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BACKGROUND

Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative tauopathy associated with repetitive head impacts (RHI) that is definitively diagnosed at autopsy

The antemortem neuropsychological profile of this condition is not well understood, hindering diagnosis in life

OBJECTIVE

To characterize antemortem objective neuropsychological test performances of 43 National Football League (NFL) players who donated their brains to the BU UNITE Brain Bank for neuropathological evaluation.

PARTICIPANTS & METHODS



NFL Concussion Settlement:

- Claims the NFL was aware of the risks of traumatic brain injuries that players sustain, but failed to protect them

- Players eligible to receive one BAP examination

- BAP = standardized pencil and paper neuropsych battery**

BAP Diagnoses:

- Level 1** Neurocognitive Impairment (moderate cognitive impairment)
- Level 1.5** Neurocognitive Impairment (early Dementia)
- Level 2** Neurocognitive Impairment (moderate Dementia)

Neuropsychological Measures by Domain

- Raw neuropsych test scores converted to z-scores using normative data accounting for age, sex, and/or education

Performance & Symptom Validity

- At least 7 validity indicators, applied Slick criteria

Learning and Memory (Verbal + Visual)

- Wechsler Memory Scale IV (WMS-IV) Logical Memory I and II
- WMS-IV Verbal Paired Associates I and II
- WMS-IV Visual Reproduction I and II

Executive Function

- Controlled Oral Word Association Test
- Trail Making Test Part B
- Booklet Category Test
- Wechsler Adult Intelligence Scale (WAIS-IV) Similarities

Attention, Visual Scanning, & Psychomotor Speed

- WAIS-IV Digit Span Total
- WAIS-IV Arithmetic
- WAIS-IV Letter Number Sequencing
- WAIS-IV Symbol Search
- WAIS-IV Cancellation

Language

- Boston Naming
- Category/Animal Fluency
- Boston Diagnostic Aphasia Examination (BDAE) Complex Ideational Material

Visuospatial Function

- WAIS-IV Block Design
- WAIS-IV Visual Puzzles
- WAIS-IV Matrix Reasoning

Neuropathological Diagnosis

Neuropathological diagnosis of CTE made using NINDS/NIBIB consensus panel neuropathological criteria; classified as “none”, “low” (stages I and II), and “high” (stages III and IV)

Regional phosphorylated tau (p-tau) rated semi-quantitatively (0 = none, 1 = mild, 2 = moderate, 3 = severe) across 11 brain regions (listed in table 2)

Statistical Analysis

- Described **impairments** by cognitive domain. A z-score of ≤ -1.5 = impaired. Domains impaired if 2+ individual tests impaired
- Multivariable linear regressions** examined associations between p-tau and composite neuropsychological test scores (derived by taking the mean of test z-scores across each domain), adjusting for age, education, and time between testing and death
- Post-hoc Spearman correlations** examined associations between p-tau severity across 9 regions and 3 composites: learning & memory, verbal memory, and visual memory
- Sensitivity Analyses:** examined **impairment patterns and regression results** excluding 8/36 participants with AD

RESULTS

Participant Sample

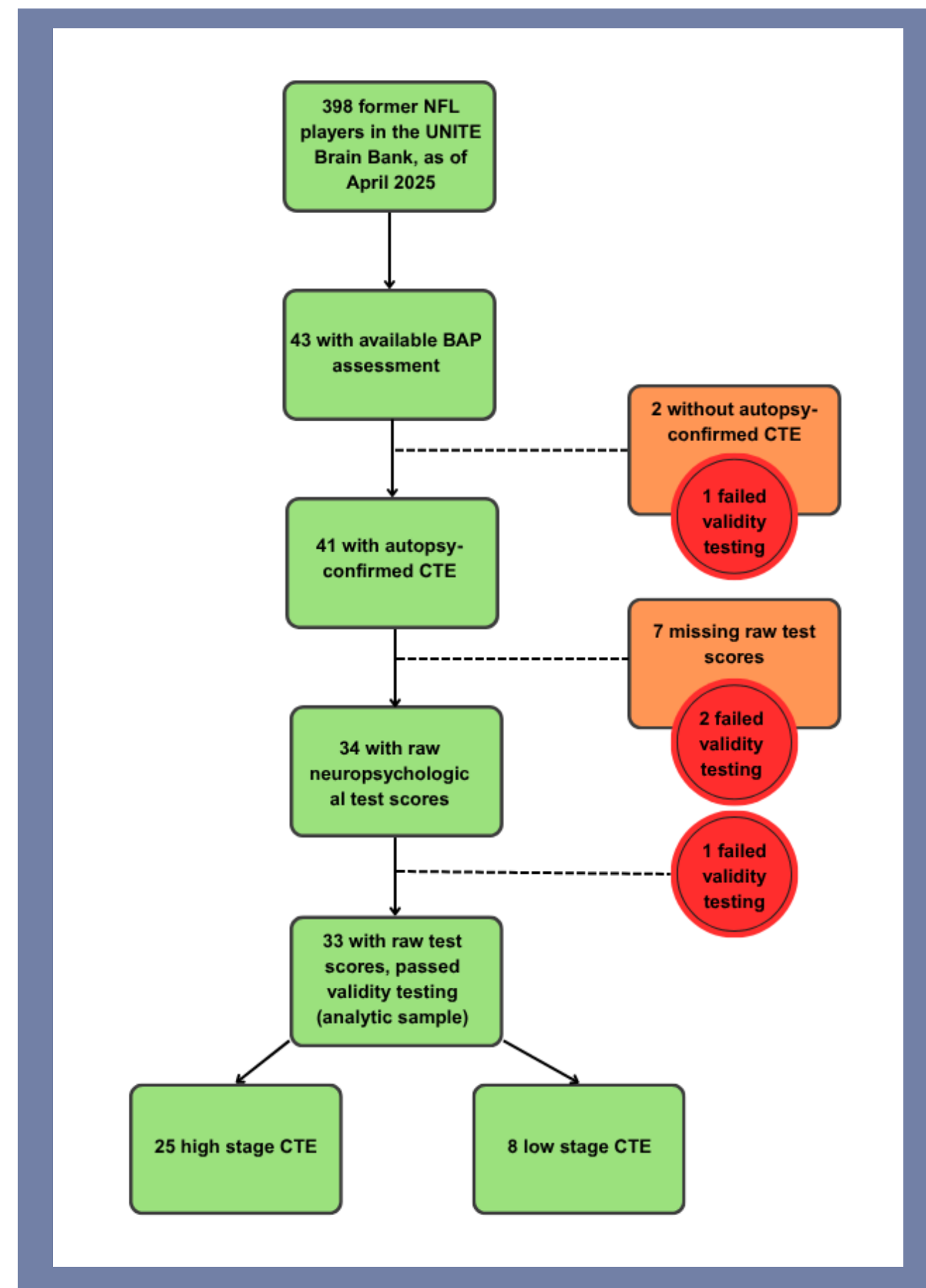


Figure 1: Derivation of Primary Analytic Sample

Neuropsychological Test Performance

Performance Validity

- 4/43 had neuropsych scores that did not accurately reflect neurocognitive functioning

Learning and Memory

- 17/27 (63.0%) impaired; 15/21 (71%) high CTE and 2/6 (33%) low stage CTE.
- Impairments more prevalent on delayed recall compared with learning, verbal compared to visual

Executive Function

- 15/29 (51.7%) impaired; 13/22 (59.1%) high and 2/7 (28.6%) low CTE
- 68% on Trail Making Test Part B

Language

- 12/29 (41%) of participants impaired; 11/22 (50%) high CTE and 1/7 (14%) low CTE
- BDAE had highest impairment

Attention, Visual Scanning, Psychomotor Speed

- 7/27 (25.9%) impaired; 6/21 (28.6%) high and 1/6 (16.7%) low stage CTE.
- WAIS-IV Cancellation most impaired

Visuospatial

- 3/27 (11.1%) of participants impaired; all high stage CTE

Table 1: Participant Characteristics

Characteristic	Low CTE (N=9)	High CTE (N=32)
Age at death, mean (SD)	56.11 (14.61)	69.19 (11.96)
Age at time of evaluation (SD)	54.22 (15.02)	66.41 (11.88)
Time between BAP examination and death, years (SD)	1.89 (1.76)	2.56 (1.39)
Race		
White	4 (44.4)	21 (65.6)
Black/African American	4 (44.4)	11 (34.4)
Pacific Islander	1 (11.1)	0
Hispanic ethnicity, n (%)	0	0
Education level		
Some college	3 (33.3)	8 (25)
College degree	6 (66.6)	18 (56.3)
More than bachelor's degree	0	1 (3.1)
Graduate degree	0	5 (15.6)
Years of total football play, mean (SD)	15 (3.61)	19.72 (4.92)
Age of first exposure to football, mean (SD)	11 (3.5)	11.03 (2.59)
Years of total NFL play, mean (SD)	4.67 (3.16)	7.66 (3.93)
NFL games played, mean (SD)	57.22 (46.08)	98.23 (53.41)
Primary position in the NFL, n (%)		
Offensive lineman	3 (33.3)	4 (12.5)
Defensive lineman	3 (33.3)	7 (21.9)
Running back	2 (22.2)	3 (9.4)
Linebacker	0	8 (25)
Defensive back	1 (11.1)	4 (12.5)
Wide receiver	0	2 (6.3)
Quarterback	0	1 (3.1)
Tight end	0	1 (3.1)
Kicker or punter	0	1 (3.1)
Multiple	0	1 (3.1)
Other contact sports, n (%)	1 (11.1)	3 (9.4)
Military veteran, n (%)	1 (11.1)	3 (9.4)
BAP Neurocognitive impairment		
Level 0 (No Impairment)	7 (77.8)	10 (31.3)
Level 1 (Moderate Cognitive Impairment)	1 (11.1)	5 (15.6)
Level 1.5 (Early Dementia)	0	3 (9.4)
Level 2 (Moderate Dementia)	1 (11.1)	14 (43.8)

Domain-Level Impairment Rates

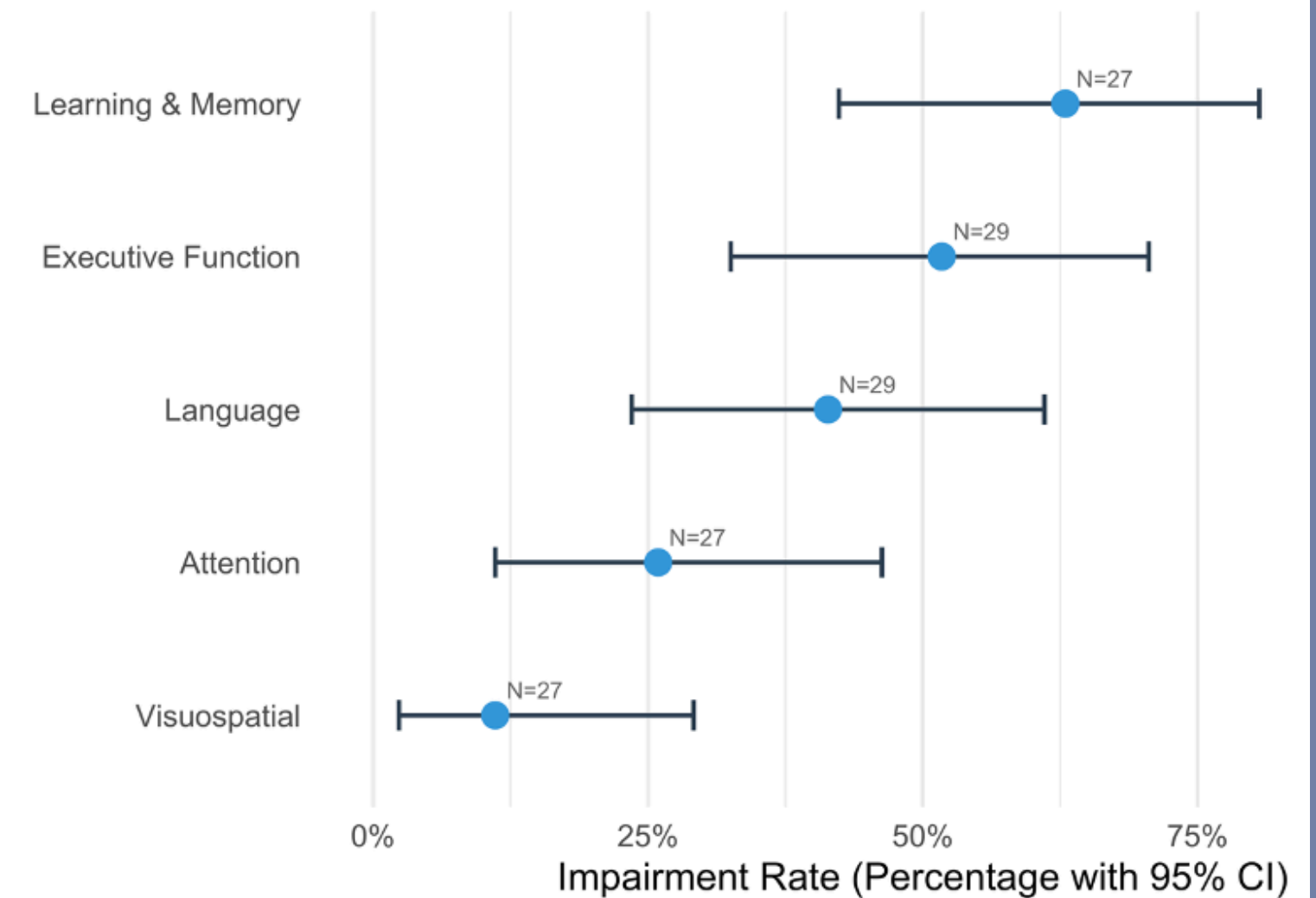


Figure 2: Domain-level impairment rates and 95% confidence intervals across neuropsychological domains. Sample sizes (N) reflect participants who completed at least 2 measures within a given domain; participants with fewer than 2 valid scores were excluded from that domain's estimate. Confidence intervals were calculated using the exact binomial method.

Table 2: Participant Neuropathological Characteristics

Neuropathology	Low CTE (N=9)	High CTE (N=32)
CTE		
Stage I	3 (33.3)	-
Stage II	6 (66.6)	-
Stage III	-	17 (53.1)
Stage IV	-	15 (46.9)
Alzheimer's disease (NIA-Reagan), n (%)	0	9 (28.1)
Lewy body disease, n (%)	1 (11.1)	4 (12.5)
Brainstem predominant	1 (11.1)	2 (6.3)
Limbic/neocortical	0	2 (6.3)
Frontotemporal lobar degeneration-tau, n (%)	0	2 (6.3)
Motor neuron disease, n (%)	0	0
White matter rarefaction, mod-severe, n (%)	2 (22.2)	17 (53.1)
Arteriolosclerosis, mod-severe, n (%)	3 (33.3)	19 (59.4)
Atherosclerosis, mod-severe, n (%)	1 (11.1)	9 (28.2)
Hippocampal sclerosis, n (%)	0	9 (28.1)
Hippocampal TDP-43 inclusions, n (%)	2 (22.2)	14 (43.8)
Presence of old infarcts, n (%)	0	5 (15.6)
Presence of old microinfarcts, n (%)	1 (11.1)	3 (9.4)
Presence of old cerebral microbleeds, n (%)	0	0

Regional Tau

- Inferior parietal p-tau associated with three learning and memory composites ($p = -0.67$ to -0.43 , all $p < 0.05$)

- Superior temporal p-tau associated with all composites ($p = -0.45$ to -0.52 , all $p < 0.05$).

Sensitivity Analysis

- Neuropsychological test patterns and rates of impairment remained similar for all domains when 8 AD participants were.
- Associations of cumulative tau & memory remained significant

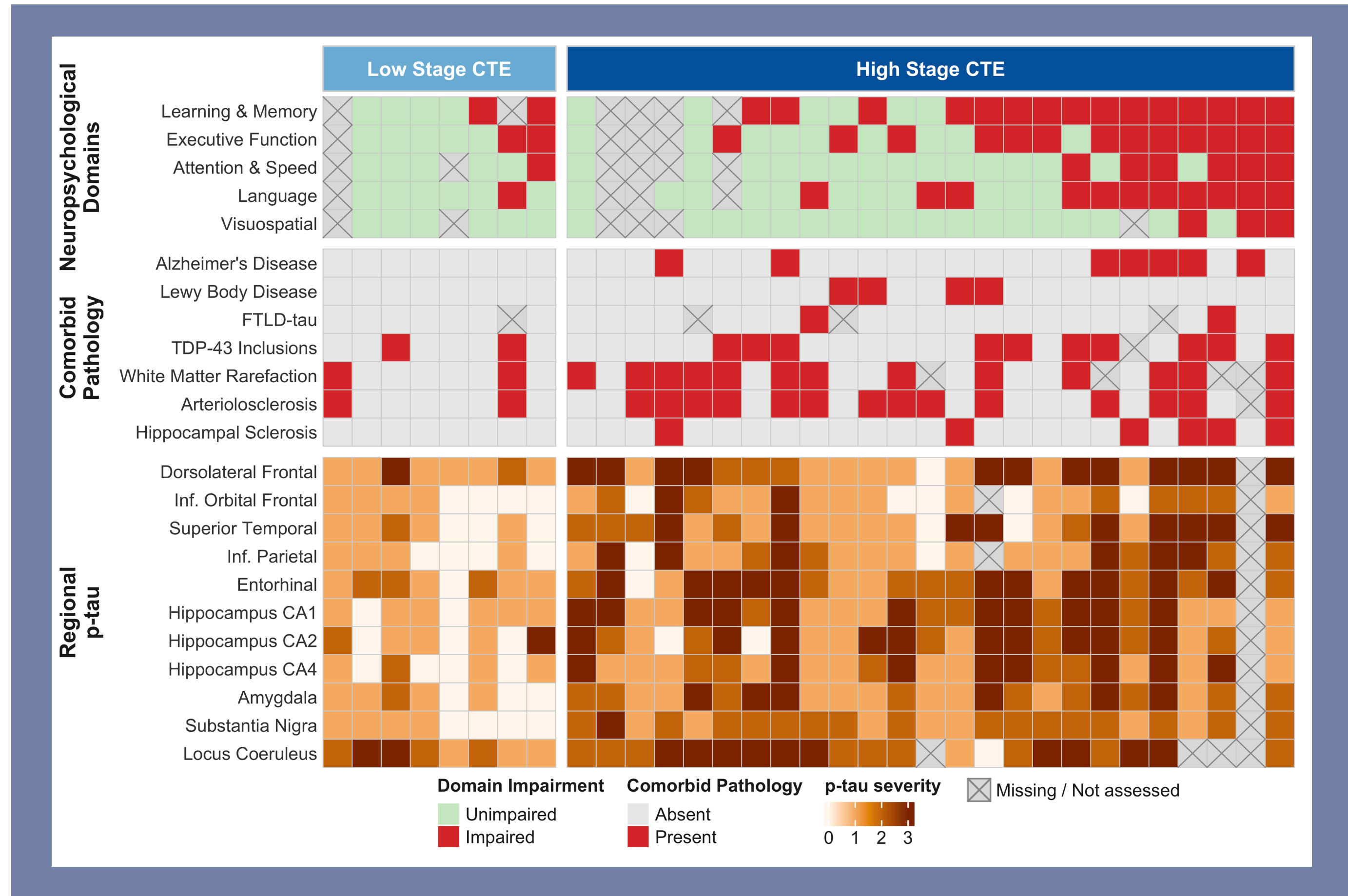


Figure 3: Columns represents a single participant (N=36). The top panel shows domain-level neuropsychological impairment across 5 domains; a domain was classified as impaired if 2 or more constituent tests were impaired. The middle panel displays comorbid neuropathological diagnoses, coded as present (red) or absent (grey): Alzheimer's disease, Lewy body disease, FTLD-tau, hippocampal sclerosis, and hippocampal TDP-43 inclusions were rated as absent or present, while white matter rarefaction and arteriolosclerosis were thresholded at moderate or severe (score ≥ 2). The middle panel shows regional phosphorylated tau (severity rated on a semi-quantitative 0-to-3 scale across 11 brain regions. Grey, cross-hatched cells indicate missing or not assessed data. Abbreviations: CA = cornu ammonis, CTE = chronic traumatic encephalopathy, FTLD = frontotemporal lobar degeneration, p-tau = phosphorylated tau, TDP-43 = transactive response DNA-binding protein 43 kDa.

CONCLUSIONS

Impairment on measures of learning and memory, executive functioning, and language were common among participants with autopsy-confirmed CTE. High stage CTE was associated with worse neuropsychological performance

P-tau burden was associated with worse memory test performance

CTE detection in life may require jointly considering age of onset, RHI exposure history, neuropsychological profile, and exclusion of AD via existing biomarkers

LIMITATIONS

- Conclusions based on test data obtained second-hand, rather than via direct examination.
- Small convenience sample of individuals whose BAP scores were available, limiting generalizability
- Missing raw neuropsychological test data reduced sample sizes across measures