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Investigating structural and perfusion deficits due to repeated head trauma in active professional fighters

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ABSTRACT

Repeated head trauma experienced by active professional fighters results in various structural, functional and perfusion damage. However, whether there are common regions of structural and perfusion damage due to fighting and whether these structural and perfusion differences are associated with neuropsychological measurements in active professional fighters is still unknown. To that end, T1-weighted and pseudocontinuous arterial spin labeling MRI on a group of healthy controls and active professional fighters were acquired. Voxelwise group comparisons, in a univariate and multivariate sense, were performed to investigate differences in gray and white matter density (GMD, WMD) and cerebral blood flow (CBF) between the two groups. A significantly positive association between global GMD and WMD was obtained with psychomotor speed and reaction time, respectively, in our cohort of active professional fighters. In addition, regional WMD deficit was observed in a cluster encompassing bilateral pons, hippocampus, and thalamus in fighters (0.49 ± 0.04 arbitrary units (a.u.)) as compared to controls (0.51 ± 0.05a.u.). WMD in the cluster of active fighters was also significantly associated with reaction time. Significantly lower CBF was observed in right inferior temporal lobe with both partial volume corrected (46.9 ± 14.93 ml/100 g/min) and non-partial volume corrected CBF maps (25.91 ± 7.99 ml/100 g/min) in professional fighters, as compared to controls (65.45 ± 22.24 ml/100 g/min and 35.22 ± 12.18 ml/100 g/min respectively). A paradoxical increase in CBF accompanying right cerebellum and fusiform gyrus in the active professional fighters (29.52 ± 13.03 ml/100 g/min) as compared to controls (19.43 ± 12.56 ml/100 g/min) was observed with non-partial volume corrected CBF maps. Multivariate analysis with both structural and perfusion measurements found the same clusters as univariate analysis in addition to a cluster in right precuneus. Both partial volume corrected and non-partial volume corrected CBF of the cluster in the thalamus had a significantly positive association with the number of fights. In addition, GMD of the cluster in right precuneus was significantly associated with psychomotor speed in our cohort of active professional fighters. Our results suggest a heterogeneous pattern of structural and CBF deficits due to repeated head trauma in active professional fighters. This finding indicates that investigating both structural and CBF changes in the same set of participants may help to understand the pathophysiology and progression of cognitive decline due to repeated head trauma.

1. Introduction

Sports-related traumatic brain injuries (TBI) amount to 21% of total TBI in the USA of which 5% of the cases are due to professional fighting (http://www.cpsc.gov/en/Research–Statistics/NEISS-Injury-Data/) (Langlois et al., 2006). Repeated head trauma, as experienced by professional fighters, has been indicated as a risk factor for neurodegenerative disorders such as dementia and various other neuropsychiatric disorders such as depression, and mood disorders (For review: Bazarian et al., 2009; Bigler, 2013; Jordan, 2013). Some individuals with chronic brain injury due to repeated head trauma have shown evidence of chronic traumatic encephalopathy (CTE) at autopsy (For review: McKee et al., 2013; Victoroff, 2013). Neuropsychological testing in boxers has revealed slower processing speed, difficulty in completing complex attentional tasks and reduction in executive functions (Bernick and Banks, 2013; Heilbronner et al., 2009). The exact pathophysiology is, however, difficult to investigate due to inherent heterogeneity among the subjects due to different injury sites, mechanical forces, and exposure to head trauma (Margulies and Hicks, 2009; Xiong et al., 2013).

Both structural and perfusion deficits have been found in animals

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and human models of repeated head trauma. The animal models of repeated head trauma have reported widespread cortical, cerebellar, hippocampal, and thalamic atrophy combined with diffuse axonal injuries of the corpus callosum and cerebellar peduncles (Xiong et al., 2013; (review)). Similar to these animal models, various structural neuroimaging studies of repeated head trauma in humans involved in repeated head trauma such as professional fighting, veterans, and combatants have shown changes in gray matter volumes in regions 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 (review); Gooijers et al., 2013; Lopez-Larson et al., 2013; Montenigro et al., 2015; Ng et al., 2014 (review)). Various diffusion tensor imaging (DTI) studies of repeated head trauma have shown increased mean diffusivity and decreased fractional anisotropy in the temporo-occipital white matter tracts and forceps major (Hulkower et al., 2013 (review); Ng et al., 2014 (review); Orrison et al., 2009 (review); Shin et al., 2014; Wintermark et al., 2015 (review); Zhang et al., 2003, 2006). Axonal diffuse injury, hippocampal atrophy, dilated perivascular spaces, cavum septum pellucidum, cerebral atrophy, increased lateral ventricular size, pituitary gland atrophy, arachnoid cysts, and contusions have been shown to be associated with repeated head injuries that were further associated with years and number of fights (Orrison et al., 2009 (review)). Perfusion studies using dynamic susceptibility contrast MRI, single photon emission computed tomography (SPECT) and arterial spin labeling (ASL) MRI in participants with repeated brain trauma has shown global perfusion deficits accompanied with lower cerebral blood flow in thalamus, cingulate gyri, cerebellum, cuneus and temporal lobes (For review: Eierud et al., 2014; Koerte et al., 2016). The perfusion deficit was further shown to be associated with neurocognitive scores (Ge et al., 2009; Koerte et al., 2016; Liu et al., 2013).

Therefore, there is an established association of both morphological and perfusion changes in fighters with repeated head trauma. However the extant neuroimaging studies in humans have investigated either structural or perfusion changes in fighters but not both in the same population. Jointly investigating both structural and perfusion changes may provide additional information about the pathophysiology and the progression of cognitive decline in participants with repeated head trauma. To that end, in the current study, we investigated both structural and perfusion changes in active professional fighters and their association with exposure to fighting and neuropsychological assessments. The data were collected as a part of Professional Fighters Brain Health Study (PFBHS) (Bernick et al., 2013). We hypothesized that repeated head trauma will induce (a) both global structural and perfusion deficits as compared to age and education-matched healthy controls, (b) there may be both overlapping and non-overlapping regions of structural and perfusion deficits due to repeated head trauma, and (c) the regions showing significant structural and perfusion deficits as compared to healthy controls will be associated with both exposure to fighting and neuropsychological assessments.

2. Materials and methods

PFBHS is a longitudinal study of active professional fighters (boxers and MMA) and age and education-matched healthy controls (Bernick et al., 2013). PFBHS was approved by the institutional review board of Cleveland Clinic and all the participants provided informed written consent. The protocols of the experiment were explained to all the subjects and were performed according to the Declaration of Helsinki guidelines and Belmont Report.

2.1. Active fighters and healthy controls recruitment and demographics

252 professional fighters (234 males (M); 18 females (F)) and 20 age-matched healthy controls (20M) were recruited at our centre. All subjects aged 18 or older licensed for professional boxing or mixed martial arts and who are fluent in English were included as professional fighters. Fighters competing in a sanctioned competition within 45 days of the visit were excluded. Control subjects could not have participated in contact sports such as rugby, football, hockey, soccer, or rodeo at the high school or above. There were 108 boxers (98M, 10F) and 144 MMA-fighters (136M, 8F). None of the fighters included for the purpose of this study suffered from hypertension, diabetes, or any other medical complications that may affect CBF measurements. All fighters who had concussion-like symptoms on the day of their visit were also excluded for the purpose of this study. Detailed information about race, educational attainment, prior involvement in other combat sports and professional fighting were recorded for most of the subjects (221 fighters, 20 controls).

Since both race and years of education (YOE) affect CBF values, those subjects that had missing information on either race (22 fighters), years of education (YOE) (seven fighters), or both race and YOE (two fighters) were removed from any further analysis. Furthermore, one control and seven fighters had registration and motion artifacts and were excluded from any analysis. This procedure yielded 19 healthy controls (19M), and 214 (14F, 200M) professional fighters (89 boxers (6F, 83M), and 125 MMA-fighters (8F, 117M)). Since there were no female controls, only male fighters and controls were used for this analysis. Therefore, 19 male healthy controls and 200 male professional fighters (83 boxers and 117 MMA-fighters) were used for the statistical analysis. Demographics of the groups are tabulated in Table 1.

2.2. Neuropsychological assessment

Cognitive tests were completed using a computer in a quiet room, supervised by a researcher. CNS Vital Signs was used to administer standardized cognitive tests (Gualtieri and Johnson, 2006). We use four tests from their battery; Finger Tapping, Symbol Digit Coding, Stroop and a Verbal Memory task involving list learning. From these tests we obtained four cognitive scores, namely verbal memory (total correct across immediate and delayed recognition tasks using a 15 item list), processing speed (total correct on a Digit Symbol Coding task), psychomotor speed (combining Digit Symbol result and average Finger Tapping on each hand) and reaction time (which uses the scores from the Stroop task) for all the participants. Table 2 tabulates the neuropsychological assessment scores.

2.3. MRI data acquisition

3T Verio Siemens MRI scanner with a 32-channel head coil was used

Table 1
Various demographics of all the participants are shown along with their mean ± SD. Results of pairwise statistical comparisons are also shown with their respective *p*-values. *p*-Values are represented by the letter "*p*". NS: Non-significant; NA: Not applicable.

Demographics	Control ($N = 19$)	Fighters ($N = 214$)	Control vs fighters
Age (years)	29 ± 7.53	28.98 ± 5.86	NS ($p = 0.95$)
Years of education (years)	14.59 ± 2.67	13.71 ± 2.47	NS ($p = 0.11$)
Race			
Unknown:	2	30	
Pacific Islander:	2	8	
Asian:	1	3	
African American:	1	56	
American Indian/ Alaskan Native:	0	3	NS ($p = 0.15$)
White:	13	100	
Number of professional fights	NA	12.69 ± 12.16	NA
Years of professional fights	NA	5.18 ± 4.03	NA
Number of knockouts	NA	0.91 ± 1.53	NA