychiatric sequelae in individuals with RHI from those sequelae induced by other medical conditions or psychosocial factors, particularly in the absence of canonical CTE symptoms such as cognitive and motor dysfunction. For example, symptoms of post-concussion syndrome (including mood and cognitive symptoms) may overlap with clinical presentation of CTE (Hadanny and Efrati, 2016; Montenigro et al., 2014). Although these are typically distinguished by symptom progression and resolution following injury, this represents a diagnostic challenge acutely following symptomatic concussion, as well as a potential confound in individuals who died soon after concussion.

Patients presenting with RHI as part of military-related activities (c.f. (Mac Donald et al., 2011)) may represent particular diagnostic difficulty for clinicians, as psychiatric sequelae resulting from PTSD (including behavioral and affective changes) share features with those found in CTE (Blake et al., 1995; Litz et al., 1997; McKee et al., 2013; Montenigro et al., 2014; Ozer et al., 2003). The psychosocial stress of coping with TBI itself may also contribute to development of psychiatric symptoms (Guskiewicz et al., 2007). Future studies refining the particular symptoms of CTE and the dynamics of their appearance, as well as development of *in vivo* imaging of CTE, will provide important information to address this diagnostic issue in clinical settings.

Not all cases of CTE present with neuropsychiatric disturbances, and psychiatric conditions also often emerge independent of head trauma (Kessler et al., 2003). As such, CTE is not identifiable solely by the presence of psychiatric symptoms coupled with a history of RHI. Additional clinical features are required for diagnosis of CTE or TES, including cognitive symptoms and a progressive course of symptoms (Reams et al., 2016). Similarly, psychiatric symptoms in high-risk cohorts of CTE such as former NFL players do not necessarily indicate that these individuals have CTE or TES, as a proportion of NFL players would have developed these same phenotypes in the absence of RHI, given the prevalence of psychiatric conditions in the general population. Professional athletes might be particularly likely to develop psychiatric sequelae post-retirement given the period of psychosocial stress and adaptation following this event, and clinically distinguishing psychosocial stress-related sequelae from CTE-related sequelae may be difficult in the absence of other symptoms. It is also possible that factors such as a genetic predisposition in athletes (c.f. Lehman (2013)), may contribute to CTE-associated psychiatric symptoms. However, the increased prevalence of depression in former NFL players (Didehbani et al., 2013; Guskiewicz et al., 2007; Kerr et al., 2012), the association between head impacts and depression and suicide (Fralick et al., 2016; Guskiewicz et al., 2007; Kerr et al., 2012; Montenigro et al., 2016), the high proportion of former players brains examined postmortem showing evidence of CTE (Bieniek et al., 2015; McKee et al., 2013), and the frequency of psychiatric sequelae identified in CTE-identified former players (Bieniek et al., 2015; McKee et al., 2013; Montenigro et al., 2016; Montenigro et al., 2014) all strongly indicate that the increased prevalence and severity of psychiatric sequelae identified in this cohort is likely related to exposure to RHI and development of CTE. Future studies will hopefully validate and clarify the nature of these associations, and a promising area of research that may resolve these challenges is the *in vivo* investigation of CTE.

This development of *in vivo* CTE diagnostic methods will allow more accurate estimates of disease prevalence, enable antemortem diagnosis, offer a temporal window of therapeutic intervention to stop symptom progression, and make possible longitudinal examination of the effectiveness of novel therapeutics. As a result, the development and refinement of *in vivo* diagnostic techniques represents a high priority. To this end, two distinct investigative strategies have been pursued: *in vivo* brain imaging, and peripheral biomarker assays.

In vivo neuroimaging for CTE relies on the principle that NFTs can be visualized using traditional positron emission tomography (PET) methods in combination with tracers that specifically target hyperphosphorylated tau-related tangles (Chien et al., 2014; Dani et al., 2016; Villemagne et al., 2015). This technique potentially allows identification of specific brain regions with CTE neuropathology. Recent PET studies show promise in their identification of tau neuropathology in a high-risk cohort for developing CTE (former professional American football players) but not in healthy controls (Barrio et al., 2015). However, *in vivo* brain imaging of phosphorylated tau has yet to be validated in a large cohort of putative clinical cases and controls (Gandy and DeKosky, 2014), or associated with particular symptom progression, and would be more expensive and less practical for large-scale CTE identification studies compared to peripheral biomarker assays. To this end, preliminary efforts to develop non-invasive *in vivo* peripheral biomarker assays have been promising (e.g. tau assays in blood), with a high degree of specificity, sensitivity, and predictive validity. Peripheral tau has been shown to be inversely associated with severity of cognitive deficits, is predicted by number of previous head impacts, and successfully discriminates between former NFL players and healthy controls (Alosco et al., 2017b; Stern et al., 2016).

In vivo assays, in tandem or individually, represent a great potential resource not only for CTE diagnosis, but for research into neuropsychiatrically-relevant phenotypes of CTE. Associating progression of ptau accumulation in imaging studies or exosomal tau in plasma with psychiatric assessments would enable researchers to determine in real time and longitudinally whether CTE pathology is associated with these symptoms, and if so, at what particular stage (and potentially in which particular brain regions) this occurs. *In vivo* studies could also inform postmortem research, identifying putative sites of neuropathology in the brains of CTE-positive individuals who had a history of neuropsychiatrically-relevant symptoms, including depression and suicidality.

6. CONCLUSIONS AND FUTURE DIRECTIONS

Focused research on CTE is relatively recent, and the precise neuropathological progression, diagnosis, and classification of CTE are still in development. Controversy exists within the CTE literature, which is to be expected for a recently-rediscovered disorder with profound implications for the play of contact sports. The identification of CTE, as well as its exact pathological hallmarks, are debated (Randolph, 2014; Wortzel et al., 2013), although a panel of expert neuropathologists convened by the National Instute of Health recently confirmed CTE as a unique neurodegeneration with distinctive pathological hallmarks (McKee et al., 2016). The preponderance of research to date indicates that CTE is found in contact sports athletes exposed to RHI (McKee et al., 2013). Given the severity of symptoms, lack of treatments or methods for *in vivo* diagnosis, and the number of individuals potentially at risk mandates accelerated research into the etiology, diagnosis, and treatment of CTE.

Among the least understood characteristics of CTE are its psychiatrically-relevant symptoms. Chief among these are depression and suicidality, which the literature suggests are overrepresented in CTE cases relative to the general population (McKee et al., 2013). Former professional football players are a high-risk population for CTE (Bieniek et al., 2015; McKee et al., 2013) and show increased prevalence of depression and severe depressive symptoms (Didehbani et al., 2013; Guskiewicz et al., 2007; Hart et al., 2013; Kerr et al., 2012). Reports indicate an association between CTE and suicidality (Corsellis et al., 1973; McKee et al., 2009; McKee et al., 2013; Montenigro et al., 2014; Omalu et al., 2011a; Omalu et al., 2011b; Omalu et al., 2006; Omalu et al., 2010a; Omalu et al., 2010b), and a high proportion of pathologically-validated CTE cases died by suicide (Bieniek et al., 2015; Omalu et al., 2011a). Selection bias in the post-mortem studies of CTE makes precise determination of the risk of suicide in CTE problematic. Epidemiologically examining the prevalence of suicide in cohorts at high risk of CTE could partially address this problem. Although a previous report examined a limited cohort of former NFL players (Lehman et al., 2016), this study needs validation using the full cohort of American football players at all football positions. Additionally, future *in vivo* diagnosis of CTE in the presence of suicidality and longitudinal assessment may provide valuable information regarding the risk of suicide amongst individuals with CTE. *In vivo* CTE studies will also be valuable in determining the clinical progression across CTE stages and the involvement of specific brain regions, and discrimination between head trauma-induced psychiatric symptoms and trauma-independent symptoms. To the extent that suicide and depression are frequent associated with CTE, research focused on early stages of CTE, before the development of widespread neuropathology, will be informative (McKee et al., 2013). Putative target brain regions of interest are the frontal cortex, hippocampus, and amygdala, as these brain regions develop dense neurofibrillary pathology and have been implicated in depression and suicide (Goswami et al., 2013; Guilloux et al., 2012; Mahar et al., 2014; Mahar et al., 2017; Maheu et al., 2013; McKee et al., 2013; Sequeira et al., 2009; Torres-Platas et al., 2014; Tripp et al., 2012; Turecki, 2014).

One important application in investigating depression and suicide in CTE may be its utility as a model for these phenotypes in the general population. Studies of depression and suicide to date have been hampered by the lack of a clearly-defined temporal etiological window, as well as the lack of a putative animal model for suicidality. If CTE represents the induction of psychiatric sequelae in individuals that would not otherwise develop these phenotypes, then the narrow temporal etiological window and clearly defined neuropathology of CTE could give important clues into brain regions, circuits, and cell types involved in these phenotypes in general. Studies differentiating between psychiatric phenotypes within CTE cohorts may be particularly informative from this perspective.

Overall, the classification, diagnosis, prevalence determination, etiology, and treatment of CTE represent unique challenges that are under active investigation. The neuropsychiatric sequelae of CTE represent endophenotypes of CTE that merit focus in future research. However, recent studies in this area have provided substantial insight into the nature of these symptoms in CTE, with clear multimodal future directions strongly indicated. Research focused on the neuropsychiatric endophenotypes of CTE, associating regional neuropathology across CTE stages with psychiatric phenotypes, epidemiological studies investigating prevalence of suicidality in high-risk cohorts for CTE, and *in vivo* studies investigating diagnosis and disease progression will be particularly informative for the future development of effective treatments and management strategies.

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Table 1. Stages of chronic traumatic encephalopathy (CTE) by symptoms and neuropathology. Arrows denote progressive nature of neurodegeneration and symptomatology throughout stages.

CTE Stages	Symptoms	Primary brain regions showing ptau pathology	Gross structural pathological changes
Stage 1	Headache; attention/concentration deficits; depression; suicidality	Depths of frontal cortical sulci; locus coeruleus. Gliosis and axonal loss in white matter tracts	None
↓			
Stage 2	Depression; suicidality; behavioral changes; memory loss; explosivity; aggression	Cortex; minimal in hippocampus, amygdala, and substantia nigra	Some mild ventricular enlargement; occasional cavum septum pellucidum
↓			
Stage 3	Cognitive/executive dysfunction; depression; explosivity; aggression; dementia; suicidality	Hippocampus; amygdala; entorhinal cortex; substantia nigra; temporal and parietal cortices	Mild cerebral atrophy and ventricular dilation; some depigmentation of substantia nigra and locus coeruleus; diencephalic and mammillary body atrophy; corpus callossal thinning
↓			
Stage 4	Dementia; memory impairment; aggression; paranoia; explosivity; motor symptoms; depression; suicidality	Throughout cortex, temporal lobe	Reduced overall brain weight; ventricular enlargement; cavum/absent septum pellucidum; depigmentation of substantia nigra and locus coeruleus

Table 2. Primary brain regions showing neuropathological changes in chronic traumatic encephalopathy (CTE), as well as type of changes observed, associated previously with depression or suicide. GM: gross morphological changes; NFT: neurofibrilary tangles; ptau: hyperphosphorylated tau. Relevant psychiatric research papers are shown at right.

Brain region affected in CTE	Psychiatric phenotype	Relevant articles
Amygdala	Depression, suicide	Maheu et al., 2013; Guilloux et al., 2012
Basal ganglia	Depression	Husain et al., 1991
Diencephalon	Depression, suicide	Mahar et al., 2014; Turecki 2014
Frontal cortex	Depression, suicide	Turecki 2014; Johnston-Wilson et al., 2000
Hippocampus	Depression, suicide	Turecki 2014; Mahar et al., 2014
Locus coeruleus	Depression	Bernard et al, 2011
White matter structures	Depression	Choi et al., 2015