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Cognitive Reserve as a Modifier of Clinical Expression in Chronic Traumatic Encephalopathy: A Preliminary Examination

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Abstract

This study conducted a preliminary examination on cognitive reserve (CR) as a modifier of symptom expression in subjects with autopsy-confirmed chronic traumatic encephalopathy (CTE). The sample included 25 former professional football players neuropathologically diagnosed with CTE stage III or IV. Next of kin interviews ascertained age of cognitive and behavioral/mood symptom onset, and demographic/athletic characteristics. Years of education and occupational attainment defined CR. High occupational achievement predicted later age of cognitive, $p = 0.02$, and behavioral/mood, $p = 0.02$, onset. Education was not an individual predictor. These preliminary findings suggest that CR may forestall the clinical manifestation of CTE.

Keywords

Chronic traumatic encephalopathy; cognitive reserve; repetitive head impacts

INTRODUCTION

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with exposure to repetitive head impacts (RHI) and is uniquely characterized by a perivascular deposition of hyperphosphorylated tau (p-tau) at the sulcal depths {1-3}. Although clinical research criteria for the *in vivo* diagnosis of CTE have been proposed {4}, currently CTE can only be diagnosed based on neuropathological examination using recently defined criteria {1,3}. The clinical presentation of CTE is heterogeneous and manifests as two variants (or a mixed combination): 1) initial behavioral/mood changes at a mean age of approximately 35, with later progression to cognitive deficits; and/or 2) initial cognitive impairment at a mean age of approximately 60, progressing to dementia {5}.

Age of symptom onset in CTE is variable even in cases with similar neuropathological severity {5}. One factor that may affect age of onset in CTE is cognitive reserve (CR). The CR theory posits that individuals with high reserve enlist pre-existing cognitive processes or compensatory strategies to cope with neuropathological insult {6}. CR has been theorized to account for inter-individual variability in the clinical course of normative aging and Alzheimer's disease (AD), with higher CR associated with delayed onset of cognitive impairment and incident dementia {7,8}. Although CR has traditionally been linked to cognitive impairment in AD, CR has been associated with reduced behavioral disturbances in frontotemporal dementia {9}.

There has been recent interest in the role of CR in the manifestation of CTE symptoms {10} due to findings that higher education decreases vulnerability to cognitive dysfunction {11} and facilitates recovery following traumatic brain injury (TBI) {12}. In our study examining the clinical presentation of neuropathologically-confirmed cases of CTE without comorbid disease, two of three asymptomatic subjects with stage II CTE neuropathology had advanced graduate degrees (the third subject was 17 years old and had stage I CTE), raising the possibility of a CR effect in CTE {5}. No study has empirically tested the role of CR in the clinical expression of CTE. This study conducted a preliminary examination on the association between CR (operationalized by years of education and occupational attainment) and age of reported cognitive and behavioral/mood symptom onset in former professional American football players with neuropathologically-confirmed CTE. The sample was restricted to subjects with stage III or IV CTE disease severity in order to limit differences in age of symptom onset due to variability in neuropathological severity. We hypothesized that higher occupational attainment and greater years of education would predict later symptom onset.

MATERIALS AND METHODS

Subjects

The sample included former professional American football players neuropathologically diagnosed with stage III or IV CTE. The former professional football players' brains were donated to the Boston University-Veteran's Affairs-Concussion Legacy Foundation Brain Bank. Brain donation was part of ongoing research at the Boston University Alzheimer's Disease and CTE Center examining the neuropathology and clinical symptoms of deceased individuals with a history of RHI exposure, with specific funding from a National Institutes of Health-funded U01 project, entitled, "Understanding Neurologic Injury and Traumatic Encephalopathy (UNITE)." A detailed description of UNITE has been outlined elsewhere {13}. Brain tissue was obtained through two methods: 1) following death, next of kin consented to brain donation of the subject's brain and spinal cord, that in many instances was facilitated through community outreach; or 2) prior to death, subjects agreed to donate their brain and spinal cord through the project's Brain Donation Registry. To optimize external validity and reduce ascertainment bias, inclusion criteria were broad and included only a history of RHI exposure. Brain donors were excluded for poor brain and spinal cord specimen quality.

Next of kin provided written informed consent for participation and brain donation at Boston University's Alzheimer's Disease Center. The institutional review boards (IRB) at Boston University Medical Center (BUMC) and the Edith Nourse Rogers Memorial Veteran's Hospital (Bedford, MA) approved brain donation procedures. The BUMC IRB approved post-mortem clinical record review, interviews with family members, and neuropathological evaluation.

Retrospective Next of Kin Interviews

Retrospective postmortem telephone interviews and online surveys with next of kin were conducted to ascertain clinical, demographic, and athletic characteristics of the decedent. See Mez et al. {13} for a detailed description of the clinical evaluations used for data collection. Briefly, data relevant to the current study was obtained through semistructured and unstructured clinical interviews, as well as an online survey with next of kin. Informants completed the telephone interviews and online surveys individually or as a group (e.g., with other family members). To facilitate informant reliability, all informants report on their relationship with the brain donor. The online survey asks about the brain donors' demographic information (e.g., educational and occupational attainment), athletic characteristics (e.g., type of sport played, position level, duration of football played, age first started playing football), and military history. Telephone interviews with next of kin were performed by behavioral neurologists and neuropsychologists trained to assess RHI and clinical manifestations of neurodegenerative diseases. Here, semistructured questions were first asked to obtain detailed demographic, psychosocial, athletic, medical, psychiatric, and traumatic brain injury history. The clinician then leads an unstructured interview to characterize the nature and course of symptoms (including age of symptom onset). Interviewers were blind to the results of the neuropathological examination and informants were interviewed before receiving the neuropathological results.

Through the above procedures, we ascertained age of onset for cognitive (e.g., episodic memory impairment, executive dysfunction), behavioral (e.g., explosivity, impulsivity, disinhibition), and mood (e.g., depression, apathy) symptoms. Behavioral and mood symptoms were combined (behavioral/mood) for consistency with clinical research criteria {4}. The earliest age of symptom onset was used to resolve discrepancies.

Cognitive Reserve

The above described methods also ascertained years of education and occupational attainment. Both variables served as proxies for CR. These variables were chosen based on epidemiological evidence in AD that shows both proxies are robust markers of reserve {8}. To ascertain occupational attainment, next of kin reported the occupation(s) of the subject. Subjects who were students at the time of death were excluded from analyses. Based on occupational category, we classified subjects as high or low using U.S. Department of Labors' Dictionary of Occupational Titles (DOT) {14}. Similar methods for classifying level of occupational attainment have been used in previous CR studies among other neurological populations {8, 15}. High attainment is defined as professional, technical, and managerial positions (DOT codes 0-1). Examples of these occupations include architect, engineer, meteorologist, teacher, professional athlete, general contractor, service industry (and other industry) managers and officials, to name a few. Low attainment is defined as clerical/sales, agricultural/fishery/forestry, processing, machine trades, benchwork, and structural occupations (DOT codes 2-8). Examples of these jobs include secretary, domestic service, food and beverage preparation and service, sales, painter, inspector, assembler, etc. There was one subject who fell in the Miscellaneous Occupations category (DOT code 9) and this subject was classified into the low occupational attainment group due to similarities to other types of occupations listed in DOT codes 2-8. In the case of multiple occupations, the highest level attained was used. **Table 1** provides a breakdown of the occupational status of the sample according to the U.S. Department of Labors' DOT.

Pathological Diagnosis of Chronic Traumatic Encephalopathy

Methodological procedures for pathological processing and evaluation are published elsewhere {16,17}. In brief, brains were hemisected and one half was sectioned and frozen and the other was fixed in periodate-lysine-paraformaldehyde for at least three weeks. The fixed tissue was dissected and processed into paraffin sections of multiple brain regions and comprehensively evaluated for neurodegenerative disease. The neuropathological diagnosis of CTE was made using neuropathological criteria recently defined by an NINDS/National Institute of Brain Imaging and Behavior (NIBIB) consensus panel {3}. CTE pathological severity was graded using a four-stage classification system based on the extent and severity of tau pathology (stage I being least severe and stage IV being most severe) {1,18}. As described previously, the sample was restricted to stage III and IV CTE disease severity. Neuropathologists were blind to all clinical data. The study cohort included all subjects with available neuropathological diagnoses.

To minimize confound due to comorbid neuropathological disease, the final sample analyzed excluded subjects that had significant comorbid neuropathology for another neurodegenerative disease or acute catastrophic brain injury. Specifically, AD, diffuse Lewy body disease, frontotemporal lobar degeneration, motor neuron disease, prion disease, and corticobasal degeneration were excluded.

Statistical Analyses

The sample of 78 former American professional football players with stage III or IV CTE was reduced to 25 following several iterative exclusions to limit differences across subjects in athletic and RHI exposure and increase generalizability to CTE. First, 32 were excluded based on neuropathological criteria, including those with significant comorbid neuropathology (as described above). Second, 17 were excluded due to history of participation in another sport. Lastly, four cases were excluded due to missing data.

Independent samples *t*-tests and chi-square analyses were conducted to determine between occupational group (high versus low) differences on sample characteristics. Because occupational attainment and years of education may represent unique aspects of CR {19}, they were examined independently. For occupational attainment and years of education, two separate linear regression analyses examined their association with age of cognitive and behavioral/mood symptom onset. Block 1 included number of years of football played in order to account for inter-individual differences in RHI exposure. In separate models, block 2 included years of education and occupational attainment (1 = high; 0 = low). To clarify effects for the CR indices that emerged significant, analysis of covariance (that accounted for duration of play) examined bonferroni adjusted estimated marginal mean differences on age of cognitive and behavioral/mood symptom onset.

RESULTS

Sample Characteristics

Table 2 presents sample characteristics. Of the 25 subjects, 24 had cognitive and behavioral/mood symptoms, and one had only cognitive symptoms. The one subject with only cognitive symptoms was thus not included in analyses examining age of behavioral/mood symptom onset. Average age of cognitive symptom onset was 56.44 (SD = 14.42) years and 47.50 (SD = 16.45) years for behavioral/mood symptoms. 11 had initial behavioral/mood symptoms, 9 initial cognitive symptoms, and the remaining subjects had the same age of onset for cognitive and behavioral/mood symptoms. All but 2 subjects were reported to have had a progressive symptom course; one subject reportedly had a stable course and another had a stepwise course.

Cognitive Reserve and Age of Symptom Onset

Regression analyses controlling for duration of football played examined the association between occupational attainment and years of education with age of cognitive and behavioral/mood symptom onset. Block 1 of the models predicted age of onset for cognitive, $p = 0.004$, but not behavioral/mood symptoms, $p = 0.76$. After controlling for duration of football play, occupational attainment predicted age of cognitive, $p = 0.02$, and behavioral/mood symptom onset, $p = 0.02$ (see **Table 3**). Greater occupational attainment correlated with later onset of symptoms. Bonferroni adjusted estimated marginal mean differences (that accounted for duration of play) showed symptom onset began more than 10 years earlier in subjects with low occupational attainment compared to those with high occupational attainment [cognitive symptom onset: mean, SE for low occupational attainment = 48.80, 3.72; high occupational attainment = 60.74, 2.78, $p = 0.02$; behavioral/mood symptom onset: mean, SE for low occupational attainment = 37.37, 5.09; high occupational attainment = 53.58, 3.92, $p = 0.02$]. Years of education was not a significant individual predictor for either symptom profile, $p > 0.05$.

DISCUSSION

The current study is the first to show that CR (i.e., occupational attainment) is associated with later symptom onset in a sample of former professional American football players with neuropathologically-confirmed CTE stage III or IV. Occupational attainment and not years of education predicted age of symptom onset. These reserve proxies have been suggested to contribute to CR through independent paths {19}, and the discrepant findings in this study may be related to the sampling of elite athletes. Educational attainment in this sample of mostly professional football players may be more reflective of athletic prowess. The limited variability in education may also explain non-significant effects. It is possible that occupational attainment may capture those subjects who continued academics post-football, remained mentally and physically active throughout their life, and/or those with a high innate intellect to achieve a high occupational status.

Higher CR was associated with onset of behavioral/mood and cognitive symptoms more than 10 years later in this sample of neuropathologically-confirmed cases of CTE. The relationship between CR and cognitive outcomes is consistent with the AD literature that shows CR attenuates and delays onset of cognitive impairment {8}. In addition to cognitive impairment, behavioral/mood symptoms are core features in CTE {4}, and we found a significant CR effect for behavioral/mood disturbances in CTE. Because nearly all subjects had both cognitive and behavioral/mood symptoms, the distinct influence of CR on each symptom profile is unclear. One study found higher CR attenuates behavioral disturbances (e.g., disinhibition) in frontotemporal dementia {9}, but minimal research has examined the relationship between CR and behavioral/mood symptoms. CR may mitigate the clinical phenotype associated with a specific neurodegenerative pathology, even if it is not cognitive in nature.

CTE is characterized pathologically by an accumulation of p-tau in neurons and astroglia distributed around small blood vessels at the cortical sulcal depths and in an irregular pattern {1-3}. As the disease progresses, p-tau accumulates in widespread cortical regions, medial temporal lobe structures, the diencephalon, and brainstem. In advanced disease, cortical atrophy is severe and there is marked neuronal loss in the hippocampus {1-3}. Other microscopic alterations include axonal loss and white matter degeneration, chronic neuroinflammation, microvascular dysintegrity, and TDP-43 inclusions. Amyloid beta is found in approximately 50% of CTE cases, and associated with age and the *APOE ε4* allele {20}. The pathological substrates underlying behavioral/mood and cognitive changes in CTE are unknown, and may involve multiple pathologies, including regional axonal damage, neuronal loss, p-tau, and TDP-43 accumulation. Based on evidence in AD, CR may modulate the clinical effects related to the neuropathological load in CTE. In a sample of 130 older Catholic clergy that underwent autopsy, greater years of education diminished the negative impact of neuritic and diffuse plaques on cognition proximate to death {21}. Past work among 165 autopsy subjects from the Rush Memory and Aging Project revealed that reduced neuronal reserve (neuronal density) in the locus coeruleus, and brain stem neurofibrillary tangles (NFT) and Lewy bodies predicted rate of cognitive decline, even after controlling for pathologic burden elsewhere in the brain {22}. Such findings are noteworthy given the brainstem, especially the locus coeruleus, raphe nuclei, and substantia nigra, show high NFT density in CTE {1}. CR may also attenuate the impact of pathology on clinical expression in CTE. Investigation of CR using *ex vivo* neuropathological data has well-defined methodological limitations {23}. Currently, we are conducting prospective studies with objective assessments proximate to death to formally test CR as a modulator of CTE pathology. In addition, CR may also attenuate the impact of RHI on the severity of cognitive impairment {24; 25} and longitudinal research in living subjects work will examine this possibility using validated metrics of RHI exposure {26}.

Lastly, longer duration of football play correlated with earlier age of cognitive symptom onset. Duration of football play has been associated with CTE stage {1}, and may thus be a critical marker of RHI exposure. Notably, we did not find a relationship between duration of football play and behavioral/mood symptom onset. Different types of RHI exposure (beyond duration) (e.g., specific types of hits) may differentially contribute to symptom phenotypes. Moreover, the relationship between RHI and CTE is complex and, risk factors beyond RHI exposure, including genetics, are likely critical in the pathogenesis of CTE.

The current study is preliminary and the generalizability of our findings is limited in several ways. Our study includes a restricted sample of deceased professional football players without any other sport history and with only neuropathologically diagnosed stage III or IV CTE. Although this methodology limits confound from differences in athletic and RHI exposure and increases generalizability to CTE, the external validity of our findings, in general, and to the larger contact sport athlete population, in particular, is limited. Once sample size permits, our findings will need to be replicated in a larger sample of former athletes with various sport (e.g., soccer) and athletic backgrounds (e.g., level played) who were neuropathologically diagnosed with CTE. Even though our study did not recruit brain donors based on the presence of symptoms, the sample may demonstrate selection bias because family members are more likely to donate if their loved ones were symptomatic. A recent study from the Mayo Clinic Jacksonville neurodegenerative disease brain bank reviewed medical records and brain tissue slides of more than 1700 male brain donors and found that 21 of 66 contact sport athletes had evidence of CTE pathology {2}. Their approach reduces ascertainment bias; thus, replication of our results in other non-CTE autopsy series would be a critical next step in the examination of a CR effect in CTE. Similarly, drawing upon other brain banks with data on sport participation history will allow for utilization of comparison (e.g., AD) and control groups (e.g., former non-contact sport professional athletes without RHI exposure) to better understand the role of CR in CTE.

Retrospective interviews introduce self-report biases (e.g., memory lapses, subjectivity). However, this approach has been shown to be reliable and valid in other dementia autopsy studies {27}. We are currently conducting longitudinal studies in living former contact sport athletes who have agreed to brain donation and, in the future, we will examine the relationship between antemortem CR and objective test data in subjects with neuropathologically-confirmed CTE. There is a lack of consensus regarding the operationalization of CR {28}. We chose educational and occupational attainment to define CR based on epidemiological evidence that they are robust markers of CR {8}. Reliability and validity of these indicators in elite athletes is unclear. In particular, there are multiple potential confounds associated with the use of occupational attainment to define CR. First, occupational attainment may be biased by athletes who died at a young age. Second, low occupational attainment may be a consequence of CTE, particularly for those with earlier onset of symptoms, rather than low cognitive reserve. Beyond these limitations, the retrospective nature of the study design precluded detailed history of lifetime occupational status (e.g., degree of responsibility). Nevertheless, this study provides initial evidence for a possible CR effect in CTE and this finding needs to be replicated with future, prospective research studies that incorporates other proxies of CR, such as socioeconomic status or engagement in social and intellectual activities. Estimated premorbid intelligence as a proxy for CR in CTE may be problematic due to the potential negative impact of childhood RHI on intellectual and brain development {29}. Recent research highlights the potential utility of residual memory variance (i.e., residual variance in episodic memory after controlling for demographic factors and brain pathology) as a potential marker of CR {30}. Our center is currently conducting prospective research to identify *in vivo* biomarkers of CTE (e.g., normal amyloid beta, elevated p-tau/tau ratio, PET tau specific ligands (e.g., [F-18]-T807), and once validated, we will utilize the residual memory variance approach (and others) to examine CR in subjects with 'Probable CTE.' Such longitudinal work will also be critical to elucidate the symptom course of CTE, and whether CR attenuates decline.

CONCLUSIONS

This study provides initial evidence that high CR may forestall the clinical manifestation of CTE. Large prospective studies of subjects at high risk for CTE that employ other CR proxies (e.g., social and intellectual enrichment) and objective symptom assessments are needed to better characterize the role of CR in the interplay among RHI, CTE pathology, and symptom presentation.

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Table 1

Breakdown of Occupational Attainment According to the U.S. Department of Labors' Dictionary of Occupational Titles (DOT)

DOT Division	Attainment Classification	N
Professional, Technical, and Managerial Occupations	High	16
Clerical and Sales	Low	4
Service Occupations	Low	3
Structural Work	Low	1
Miscellaneous Occupations	Low	1

Table 2

Characteristics of 25 Former American Professional Football Players with Neuropathologically-Confirmed Stage III or IV CTE

	Total Sample (N = 25)	High Occup. (n = 16)	Low Occup. (n = 9)	P value
Demographic/Athletic Characteristics				
Age at death, mean (SD) years	65.00 (14.07)	67.75 (13.51)	60.11 (14.47)	0.20
Race, n (%) white	16 (64.0)	9 (56.3)	7 (77.8)	0.28
Education, mean (SD) years	15.70 (1.22)	15.75 (1.48)	15.61 (0.60)	0.79
Football Primary Position, n (%): Lineman (OL/DL) Linebacker Defensive back/safety Running back Quarterback Other/multiple	10 (40.0) 2 (8.0) 3 (12.0) 7 (28.0) 1(4.0) 2(8.0)	5 (31.3) 1 (6.3) 3 (18.8) 7 (43.8) 0 0	5 (55.6) 1 (11.1) 0 0 1(11.1) 2(22.2)	--
Duration of play, mean (SD) years	19.24 (3.27)	19.69 (2.73)	18.44 (4.13)	0.37
Military, n (%) yes	8 (32.0)	5 (31.3)	3 (33.3)	0.92
CTE Characteristics				
CTE stage, n (%) III IV	14 (56.0) 11 (44.0)	8 (50.0) 8 (50.0)	6 (66.7) 3 (33.3)	0.42

CTE = chronic traumatic encephalopathy; occup. = occupational attainment

Table 3

Linear Regression Examining Occupational Attainment and Age of Cognitive and Behavioral/Mood Symptom Onset

	Age of Cognitive Impairment Onset							
	ß	**b**	**SE b**	***F***	**Δ *F***	***R^2***	**Δ *R^2***	**95% CI for unstandardized b**
Block 1	--		--	10.04**	--	0.30	--	
Duration of Play (years)	−0.55**	−2.43	0.77	--	--	--	--	−4.02, −0.84
Block 2	--		--	9.47**	6.50*	0.46	0.16	
Occup. Attainment (1 = high; 0 = low)	0.41*	11.94	4.68	--	--	--	--	2.23, 21.65
	Age of Behavioral/Mood Symptom Onset							
	ß	**b**	**SE b**	***F***	**Δ *F***	***R^2***	**Δ *R^2***	**95% CI for unstandardized b**
Block 1	--		--	0.09	--	0.004	--	
Duration of Play (years)	−0.07	−0.32	1.05	--	--	--	--	−2.49, 1.85
Block 2	--		--	3.19	6.26*	0.23	0.23	
Occup. Attainment (1 = high; 0 = low)	0.49*	16.20	6.48	--	--	--	--	2.73, 29.67

Note.

SE b = standard error of unstandardized beta coefficient; Occup = occupational

* $p < 0.05$;

** $p < 0.01$;