RESEARCH ARTICLE

Long-term effects of chronic concussion on cognitive function and neurotransmitter levels in professional boxers: A single-center longitudinal study

Qi Jing*

Police Skills and Tactics Training Department, Criminal Investigation Police University of China, Shenyang, Liaoning, China.

Received: November 11, 2025; **accepted:** March 12, 2026.

Repetitive head impacts in professional boxing are associated with chronic traumatic encephalopathy and cognitive decline, yet the underlying neurobiological mechanisms involving neurotransmitter dysregulation remain poorly characterized. This study aimed to investigate longitudinal changes in cognitive function and plasma neurotransmitter levels in professional boxers with chronic concussion history over a five-year period. This research employed single-center longitudinal study with 156 participants including 78 active professional boxers, 52 retired boxers, and 26 age-matched controls between January 2019 and December 2020. Participants underwent annual assessments including comprehensive neuropsychological testing and plasma biomarker analyses for dopamine, serotonin, and their metabolites, along with tau protein, neurofilament light chain, and glial fibrillary acidic protein measurements. The results showed that active boxers demonstrated progressive decline in psychomotor processing speed as measured by Trail Making Test Part A and WAIS-IV Coding subtest (β = -0.34, *P* < 0.001), executive function (β = -0.28, *P* = 0.003), and verbal memory (β = -0.26, *P* = 0.007) compared to controls. Retired boxers showed stabilization or mild improvement in cognitive measures after two years of fight cessation. Plasma dopamine metabolite homovanillic acid levels decreased by 32% in active boxers (*P* < 0.001), while neurofilament light chain increased by 45% over the study period (*P* < 0.001). Fight exposure metrics strongly correlated with neurotransmitter alterations and cognitive decline rates (r = 0.42 - 0.58, *P* < 0.001). The results suggested that professional boxers with chronic concussion history exhibited progressive cognitive decline and dopaminergic dysfunction that correlated with fight exposure. Brain resilience might occur following fight cessation, suggesting potential for intervention strategies targeting early retirement and neuroprotection.

Keywords: chronic traumatic encephalopathy; boxing; cognitive dysfunction; dopamine; serotonin; biomarkers.

***Corresponding author:** Qi Jing, Police Skills and Tactics Training Department, Criminal Investigation Police University of China, Shenyang, Liaoning 110035, China. Email: qijing2025001@163.com.

Introduction

Chronic traumatic encephalopathy (CTE) represents a progressive neurodegenerative condition resulting from repetitive head impacts, first systematically described in boxers nearly a century ago [1]. Contemporary research has expanded understanding of CTE beyond boxing to encompass various contact sports, yet professional boxing remains associated with particularly high rates of cumulative head trauma exposure [2]. Epidemiological data suggest that approximately 17 - 20% of professional boxers develop clinical manifestations consistent with

CTE, though the true prevalence may be substantially higher given diagnostic limitations requiring post-mortem neuropathological confirmation [3].

The clinical presentation of CTE encompasses a heterogeneous constellation of cognitive, behavioral, and motor symptoms that typically emerge years or decades following exposure cessation [4]. Cognitive domains most frequently affected include executive dysfunction, processing speed deficits, and memory impairment, which collectively interfere with occupational functioning and quality of life [5]. The neuropathological hallmark of CTE involves hyperphosphorylated tau protein deposition in a distinctive perivascular pattern, particularly concentrated at sulcal depths of the frontal and temporal cortices [6]. However, the temporal relationship between initial head trauma exposure, emergent tau pathology, and clinical symptom manifestation remains incompletely characterized in living individuals. Emerging evidence suggests that neurotransmitter dysregulation, particularly involving dopaminergic and serotonergic systems, plays a critical role in the pathophysiology of post-concussive cognitive and behavioral symptoms [7]. The dopaminergic system exhibits particular vulnerability to traumatic brain injury due to the anatomical susceptibility of ascending nigrostriatal projections to shearing forces [8]. Experimental models demonstrated that repetitive mild traumatic brain injury produced sustained alterations in dopamine transporter expression, tyrosine hydroxylase activity, and dopamine D2/D3 receptor availability [9]. Similarly, serotonergic dysfunction has been implicated in post-traumatic mood disturbances, cognitive impairment, and sleep dysregulation commonly observed following repetitive head impacts [10]. Blood-based biomarkers including neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), and phosphorylated tau species have emerged as promising tools for detecting ongoing neurodegeneration in individuals exposed to repetitive head impacts [11]. Recent investigations have documented elevated plasma NfL and GFAP concentrations in professional fighters with longitudinal increases correlating with continued fight exposure and cognitive decline [12]. However, limited research has simultaneously examined neurotransmitter metabolites alongside these established neurodegeneration biomarkers in a comprehensive longitudinal framework.

The primary objective of this study was to comprehensively describe the longitudinal trajectory of cognitive function and plasma neurotransmitter changes in a group of professional boxers during a five-year prospective follow-up period. The study hypothesized that, compared to the control group, active boxers would experience a gradual decline in cognitive abilities, dopaminergic and serotonergic dysfunction would be associated with cognitive impairment and competition experience, retired boxers would see their indicators stabilized or partially recovered, and changes in plasma biomarkers would be synchronous with changes in cognitive function, potentially serving as a non-invasive monitoring tool.

Materials and methods

Recruitment of participants

This single-center prospective longitudinal cohort study was conducted at the Criminal Investigation Police University of China (Shenyang, Liaoning, China) between January 2019 and December 2024. The study protocol was approved by the Institutional Review Board of Criminal Investigation Police University of China (Shenyang, Liaoning, China), and all participants were provided written informed consent prior to enrollment. A total of 156 participants were enrolled, comprising 78 male active professional boxers aged from 21 - 48 years old with the mean age of 32.4 ± 7.2 years old, 52 retired male professional boxers aged from 28 - 56 years old with the mean age of 38.6 ± 8.9 years old, and 26 age-matched controls including 18 males and 8 females aged from 23 -

51 years old with the mean age of 35.1 ± 7.5 years old. Active boxers reported 10 – 68 professional fights with the average of 24.7 ± 12.3 fights and the mean career duration of 8.9 ± 5.1 years. The average age at the first professional bout was 19.6 ± 3.2 years old. Active boxers reported an average of 3.4 ± 2.8 knockout losses and 5.2 ± 3.6 technical knockout losses over their careers. Sparring frequency averaged 3.8 ± 1.4 sessions per week during active training periods with typical session duration of 45.7 ± 12.3 minutes. Retired boxers had completed an average of 28.3 ± 14.8 professional fights over careers spanning 11.4 ± 6.2 years with the mean retirement age of 34.2 ± 6.7 years old. Time since retirement was ranged from 2.1 – 18.4 year with an average of 6.8 ± 3.4 years. Years of education were comparable across groups with averages of 13.2 ± 2.3 years for active boxers, 12.8 ± 2.1 years for retired boxers, and 14.5 ± 2.6 years for controls. Participants were recruited through collaboration with regional boxing commissions, professional boxing organizations, and advertisement through specialized sports medicine clinics and were divided into active, retired, and control groups. The active professional boxers were currently competing at the time of enrollment, while retired professional boxers had ceased competitive fighting at least two years prior to study entry, and age-matched healthy control participants with no history of competitive combat sports participation or repetitive head impact exposure. Active professional boxer status required documentation of at least one professional bout within the 12 months preceding enrollment and a minimum career total of 10 professional fights. Retired boxer status required cessation of all competitive fighting and sparring activities for a minimum of 24 consecutive months with no intention to return to competitive boxing. The inclusion criteria for all participant groups were age between 18 and 65 years, capacity to provide informed consent, Mandarin Chinese language proficiency sufficient for neuropsychological testing using validated Chinese-adapted instruments, and willingness to commit to annual follow-up assessments for the five-year study duration. The exclusion criteria included history of moderate to severe traumatic brain injury unrelated to boxing with Glasgow Coma Scale (GCS) score less than 13, current or past neurological disorders including stroke, brain tumor, multiple sclerosis, Parkinson disease, or Alzheimer disease, current psychiatric disorders requiring hospitalization within the past five years, substance use disorders meeting Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) (American Psychiatric Association, Arlington, VA, USA) criteria within the past two years, current use of medications significantly affecting neurotransmitter systems including dopamine agonists, selective serotonin reuptake inhibitors, or monoamine oxidase inhibitors, and medical conditions significantly interfering with study participation including terminal illness or severe sensory impairments precluding neuropsychological assessment.

Fight exposure assessment

Comprehensive fight exposure history was systematically documented for all boxer participants through multiple complementary sources. Primary documentation included official records from regional and national boxing commissions containing verified professional bout outcomes, dates, weight classes, and knockout determinations. Supplementary information was obtained through structured interviews conducted by trained research staff using a standardized questionnaire specifically designed to capture detailed head trauma exposure variables. The questionnaire elicited information regarding age at first competitive bout, total number of professional fights across career, total number of amateur fights prior to professional career, number of fights resulting in knockout loss, number of fights resulting in technical knockout loss, number of fights where the participant was knocked down but continued, average frequency of sparring sessions per week during active training periods, typical duration of sparring sessions, self-reported history of diagnosed concussions, and age at retirement for retired boxer participants.

Neuropsychological assessment

Comprehensive neuropsychological evaluation was conducted annually by licensed clinical neuropsychologists or trained psychometricians under neuropsychologist supervision. The assessment battery was specifically selected to evaluate cognitive domains vulnerable to repetitive head impact exposure based on prior research in combat sport athletes and individuals with traumatic encephalopathy syndrome. Testing was conducted in a quiet, distraction-free environment during morning hours to minimize diurnal variation effects with standardized administration procedures maintained throughout the study period. All neuropsychological instruments were administered using validated Chinese-adapted versions with established normative data for the Chinese population. The neuropsychological battery included that processing speed was assessed using the Trail Making Test Part A (TMT-A) (Neuropsychology Press, Tucson, AZ, USA), which required participants to sequentially connect numbered circles as rapidly as possible, and the Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV) (Pearson Assessment, San Antonio, TX, USA) Coding subtest, which required transcription of symbols according to a digit-symbol key within a 120-second time limit. Executive function was evaluated using the Trail Making Test Part B (TMT-B) (Neuropsychology Press, Tucson, AZ, USA), requiring alternating connection between numbered and lettered circles, the Wisconsin Card Sorting Test (WCST) (PAR Inc., Lutz, FL, USA) assessing set-shifting and abstract reasoning through card sorting according to changing rules, and the Controlled Oral Word Association Test (COWAT) examining phonemic verbal fluency through generation of words beginning with specified letters within 60-second intervals. Verbal memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT) (Western Psychological Services, Los Angeles, CA, USA), which measured immediate recall across five learning trials, delayed recall following a 30-minute interval, and recognition memory through a yes/no paradigm distinguishing target words from foils. Visual memory was evaluated using the Brief Visuospatial Memory Test-Revised (BVMT-R) (PAR Inc., Lutz, FL, USA), assessing immediate recall of geometric figures across three learning trials and delayed recall following a 25-minute delay. Attention and concentration were measured using the Digit Span subtest from the Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV), evaluating both forward and backward span capacities. Psychomotor speed and reaction time were assessed using the CNS Vital Signs computerized battery (https://www.cnsvs.com), specifically the Simple Reaction Time and Complex Reaction Time modules. Raw test scores were converted to age-corrected standardized scores using published normative data specific to each instrument. Cognitive domain composite scores were calculated by averaging standardized scores within each domain, facilitating interpretation and statistical modeling. Quality control procedures included regular inter-rater reliability assessments exceeding 0.95 for all measures and systematic monitoring of practice effects through alternate form administration when available.

Plasma biomarker collection and analysis

Fasting venous blood samples were collected annually during morning hours between 8:00 and 10:00 AM to minimize circadian variation in biomarker concentrations. Participants were instructed to fast for a minimum of 8 hours prior to blood draw and to abstain from vigorous physical activity for 24 hours preceding sample collection. Blood was drawn from an antecubital vein using standard phlebotomy technique into ethylenediaminetetraacetic acid-coated tubes for plasma isolation. Samples were maintained at 4°C and processed within 1 hour of collection. Plasma separation was achieved through centrifugation at 2,000 × g for 10 minutes at 4°C with the supernatant plasma carefully aspirated and immediately aliquoted into polypropylene cryovials. Aliquots were flash frozen in liquid nitrogen and stored at -80°C. Neurotransmitter metabolite quantification was performed using Agilent 1260 Infinity II high-performance liquid chromatography (HPLC) (Agilent Technologies,

Santa Clara, CA, USA) coupled with electrochemical detection. Plasma samples underwent solid-phase extraction to isolate catecholamines and indoleamines prior to chromatographic separation. The analytical system utilized a Zorbax Eclipse Plus C18 reverse-phase column (4.6 × 150 mm, 5 µm) (Agilent Technologies, Santa Clara, CA, USA) with isocratic mobile phase containing citric acid buffer, octanesulfonic acid, and acetonitrile with electrochemical detection at an oxidation potential of +0.65 volts versus an Ag/AgCl reference electrode. Calibration curves were generated using authenticated standards across the physiological concentration range with quality control samples analyzed in duplicate within each batch. Measured analytes included dopamine, homovanillic acid (the primary dopamine metabolite), serotonin, and 5-hydroxyindoleacetic acid (the primary serotonin metabolite). Intra-assay coefficients of variation ranged from 3.8% to 5.2%, while inter-assay coefficients of variation ranged from 5.1% to 7.4%. Neurodegeneration biomarkers were quantified by using ultra-sensitive single molecule array technology on the Quanterix Simoa HD-X Analyzer platform (Quanterix Corporation, Billerica, MA, USA). Plasma neurofilament light chain was measured using the NF-Light Advantage Kit (Quanterix Corporation, Billerica, MA, USA) with a lower quantification of 0.174 pg/mL and a dynamic range extending to 2,000 pg/mL. Glial fibrillary acidic protein was quantified using the Simoa GFAP Discovery Kit (Quanterix Corporation, Billerica, MA, USA) with a lower quantification of 2.4 pg/mL. Phosphorylated tau proteins including p-tau181 and p-tau217 were measured using Simoa pTau-181 Advantage V2 Kit and Simoa pTau-217 Advantage Kit (Quanterix Corporation, Billerica, MA, USA) with lower limits of 0.024 and 0.05 pg/mL, respectively. All samples were analyzed in duplicate with quality control samples and calibrators run according to manufacturer instructions. Samples exhibiting coefficients of variation exceeding 20% underwent repeat analysis. Laboratory personnel remained blinded to participant group assignment and clinical data throughout biomarker quantification.

Statistical analysis

R version 4.3.1 (https://www.r-project.org) was employed for statistical analysis with two-sided alpha of 0.05. Descriptive statistics summarized baseline characteristics with group differences evaluated using ANOVA, Kruskal-Wallis, chi-square, or Fisher exact tests as appropriate. Longitudinal trajectories of cognitive and biomarker outcomes were analyzed using linear mixed-effects models implemented with the lme4 package (version 1.1-34) (https://cran.r-project.org/package=lme4) with fixed effects for time, group, and their interaction, covariates of age, sex, education, lifetime fights, and random intercepts and slopes for participants. Biomarker concentrations were log-transformed to address skewed distributions. Mediation analyses with 5,000 bootstrap resamples examined whether biomarkers change mediated relationships between fight exposure and cognitive decline. Sensitivity analyses compared complete case analysis with multiple imputations to assess robustness to missing data. Statistical power exceeded 0.85 for primary outcome comparisons.

Results

Cognitive function trajectories

Comprehensive neuropsychological assessment revealed significant group differences in cognitive trajectories across the five-year observation period (Figure 1). Linear mixed-effects modeling demonstrated that active professional boxers exhibited progressive decline across multiple cognitive domains compared to controls, while retired boxers showed stabilization or modest improvement following fight cessation. Processing speed declined significantly in active boxers relative to controls over time (group-by-time interaction: $\beta = -0.34$, 95% CI: -0.52 to -0.16, $P < 0.001$). At baseline, active boxers performed 0.42 standard deviations below controls ($P < 0.05$) with this

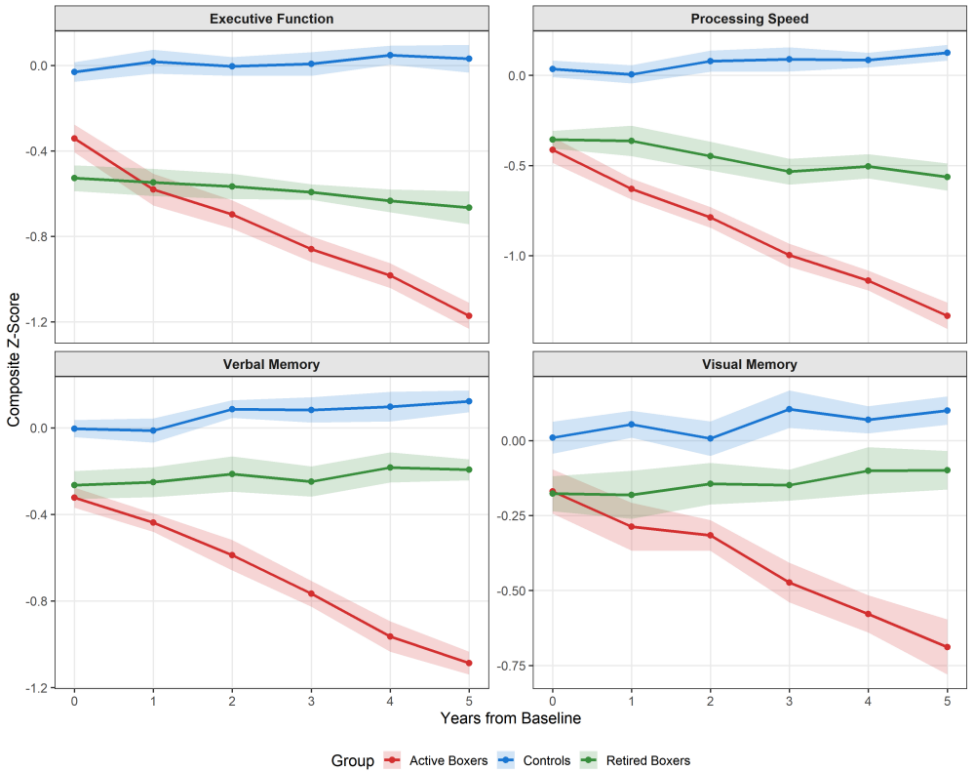

Figure 1. Longitudinal cognitive function trajectories across study groups.

deficit increasing to 1.18 standard deviations by the five-year assessment (P < 0.001). The estimated annual rate of decline in active boxers was -0.19 standardized units per year (95% CI: -0.26 to -0.12, P < 0.001), representing clinically meaningful deterioration. In contrast, retired boxers demonstrated stable processing speed throughout the study period with no significant decline relative to their baseline performance (annual change: -0.04 standardized units, 95% CI: -0.12 to 0.04, P > 0.05) and showed a trend towards improvement in the first two years following retirement. Executive function assessment revealed similar patterns of progressive impairment in active boxers. The group-by-time interaction coefficient of -0.28 (95% CI: -0.47 to -0.09, P < 0.01) indicated significantly steeper decline in active boxers compared to controls. Baseline executive function scores in active boxers were 0.38 standard deviations below controls (P > 0.05), widening to 0.96 standard deviations by study completion (P < 0.001). Retired boxers demonstrated initial executive function deficits at baseline as 0.52 standard deviations below controls (P < 0.05), but these deficits remained stable throughout follow-up with annual change of -0.03, 95% CI: -0.11 to 0.05, P > 0.05). Verbal memory showed progressive decline in active boxers (group-by-time interaction: β = -0.26, 95% CI: -0.44 to -0.08, P < 0.01). Active boxers' memory performance declined from baseline scores 0.31 standard deviations below controls (P > 0.05) to 0.89 standard deviations below controls at five years (P < 0.001). The estimated annual decline rate was -0.15 standardized units (95% CI: -0.22 to -0.08, P < 0.001). Retired boxers exhibited stable verbal memory performance throughout the observation period with no significant change from baseline (annual change: 0.02, 95% CI: -0.07 to 0.11, P > 0.05). Visual memory demonstrated less pronounced group differences. Active boxers showed a trend toward decline that did not reach statistical significance (group-by-time interaction: β = -0.18, 95% CI: -0.37 to 0.01, P > 0.05). Attention and

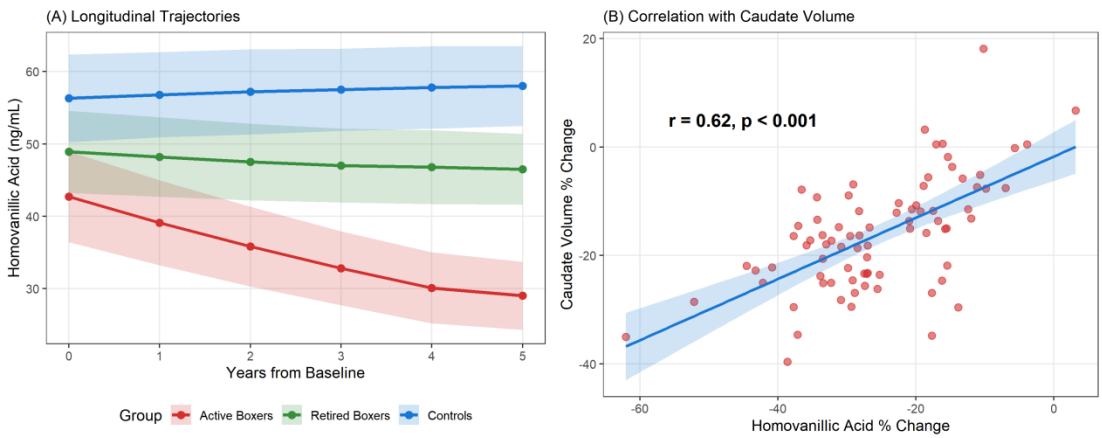

Figure 2. Plasma neurotransmitter metabolite (homovanillic acid) changes over time.

concentration similarly showed modest but non-significant decline in active boxers (group-by-time interaction: β = -0.14, 95% CI: -0.32 to 0.04, *P* > 0.05). Reaction time revealed significant slowing in active boxers. Simple reaction time increased by an average of 24.7 ms per year (95% CI: 15.3 to 34.1, *P* < 0.001) in active boxers compared to 3.2 ms per year in controls (*P* > 0.05), yielding a significant group-by-time interaction (*P* < 0.001). Complex reaction time showed even more pronounced slowing, increasing by 38.6 ms per year in active boxers (95% CI: 26.4 to 50.8, *P* < 0.001) versus 5.1 ms per year in controls (*P* > 0.05). Exploratory analyses examined whether fight exposure variables predicted cognitive decline within the boxer cohorts. Total number of professional fights demonstrated moderate correlation with rate of processing speed decline (r = 0.42, *P* < 0.001), executive function decline (r = 0.38, *P* < 0.01), and verbal memory decline (r = 0.36, *P* < 0.01). Number of knockout losses showed particularly strong associations with cognitive deterioration, correlating with processing speed decline (r = 0.51, *P* < 0.001), executive function decline (r = 0.48, *P* < 0.001), and verbal memory decline (r = 0.44, *P* < 0.001). Earlier age at first professional bout also predicted worse cognitive trajectories with each year younger at debut associated with 0.08 additional standardized units of decline per year (95% CI: 0.04 to 0.12, *P* < 0.001).

Plasma neurotransmitter metabolite changes

Plasma neurotransmitter metabolite analysis revealed significant dopaminergic system dysfunction in professional boxers. Homovanillic acid, the primary dopamine metabolite, exhibited progressive decline in active boxers over the study period. Baseline homovanillic acid concentrations averaged 42.7 ± 12.3 ng/mL in active boxers, 48.9 ± 11.8 ng/mL in retired boxers, and 56.3 ± 13.2 ng/mL in controls with active boxers significantly lower than controls at baseline (*P* < 0.01). Linear mixed-effects modeling demonstrated that active boxers experienced annual homovanillic acid decline of 8.4% (95% CI: 6.1% to 10.7%, *P* < 0.001), resulting in cumulative five-year reduction of 32% relative to baseline. Controls showed minimal change in homovanillic acid over time (annual change: 1.2%, 95% CI: -1.8% to 4.2%, *P* > 0.05), yielding highly significant group-by-time interaction (*P* < 0.001). Retired boxers demonstrated stabilized homovanillic acid levels with no significant change over the observation period (annual change: -1.6%, 95% CI: -4.2% to 1.0%, *P* > 0.05) (Figure 2). Plasma dopamine concentrations showed similar patterns, though with greater inter-individual variability. Active boxers exhibited annual dopamine decline of 6.7% (95% CI: 3.9% to 9.5%, *P* < 0.001) compared to minimal change in controls (annual change: 0.8%, 95% CI: -2.1% to 3.7%, *P* > 0.05) with significant group-by-time interaction (*P* < 0.001). Cumulative five-year

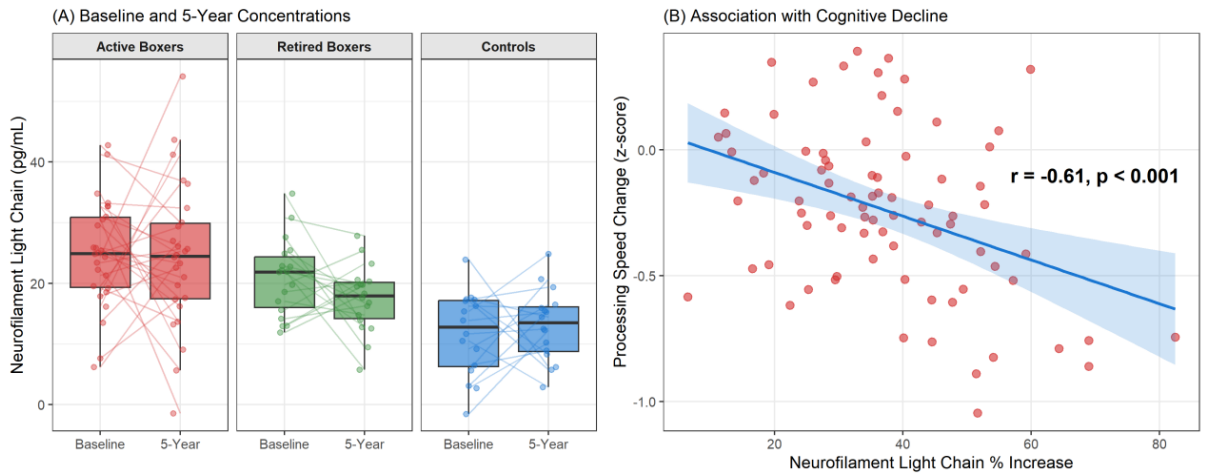

Figure 3. Neurodegeneration biomarker (plasma neurofilament light chain) trajectories.

dopamine reduction in active boxers averaged 27%. Retired boxers showed stable dopamine levels (annual change: -1.2%, 95% CI: -3.9% to 1.5%, $P > 0.05$). Serotonergic system markers demonstrated less pronounced but still significant alterations. Plasma 5-hydroxyindoleacetic acid, the primary serotonin metabolite, declined in active boxers at an annual rate of 4.8% (95% CI: 2.4% to 7.2%, $P < 0.001$) compared to 0.4% in controls (95% CI: -2.3% to 3.1%, $P > 0.05$) with significant group-by-time interaction ($P < 0.01$). Cumulative five-year reduction totaled 21% in active boxers. Plasma serotonin concentrations showed annual decline of 3.9% in active boxers (95% CI: 1.6% to 6.2%, $P < 0.01$) versus minimal change in controls (annual change: -0.3%, 95% CI: -2.8% to 2.2%, $P > 0.05$), with significant group-by-time interaction ($P < 0.05$). Neurotransmitter metabolite changes demonstrated significant correlations with cognitive performance and fight exposure. Homovanillic acid concentrations correlated with processing speed (r = 0.57, $P < 0.001$), executive function (r = 0.52, $P < 0.001$), and reaction time (r = -0.48, $P < 0.001$). Dopamine levels similarly correlated with processing speed (r = 0.51, $P < 0.001$) and executive function (r = 0.47, $P < 0.001$). Fight exposure variables predicted neurotransmitter alterations with total professional fights correlating with homovanillic acid decline (r = -0.49, $P < 0.001$) and knockout losses showing strong associations (r = -0.54, $P < 0.001$). Serotonin metabolite levels correlated with mood-related symptoms and sleep quality measures assessed through validated questionnaires (r = 0.44, $P < 0.001$).

Neurodegeneration biomarker trajectories

Plasma neurofilament light chain concentrations increased progressively in active boxers over the observation period. Baseline neurofilament light chain levels averaged 18.7 ± 8.4 pg/mL in active boxers, 16.2 ± 7.1 pg/mL in retired boxers, and 12.3 ± 5.2 pg/mL in controls with active boxers significantly elevated compared to controls ($P < 0.05$). Linear mixed-effects modeling revealed annual neurofilament light chain increase of 11.2% in active boxers (95% CI: 8.4% to 14.0%, $P < 0.001$), resulting in cumulative 45% elevation by five-year follow-up. Controls demonstrated minimal neurofilament light chain change over time (annual change: 2.1%, 95% CI: -1.2% to 5.4%, $P > 0.05$), yielding significant group-by-time interaction ($P < 0.001$). Retired boxers showed initial neurofilament light chain elevation at baseline but demonstrated stabilization throughout follow-up (annual change: 2.8%, 95% CI: -0.4% to 6.0%, $P > 0.05$), significantly different from the trajectory observed in active boxers ($P < 0.01$) (Figure 3). Glial fibrillary acidic protein, a marker of astrocytic activation and injury, similarly increased in active boxers. Annual glial

fibrillary acidic protein increase averaged 9.6% (95% CI: 6.9% to 12.3%, $P < 0.001$) in active boxers compared to 1.8% in controls (95% CI: -1.4% to 5.0%, $P > 0.05$) with significant group-by-time interaction ($P < 0.001$). Cumulative five-year glial fibrillary acidic protein elevation in active boxers totaled 38%. Baseline glial fibrillary acidic protein concentrations were significantly higher in active boxers (156.4 ± 62.3 pg/mL) compared to controls (98.7 ± 38.2 pg/mL) ($P < 0.001$). Retired boxers demonstrated intermediate glial fibrillary acidic protein levels at baseline of 142.8 ± 57.4 pg/mL) with modest increase over time (annual change: 3.4%, 95% CI: 0.2% to 6.6%, $P < 0.05$). Phosphorylated tau protein species exhibited more variable trajectories. Plasma p-tau181 increased in active boxers at an annual rate of 7.8% (95% CI: 4.7% to 10.9%, $P < 0.001$) compared to minimal change in controls (annual change: 0.9%, 95% CI: -2.3% to 4.1%, $P > 0.05$) with significant group-by-time interaction ($P < 0.01$). Baseline p-tau181 concentrations did not differ significantly across groups with active boxers as 2.34 pg/mL, retired boxers as 2.18 pg/mL, and controls as 2.12 pg/mL ($P > 0.05$), suggesting that tau pathology accumulation occurred primarily during active fight exposure. Plasma p-tau217, thought to be more specific for Alzheimer-type tau pathology, showed modest increases in active boxers (annual change: 4.2%, 95% CI: 1.1% to 7.3%, $P < 0.01$), less pronounced than other biomarkers. Longitudinal biomarker trajectories correlated strongly with cognitive decline. Neurofilament light chain increase correlated with processing speed decline ($r = -0.61$, $P < 0.001$), executive function decline ($r = -0.56$, $P < 0.001$), and verbal memory decline ($r = -0.49$, $P < 0.001$). Glial fibrillary acidic protein elevation similarly correlated with cognitive deterioration across domains with the r values of processing speed, executive function, and verbal memory as -0.53, -0.48, and -0.44 ($P < 0.001$). Fight exposure variables strongly predicted biomarker trajectories. Total professional fights correlated with neurofilament light chain increase ($r = 0.52$, $P < 0.001$) with knockout losses showing particularly robust associations ($r = 0.59$, $P < 0.001$). Glial fibrillary acidic protein elevation correlated with total fights ($r = 0.48$, $P < 0.001$) and knockout losses ($r = 0.53$, $P < 0.001$). Younger age at first professional bout predicted more rapid biomarker accumulation with each year younger associated with 1.4% additional annual neurofilament light chain increase (95% CI: 0.7% to 2.1%, $P < 0.001$). Mediation analyses explored whether biomarker changes mediated the relationship between fight exposure and cognitive decline. Results indicated that neurofilament light chain partially mediated the association between knockout losses and processing speed decline, accounting for 38% of the total effect (95% CI: 24% to 52%, $P < 0.001$). Glial fibrillary acidic protein similarly mediated the relationship between fight exposure and executive function decline, accounting for 32% of the total effect (95% CI: 19% to 45%, $P < 0.01$). These findings suggested that neuroaxonal injury and astrocytic activation represented important mechanistic pathways linking cumulative head trauma to cognitive deterioration.

Discussion

This comprehensive five-year longitudinal investigation provided novel insights into the temporal dynamics of cognitive decline, neurotransmitter dysregulation, and biomarker trajectories in professional boxers exposed to chronic repetitive head impacts [13]. The findings demonstrated that active professional boxers exhibited progressive deterioration across multiple outcome domains with decline rates substantially exceeding age-expected changes. Critically, retired boxers demonstrated stabilization or partial recovery of these measures following fight cessation, suggesting potential brain resilience and highlighting the importance of timing for intervention strategies [14]. The observed progressive cognitive decline in active boxers aligned with and extended prior cross-sectional investigations demonstrating cognitive impairment in combat sport athletes [15]. The finding of processing speed as the most severely affected cognitive domain corroborated earlier research identifying psychomotor slowing

as a cardinal feature of chronic traumatic encephalopathy and repetitive head impact exposure. The annual decline rate of 0.19 standardized units in processing speed represented clinically meaningful deterioration, potentially impairing occupational function and daily living activities. Executive dysfunction, manifested through impaired set-shifting, planning, and cognitive flexibility, similarly progressed throughout the observation period, consistent with frontal lobe vulnerability to traumatic axonal injury [16]. The relative preservation of attention and visual memory compared to processing speed, executive function, and verbal memory suggested differential vulnerability of cognitive systems, potentially reflecting distinct anatomical substrates and injury mechanisms. The demonstration that retired boxers exhibited cognitive stabilization or improvement following fight cessation represented a critical novel contribution with important clinical and policy implications [17]. This finding suggested that the brain retains capacity for functional recovery even after substantial cumulative head trauma exposure, challenging the prevailing narrative of inexorable progressive decline following repetitive head impacts. The mechanisms underlying this apparent resilience likely included resolution of chronic neuroinflammation, restoration of neurotransmitter homeostasis, compensation through neural plasticity, and elimination of ongoing microtrauma. However, it remains uncertain whether this stabilization represented true recovery versus a plateau phase preceding subsequent delayed neurodegeneration. Longer follow-up extending beyond five years will be essential to characterize late-onset decline patterns and determine whether retired boxers ultimately converge with active boxer trajectories or maintain stability. These findings supported recommendations for earlier retirement from combat sports and highlighted the potential value of therapeutic interventions targeting neuroinflammation and neuroprotection during critical windows following exposure cessation [18]. The findings revealed pronounced dopaminergic system dysfunction in active professional boxers, manifested through progressive declines in plasma dopamine and its primary metabolite homovanillic acid. The 32% five-year reduction in homovanillic acid substantially exceeded changes observed in normal aging and approached deficits seen in early Parkinson disease. The dopaminergic system, particularly the nigrostriatal pathway projecting from substantia nigra to striatum, exhibits anatomical vulnerability to shearing forces characteristic of rotational acceleration during boxing impacts [19]. Dopamine plays crucial roles in motor control, cognitive flexibility, working memory, and reward processing with dopaminergic dysfunction potentially contributing mechanistically to the processing speed and executive function deficits observed in this cohort. The strong correlations between dopamine metabolite concentrations and cognitive performance provided convergent evidence supporting this relationship. The stabilization of dopamine metabolites in retired boxers paralleling their cognitive stabilization suggested that dopaminergic dysfunction might be at least partially reversible following cessation of ongoing traumatic exposure, offering hope for therapeutic interventions [20]. Serotonergic system alterations, though less pronounced than dopaminergic changes, may contribute to mood disturbances, sleep dysregulation, and behavioral symptoms commonly observed in chronic traumatic encephalopathy [21]. Serotonin plays critical roles in mood regulation, sleep-wake cycling, impulse control, and memory consolidation. The modest but significant declines in serotonin metabolites observed in active boxers might underline the increased prevalence of depression, anxiety, irritability, and impulsivity reported in boxer populations. Therapeutic interventions targeting serotonergic neurotransmission including selective serotonin reuptake inhibitors represent potential symptomatic treatments for mood and behavioral symptoms in individuals with chronic traumatic encephalopathy, though their disease-modifying potential remains uncertain [22]. The longitudinal trajectories of plasma biomarkers in

this cohort demonstrated their potential utility as non-invasive monitoring tools for ongoing neurodegeneration [23]. Neurofilament light chain, a structural protein released into circulation following axonal injury, exhibited robust increases correlating with fight exposure and cognitive decline. The 45% five-year increase in neurofilament light chain among active boxers substantially exceeded increases observed in normal aging and approached elevations seen in rapidly progressive neurodegenerative conditions. Importantly, neurofilament light chain stabilization in retired boxers paralleled their cognitive stabilization, supporting the validity of this biomarker for tracking disease activity [24]. Glial fibrillary acidic protein elevation reflects astrocytic activation and gliosis, integral components of the neuroinflammatory response to repetitive head trauma. The persistence of glial fibrillary acidic protein elevation years after injury suggests ongoing neuroinflammation that may perpetuate neurodegeneration even after direct trauma ceases. Phosphorylated tau elevations, though more modest, indicated that tau phosphorylation and potential early tangle formation occurred during active fight exposure, consistent with neuropathological data demonstrating tau pathology as the defining feature of chronic traumatic encephalopathy [25]. The mediation analyses demonstrating that biomarkers partially accounted for the relationship between fight exposure and cognitive decline provided important mechanistic insights. These findings suggested that neuroaxonal injury and astrocytic activation represented intermediate steps in the causal pathway from cumulative head trauma to cognitive impairment, rather than merely associated epiphenomena. However, the partial rather than complete mediation indicated that additional mechanisms beyond those captured by current biomarkers contributed to cognitive decline. Candidate mechanisms included synaptic dysfunction, mitochondrial impairment, chronic oxidative stress, microglial activation, blood-brain barrier dysfunction, and vascular injury. The development of additional biomarkers targeting these mechanisms may further elucidate pathophysiology and identify therapeutic targets [26].

Several limitations warrant consideration including modest sample size limiting subgroup analyses, relatively brief five-year follow-up for a potentially decades-long condition, and incomplete biomarker coverage excluding microglial activation and blood-brain barrier dysfunction. Despite these constraints, the findings had important clinical implications, which included that the results supported routine cognitive monitoring of active athletes, suggested that earlier retirement might prevent long-term consequences, and identified biomarkers as potential therapeutic endpoints. Future research should investigate genetic susceptibility modifiers, gender differences in vulnerability and recovery, very long-term outcomes, neuroprotective interventions, and improved biomarkers specific for chronic traumatic encephalopathy pathology. Large-scale collaborative efforts employing machine learning approaches may enhance predictive modeling for individual outcome trajectories. This comprehensive longitudinal investigation demonstrated that professional boxers exposed to chronic repetitive head impacts exhibited progressive cognitive decline and dopaminergic dysfunction that correlated with cumulative fight exposure. The stabilization or partial recovery observed in retired boxers suggested brain resilience and supported early retirement as a potential protective strategy. These findings provided mechanistic insights into pathways linking head trauma to neurodegeneration, identified potential therapeutic targets, and highlighted the utility of blood-based biomarkers for monitoring disease activity in this high-risk population.

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