RESEARCH ARTICLE

Understanding white matter structural connectivity differences between cognitively impaired and nonimpaired active professional fighters

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Abstract

Long-term traumatic brain injury due to repeated head impacts (RHI) has been shown to be a risk factor for neurodegenerative disorders, characterized by a loss in cognitive performance. Establishing the correlation between changes in the white matter (WM) structural connectivity measures and neuropsychological test scores might help to identify the neural correlates of the scores that are used in daily clinical setting to investigate deficits due to repeated head blows. Hence, in this study, we utilized high angular diffusion MRI (dMRI) of 69 cognitively impaired and 70 nonimpaired active professional fighters from the Professional Fighters Brain Health Study, and constructed structural connectomes to understand: (a) whether there is a difference in the topological WM organization between cognitively impaired and nonimpaired active professional fighters, and (b) whether graph-theoretical measures exhibit correlations with neuropsychological scores in these groups. A dMRI derived structural connectome was constructed for every participant using brain regions defined in AAL atlas as nodes, and the product of fiber number and average fractional anisotropy of the tracts connecting the nodes as edges. Our study identified a topological WM reorganization due to RHI in fighters prone to cognitive decline that was correlated with neuropsychological scores. Furthermore, graph-theoretical measures were correlated differentially with neuropsychological scores between groups. We also found differentiated WM connectivity involving regions of hippocampus, precuneus, and insula within our cohort of cognitively impaired fighters suggesting that there is a discernible WM topological reorganization in fighters prone to cognitive decline.

KEYWORDS

cognitive impairment, DTI, graph-theoretical analysis, repeated head impacts, RHI, rich-club analysis

1 | INTRODUCTION

Exposure to repeated head impacts (RHI) has been shown to be a risk factor for neurodegenerative disorders (Bazarian, Cernak, Noble-Haeusslein, Potolicchio, & Temkin, 2009; Jordan, 2013; Koerte et al., 2015). The

pathological neurodegenerative changes associated with RHI include diffuse axonal injury, cerebral atrophy, shrinkage of the mammillary bodies, and cavum septum pellucidum combined with clinical changes in behavior, personality, executive function, and memory (Banks, 2017; Gavett, Stern, & McKee, 2011).

Magnetic resonance imaging (MRI) can be used to investigate changes in regional brain volumes, perfusion, structural connectivity [derived using diffusion-weighted MRI (dMRI)], and functional connectivity in participants exposed to RHI. For instance, various structural neuroimaging studies of RHI due to combat sports and in veterans with blast injuries have shown changes in various gray matter volumes such as thalamus, ventromedial prefrontal cortices, right fusiform gyrus, and frontotemporolimbic regions involving hippocampus, medial temporal lobe, and frontal lobes (Bernick et al., 2015; Bigler, 2013; Gooijers et al., 2013; Lopez-Larson et al., 2013; Mishra et al., 2017, 2018; Montenegro, Bernick, & Cantu, 2015; Ng et al., 2014). Similarly, voxelwise dMRI-derived measures such as fractional anisotropy (FA) and mean diffusivity (MD) have shown differences in the temporo-occipital white matter tracts and forceps major (Hulkower, Poliak, Rosenbaum, Zimmerman, & Lipton, 2013; Mishra et al., 2017; Ng et al., 2014; Orrison et al., 2009; Shin et al., 2014; Wintermark, Sanelli, Anzai, Tsiouris, & Whitlow, 2015; Zhang et al., 2003; Zhang, Heier, Zimmerman, Jordan, & Ulug, 2006). Finally, perfusion measures using arterial spin labeling (ASL) MRI has also shown significant deficits in the thalamus, cingulate gyri, cerebellum, cuneus, and temporal lobes (Eierud et al., 2014; Koerte et al., 2015; Mishra et al., 2018). Even multivariate MRI measures combining voxelwise volumetric, perfusion, and dMRI-derived measures (Mishra et al., 2018, 2017) have identified deficits in several brain regions that were correlated with exposure and neuropsychological scores in participants with RHI.

Although these studies have improved our knowledge regarding both gray matter and white matter (WM) abnormalities at a regional level in participants exposed to RHI, there are no studies that attempt to understand topological WM structural connectivity changes due to RHI, despite RHI being thought of as a "disconnection syndrome" (Guye, Bettus, Bartolomei, & Cozzone, 2010). Furthermore, studies have suggested that there are dose-dependent effects of violent head displacement in some participants exposed to RHI, thereby making them predisposed to dementia with a possibility of propagation of abnormal proteins along with damaged WM structural connectivity networks (Mendez, 2017). WM structural connectivity differences can be studied using a network neuroscience approach. This approach conceptualizes the structure and function of the brain as a large-scale neural network, and has contributed to our understanding of brain organization from birth (Huang et al., 2015; Song et al., 2017; Zhao et al., 2018) to healthy aging (Sala-Llonch, Bartrés-Faz, & Junqué, 2015), as well as in various neurological disorders such as Alzheimer's Disease (Bachmann et al., 2018; Jalili, 2017), TBI (van der Horn et al., 2017), multiple sclerosis (Kocevar et al., 2016; Rocca et al., 2016), epilepsy (Garcia-Ramos et al., 2016; Jiang, Li, Chen, Ye, & Zheng, 2017; Sone et al., 2016), and schizophrenia (Lo et al., 2015; Olejarczyk & Jernajczyk, 2017; van den Heuvel, Mandl, Stam, Kahn, & Hulshoff Pol, 2010). Various network measures can be derived using graph-theoretical approaches such as modularity, clustering coefficient, path length, and small-worldness that can inform both network segregation and integration (Rubinov & Sporns, 2010). A network is

thought to be efficient in information transfer if it is efficient in both network segregation and integration.

Contrasting WM networks between cognitively impaired and non-impaired participants exposed to RHI may provide insights into the clinical correlates of topological WM organization. In addition, establishing the correlation between changes in the WM structural connectivity measures and neuropsychological test scores might help to identify the neural correlates of the test batteries that are used in clinical setting to investigate deficits in attention and executive functions in participants with exposure to RHI. Since, active professional fighters, both boxers and mixed martial arts (MMA) fighters are exposed to RHI, they are an interesting cohort (Bernick & Banks, 2013) to establish such a correlation between neuropsychological test scores and dMRI derived topological WM organization in participants exposed to RHI.

Both functional connectivity derived using functional MRI (fMRI) and structural connectivity derived using dMRI, could be investigated to understand the neural correlates of neuropsychological scores in active professional fighters. However, fMRI connectivity findings might suffer from various confounds, both due to inter-subject variability (Seghier & Price, 2018) and intra-subject variability (Rangaprakash, Wu, Marinazzo, Hu, & Deshpande, 2018). Hence, in the current study, we only focused on WM structural connectivity difference which may be more robust when compared to functional connectivity.

Utilizing the high angular dMRI of active professional fighters from the Professional Fighters Brain Health Study (PFBHS; Bernick et al., 2013), we investigated whether there are discernible WM structural connectivity differences between cognitively impaired and non-impaired active professional fighters. We applied the network neuroscience approach on the WM structural connectivity derived using dMRI and (a) compared whether there is a global difference in the WM structural connectivity between the groups; (b) compared global and local graph-theoretically derived topological measures of path length, clustering coefficient, and efficiency between the groups; and (c) investigated the correlation of these measures with neuropsychological assessments in cognitively impaired and nonimpaired active professional fighters. We also computed and compared "rich-club" measures (van den Heuvel & Sporns, 2011) in the WM structural connectivity of these active professional fighters to understand whether there is a differential recruitment of brain regions between cognitively impaired and nonimpaired active professional fighters, in addition to investigating the correlation of rich-club properties with neuropsychological scores in both groups.

2 | MATERIALS AND METHODS

PFBHS was approved by the institutional review board of Cleveland Clinic and all the subjects provided informed written consent. The protocol was explained to all the subjects and was performed according to the Declaration of Helsinki guidelines and the Belmont Report.

2.1 | Participant characteristics

Two hundred and fifty-two professional fighters (18 Women [F]) who were licensed and competed in professional boxing or mixed martial arts (MMA) underwent dMRI data acquisition at our center. There were 108 boxers (10F) and 144 MMA-fighters (8F). MMA fighters were those fighters that were permitted to use fighting techniques of boxing, wrestling, kickboxing, jiu-jitsu, and other forms of martial arts. Fighters with a current or past history of psychiatric or neurological disorders, age less than 18 years and greater than 35 years, and a sanctioned competition within 45 days of the visit were excluded. Detailed information about the race, educational attainment, prior involvement in other contact sports, and professional fighting were recorded for most of the subjects (221 fighters).

2.2 | MRI and neuropsychological data acquisition

High angular resolution dMRI data were acquired for all the participants using a 3 T Siemens MRI scanner with a 32-channel head coil with the following imaging parameters: Resolution: $2.5 \times 2.5 \times 2.5 \text{ mm}^3$; TR: 7,000 ms; TE: 91 ms; *b*-value: $1,000 \text{ s/mm}^2$; number of diffusion-encoding gradients: 71; number of nondiffusion weighted (*b*₀) volumes: 8. In addition, 3D magnetization prepared rapid gradient echo (MPRAGE) T1-weighted scan was also acquired within the same imaging session with the following imaging parameters: Resolution: $1 \times 1 \times 1.2 \text{ mm}^3$; TR: 2,300 ms; TE: 2.98 ms; TI: 900 ms and flip angle = 9° . Total imaging scan duration was 15 min.

Computerized cognitive tests were conducted on every participant using CNS Vital Signs (Gualtieri & Johnson, 2006) during the same visit as MRI data acquisition. We used two tests from their battery; Finger Tapping, and Symbol Digit Coding. From these tests, we obtained processing speed (total correct on a Symbol Digit Coding task) and psychomotor speed (combining Symbol Digit result and average Finger Tapping on each hand) for all the participants. Symbol Digit Coding requires the participant to “decode” as many symbols into the correct digits (using a key) in a set time, thus it measures processing speed. Since Symbol Digit Coding and Finger Tapping are both psychomotor speed test, CNS Vital Signs program combines aspects of these tests into one psychomotor score. Psychomotor speed is computed as an arithmetic sum of the total of right and left taps from Finger Tapping and total correct responses on the Symbol Digit Coding (Gualtieri & Johnson, 2006).

2.3 | Classification of fighters into cognitively impaired and nonimpaired fighters

Heilbronner et al. (2009) have shown a correlation between exposure to contact sports and impairment in memory and executive functions using neuropsychological test scores. Hence, our cohort was segregated into cognitively impaired and nonimpaired active professional fighters using both processing and psychomotor speed using the following criteria: The raw neuropsychological scores of every participant were standardized by converting to z-scores and those fighters

that had both standardized processing and psychomotor speed 2 standard deviations below the mean (Schinka et al., 2010) were classified as cognitively impaired fighters. The remaining fighters formed the nonimpaired group yielding a total of 70 impaired fighters and 151 nonimpaired fighters.

Since there was a significant difference in educational attainment between these impaired and nonimpaired fighters, we selected 70 nonimpaired fighters from our cohort of 151 nonimpaired fighters that were matched for years of education, and other demographics such as age, gender, race, and type of fighting.

2.4 | dMRI data processing and quality control

Each participant's dMRI scans were first inspected for signal dropouts or other noticeable artifacts, before preprocessing. Eddy current distortion correction was subsequently performed to minimize the influence of diffusion-sensitizing gradients using *eddy_correct* in FSL using FMRIB software library version 5.0.9 (FSL, <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). This procedure performs affine registration between *b*₀ images and diffusion-weighted imaging volumes. A single tensor was finally fitted for every single voxel inside the brain using *dtifit* module of FSL. Various dMRI-derived metrics such as FA and MD were estimated in each voxel of every participant. *bet* was used before estimating tensors to ensure the fitting is conducted only inside the brain voxels.

An average estimate of total translational motion during the dMRI scan was calculated from *eddy_correct* by taking the root mean square of the estimated translation in the X, Y, and Z directions obtained with affine registration. Participants with the average mean + standard deviation of translation motion greater than a voxel movement in the slice-encoding direction were identified and removed from further analysis. Since rotation and translation are highly correlated during dMRI scan (Rae et al., 2012), rotational motion was not included in our quality control procedure. This quality control procedure removed one impaired fighter from our analysis cohort.

Table 1 summarizes the brief demographics of the impaired and nonimpaired fighters used in the current study.

2.5 | Generation of dMRI-derived WM structural connectome

Nodes and edges required to build the dMRI-derived WM structural connectome in every participant were obtained using the following steps.

First, the MNI152 template was registered to each subject's *b*₀ image in native space using both linear (*flirt*) and nonlinear (*fnirt*) registration in FSL. Then AAL atlas (Tzourio-Mazoyer et al., 2002) in the MNI152 space was transformed to each subject's native space by using the registration parameters obtained from *flirt* and *fnirt* commands with nearest-neighbor interpolation. The cortical and subcortical AAL regions were treated as nodes of the connectome.

Whole-brain deterministic tractography was conducted using TrackVis (Wang & Wedeen, 2007) for every participant using the

TABLE 1 Various demographics along with the neuropsychological assessment test results of all subjects are shown along with their mean $\pm$ SD

Demographics	Impaired fighters (N = 69)	Nonimpaired fighters (N = 70)	Impaired versus nonimpaired fighters
Gender			
Women	3	7	NS ($p = .2$)
Men	66	63	
Age (years)	29.77 $\pm$ 6.22	29.2 $\pm$ 6.5	NS ($p = .63$)
Years of education (years)	13.17 $\pm$ 2.16	13.66 $\pm$ 1.68	NS ($p = .16$)
Race			
Unknown	12	9	
Pacific Islander	2	6	
Asian	1	0	
African American	21	28	
American Indian/Alaskan Native	2	1	NS ($p = .39$)
White	31	26	
Number of professional fights	14.43 $\pm$ 12.73	13.76 $\pm$ 12.57	NS ($p = .7$)
Years of professional fights	5.81 $\pm$ 4.3	5.08 $\pm$ 4.1	NS ($p = .22$)
Processing speed ^a	40.64 $\pm$ 8.44	57.66 $\pm$ 7.61	$p < .0001$
Psychomotor speed ^a	151.36 $\pm$ 21.4	181.89 $\pm$ 17.01	$p < .0001$
Diffusion motion	1.21 $\pm$ 0.25	1.2 $\pm$ 0.26	NS ($p = .93$)

Results of pairwise statistical comparisons are also shown as p values.

Abbreviation: NS, nonsignificant.

^aFor Processing Speed, $p = 1.58 \times 10^{-19}$, and for Psychomotor Speed, $p = 2.41 \times 10^{-16}$.

tensor maps obtained from FSL. An angle threshold of 35° (Cheng et al., 2012) was used to control for sharp bending of the WM tracts. A fiber length threshold of 10 mm (Cheng et al., 2012) was further applied to remove apparently spurious WM tracts. This procedure generated the edges to build the WM structural connectome.

A weighted structural connectome was finally obtained for every participant using the nodes and edges generated from the above procedure. Briefly, two nodes (m, n) were said to be structurally connected if and only if there is a WM tract with its endpoints in both nodes. The number of WM tracts between the nodes (FN) was then multiplied by the average FA of those WM tracts to minimize the influence of noise in deterministic tracking. Outlier detection was further applied within each participant's connectome using the interquartile range (Rousseeuw & Croux, 1993) of the connectome to further minimize the influence of noise. Self-connectivity of the nodes was ignored in this study.

Figure 1 shows the basic flowchart for constructing the connectome of every participant.

2.6 | Global subject-level connectivity score

A global WM connectivity strength was obtained for every participant by computing the summation of the inner dot product of the structural connectome matrix (M) as, $\sum(M * M^T)$. Briefly, this score represents the total WM connectivity strength of each subject, and this global WM strength was used as a surrogate for each participant's global WM connectivity score.

2.7 | Graph-theoretical analysis

Multiple global and local network topological properties can be used to characterize the topology of a weighted connectome using graph-theoretical approaches (Rubinov & Sporns, 2010). In the current study, we only focused on network integration and segregation of information flow between nodes of the network. Normalized clustering coefficient (γ) and normalized path length (λ) can be used as a surrogate of network segregation and integration (Rubinov & Sporns, 2010), respectively.

γ is defined as the ratio of the average clustering coefficient (C_p) of the connectome to that of an average C_p of 1,000 equivalent random networks. C_p denotes the likelihood that neighbors of a node are connected to each other and hence describes the tendency of the nodes to form local clusters. λ is defined as the ratio of the average shortest path length (L_p) to that of an average L_p of 1,000 equivalent random networks. L_p is measured from the harmonic mean of the shortest paths among all possible vertex pairs in the network. Since C_p and L_p are computed both locally and globally, we compared C_p and L_p to understand differences in clustering coefficient and path length between the groups if any at both global and local levels.

Global and local efficiency were also computed and compared between the groups as a measure of global and local network topological properties. Global efficiency measures the efficiency of the parallel information transfer in the network while local efficiency measures the efficiency of the information flow among the first neighbors of a node, m , when it is removed.

FIGURE 1 A brief flowchart describing the generation of structural connectivity matrix for every subject. Briefly, MNI152 template was registered to nondiffusion weighted, b0, image in every subject. AAL atlas was then transformed to subject's native space using these registration parameters with nearest-neighbor interpolation, to obtain the nodes of the connectivity matrix. Of note, only cortical and subcortical regions in AAL atlas were retained. Edges were obtained using deterministic tractography. Structural connectivity matrix was then generated for every subject using the product of the average fractional anisotropy (FA) of the tracts and the number of tracts (FN) connecting two distinct nodes. Average symmetric connectivity matrix for the impaired and nonimpaired group is shown. The color map indicates the average strength of connections between any two nodes in the connectivity matrix [Color figure can be viewed at wileyonlinelibrary.com]

Local topological properties were compared at the minimum sparsity level at which there is no significant difference between the numbers of nodes required to execute complete information transfer in the participants of each group.

2.8 | Rich-club analysis

Rich-club is a network phenomenon that is said to be present when the hubs of a network tend to be more densely connected among themselves rather than the nodes with a lower degree. The presence or absence of a rich-club organization can provide insights into the higher-order structure of a network, thereby providing information about the network's resilience, hierarchical ordering, and specialization (van den Heuvel & Sporns, 2011), and its correlation with the neuropsychological score might suggest the topological preference of connections with cognition. Mathematically, rich-club computes the number of edges present between nodes of degree greater than or equal to k , and is mathematically represented by $\Phi^w(k) = \frac{W_{>k}}{\sum_{i=1}^{E_{>k}} W_i^{\text{ranked}}}$

where $\Phi^w(k)$ is the weighted rich-club parameter. W^{ranked} represents the connections of the network ranked with respect to weight, and $E_{>k}$ represents the number of links with degree greater than k (Opsahl, Colizza, Panzarasa, & Ramasco, 2008; van den Heuvel & Sporns,

2011). The rich-club hence obtained was normalized with respect to 1,000 random networks of equal size and similar connectivity distribution (Colizza, Flammini, Serrano, & Vespignani, 2006; van den Heuvel & Sporns, 2011), yielding a normalized rich-club coefficient Φ_{norm} for every participant. An increasing normalized coefficient $\Phi_{\text{norm}} > 1$ over a range of k was said to reflect the existence of a rich-club organization in a network.

Rich-club nodes, feeder nodes, and local nodes were identified for each participant using Φ_{norm} for a given k , and the edges associated with these nodes were categorized into rich-club edges, feeder edges, and local edges (van den Heuvel & Sporns, 2011), respectively. Briefly, rich-club nodes are those nodes that are more densely connected among themselves than nodes of a lower degree. Feeder and local nodes are those nodes that are either directly (feeder) or indirectly (local) connected to rich-club nodes. Average rich-club edge strength, feeder edge strength, and local edge strength were then computed and compared among the groups to understand whether there is a difference in the rich-club structural organization and whether edge strengths of the rich-club, feeder, and local nodes are correlated with neuropsychological scores.

All network measures were generated by using in-house MATLAB[®] codes and GREYNA toolbox (Wang et al., 2015).

2.9 | Statistical analysis

Chi-square (χ^2) test was used to test the significance of categorical demographic variables, and the Kruskal–Wallis test was used to determine the statistical significance of continuous demographic and neuropsychological variables. Significance was established at $p < .05$ and the values were reported as the mean $\pm$ standard deviation for each demographic and neuropsychological variable. Diffusion motion between the groups was also compared using the nonparametric Kruskal–Wallis test and significance was established at $p < .05$.

Network-based statistic (NBS; Zalesky, Fornito, & Bullmore, 2010) was used to perform nonparametric statistical tests to identify whether there was a difference in WM structural connectivity between cognitively impaired and nonimpaired professional fighters. No sparsity threshold was applied during NBS comparison. Briefly, NBS performs permutation testing using unpaired t tests with 5,000 permutations. A test statistic is then computed for each connection, and a threshold of $t = 1.6$ (uncorrected $p = .05$) was then applied to identify a set of suprathreshold connections which showed significant differences ($p_{\text{corr}} < .05$) in structural connectivity between the groups.

We used well-established principles of general linear modeling (GLM) to perform: (a) two-sample t test for determining whether there is a mean difference between rich-club measures, global network properties, and local network properties among the groups; (b) linear regression to investigate whether there is a correlation between the neuropsychological scores, and the network measures (rich-club measures, global and local network measures) in each group; and (c) linear regression to determine whether there is a correlation between the number of professional fights and years of professional fighting, and the network measures (rich-club measures, global and local network measures) in each group. We also tested whether the slope obtained through linear regression model between various network measures and clinical measures differed between groups. All statistical tests were conducted with the nonparametric statistical analysis using the permutation analysis of linear models (PALM) toolbox in FSL (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). Briefly, PALM is a tool that allows statistical inference using permutation methods thereby allowing freedom to both independent and dependent variables from Gaussian distribution. Significance for PALM was established with family-wise error correction of $p_{\text{corr}} < .05$.

3 | RESULTS

3.1 | Demographics and neuropsychological scores

The neuropsychological scores and the demographical information about the cognitively impaired and nonimpaired active professional fighters are outlined in Table 1. As can be observed, means of none of the demographical information exhibited a statistical difference between the groups ($p > .05$), except for the processing and the psychomotor speed as expected. Statistically significant ($p < .0001$) lower processing speed and psychomotor speed was observed for cognitively impaired active professional fighters. Motion during the dMRI scan was also found to be nonsignificant between groups.

3.2 | WM structural connectivity between cognitively impaired and nonimpaired active professional fighters

Out of 4005, 92 paths showed a significantly ($p_{\text{corr}} < .05$) lower connectivity strength in cognitively impaired fighters, as shown in Figure 2. The paths comprised both cortical and subcortical brain regions and no laterality was observed in our cohort. Briefly, paths comprised regions of supplementary motor area, cingulum, hippocampus, striatum, frontal cortices, and occipital regions. Most of the paths showing a significantly lower strength in impaired fighters had a small effect size (Cohen's d between 0.3 and 0.5), and only two paths, namely, between left superior parietal gyrus and inferior parietal gyrus ($d = 0.55$), and between right fusiform and right superior temporal pole ($d = 0.53$) had a medium effect size. All the paths at $p_{\text{corr}} < .05$ with the corresponding effect sizes are outlined in Table S1.

3.3 | Correlation between subject global connectivity score and the neuropsychological scores

Significantly ($p < .05$) lower subject global connectivity score, a surrogate of global WM structural connectivity, was observed in our cohort of cognitively impaired active professional fighters (Figure 3a). Furthermore, a differential pattern of correlation between the subject's global connectivity score and the neuropsychological score was also observed (Figure 3b) between impaired and nonimpaired fighters. While nonimpaired active professional fighters showed a significantly negative correlation with both processing speed ($r = -.18$, $p_{\text{corr}} = .02$) and psychomotor speed ($r = -.16$, $p_{\text{corr}} = .03$), a significantly positive correlation between subject global connectivity score and processing speed ($r = .19$, $p_{\text{corr}} = .02$) was observed in cognitively impaired active professional fighters.

In addition, while the slope between subject global connectivity score and processing speed was significantly greater ($p_{\text{corr}} < .001$) in impaired fighters, the slope between subject global connectivity score and psychomotor speed was significantly lower ($p_{\text{corr}} < .002$) in impaired fighters.

3.4 | Correlation between local topological network measures and the neuropsychological scores

As the structural connectome was fully connected for both groups at a minimum sparsity level of 11% (Figure 4), local topological network properties were extracted and compared between groups only at this sparsity level.

No difference in any global network properties was observed between groups. Although a significantly different pattern of correlation between local efficiency of the entire network and processing speed ($r_{\text{impaired}} > r_{\text{nonimpaired}}$; $p_{\text{corr}} = .04$) was observed between groups (top left panel of Figure 5) at the sparsity level of 11%, no significant correlations between local efficiency and processing speed were observed within our cohort of cognitively impaired and nonimpaired active professional fighters.

No statistical difference was observed between the means of any local network properties between groups. The path length of left

FIGURE 2 Network-based statistical (NBS) results are only shown for those paths where the structural connectivity in impaired fighters was significantly ($p_{corr} < .05$) less than the nonimpaired fighters. No sparsity threshold was used for NBS. An uncorrected threshold of $t = 1.6$ (uncorrected $p = .05$) was applied to identify a set of suprathreshold connections that showed significant differences ($p_{corr} < .05$) in structural connectivity between the groups. The blue circles and the yellow stick represent the nodes and edges connecting the nodes respectively. The nodes and edges were visualized on an MNI152 template. L and R represent the left and right hemisphere, respectively [Color figure can be viewed at wileyonlinelibrary.com]

paracentral lobule showed a statistically significant ($r = -.31$; $p_{corr} = .04$) negative correlation with processing speed in impaired fighters (right top panel of Figure 5). Furthermore, while slope between local efficiency of right rolandic operculum and processing speed was significantly greater ($p_{corr} = .04$) in impaired fighters, the slope between path length of right rolandic operculum and processing speed was significantly lower ($p_{corr} = .04$) in impaired fighters. There was, however, no statistically significant correlations observed between local efficiency and path length of right rolandic operculum, and processing speed in any group. None of the other independent variables such as number of professional fights, years of professional fights, and psychomotor speed exhibited any correlation with the graph-theoretical measures in any group.

3.5 | Correlation between rich-club network measures and the neuropsychological scores

Both impaired and nonimpaired active professional fighters exhibited a presence of rich-club from $k \geq 3$ to $k \geq 11$ (Figure 6a). To maximize the connections between the nodes with the highest nodal degree, all

rich-club measures were extracted and compared for differences in the rich-club properties and correlation with neuropsychological scores at $k \geq 11$. Six nodes were identified as rich-club nodes in our cohort of impaired and nonimpaired active professional fighters. While bilateral caudate, left insula and left hippocampus were identified as rich-club nodes in both impaired and nonimpaired professional fighters; right insula, and right precuneus were identified as rich-club nodes in impaired fighters, and right middle cingulate gyrus and right hippocampus were identified as rich-club nodes in nonimpaired fighters (Figure 6b).

Statistically significant ($p_{corr} < .05$) weaker rich-club edge strength and weaker local edge strength was found in our cohort of cognitively impaired active professional fighters (Figure 7a). Additionally, a statistically significant positive correlation was observed between feeder edge strength and processing speed in impaired fighters ($r = .18$; $p_{corr} = .02$) and showed a statistically significant negative correlation was observed between feeder edge strength and processing speed in nonimpaired fighters ($r = -.17$; $p_{corr} = .02$) as shown in the left panel of Figure 7b. Furthermore, the difference in the pattern of correlation

FIGURE 3 (a) Boxplot of the subject global connectivity score, derived from the structural connectivity matrix, of impaired and nonimpaired fighters is shown. (b) The relationship between the subject's global connectivity score and the neuropsychological scores (processing and psychomotor speed) is shown as a scatter plot. Impaired and nonimpaired fighters are represented as blue circle and orange triangle respectively. The regression line for the impaired and nonimpaired group is shown as blue and orange lines respectively. Each scatter represent data from every participant. The slopes were corrected for multiple comparisons and were considered significant at $p_{corr} < .05$. Dashed regression line indicates nonsignificant relationship and solid regression line indicates a significant relationship [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 4 Relationship between the sizes of the largest connected component as a function of sparsity is shown. The dashed line represents the minimum sparsity (11%) at which nodal graph-theoretical properties were compared between impaired and nonimpaired fighters. Impaired and nonimpaired fighters are represented as blue and orange lines, respectively. The error bars indicate the standard deviation of the size of the largest connected component at the given sparsity level for each group and are plotted as blue and orange error bars for impaired and nonimpaired fighters respectively [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 5 Relationship between graph-theoretical properties and processing speed is shown for both impaired fighters (blue circles) and nonimpaired fighters (orange triangles) as a scatter plot. Each scatter represents data from every participant. The slopes were corrected for multiple comparisons and were considered significant at $p_{corr} < .05$. The regression line for the impaired and nonimpaired group is shown as blue and orange, respectively. Of note, the local efficiency of the entire network was corrected across various sparsity thresholds and other measures simultaneously. The relationship between local efficiency of the entire network and processing speed was significant ($p_{corr} < .05$) from sparsity of 10–40%, but the result is only shown for the chosen sparsity threshold of 11% at which nodal properties were compared. Furthermore, the nodal graph-theoretical properties were corrected across all nodes and measures simultaneously. Dashed regression line indicates nonsignificant relationship and solid regression line indicates a significant relationship [Color figure can be viewed at wileyonlinelibrary.com]

between feeder edge strength and processing speed in the two groups was statistically significant ($r_{impaired} > r_{nonimpaired}$; $p_{corr} = .001$). While the correlation between local edge strength and psychomotor speed was not statistically significant within the groups, a significantly different pattern of correlation between local edge strength and psychomotor speed ($r_{impaired} < r_{nonimpaired}$; $p_{corr} = .02$) was observed as shown in the right panel of Figure 7b.

4 | DISCUSSION

Utilizing high-angular resolution dMRI data in a cohort of active professional fighters, our study identified: (a) weak global WM structural connectivity in cognitively impaired fighters that correlated with neuropsychological scores; (b) a differential correlation between local topographically computed network-derived measures and neuropsychological scores among cognitively impaired and nonimpaired fighters; and (c) a discernible reorganization in the network topology that correlated with neuropsychological scores among cognitively impaired and nonimpaired fighters.

4.1 | Global WM connectivity changes due to RHI

Our study identified widespread structural connectivity damage in regions involved in executive memory, working memory, language, social interactions, and empathy, which has been shown to be affected in participants with TBI (de Sousa, McDonald, & Rushby, 2012; Hanks, Temkin, Machamer, & Dikmen, 1999; McDonald, 1998; McDowell, Whyte, & D'Esposito, 1997; Wood & Worthington, 2017). For instance, paths involving superior and inferior parietal lobule, which are considered to be a part of the "default mode network" (Johns, 2014; Philippi et al., 2015) showed a significantly weaker connectivity in our cohort of cognitively impaired fighters with the maximum effect. Superior and inferior parietal lobule have also been speculated to be involved in attention and visuospatial perception (Johns, 2014). Left inferior parietal lobule, specifically, has been shown to be involved in the arithmetic components in the left hemisphere (Johns, 2014). Furthermore, paths involving fusiform and right temporal pole were also found to be significantly lower in cognitively impaired fighters, and these regions have been shown to be associated with processing facial emotions (Zevin, 2009), empathy and cognitive perspective-taking (Meyer et al., 2013; Rascovsky et al., 2011).

FIGURE 6 (a) Relationship between rich-club measure (Φ_{norm}) and degree (k) is shown for both impaired (blue circles) and nonimpaired fighters (orange triangles). The error bar indicates the standard deviation of Φ_{norm} at each k for impaired (blue) and nonimpaired fighters (orange). The rich-club was found for both groups from $k \geq 3$ to $k \geq 11$ and is shown as a gray rectangular box. (b) All nodes with $k \geq 11$ were extracted from both groups. The nodes are overlaid for both impaired and nonimpaired fighters on an MNI152 template. The rich club nodes are represented as yellow circles. The thickness of the edge connecting the nodes in both groups represents the average edge strength between the nodes in impaired and nonimpaired fighters. L and R represent the left and right hemisphere respectively [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 7 (a) Significantly ($p_{\text{corr}} < .05$) higher rich-club edge strength and local edge strength was found for nonimpaired fighters and is represented as a bar plot. The error bar indicates the standard deviation of the edge strengths in each group. (b) The relationship between feeder edge strength and processing speed along with the relationship between local edge strength and psychomotor speed is shown for both impaired fighters (blue circles) and nonimpaired fighters (orange triangles) as scatter plot. Each scatter represents data from every participant. The slopes were corrected for multiple comparisons and were considered significant at $p_{\text{corr}} < .05$. Dashed regression line indicates nonsignificant relationship and solid regression line indicates a significant relationship [Color figure can be viewed at wileyonlinelibrary.com]

In addition, paths involving cingulum, hippocampus, parahippocampus, amygdala, and thalamus showed a significantly lower WM connectivity in cognitively impaired fighters, and all these regions have been implicated to be involved in memory (Johns, 2014). Furthermore, in this same cohort, volumetric loss in thalamus and its association with neuropsychological outcomes (Bernick et al., 2015) has been indicated to predict cognitive decline (Mishra et al., 2017) due to RHI. These findings suggest that the RHI in fighters exhibiting cognitive decline had a significant WM connectivity damage in regions involving executive and working memory which may be responsible for their poor functional outcome. However, it should be noted that our cohort of cognitively impaired fighters were defined using a combination of working and executive memory. Future studies with multi-modal dMRI with resting-state fMRI or task-based fMRI probing working (Archer, Lee, Qiu, & Chen, 2018) and executive memory (Osaka, Komori, Morishita, & Osaka, 2007) regions are warranted to understand the correlation between anatomical and functional connectivity, and their combined effect on neuropsychological scores.

Furthermore, an integrated measure of the global WM structural connectivity was weaker in impaired fighters and was observed to be correlated differentially with the neuropsychological scores as compared to nonimpaired fighters. Taken together, this finding suggests that global WM damage in cognitively impaired fighters might point to inefficient information transfer as there was a significantly different slope observed between global WM connectivity strength and neuropsychological scores in nonimpaired fighters.

However, our findings appear to be driven by the fighters with extreme neuropsychological scores in both groups since an inverted U-shape weak correlation of global WM structural connectivity and neuropsychological scores (Figure S1) was observed when the entire fighters population was compared as a whole. Longitudinal analyses of the dMRI acquired in the participants of this study in conjunction with fMRI will help to tease out the importance of the global WM connectivity, since hyper-connectivity between cortical-subcortical regions derived using fMRI has been indicated as a potential biomarker for monitoring progression of clinical symptoms (for review, Caeyenberghs, Verhelst, Clemente, & Wilson, 2017) in participants exposed to RHI.

4.2 | Insights into changes in brain architecture with RHI

To the best of our knowledge, there have been no studies comparing the change in the brain topological organization between participants who are cognitively impaired and nonimpaired where the participants in both groups are exposed to RHI. Nevertheless, when compared to healthy controls, Zhou (2017) showed that graph-theoretical measures in participants with mild TBI showed a decreased betweenness-centrality but a higher clustering coefficient. However, no significant difference in any graph-theoretical measures was observed in our cohort of impaired and nonimpaired professional fighters. This suggests that while graph-theoretical measures may be significantly different when compared to healthy controls, they are not a powerful

measure to differentiate among participants that are exposed to RHI but are prone to cognitive decline.

Rich-club measures and betweenness-centrality could be loosely linked as both measures attempt to find the nodes of the graph that are centrally important to information transfer between various cortico-subcortical regions. While our study did not find any significant difference in the rich-club organization between groups, we did find that both cognitively impaired and nonimpaired fighters exhibit a rich-club property sharing four out of six rich-club nodes identified in both groups. Our study also observed a spatial reorganization of the WM connections traversing through bilateral hippocampus and left cingulate gyrus in nonimpaired fighters to right precuneus, right insula, and left hippocampus in cognitively impaired fighters. All these differentiated rich-club nodes within impaired fighters are thought to be responsible for cognition (Cavanna & Trimble, 2006; Rubin, Watson, Duff, & Cohen, 2014; Uddin, Nomi, Hébert-Seropian, Ghaziri, & Boucher, 2017). Furthermore, we also found that the strength of the WM connections within the rich-club nodes, and nonrich-club nodes were weaker in impaired fighters.

Overall, this finding suggests that there is a reorganization of the topology of the WM structure due to RHI which is differentiated between cognitively impaired and nonimpaired active professional fighters and may explain the poor functional outcome in the fighters with significant cognitive decline. However, these topological measurements when translated to graph-theoretical measures were neither different nor associated with exposure to fighting and neuropsychological scores. One possible explanation to these unanticipated finding would be that processing speed or psychomotor measures are high-level functional outcome measure (Rath et al., 2004) that involves a complex interplay between various cortical-subcortical regions while graph-theoretical measures are derived as an ensemble of the average connectivity strength between various cortical regions but taken one-node at a time. As recently speculated by Kaminski and Blinowska (2018), this simple bivariate method to compute graph-theoretical measures may not be able to capture the complicated clinical measures which may be responsible for the lack of association between the graph-theoretical measures and neuropsychological scores.

4.3 | Correlation between network measures and neuropsychological scores

Our study identified that while the slope of correlation of graph-theoretical measures and neuropsychological scores was significantly different between groups for almost all graph-theoretical measures utilized in this study, the network measures were not correlated with the neuropsychological scores within the group. Furthermore, we found no correlation with the graph-theoretical measures with exposure to RHI in any group. Longitudinal evaluation in conjunction with fMRI derived graph-theoretical measures might help us to understand whether a joint analysis might reveal the correlation between graph-theoretical measures and neuropsychological scores and allow us to

understand the interplay between functional and structural topological organization and any disruptions thereof with RHI.

4.4 | Limitations of the current study and future work

Potential contributing factors such as time since last injury, past history of drug usage, childhood environmental factors, or other comorbidities were not explicitly controlled in our statistical analysis, and hence studies considering their effects on the neural architecture are warranted. Furthermore, repeated TBI is known to cause diffuse axonal injury and has been shown to induce a continuous axonal change in a rat model of repeated mild TBI (Donovan et al., 2014) which will modulate average FA across the tracts. The average FA of the fibers connecting two distinct nodes will also be modulated due to crossings and possible axonal changes (Wheeler-Kingshott & Cercignani, 2009) when computed using a single tensor DTI model like in our study. Future studies should evaluate whether tract-specific FA (Mishra, Guo, Delgado, & Huang, 2015) or free-water corrected FA (Mishra et al., 2015; Pasternak, Sochen, Gur, Intrator, & Assaf, 2009) might reduce the bias induced due to single tensor model and improve detection of any changes in graph-theoretical measures between groups. There is still no consensus regarding the choice of tracking algorithms to be used to generate a structural connectome. Probabilistic tracking suffers from false positives (Zolal et al., 2017) but robust in tracking through crossing fibers (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007) while deterministic tractography suffers from its inability to track through crossing fibers (Christidi et al., 2016) and hence can result in false negatives. The effect of both the tracking algorithms and the choice of the edge weights should be evaluated in future work to understand their impact on the topological WM organization. Longitudinal evaluation of the graph-theoretical measures and neuropsychological scores is warranted to understand the utility of graph-theoretical measures in understanding changes in cognition with RHI, as our findings suggest that differentiated topological change may be more sensitive in understanding the functional outcome measures rather than the graph-theoretical measures. The cognitive battery in the current study was limited and hence future studies should use more comprehensive testing of different domains to better understand the cognitive implications of RHI, and their association with graph-theoretical measures and WM topology. Distortion correction in the current study was performed using only the affine registration of the diffusion-weighted volumes to the nondiffusion-weighted b0 map due to the lack of field map. Future studies should validate our findings with advanced distortion correction techniques to investigate the potential bias induced by off-resonance effects (Andersson & Sotiropoulos, 2016). Finally, as mentioned earlier, joint fMRI and dMRI graph-theoretical measures in a longitudinal cohort will help to understand the comprehensive reorganization in brain topology within cognitively impaired active professional fighters with exposure to RHI.

5 | CONCLUSION

In conclusion, our study identified a topological WM reorganization due to RHI in fighters prone to cognitive decline that was weakly correlated with neuropsychological scores. Our study identified a global reorganization in the WM topological connectivity involving regions of hippocampus, precuneus, and insula within our cohort of cognitively impaired fighters suggesting that there is a discernible difference in the WM connectivity within fighters prone to cognitive decline. Although graph-theoretical measures were correlated differentially with neuropsychological scores in our cohort, we found neither a group difference in the average graph-theoretical measures nor correlation of the graph-theoretical measures with neuropsychological scores within the group.

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CONFLICT OF INTEREST

The authors declare no conflict of interest relevant to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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