RESEARCH ARTICLE OPEN ACCESS

Longitudinal Changes in Cognitive Functioning and Brain Structure in Professional Boxers and Mixed Martial Artists After They Stop Fighting

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Neurology® 2022;99:e2275-e2284. doi:10.1212/WNL.0000000000201158

Abstract

Background and Objectives

This study compares longitudinal changes in cognitive functioning and brain structures in male fighters who transitioned to an inactive fighting status without any further exposure to repetitive head impacts (RHIs) and fighters remaining active with continual exposure to RHIs.

Methods

Participants were recruited from the Professional Fighters Brain Health Study. At time point (TP)1, all fighters were active, with continual exposure to RHIs. At TP2, fighters were considered "transitioned" if they had no sanctioned professional fights and had not been sparring for the past 2 years. Fighters were considered "active" if they continued to train and compete. All fighters underwent cognitive testing and 3T MRI at both TPs. A subset of our fighters (50%) underwent blood sampling for the characterization of neurofilament light (NfL) levels at both TPs. Linear mixed-effect models were applied to investigate the potentially different longitudinal trajectories (interaction effect between group and time) of cognitive function measures, NfL levels, and regional thickness measures (derived from structural MRI) between transitioned and active fighters.

Results

Forty-five male transitioned fighters (aged 31.69 ± 6.27 years [TP1]; 22 boxers, 22 mixed martial artists, and 1 martial artist) and 45 demographically matched male active fighters (aged 30.24 ± 5.44 years [TP1]; 17 boxers, 27 mixed martial artists, and 1 martial artist) were included in the analyses. Significantly different longitudinal trajectories between transitioned and active fighters were observed in verbal memory (p_{FDR} = 4.73E-04), psychomotor speed (p_{FDR} = 4.73E-04), processing speed (p_{FDR} = 3.90E-02), and NfL levels (p = 0.02). Transitioned fighters demonstrated longitudinally improved cognitive functioning and decreased NfL levels, and active fighters demonstrated declines in cognitive performance and stable NfL levels. Of 68 cortical regions inspected, 54 regions demonstrated a consistently changing trajectory, with thickness measures stabilizing on a group level for transitioned fighters and subtly declining over time for active fighters.

Discussion

After fighters' cessation of RHI exposure, cognitive function and brain thickness measures may stabilize and blood NfL levels may decline. This study could be a starting point to identify potential predictors of individuals who are at a higher risk of RHI-related long-term neurologic conditions.

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The Article Processing Charge was funded by Cleveland Clinic.

Glossary

CTE = chronic traumatic encephalopathy; **FDR** = false discovery rate; **LME** = linear mixed effect; **MA** = martial artist; **MMA** = mixed martial artist; **NfL** = neurofilament light; **PFBHS** = Professional Fighters Brain Health Study; **PSS** = processing speed; **PSY** = psychomotor speed; **rACC** = rostral-anterior-cingulate gyrus; **RHI** = repetitive head impact; **rMFG** = rostral-middle-frontal gyrus; **ROI** = regions of interest; **RT** = reaction time; **TP** = time point; **VM** = verbal memory.

Repetitive head impacts (RHIs) common in combat sports have been considered as a severe risk factor for multiple long-term neurologic conditions, including chronic traumatic encephalopathy (CTE), cognitive and behavioral impairments, and post-traumatic parkinsonism.[1-4] RHIs have been associated specifically with a wide range of cognitive changes in professional fighters,[5-8] who experience RHIs in both sanctioned matches and daily trainings, and RHIs may increase their risk for the development of a neurodegenerative condition. What remains unclear after fighters' transitions from active to inactive fighting status at a relatively young age (in their early 30s) is whether the noted cognitive changes will progress further, remain stable, or recover after the discontinuation of RHI exposures. Understanding the clinical trajectory during this transition period in a well-characterized fighters' cohort may have direct implications to several other groups experiencing RHIs in our society, such as other contact sports athletes and military veterans with multiple blast exposures.

Previous neuroimaging studies have identified various structural abnormalities in fighters' brains that have been associated with both exposure to RHIs and subsequent declines in neuropsychological performance.[9-14] Changes in fighters' regional thalamic volumes have been reported both cross-sectionally and longitudinally in structural MRI data,[11,12] with greater regional volume loss associated with declines in cognitive functioning.[11,14] Gray matter morphometry changes encompassing the caudate, putamen, and thalamus have also been identified in fighters with declines in cognitive performance.[15] Building from these works, we hypothesize that, after active fighters' transitions to inactive status, their brain regional measures derived from structural MRI data will stabilize or change differently from fighters who remain active, and these changes will correspond with the stabilization of their cognitive functions.

The Professional Fighters Brain Health Study (PFBHS) is a longitudinal study launched at our center in 2011, which aims to understand the long-term clinical, neuropsychological, and neurophysiologic effects of exposure to RHI in active professional fighters.[16] A wide array of neuropsychological test results, blood biomarkers, and MRI data have been collected annually from fighters. In this study, using this cohort and a longitudinal mixed-effects statistical model, we investigate the longitudinal changes in cognitive functioning, blood biomarkers, and structural brain measures in fighters who have transitioned from active to inactive fighting status. We then compare these changes with fighters who continue to actively fight to test our hypotheses.

Methods

Standard Protocol Approvals, Registrations, and Participant Consents

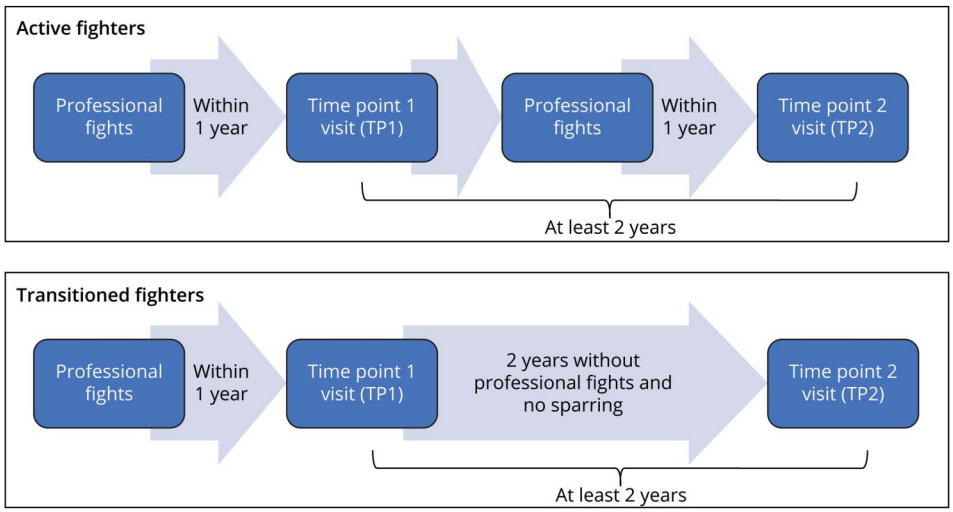
This study is part of the PFBHS that is approved by the Cleveland Clinic Institutional Review Board (IRB protocol no. 10-944), and written informed consent has been obtained from all participants. The protocols of the experiment have been explained to all participants and performed according to the Declaration of Helsinki guidelines and Belmont Report.

Participants

The recruitment of PFBHS participants has been continuous since 2011 at our center and includes boxers, mixed martial artists (MMAs), and martial artists (MAs). Fighters enrolled in the PFBHS must not have any current or previous psychiatric or neurologic disorders and be older than 18 years. Fighters' annual assessments are not scheduled within 45 days after any matches. A total of 845 participants have been recruited for at least 1 visit in PFBHS. During each visit, participants' demographics, fighting histories, neuropsychological performances, and MRI data were collected. The number of professional fights each fighter has participated in and the date of each fighter's most recent professional fight before each annual visit were manually verified with online records through Boxrec[17] for boxers and Sherdog[18] for MMAs and MAs. Further details of the recruitment and study design of PFBHS have been previously reported.[16]

At time point (TP)1, both transitioned and active fighters actively participated in professional matches, with at least 1 professional fight within 1 year before their TP1 visits. At TP2, transitioned fighters were required to have had no sanctioned fights for 2 years, have no intention to return to competition, and not be sparring. These criteria shrink our sample size of transitioned fighters to 45 in the entire PFBHS database. Active fighters were required to have at least 1 professional fight within 1 year before their TP2 visits. Figure 1 shows the detailed longitudinal data collection design for transitioned and active fighters' groups. Finally, active fighters were matched to transitioned fighters using demographic variables (e.g., age, years of education, and race), types of fighters (boxers, MMA, and MA), number of professional fights at TP1, and time differences between TP1 and TP2 (Table 1).

Figure 1 Longitudinal Study Design for Active Fighters and Transitioned Fighters



Both groups of fighters were matched for time differences between time point 1 (TP1) and time point 2 (TP2) visits.

Neuropsychological Assessment

For every fighter at each visit, CNS vital signs tests,[19] a computerized battery, including measures of verbal memory (VM), executive functioning, motor speed, and processing speed (PSS) were conducted on the same day their MRI data were collected. Results from these tests were used to evaluate fighters' performance across 4 index score domains, including VM, PSS, psychomotor speed (PSY), and reaction time (RT).

Blood Biomarkers

A subset of fighters underwent blood sampling for the characterization of neurofilament light (NfL) levels. Venipuncture was performed on the same day of fighters' annual MRI visit. Blood samples were collected in EDTA tubes and centrifuged at 3,200 rpm for 10 minutes to separate plasma from blood cells. The supernatant was aliquoted in 2 mL portions and immediately frozen and stored at −80°C. NfL concentrations were measured using ultrasensitive single-molecule array (Simoa) assays as previously described in detail.[20,21] All analyses were performed by board-certified laboratory technicians who were blinded to clinical data.

MRI Data Collection and Analyses

For each visit, MRI data were collected on a 3T Siemens scanner (Verio: from April 2011 through August 2016 and Skyra: from December 2016 through now) with a 32-channel head coil. Detailed scanner types for both groups at each TP are listed in Table 1. A high-resolution T1-weighted structural MRI was acquired using a 3-dimensional MPRAGE sequence with the following parameters: repetition time 2,300 milliseconds, echo time 2.98 milliseconds, inversion time 900 milliseconds, flip angle 9°, in-plane resolution 1 × 1 mm, and slice thickness 1.2 mm.

T1-weighted image at both visits for each participant were input to the FreeSurfer 6.0 longitudinal processing pipeline[22] to generate subject-specific anatomical labeling from the Desikan-Killiany atlas,[23] yielding 68 cortical regions and 12 subcortical regions of interest (ROIs) for every participant at each visit. Thickness measures of 68 cortical regions and volume measures of 80 cortical and subcortical regions were calculated for each visit. A quality control step was also performed using the FreeSurfer's quality analysis tools[24] to guarantee only data with high-quality cortical reconstruction were included in the following analyses. We primarily focused our analyses on cortical thickness measures, and additional analyses for volume measures were specifically performed at (1) regions demonstrating significant effects in cortical thickness analysis and (2) bilateral thalamus because both cross-sectional and longitudinal volume loss of bilateral thalamus have been previously reported in this fighter's cohort.[12,14,15]

Details of MRI data analyses are included in eMethods (links.lww.com/WNL/C312). Labels, abbreviations, and corresponding brain lobes of each ROI are listed in eTable 1.

Statistical Analyses

Group Differences of Demographic Variables

Group differences for each demographic variable at TP1 were assessed between transitioned and active fighters group using the χ^2 tests for categorical variables and 2-sample t tests for continuous variables.

Longitudinal Changes

A linear mixed-effect (LME) model was applied to investigate the longitudinal changes for each neuropsychological score, NfL level, and brain regional measure derived from MRI data. Fixed effects in the LME model included group effect (transitioned fighters vs active fighters), time effect (TP1 vs TP2), and interaction effect between group and time (group × time). Additional fixed effects of age, years of education, and

Table 1 Demographics of Transitioned Fighters and Active Fighters

	Transitioned fighters	Active fighters	Transitioned vs active fighters (*p* values)
No. of subjects	45	45	
Age at TP1, y	31.69 ± 6.27	30.24 ± 5.44	0.25
Sex, male	45	45	
Years of education at TP1, y	12.98 ± 1.75	13.27 ± 1.96	0.46
Race			
American Indian/Alaskan native	1	1	0.65
Asian	1	0	
African American	11	12	
White	23	21	
Pacific Islander	6	5	
Other/multiple	3	6	
Type of fighting			
Boxers	22	17	0.81
Mixed martial artists	22	27	
Martial artists	1	1	
No. of fights at TP1	14.98 ± 12.51	10.62 ± 10.8	0.08
Years of professional fights at TP1	7.00 ± 5.45	4.93 ± 4.35	0.05[a]
Time differences between TP1 and TP2, y	2.76 ± 0.93	2.89 ± 1.24	0.58
Scanner types at TP1	37 Verio/8 Skyra	40 Verio/5 Skyra	0.37
Scanner types at TP2	11 Verio/34 Skyra	16 Verio/29 Skyra	0.25
SNR on T1 images	19.22 ± 2.16	19.78 ± 1.77	0.06

Abbreviations: SNR = signal-to-noise ratio; TP1 = time point 1; TP2 = time point 2.
Two-sample *t* test and χ^2 test were used to compare continuous and categorical variables between 2 groups, respectively.
[a] Statistically significant.

race were also included in the LME model as covariates. The intercept and time varying by subject were considered as random effects in the LME model. Total intracranial volume was added as another covariate when analyzing brain regional volume features. A scanner upgrade occurred during the longitudinal MRI data collection (Table 1), and scanner type was also included as an additional covariate with fixed effect in the LME model when analyzing MRI-derived features. We chose the LME model over other simpler but more powerful models (such as comparing longitudinal changes (Δ = TP2 – TP1) of each measure between groups using 2-sample *t* tests) simply because that scanner type effect could easily be addressed in the LME model where measurements at both time points were treated as individual entries to the model. Detailed LME models for each measure could be found in eMethods (links.lww.com/WNL/C312).

To test our hypotheses of differences in longitudinal changing trajectories between groups, we focused on the interaction term (group × time) in the LME model. A false discovery rate (FDR) correction method (p_{FDR}) was performed on raw *p* values of the interaction term to adjust for multiple comparisons of cognitive function measures ($N_{comparison} = 4$), cortical thickness measures ($N_{comparison} = 68$), and regional volume measures ($N_{comparison} = 5$). The raw *p* value was reported for NfL level ($N_{comparison} = 1$).

To further demonstrate the effect of longitudinally changing differences between transitioned and active fighters, we computed effect sizes of differences in longitudinal changes between these 2 groups after adjusting for covariates. In brief, residuals after removing covariate effects in the LME models were obtained for every participant at every time point. Longitudinal changes between 2 time points ($\Delta = TP1_{res} - TP2_{res}$) were further computed for each participant and compared using a post hoc 2-sample *t* test between transitioned and active fighters (transitioned vs active fighters). Effect sizes for Cohen *d* were computed accordingly.

Associations between longitudinal changes in cognitive function and brain structure measures were further evaluated. A linear regression model was used to investigate (1) whether any cognitive function changes might be associated with brain structure changes longitudinally in fighters; and (2) whether this association (i.e., slope) differed between transitioned and active fighters. Details of this analysis are included in eMethods (links.lww.com/WNL/C312).

Repeated Analysis With *ApOE* as an Additional Covariate

As a significant genetic risk factor for dementia,[25] *ApoE* status might influence rates of cognitive declines in general. Therefore, we have repeated our LME analysis with 41 active and 41 transitioned fighters who have their *ApoE* status genotyped. A categorical variable representing *ApoE* genotypes was included in all LME models as an additional covariate (also see eMethods, links.lww.com/WNL/C312). All statistical analyses were performed using MATLAB functions and in-house scripts.

Data Availability

Anonymized data will be shared on reasonable request from a qualified investigator.

Results

Demographics

Fort-five male transitioned fighters and 45 matched male active fighters from PFBHS were included in this study. Because sex significantly affects brain structures in fighters with RHI,[26] only male fighters were used in our analyses. Table 1 summarizes the detailed demographics at TP1 for transitioned and active fighters. Values are reported as the mean ± SD for each variable. As designed, both groups were matched for age, education, race, and types of fighting at TP1. Transitioned fighters have trend-level more professional fights (p = 0.08) and border line more years of fighting than active fighters at TP1 (p = 0.05). Time differences between TP1 and TP2 and signal-to-noise ratio on T1 images input to FreeSurfer were not significantly different between the 2 groups. Scanner types are also detailed in Table 1 and do not differ between 2 groups at either TP1 (p = 0.37) or TP2 (p = 0.25).

Neuropsychological Measures

LME results demonstrate different trajectories of cognitive functioning between transitioned and active fighters. At TP2, improvements across VM, PSS, and PSY scores and a faster RT are observed among transitioned fighters when compared with TP1 performance, whereas active fighters' performances are largely stable, with subtle declines across VM and PSY scores between time points (Figure 2A, eTable 2, links.lww.com/WNL/C312). After FDR corrections for multiple comparisons, significant interaction effects remain for VM (p_{FDR} = 4.73E-04), PSY (p_{FDR} = 4.73E-04), and PSS (p_{FDR} = 3.90E-02) scores in the LME model. These results suggest a recovery of cognitive functioning in fighters who are no longer exposed to RHI.

NfL Measure

Twenty-five transitioned and 20 active fighters have their blood samples collected and NfL levels quantified at both TP1 and TP2. Significantly different changing trajectories across 2 TPs are observed between these transitioned fighters and active fighters (p = 0.02) from the LME analysis, with a continuous declined NfL level observed in transitioned fighters and a stable NfL level observed in active fighters (Figure 2B, eTable 3, links.lww.com/WNL/C312).

Structural Brain Measures

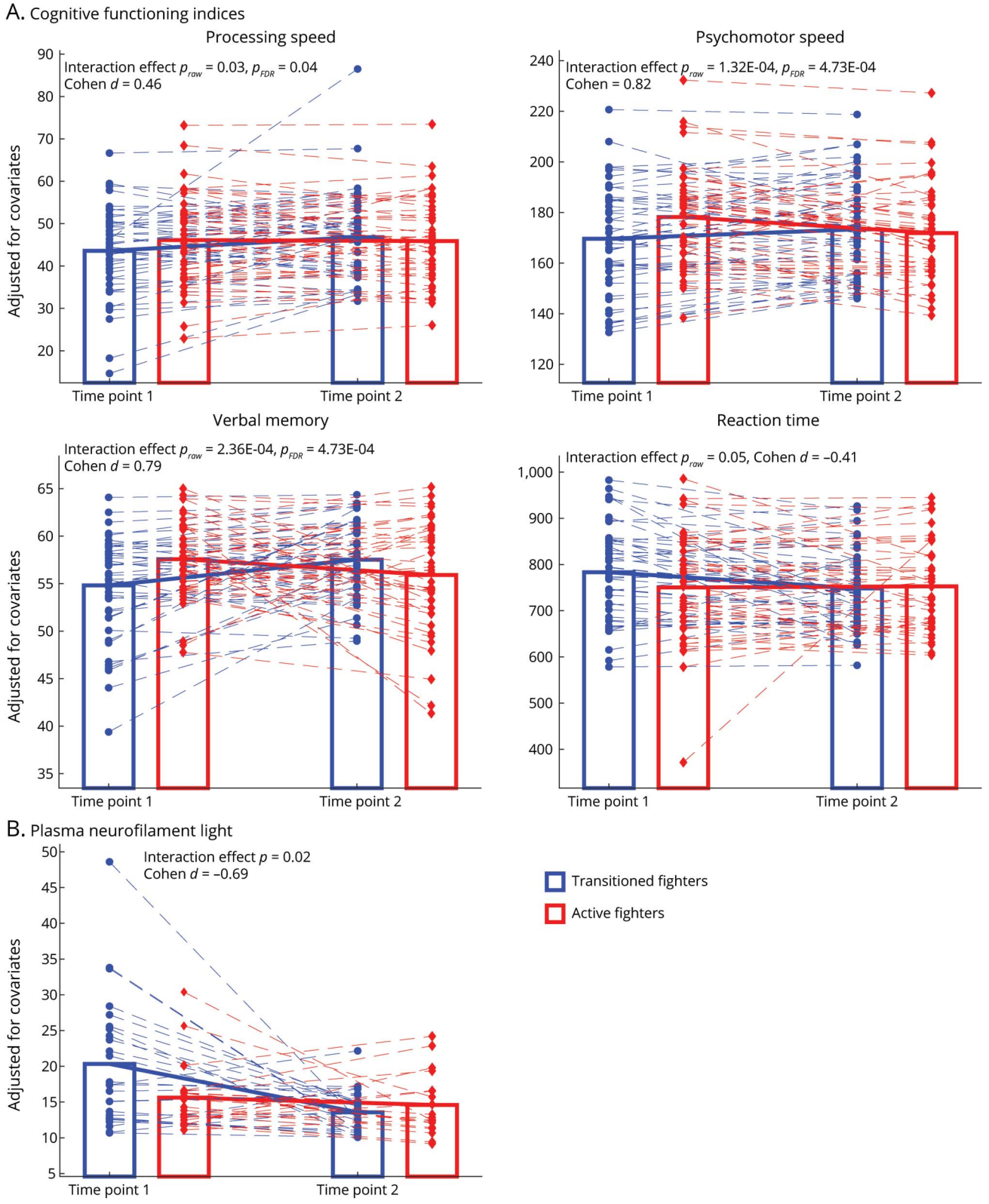
For 68 cortical thickness measures, the most significant results are observed at the right rostral-anterior-cingulate cortex (right rACC, p_{FDR} = 0.11) and the right rostral-middle-frontal gyrus (right rMFG, p_{FDR} = 0.11), with transitioned fighters showing stable thickness measures on a group level and active fighters showing subtle declines over time (Figure 3A). Rather than limiting our analysis to any preselected brain regions, we conducted an unbiased whole-brain analysis on all 68 cortical regions to identify any potential differences in changing trajectories between transitioned and active fighters. Consequently, the high number of comparisons has reduced our statistical power, particularly after adjusting for multiple comparisons. However, of the 68 cortical regions inspected, 54 regions show longitudinal changing trajectories along the same direction as rACC and rMFG (Figure 3, A and B). The probability of at least 54 of 68 regions changing along the same direction in a theoretical binomial distribution Bin(68,0.5) can be computed as $P_{Bin}(X \geq 54|N = 68, p = 0.5)$ = 5.55E-07, indicating that the direction of observed changing trajectory differences between 2 groups cannot be random, that is, is statistically significant at a whole-brain level.

Figure 3B plots the histogram of effect sizes (Cohen d) of differences in changing trajectories between transitioned and active fighters for all 68 regions. As shown in Figure 3B, positive effect sizes indicating less declines in transitioned fighters when compared with active fighters were observed for 54 regions, and medium effect sizes ($d \geq 0.5$) were further observed for the right rACC (d = 0.63), right rMFG (d = 0.63), and left medial orbital frontal cortex (d = 0.54, Figure 3A, eTable 4, links.lww.com/WNL/C312).

These 3 regions (N = 3), together with bilateral thalamus (N = 2), have been further evaluated for volumetric changing trajectories in the LME model. After FDR corrections for 5 comparisons, significant interaction effects in the LME model remain for the right rMFG volume (p_{FDR} = 0.01, d = 0.66, Figure 3C, eTable 4, links.lww.com/WNL/C312).

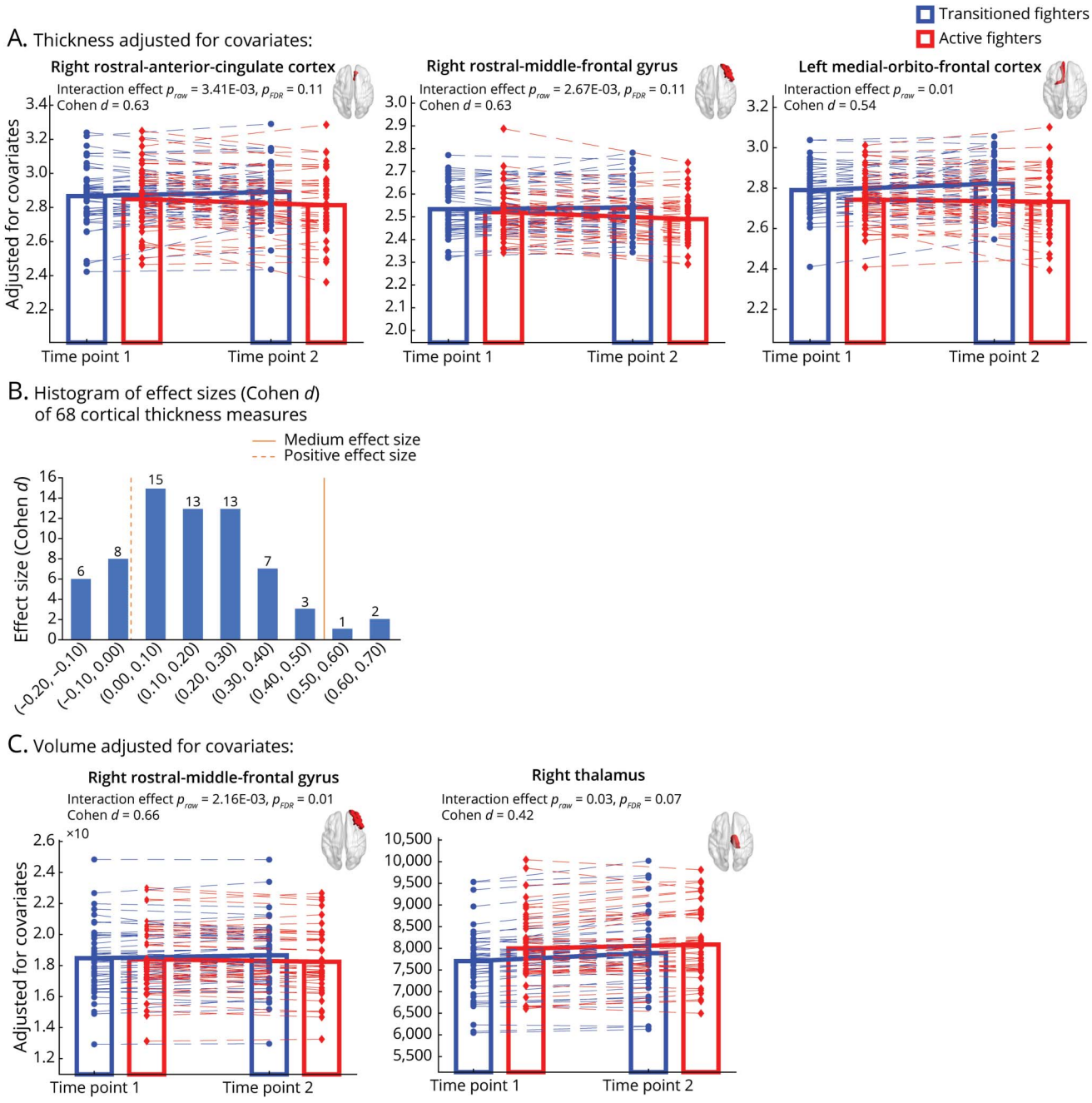
Association analyses between longitudinal changes reveal a trend-level association between VM changes (Δ_{VM}) and right-rMFG-thickness changes ($\Delta_{right\text{-}rMFG\text{-}thickness}$, p_{raw} = 0.01, p_{FDR} = 0.08, eTable 5, links.lww.com/WNL/C312), with a positive and a negative relationship between Δ_{VM} and $\Delta_{right\text{-}rMFG\text{-}thickness}$ observed for transitioned and active fighters, respectively (p_{raw} = 0.01, p_{FDR} = 0.08, eFigure 1, eTable 5).

Figure 2 Cognitive Functioning and Blood Biomarker Findings



Changing trajectories of cognitive functioning indices (CNS Vital Signs scores, A) and plasma NfL levels (B) for both transitioned fighters (blue) and active fighters (red). Raw and FDR corrected *p* values for the interaction effect in the LME model are listed in inset boxes. Effect sizes of between-group differences in longitudinal changes (Cohen *d*) are also listed. Bar plots and solid lines represent group averages at each time point, whereas scatter dots and discrete lines represent individual changing trajectories. All values plotted are residuals adjusted for covariates. FDR = false discovery rate; LME = linear mixed effect.

Figure 3 Brain MRI Findings



(A) Changing trajectories of cortical thickness measures in transitioned fighters (blue) and active fighters (red). Three regions with medium interaction effect (Cohen $d \geq 0.5$) are shown here (p_{FDR} are corrected over 68 regions). (B) Histogram of effect sizes of differences in longitudinal changes between transitioned and active fighters for all 68 cortical thickness measures. Fifty-four regions demonstrating positive effect sizes, with active fighters showing severer declines than transitioned fighters. (C) Changing trajectories of volume measures of the regions with interaction effect of $p_{raw} < 0.05$ in the LME model (p_{FDR} are corrected over 5 input volume measures). In (A) and (C), Bar plots and solid lines represent group averages at each time point, whereas scatter dots and discrete lines represent individual changing trajectories. All values plotted are residuals adjusted for covariates. FDR = false discovery rate; LME = linear mixed effect.

Repeated Analyses With *ApoE* Genotype as an Additional Covariate

Overall, the *ApoE* genotype does not contribute significantly to the LME model, except for the PSY score (p_{raw} = 0.03, eTable 6, links.lww.com/WNL/C312) and the right-thalamic volume measure (p_{raw} = 0.04, eTable 6), and does not change our results, that is, p values of the interaction effect in the LME model stay at the same level before and after including *ApoE* as a covariate, with a Pearson correlation value of 0.90 (eFigure 2).

Discussion

RHIs, both concussive and subconcussive, increase the risk of long-term neurologic conditions.[1,4] However, the outcome

remains unclear for individuals who have been exposed to RHIs and then discontinued the exposure. Investigating cognitive functioning, axonal damage marker, and brain structure changes during this transition period in fighters with previous RHI exposures could improve our understandings on potential predictors of fighters who experience RHI and are at a greater risk of developing a long-term progressive neurodegenerative condition. Results from these types of analyses may also have direct implications to other groups with RHI exposure, including other contact sports athletes and military veterans with multiple blast exposures.

Our study examined longitudinal changes in cognitive functioning, NfL, and brain structure measures after cessation of exposures to RHI in a specific and well-characterized cohort of professional fighters. Unlike our hypothesis that transitioned fighters would show stable cognitive functioning, we observed some degree of improvement in cognitive scores at a group level in transitioned fighters who stop fighting. By contrast, fighters who remain active demonstrate continued declines in performance across measures of attention, memory, and executive functioning. The longitudinal change of available blood NfL levels is in line with these cognitive findings. In addition, stable cortical thickness measures derived from structural MRI are found in transitioned fighters, whereas subtle declines in these measures are observed in active fighters in a period of approximately 3 years.

Previous studies, including our own studies, have reported cognitive impairments in active professional fighters that further correlate with fighters' RHI exposures.[7,8,14] In this study, fighters who stopped fighting in their early 30s demonstrated improvements across measures of VM, PSS, and PSY. By contrast, fighters who remained active were observed to have a continued decline (VM and PSY) or stable performance (PSS) across cognitive measures between the 2 time points (Figure 2A). Several potential mechanisms could be contributing to this finding. Various repair processes could occur in those who stopped exposures to RHIs, including beneficial changes in neuroinflammatory response[4,27,28] and/or axonal regreneration.[4,29] However, other factors that may affect cognitive performance such as less fatigue from not training and different psychosocial factors, including stress and depression, have to be considered as well.

It is also worth noting that at TP1, transitioned fighters had lower VM ($p = 0.01$, 2-sample t test) and PSY scores ($p = 0.04$, 2-sample t test), when compared with active fighters, which might reflect greater cognitive impairments in transitioned fighters and might have contributed to these fighters' decisions to stop competing.

As we stated earlier and others have previously reported, a wide range of cognitive disturbances, including memory, attention, and executive function, are common in individuals after traumatic brain injuries[30,31] and with RHIs.[3,6] At the cellular level, these cognitive disturbances may be caused by damage to white matter connections induced by diffuse axonal injury including stretching and tearing of axons.[32-35] NfL is a cytoskeletal protein expressed highly in large-caliber myelinated axons of the white matter and has emerged as a blood biomarker to capture a wide variety of neurologic conditions related to axonal injuries.[36-38] In those with RHIs, serum NfL concentrations have been found to increase in boxers 7–10 days after a sanctioned game and then decrease after 3 months of rest.[39] In PFBHS, we have also reported elevated serum NfL levels in active fighters, when compared with retired fighters.[12,21] Consistent with these previous findings and our hypothesis, transitioned fighters with recovered cognitive functioning show decreased NfL concentrations after their discontinuation of RHI exposures, whereas in fighters remaining active, stable NfL levels are observed across 2 time points (Figure 2B). This finding supports that axonal damage or injury can potentially be ceased or decreased once exposure to RHI stops.

We also noted that active fighters showed a lower NfL than transitioned fighters at TP1, which might also be in line with their higher VM and PSY scores at TP1. Because not every fighter underwent the venipuncture at every time point, future analyses with full or even larger samples are needed to further investigate this finding.

Neuroimaging techniques may also contribute to understanding the underlying mechanisms that accompany cognitive improvements (or declines) in individuals with RHI.[40,41] In our unique transitioned and active fighters' cohort with distinct cognitive changing trajectories, the most prominent differences in structural changes were seen in the trajectories of cortical thickness measures of frontal areas (middle frontal, orbitofrontal, and anterior cortex) and in the volumetric measures of middle frontal gyrus (Figure 3, A and B). We also observed a trend-level significance for the right thalamic volume measure ($p_{FDR} = 0.07$, Figure 3C). The decline across 2 time points of these cortical thickness and volumes in active fighters (continuing fighting) are consistent with previous studies reporting both cross-sectional and longitudinal thalamic volume loss in active fighters,[11,12] and widespread cortical thinning in frontal areas in other contact sports athletes,[42,43] both of which are attributed to the fiber loss resulted from physical injury to axons during head trauma.[29] The stable structural measures in transitioned fighters are as expected and could be interpreted as no further axonal/neuronal damage in transitioned fighters after cessation of RHI exposures.

Only a trend-level association was observed between longitudinal changes in cognitive function and brain structure measures in our study (eTable 5, links.lww.com/WNL/C312). This association further differed between transitioned and active fighters (eFigure 1), which might indicate a more complicated (potentially nonlinear) damage profile with continued RHI exposures. Future and longer longitudinal monitoring might allow us to further understand the interplay between cognition and brain structural changes.

In our main analyses, the *ApoE* genotype was not included as a covariate because (1) not every fighter has been genotyped in our sample and (2) previous publication using general PFBHS cohort has reported no effect of the *ApoE* genotype on the association between exposure to professional fighting and brain structures or aspects of cognition.[44] Nonetheless, we also recognized that as a major genetic risk factor for dementia, *ApoE* status might influence rates of cognitive declines in general.[25] In repeating LME analysis with the *ApoE* genotype as an additional covariate, we found that in most cases, the *ApoE* genotype does not contribute significantly to the LME model or change our results (eFigure 2 and eTable 6, links.lww.com/WNL/C312). Therefore, *ApoE* status does not bias our results.

At TP1, transitioned fighters have on average 2.07 more years of professional fights than active fighters (Table 1), which leads to generally comparable years of professional fights between transitioned and active fighters at TP2. Therefore, our results, such as improved cognitive functioning in transitioned fighters at TP2 when compared with that in active fighters, are less likely to be biased by the different years of professional fights in these 2 groups.

It is also unlikely that the upgrade of scanner in October 2016 is altering/driving our results. First, the scanner type does not differ between transitioned and active fighters' groups at either time point (Table 1), and the scanner type variable is included as a covariate in the LME model for MRI-derived features. In addition, we further ran the same LME model on the scanner type variable itself to evaluate whether the scanner type changed differently from TP1 to TP2 between 2 groups. The interaction effect of group × time remains not significant in this analysis ($p_{raw} = 0.67$).

While it is not surprising that at a group level, clinical measures and biomarker improve or stabilize with cessation of exposure to cumulative RHI, these findings raise a number of important clinical issues and questions. For instance: (1) do these results apply to individuals exposed to RHI in settings such as other contact sports or military blast exposures? (2) are there some individuals who do not improve clinically after removal from RHIs, and are they at higher risks of developing a progressive disorder such as CTE? and (3) is there a certain threshold of exposure to RHI where it becomes unlikely to see clinical improvement with cessation of the exposure? If so, surveillance and policies would need to be developed to reduce the risk of long-term neurologic impairment. Therefore, although our findings might not have direct clinical implications, our study serves as the starting point for these important clinical issues, and future research designed to answer these questions is necessary before clinical actions.

Despite the unique sample of transitioned and active fighters included in this study, there are several limitations of our study. One limitation is the inability to quantify the precise amount of RHIs each participant sustained, that is, the number of head impacts. It is not possible to obtain this information because many head impacts occur during training, and there is no generally accepted way of measuring it. We used the number of professional fights as a surrogate of cumulative exposure to RHI based on our previous work.[11,26,45] A second limitation of this study is that no women fighters were included in the analysis, which limits the interpretation of our findings to male fighters only. In addition, no normal controls were included in current analyses, which also restrict us from relating observed longitudinal changes of cognitive function and structural brain measures in fighters to general populations. Furthermore, our sample size, while not insignificant, was small, especially for whole-brain analyses. No sensitivity analysis has been performed because of this limited sample size. A number of other factors aside from exposure to RHI that may occur when an individual retires from a sport were not included in our analyses such as fatigue levels, substance usage, and mood status. Finally, to further delineate the brain changes underlying cognitive function changes in these fighters, it would be ideal to follow both active and transitioned fighters in the long term and to further evaluate functional brain network changes in this same cohort.

Overall, this study incorporates a unique cohort of transitioned fighters who have stopped fighting in their early 30s and compares their longitudinal cognitive functioning, blood biomarkers, and structural brain changes afterward with fighters remaining active. Improved memory, executive and attentional functioning scores, lower NfL levels, and stable cortical thickness were observed in transitioned fighters, whereas declined cognitive measures, stable NfL levels, and slightly decreased cortical thickness were found in active fighters. These findings suggest that individuals exposed to RHIs can improve their neurologic functioning once they cease exposures to RHIs. However, although this study is a starting point, future research is necessary to determine whether there is a point where recovery is less likely to happen or identify characteristics that might indicate a greater risk for the development of a progressive neurodegenerative condition.

Study Funding

This study is supported by the NIH (NIA-grant 1RF1AG071566, NIGMS-grant P20GM109025, and NIA-grant P20AG068053). This study, as part of the PFBHS, is supported by Lincy Foundation, Belator, Ultimate Fighting Championship Company (UFC), the August Rapone Family Foundation, Top Rank, and Haymon Boxing.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* January 14, 2022. Accepted in final form July 11, 2022. Submitted and externally peer reviewed. The handling editor was Brad Worrall, MD, MSc, FAAN.

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Lauren Bennett, PhD	Pickup Family Neurosciences Institute, Hoag Memorial Hospital Presbyterian, Newport Beach, CA	Drafting/revision of the article for content, including medical writing for content; study concept or design
Rajesh Nandy, PhD	Department of Biostatistics & Epidemiology, School of Public Health, University of North Texas Health Science Center, Fort Worth	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Dietmar Cordes, PhD	Lou Ruvo Center for Brain Health, Cleveland Clinic, Las Vegas, NV; University of Colorado Boulder	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Charles Bernick, MD	Lou Ruvo Center for Brain Health, Cleveland Clinic, Las Vegas, NV; UW Medicine, Seattle	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Aaron Ritter, MD	Lou Ruvo Center for Brain Health, Cleveland Clinic, Las Vegas, NV	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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Longitudinal Changes in Cognitive Functioning and Brain Structure in Professional Boxers and Mixed Martial Artists After They Stop Fighting

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Neurology 2022;99;e2275-e2284 Published Online before print September 14, 2022
DOI 10.1212/WNL.0000000000201158