Lasting consequences of concussion on the aging brain: Findings from the Baltimore Longitudinal Study of Aging

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Abstract

Studies suggest that concussions may be related to increased risk of neurodegenerative diseases, such as Chronic Traumatic Encephalopathy and Alzheimer's Disease. Most neuroimaging studies show effects of concussionsin frontal and temporal lobes of the brain, yet the long-term impacts of concussions on the aging brain have not been well studied. We examined neuroimaging data from 51 participants (mean age at first imaging visit = 65.1±11.23) in the Baltimore Longitudinal Study of Aging (BLSA) who reported a concussion in their medical history an average of 23 years prior to the first imaging visit, and compared them to 150 participants (mean age at first imaging visit = 66.6 ± 10.97) with no history of concussion. Participants underwent serial structural MRI overa mean of 5.17 ± 6.14 years and DTI over a mean of 2.92 ± 2.22 years to measure brain structure, as well as ^{15}O-water PET over a mean of 5.33 ± 2.19 years to measure brain function. A battery of neuropsychological tests was also administered over a mean of 11.62 ± 7.41 years. Analyses of frontal and temporal lobe regions were performed to examine differences in these measures between the concussion and control groups at first imaging visit and in change over time. Compared to those without concussion, participants with a prior concussion had greater brain atrophy in temporal lobe white matter and hippocampus at first imaging visit, which remained stable throughout the follow-up visits. Those with prior concussion also showed differences in white matter microstructure using DTI, including increased radial and axial diffusivity in the fornix/stria terminalis, anterior corona radiata, and superior longitudinal fasciculus at first imaging

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Danielle June: Formal analysis, Data curation, Visualization, Writing - original draft. **Owen A. Williams:** Formal analysis, Data curation, Writing - original draft. **Chiung-Wei Huang:** Formal analysis, Data curation, Writing - review & editing. **Yang An:** Formal analysis, Data curation, Writing - review & editing. **Bennett A. Landman:** Software, Validation, Writing - review & editing. **Christos Davatzikos:** Software, Validation, Writing - review & editing. **Murat Bilgel:** Formal analysis, Data curation, Visualization, Writing - review & editing. **Susan M. Resnick:** Project administration, Funding acquisition, Supervision, Writing - review & editing. **Lori L. Beason-Held:** Conceptualization, Methodology, Formal analysis, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors report no competing interests.

visit. In ^{15}O-water PET, higher resting cerebral blood flow was seen at first imaging visit in orbitofrontal and lateral temporal regions, and both increases and decreases were seen in prefrontal, cingulate, insular, hippocampal, and ventral temporal regions with longitudinal follow-up. There were no significant differences in neuropsychological performance between groups. Most of the differences observed between the concussed and non-concussed groups were seen at the first imaging visit, suggesting that concussions can produce long-lasting structural and functional alterations in temporal and frontal regions of the brain in older individuals. These results also suggest that many of the reported short-term effects of concussion may still be apparent later in life.

1. Introduction

Approximately 42 million people worldwide suffer a concussion every year (Gardner and Yaffe, 2015), making it the most common form of brain injury (Cassidy et al., 2004). Research conducted in concussed individuals reveals alterations in the brain within a few days of the injury, including differences in brain activity and white matter microstructure (Bazarian et al., 2007; Bazarian et al., 2012; Churchill et al., 2017b; Mayer et al., 2010). These alterations are accompanied by possible cognitive deficits such as poor concentration and difficulty remembering new information (Ruff et al., 2009). Although the majority of concussions and the associated symptoms are thought to resolve within a two-week period (McCrory et al., 2013), there has been growing concern regarding the long-term effects of concussion because of the associations with neurodegenerative diseases, such as Chronic Traumatic Encephalopathy (Goldstein et al., 2012; McKee et al., 2013) and age-related dementias (Abner et al., 2014; Schofield et al., 1997).

Literature on the effects of concussion has grown exponentially in the recent years, largely due to professional athletes and military personnel who have brought this issue to the forefront of national attention (Omalu et al., 2011). Evidence of long-term concussive effects has been associated with a neurodegenerative disease known as CTE, which is caused by repetitive sub-concussive hits to the head and is marked by widespread cerebral atrophy and progressive tauopathy in frontal, temporal and limbic brain regions (McKee et al., 2013; Sundman et al., 2015). Due to similarities in pathology with CTE (McKee et al., 2013; Stern et al., 2013; Sundman et al., 2015), Alzheimer's Disease (AD) and age-related dementias have also been studied in relation to concussion. Several studies have found associations between concussions and increased risk of dementia (Abner et al., 2014; Schofield et al., 1997), with one longitudinal aging study demonstrating increased risk of incident dementia in those with only a single, self-reported concussion (Abner et al., 2014). While these studies suggest associations between neurodegenerative disease and concussion, few studies have yet to establish significant causality between the two.

In order to bridge the gap between an initial concussive event and subsequent neurodegeneration, researchers have begun to utilize in-vivo neuroimaging alongside cognitive testing in order to investigate potential lasting alterations to the brain. Studies examining chronic phases of concussion, or more than a year post concussive event, have examined abnormalities in the brain that mimic and extend from brain regions that were also affected within a week of the concussive event. For example, differences in white matter diffusivity and fractional anisotropy seen in the corpus callosum, fasciculi, and corona radiata during the acute phase of concussion continue to be observed more than 2 years after the concussive event (Bazarian et al., 2007, 2012; Mayer et al., 2010), with additional involvement of the fornix and cingulate cortex (Kinnunen et al., 2011). Increases and decreases in brain metabolism at rest have also been seen in similar regions up to 5 years post-concussive event, again in areas observed in the acute phase such as temporal, frontal and limbic regions (Gross et al., 1996; Peskind et al., 2011). However, directionality of these results is variable, with some studies showing increases in these measures and others showing decreases, further highlighting the complexity of concussive outcomes. Nevertheless, morphologic and functional changes in those with a prior concussion have been associated with memory, executive, and attentional deficits (Koerte et al., 2016; Peskind et al., 2011; Wilde et al., 2016).

Significant progress has been made in understanding the morphologic and cognitive effects of concussions, yet few studies have examined the longitudinal effects of a prior concussion on the aging brain. While certain studies have examined alterations to the brain decades after a concussive event (Koerte et al., 2016; Tremblay et al., 2013), these findings were limited by the availability of only cross-sectional data. Additionally, while these studies were conducted cross-sectionally, both reported a significant effect of age when advancing from middle- to older age in those with a prior concussion (Koerte et al., 2016; Tremblay et al., 2013), further confirming the need to understand implications in the aging brain.

To explore the long-term impact of concussion on subsequent neurodegeneration, this study examines baseline and longitudinal brain alterations more than 20 years post-concussive event (23.03 (18.64 SD mean years) in cognitively normal older adults from the Baltimore Longitudinal Study of Aging (BLSA). Based on previous findings of frontal and temporal lobe effects of concussion in both earlier and chronic stages (Churchill et al., 2017a; Kinnunen et al., 2011; McKee et al., 2013; Sundman et al., 2015; Tremblay et al., 2013), we investigate these regions of the aging brain. We examine structural and functional brain alterations using MRI, DTI and ^{15}O-water PET in frontal and temporal areas, as well as examine differences in cognitive performance over time. In order to assess differences between concussed and non-concussed participants, we examine differences at the first imaging visit as well as subsequent changes over a follow-up interval of 11 years on average.

Based on previous studies that have shown both acute and chronic structural and functional effects in frontal and temporal regions, including the hippocampus, amygdala, cingulate and orbitofrontal cortex (Bazarian et al., 2007, 2012; Churchill et al., 2017b; Gross et al., 1996; Kinnunen et al., 2011; Mayer et al., 2010; Peskind et al., 2011; Tremblay et al., 2013), we hypothesize that differences may be still be apparent in these regions at initial imaging visit,

long after the concussive event. We further explore whether continued change in these regions can be detected over longitudinal follow-up. Although cognitive findings related to concussion are more variable, we hypothesize that memory, executive function or attentional performance could show differences between the groups, especially in relation to the hypothesized brain effects (Goswami et al., 2016; Wilde et al., 2016).

2. Methods

2.1. Participant pool

Participants in the neuroimaging substudy (Resnick et al., 2003) of the BLSA (Shock, 1984) underwent neuroimaging sessions where volumetric MRI, DTI and/or ^{15}O-water PET scans were collected, and cognitive testing was administered. Within this substudy, 51 older participants self-reported a concussion in their medical history (mean age at first imaging visit 65.14 (11.23 SD)). If loss of consciousness was reported, only those with reports of < 30 min unconsciousness were included in the analyses. For each imaging modality, a 2:1 control:concussion age, sex and race matched subject ratio was determined, resulting in a total pool of 150 participants (mean age at first imaging visit 66.64 (10.97 SD)) with no history of concussion, referred to as the control group in each analysis (Table 1).

All participants were free of other significant health conditions that could affect brain structure (i.e. stroke, brain surgery, malignant cancer, meningiomas and cysts with brain tissue displacement, seizure and bipolar disorders). Participants were excluded if they had a clinical diagnosis of mild cognitive impairment, Alzheimer's Disease, dementia, or Parkinson's disease at first imaging visit. If they received a clinical diagnosis during the follow-up interval, any visits after symptom onset were excluded from the analyses ($n = 18$; 11 controls, 7 concussion). Cognitive status was determined by consensus case conference using the Petersen criteria (Petersen, 2004) for mild cognitive impairment, and Diagnostic and Statistical Manual, third edition, revised (DSM-III-R)(American Psychiatric Association, 1987) and the National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984) for dementia and Alzheimer's Disease, respectively. The local Institutional Review Board approved the research protocol for this study, and written informed consent was obtained at each visit from all participants.

Of the 51 participants, two participants reported two concussions and two reported three concussions. Furthermore, 40 out of the 51 participants also reported the year that the concussion was sustained. Of these 40, 35 participants received a concussion prior to the initial start of the neuroimaging study in 1994. The remaining five participants whose concussion occurred after their first imaging visit were censored to only include visits after the year their concussion was sustained. The average age at which a concussion was sustained was 33.05 (22.25 SD) years old (Fig. 1). In addition, a concussion was sustained on average 23.03 (18.64 SD) years prior to initial volumetric MRI and PET scanning which began in 1994, and 37.18 (19.85 SD) years prior to DTI imaging beginning in 2009. Furthermore, a concussion was sustained on average 30.78 (18.71 SD) years prior to cognitive testing.

2.2. MRI

2.2.1. Participant subset—Within the concussion group, all 51 participants (mean age at first imaging visit 65.14 (11.23 SD)) underwent MRI scanning, and of these, 37 had longitudinal MRI data (2 or more visits) over a mean of 5.17 years (6.14 SD). A 2:1 control matching ratio resulted in 102 age, sex, and race matched controls (mean age at first imaging visit 65.2 (11.25 SD)), and of these, 63 had longitudinal MRI data over a mean of 4.45 years (5.78 SD) (Table 1). Thus, the first visit assessment included data from 102 controls and 51 concussion participants, and the longitudinal assessment included data from 63 controls and 37 concussion participants. The analyses were performed using linear mixed effects (LME) models that accommodate an unbalanced data structure which allows for the use of all available data for each subject.

2.2.2. MRI acquisition—MRI was performed on a General Electric (GE) Signa 1.5 T scanner ($n = 16$ concussion with 109 total scans, $n = 32$ controls with 235 total scans) or a 3T Philips Achieva ($n = 42$ concussion with 100 total scans, $n = 79$ controls with 171 total scans). GE 1.5-T scans used a high-resolution volumetric spoiled gradient recalled acquisition in a steady state series (axial acquisition, repetition time = 35msec, echo time = 5msec, flip angle = 45°, field of view = 24 cm, matrix = 256 × 256, number of excitations = 1, voxel dimensions = 0.94 × 0.94 × 1.5 mm slice thickness). T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) scans were acquired on a 3T Philips Achieva (repetition time [TR] = 6.8msec, echo time [TE] = 3.2msec, flip angle = 8°, image matrix = 256 256, 170slices, pixel size = 1 × 1 mm, slice thickness = 1.2 mm).

2.2.3. Harmonization of MUSE anatomical labels across 1.5-T SPGR and 3-T MPRAGE—An automated labeling method specifically designed to achieve a consistent parcellation of brain anatomy in longitudinal MRI studies with scanner and imaging protocol differences was used to harmonize MR data in the BLSA from 1994 to 2017. This method combines the MUSE anatomical labeling approach (Doshi et al., 2016) with harmonized acquisition-specific atlases which leverage the availability of brain scans from the same individuals with both 1.5T and 3T images to harmonize the labeling process (Erus et al., 2018). In this framework, multiple atlases with semi-automatically extracted ground-truth ROI labels were individually warped through deformable registration to the target image. A spatially adaptive weighted voting strategy was then applied to fuse the ensemble into a final segmentation. In order to obtain a more robust segmentation, we fused labels from multiple atlases using DRAMMS (Ou et al., 2011) and ANTS (Avants et al., 2008) deformable registration algorithms with two smoothness parameters for each algorithm. DRAMMS was used with smoothness weights g=[0.1, 0.2]; ANTS 1,9.x was used with symmetric normalization (SyN) transformation using smoothness parameters gradstep = [0.25, 0.5]. Using this method, we deformably registered each participant's 1.5-T SPGR image to their 3-T MPRAGE image. This approach was validated (Erus et al., 2018) and was shown to significantly mitigate the difference between 1.5T and 3T volumetric measurements, a problem that has been described before in (Chu et al., 2016). Moreover, by using scanner as a covariate, we further reduced effects of inter-scanner differences.

2.2.4. MRI statistical analysis—Volumes of 21 brain regions of interest (ROIs) were used for this study. Total brain and ventricular volume were used to assess generalized brain atrophy. Frontal ROIs included frontal gray matter, frontal white matter, superior, middle and inferior frontal gyri, medial frontal cortex, and orbitofrontal gyrus. Temporal ROIs included temporal gray matter, temporal white matter, superior, middle and inferior temporal gyri, hippocampus, parahippocampal gyri, entorhinal cortex, and the amygdala. Anterior, posterior and middle cingulate gyri were also examined. We used linear mixed effects models to estimate the cross-sectional difference of brain volume at first imaging visit and longitudinal volumetric change between concussion and control groups. The fixed effects of the model included ICV (intra-cranial volume), scanner type, concussion/control groups (control group as a reference group), time (follow up time since the first MRI scan) and two-way interaction of group x time. Random effects included intercept and time with unstructured covariance. Analyses were performed in SAS 9.4 (Cary, NC). As this was an exploratory analysis, we report uncorrected p-values. A significance level of p 0.05, uncorrected was used for the analyses. The slope of change in regional MRI volumes was also calculated for regions showing significant differences at baseline to determine the subsequent trajectory of volume change in these areas over time. A sensitivity analysis was also performed, excluding those individuals who reported more than 1 concussion ($n = 4$).

2.3. DTI

2.3.1. Participant subset—Within the concussion group, 40 participants (mean age at first imaging visit 65.45 (12.25 SD)) underwent DTI scanning, and of these, 28 had longitudinal DTI data over a mean follow-up of 2.92 years (2.22 SD). While a 2:1 control matching ratio was attempted, the sample of participants with DTI data was smaller, resulting in 76 ages, sex, and race matched controls (mean age at first imaging visit 65.63 (12.37 SD)), and of these, 51 had longitudinal DTI data over a mean of 2.54 years (2.20 SD) (Table 1). Thus, the first visit assessment included data from 76 controls and 40 concussion participants, and the longitudinal assessment included data from 51 controls and 28 concussion participants.

2.3.2. DTI image acquisition and processing—DTI data were acquired on three different 3 Tesla Philips Achieva scanners (scanners 1 and 2 at the Kennedy Krieger Institute and scanner 3 at the National Institute on Aging). DTI acquisition protocol was identical for scanners 1 and 2 but was different for scanner 3.

DTI acquisition, Scanners 1 and 2: number of gradients=32, number of b0 images=1, max b-factor=700 s/mm^2, TR/TE=6801/75 msec, number of slices=65, voxel size=0.83 × 0.83 × 2.2 mm, reconstruction matrix=256 × 256, acquisition matrix=96 × 95, field of view=212 × 212 mm, flip angle=90° DTI acquisition, Scanner 3: number of gradients=32, number of b0 images=1, max b-factor=700 s/mm^2, TR/TE=7454/75 msec, number of slices=70, voxel size=0.81 × 0.81 × 2.2 mm, reconstruction matrix=320 × 320, acquisition matrix=116 × 115, field of view=260 × 260 mm, flip angle=90° To improve signal to noise ratio, two separate DTI scans were acquired for each session and subsequently combined for tensor fitting (Lauzon et al., 2013; Williams et al., 2019).

Tensor fitting and quality assessment was carried out using a protocol described previously (Lauzon et al., 2013; Williams et al., 2019). Briefly, diffusion-weighted volumes were affine co-registered to a b0 image target to correct for eddy current and physiological motion effects. The gradient tables were corrected for the identified rotational component using finite strain (Alexander et al., 2001). To combine the two DTI sessions that had different unknown intensity normalization constants, each diffusion-weighted image was normalized by its own reference image prior to tensor fitting. To improve robustness, iteratively reweighted least squares fitting with outlier rejection (in the form of RESTORE (Chang et al., 2005) from the Camino toolkit (Cook et al., 2006) was used to estimate tensors on a voxel-wise basis.

2.3.3. White matter regions of interest—White matter regions examined were restricted to regions with connections to frontal and temporal areas of the brain. Frontal connecting regions included the superior longitudinal fasciculus, superior fronto-occipital fasciculus, inferior fronto-occipital fasciculus, sagittal stratum, genu of the corpus callosum, anterior corona radiata, and the anterior limb of the internal capsule. Temporal connecting regions included the uncinate fasciculus, cingulum, fornix/stria terminalis, body of the corpus callosum, anterior commissure, and superior corona radiata. To segment our 15 white matter ROIs the Eve white matter atlas (Mori et al., 2008) was combined with corresponding white matter labels from a multi-atlas segmentation using 35 manually labeled atlases from NeuroMorphometrics with the BrainCOLOR protocol (Klein et al., 2010) and FA mapped MRI. The white matter labels were intersected with the white matter segmentation and the resultant labels were iteratively grown to fill the remaining white matter space from the multi-atlas labels. The white matter ROI labels obtained from the T1-weighted image for each visit were affine registered to the fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD) and mean diffusivity (MD) images and used to extract average FA, RD, AD and MD values for each ROI. DTI metrics were averaged across hemispheres for each ROI.

2.3.4. DTI statistical analysis—We used linear mixed effects models to estimate the cross-sectional difference of DTI metrics at first imaging visit and longitudinal change between concussion and control groups. The fixed effects of the model included concussion/ control groups (control group as a reference group), time (follow-up time since the first DTI scan) and a two-way interaction of group x time, adjusted for scanner (1 and 2 vs. 3) as a covariate. Random effects included intercept and time with unstructured covariance. Analyses were performed using the LME function from the NLME package in R (Bates,2007). A significance level of p 0.05, uncorrected was used for the analyses. The slope of change in regional FA, RD, AD and MD was also calculated for regions showing significant differences at baseline to determine the subsequent trajectory of volume change in these areas over time. A sensitivity analysis was also performed, excluding those individuals who reported more than 1 concussion ($n = 4$).

2.4. ^{15}O-water PET

2.4.1. Participant subset—Within the concussion group, 15 participants (mean age at first imaging visit 66.92 (7.47 SD)) underwent PET scanning, and of these, 12 had

longitudinal PET data over a mean of 5.33 years (2.19 SD). A 2:1 control matching ratio resulted in 30 age, sex, and race matched controls (mean age at first imaging visit 67.64 (7.00 SD)), and of these, 29 had longitudinal PET data over a mean of 6.77 years (2.25 SD) (Table 1). Thus, the first visit assessment included data from 30 controls and 15 concussion participants, and the longitudinal assessment included data from 29 controls and 12 concussion participants.

2.4.2. PET imaging acquisition—Annual ^{15}O-water PET scans were used to assess regional cerebral blood flow (rCBF) as an index of brain function (Jueptner and Weiller, 1995), as rCBF is an indirect measure of localized neuronal activity. During each imaging session, a resting state PET scan was performed. During rest, participants were instructed to keep their eyes open and focused on a computer screen covered by a black cloth. PET measures of rCBF were obtained using [^{15}O] water. For each scan, 75 mCi of [^{15}O] water was injected as a bolus. Scans were performed on a GE 4096+ scanner, which provides 15 slices of 6.5-mm thickness. Images were acquired for 60 s from the time the total radioactivity counts in brain reached threshold level. Attenuation correction was performed using a transmission scan acquired prior to the emission scans. Head positioning and immobilization were accomplished using a thermoplastic mask custom fit to each individual.

2.4.3. PET statistical analysis—For each subject, the PET scans were realigned, resliced to a voxel size of $2 \times 2 \times 2$ mm, spatially normalized into standard stereotactic, and smoothed to a full width at half maximum of 12, 12, and 12 mm in the x, y, and z planes. To control for variability in global flow, rCBF values at each voxel were ratio adjusted and scaled to a mean global flow of 50 mL/100 g/min for each image. The image data were analyzed using Statistical Parametric Mapping (SPM12; Welcome Department of Cognitive Neurology, London, England), where voxel by voxel comparisons within frontal, temporal and cingulate regions determined significant differences between the groups at first imaging visit (*t*-test) and in longitudinal rCBF change over time (ANOVA). Differences in longitudinal change was assessed using a group x time interaction. Significant effects for each contrast were based on the uncorrected magnitude (p 0.005) and spatial extent (>50 voxels) of activity. The slope of change in regional rCBF was also calculated for regions showing significant differences at baseline to determine the subsequent trajectory of rCBF change in these areas over time. All participants in the PET studies reported only 1 concussive event.

2.5. Cognition

2.5.1. Participant subset—Within the concussion group, all 51 participants (mean age at first cognition visit 60.08 (9.43 SD)) underwent comprehensive neuropsychological assessments, and of these, 46 had longitudinal cognitive data (two or more visits) over a mean of 11.62 years (7.41 SD). The control sample was selected from the controls available in the MRI dataset, which resulted in 102 age, sex, and race matched controls (mean age at first cognition visit 66.67 (10.89 SD)), and of these, 88 had longitudinal cognitive data over a mean of 9.44 years (6.62 SD) (Table 1). Thus, the first visit assessment included data from 102 controls and 51 concussion participants, and the longitudinal assessment included data from 88 controls and 46 concussion participants. All available cognitive data was used in the

analyses, with initial assessments beginning an average of 4.13 (14.67 SD) years before the first imaging visit, contributing to the difference in the mean baseline age.

2.5.2. Cognitive domains—We constructed five cognitive domains based on guidelines of the Neurocognitive Work Group of the DSM-5 (Sachdev et al., 2014): memory, executive function, attention, verbal fluency and visuospatial perceptual/motor abilities using 11 cognitive measures that were administered for each participant on each visit. The domains scores were composite z-scores of individual cognitive measures. Memory was the composite z-scores of California Verbal Learning Test (CVLT) (Delis et al., 1987) immediate and long-delay free recall. Attention was the composite z-score of Trail Making Test (TMT) (Reitan, 1992) Part A and Digit Span Forward (Blackburn and Benton, 1957). Executive function was the composite z-scores of Trail Making Test Part B and Digit Span Backwards (Blackburn and Benton, 1957). Verbal fluency was the composite z-scores of Category (Newcombe, 1969) and Letter Fluency (Benton, 1968). Lastly, visuospatial perceptual/motor ability was the composite z-score of Card Rotations Test (Wilson et al., 1975) with the measure of total number correct minus total number incorrect across the two parts (14 targets per part) as well as the Clock Drawing Test (Freedman et al., 1994) with 11:10 and 3:25 as times drawn on a clock. For measures of TMT Part A and TMT part B, due to the distribution, they were log-transformed, z-scored and then signed reversed so that higher scores indicated better performance.

2.5.3. Cognition statistical analysis—We used linear mixed models to estimate the cross-sectional difference of each cognitive domain score at first visit and longitudinal cognitive change between concussion and control groups. The fixed effects of the model included concussion/control groups (control group as a reference group), time (follow up time since the first cognitive assessment), age at first visit, first visit age squared, education, and interactions of time with group, age at first visit and education. Random effects included intercept and time with unstructured covariance. Age at first visit and education were mean centered. Analyses were performed in SAS 9.4 (Cary, NC). A significance level of p 0.05, uncorrected was used for the analyses.

2.6. Data availability

Data from the BLSA are available on request by proposal submission through the BLSA website (blsa.nih.gov). All requests are reviewed by the BLSA Data Sharing Proposal Review Committee and are also subject to approval from the NIH Institutional Review Board.

3. Results

3.1. MRI

Table 2 summarizes the regional brain volume differences between groups. In comparison to controls, the concussion group had smaller volumes of the temporal white matter and hippocampus at first imaging visit as well as larger ventricular volume. These differences remained stable over the follow-up visits (Fig. 2). There were no significant differences in

the rate of change between groups during longitudinal follow-up. In the sensitivity analyses, restricting the participants to those with only 1 concussion did not change the results.

3.2. DTI

Table 3 summarizes the DTI white matter microstructural differences between groups. In comparison to controls, the concussion group showed higher RD in the fornix/stria terminalis, and higher AD in the superior longitudinal fasciculus and anterior corona radiata at first DTI visit. These differences remained stable over the follow-up years. There were no significant differences in the rate of change between groups during longitudinal follow-up. In the sensitivity analyses, restricting the participants to those with only 1 concussion did not change the AD results, but the greater RD seen in the fornix was no longer significant (β=<0.001, t = 1.78, p = 0.078).

3.3. ^{15}O-water PET

Table 4 summarizes ^{15}O rCBF differences between groups. We examined differences in frontal and temporal regions of the brain at first ^{15}O visit. In comparison to controls, the concussion group showed lower rCBF in the left superior frontal gyrus (Brodmann Area 9). We also observed higher rCBF in the right middle frontal gyrus (BA 44), left orbitofrontal cortex (BA 47), right middle temporal gyrus (BA 20/21), left middle temporal gyrus (22) and right precentral gyrus (BA 4) (Fig. 3). All regions showed stable differences over time except for the left superior frontal gyrus (BA 9) and left orbitofrontal cortex (BA 47), which reached the levels of the controls by the last visit.

We also found differences in the rate of change over time, predominately in frontal and temporal lobes, including limbic regions (Fig. 3). Compared to controls, increases in rCBF were steeper in the concussion group in the left (BA 45) and right (BA 44) inferior frontal gyrus, right superior frontal gyrus (BA 10/11), right middle temporal gyrus (BA 21), right temporal pole (BA 20), right hippocampus, and the right anterior and posterior insula. Decline in rCBF was also steeper in the concussion group in the left lingual gyrus (BA 19), left superior temporal gyrus (BA 22), left anterior (BA 32) and right posterior (BA 30) cingulate, andleft fusiform gyrus (BA 37).

3.4. Cognition

Differences in memory, attention, executive function, language and visuospatial abilities were also examined between the concussion and control groups. There were no significant differences between the groups regarding neuropsychological performance in any of the 5 cognitive domains at first imaging visit or longitudinal follow-up.

4. Discussion

The long-term effects of concussions on the aging brain are poorly understood. The present study provides insight into these long-term consequences by examining differences in neuroimaging measures and cognitive performance over time. Approximately 20 years after a concussive event, we observed differences in brain volume, white matter microstructure, and brain activity relative to those with no history of concussion. A prior concussion was

associated with differences between groups in both temporal and frontal regions of the brain, including the hippocampus, orbitofrontal cortex and cingulate cortex limbic regions. Despite these group differences in brain structure and function, we found no concussion-associated group differences in cognitive performance. Together, these results suggest that concussions result in long-term functional and structural alterations in the brain, but these differences did not significantly impact cognitive performance in our sample.

We observed differences in brain volume in those who had sustained a concussion compared to controls when assessed at the first imaging visit. We found that those with a prior concussion had greater ventricular volume, as well as smaller volume of the temporal white matter and the hippocampus. Previous studies have reported similar findings, including differences in ventricular and temporal volume cross-sectionally up to 5 years post-injury (Koerte et al., 2016; Tremblay et al., 2013). Our study suggests that the brain atrophy can continue to be observed an average of 20 years after the concussive event, and these atrophic changes remain stable beyond that time. Furthermore, although hippocampal atrophy has commonly been observed in more moderate to severe traumatic brain injury (Bigler et al., 1997), our results suggest that hippocampal atrophy also is associated with in mild TBI when examined over a much longer timescale.

We next examined differences in white matter microstructure in those with a concussion compared to controls. Those with a prior concussion had greater radial diffusivity in the fornix/stria terminalis. We also observed greater axial diffusivity in the anterior corona radiata and superior longitudinal fasciculus. These differences observed at first imaging visit remained constant throughout the follow-up interval. While the diffusivity findings are often variable across studies, the specific regions affected in our study are well-documented.

Due to its sensitivity, DTI can detect alterations in white matter microstructure and within days of a concussive event (Bazarian et al., 2007, 2012; Murugavel et al., 2014; Yin et al., 2019). Studies have also examined similar alterations occurring up to 2 years after a concussion (Kinnunen et al., 2011; Mayer et al., 2010; Murugavel et al., 2014), suggesting that some white matter regions may be affected at an early stage after a concussive event, as well as long after the injury. Overall, our results suggest that those with a prior concussion may have impaired white matter microstructure, as shown by higher radial diffusivity, in comparison to the normal age-related microstructural damage seen in the controls (Bender and Raz, 2015). Although the differences in axial diffusivity were not in the direction hypothesized, others have reported a similar elevation in chronic TBI (Kinnunen et al., 2011), where the increase in axial diffusivity was positively correlated with time since traumatic brain injury. The pathological significance of the rise in axial diffusivity remains unclear, though it is speculated to be due to normalization, or axonal recovery, following a decrease in diffusivity seen in the acute stages of brain injury (Kinnunen et al., 2011).

In addition, we examined differences in brain activity measured with regional cerebral blood flow at rest in those with a prior concussion compared to controls. At first imaging visit, those with a prior concussion had lower relative brain activity in the superior frontal gyrus. We observed greater relative activity at first imaging visit, predominantly right hemisphere dominant, in temporal and frontal regions. We also examined greater activity in the left

middle temporal gyrus and left orbitofrontal cortex. These regions observed at the first imaging visit showed consistent differences over time except for the left superior frontal gyrus (BA 9) and left orbitofrontal cortex (BA 47), which reached the levels of the control group over the follow-up interval. Longitudinally, significant rates of decline in rCBF extended to regions in left hemisphere of the brain including the fusiform gyrus and areas of the cingulate cortex. Increases in rCBF were steeper in those with a prior concussion, predominantly in the right hemisphere, in temporal regions including the hippocampus, as well as frontal gyri.

PET scanning has been used to observe brain metabolism and activity in acute stages of brain injury (Churchill et al., 2017b) and chronic stages of brain injury, with changes in brain activity seen between 1 week and 5 years (Gross et al., 1996; Peskind et al., 2011). These previous studies have also observed differences in temporal and frontal regions gions of the brain including the cingulate and hippocampus. Although the majority of PET studies observe hypometabolism following brain injury, especially in those with poorer clinical outcomes (Gross et al., 1996; Peskind et al., 2011; Ruff et al., 1994), studies focusing on brain activity during the chronic stages of injury find both increased and decreased activity levels in frontal and temporal regions (Gross et al., 1996) which support the current findings.

Although we found brain alterations in our concussion group, our sample maintained normal cognitive performance. One reason may be related to the extent and severity of the alterations. While we examine changes on average more than 20 years after a concussion, our sample may not have reached the critical stage of pathologic change where functional outcomes are affected. It may also be that the preservation of cognitive performance in this study is related to our rCBF findings, in that some of these differences may be a compensational rather than detrimental. For instance, previous PET studies have shown that individuals with hypometabolism in temporal, frontal and parietal regions can have persistent concussive symptoms and poor cognitive outcomes (Gross et al., 1996; Peskind et al., 2011; Provenzano et al., 2010), therefore, the rCBF increase seen in these regions may counter these effects. Because our concussion sample maintains normal cognitive performance, it may be that the alterations in brain activity support cognitive function in the face of structural damage. However, without a sufficiently large cognitively impaired group for comparison, further investigation is needed to understand the possible compensational effects in this cohort.

While our study provides further evidence of long-term consequences that often mimic the acute and chronic phases of concussion, our results also somewhat support the regional specificity of neurodegeneration seen in Chronic Traumatic Encephalopathy and Alzheimer's Disease. Chronic Traumatic Encephalopathy has been classified by its progression of tau, which begins in temporal and frontal regions of the brain (McKee et al., 2013). In the later stages of Chronic Traumatic Encephalopathy, extensive atrophy is seen in medial temporal and frontal lobes. In contrast, brain atrophy can be seen in the early and preclinical stages of Alzheimer's Disease, predominately in temporal regions of the brain, including the hippocampus (Frisoni et al., 2010). Our results suggest that there may be selective vulnerability of temporal and frontal lobe regions following a concussion, however we did not observe significant atrophy of temporal lobe gray matter commonly seen in

Chronic Traumatic Encephalopathy, but did observe atrophy of the hippocampus and temporal lobe white matter. The lack of cognitive differences between the groups at present also suggests that further follow-up is needed to fully assess the effects of these findings on future cognitive trajectories and rate of dementia onset in this group.

The results of this study should be considered with several limitations. First, our sample includes classification of concussion based on self-reported history, allowing for the potential of moderate TBI to be included. Our inclusion criteria attempted to minimize moderate TBI by following the CDC (Center for Disease Control and Prevention) criterion for mild traumatic brain injury and excluding any participant with known loss of consciousness exceeding 30 min (Carroll et al., 2004). There were also participants in the concussion group who went on to develop cognitive impairment ($n = 7$). However, due to the small sample size, we were unable to perform a separate assessment of this group alone. Future studies with a larger sample size could provide additional information regarding the role of concussion and the onset of age-related cognitive decline. Additionally, as this is an exploratory study with a relatively small sample size, the analyses also used uncorrected statistical thresholds. In sensitivity analyses, these results did not withstand FDR correction. Although the limited statistical power in this sample should certainly be taken into consideration, these preliminary results provide targets for future studies with larger subject numbers, allowing for more hypothesis driven assessment of the long-term effects of concussion on the brain. Finally, the BLSA cohort is highly educated and mostly Caucasian, thus limiting generalizability to the general population. However, the BLSA provides a considerable amount of cognitive testing and neuroimaging data allowing us to consider these changes longitudinally.

Our study provides evidence that a concussion is not a transient brain injury, but rather has long lasting consequences on the aging brain. These consequences include long-term structural degeneration and functional abnormalities in temporal and frontal regions of the brain, including regions within the limbic system. Because most of the differences observed between the concussed and non-concussed groups were seen at the first imaging visit with few differences seen during continued longitudinal follow-up, these results also suggest that advancing age may not necessarily compound the effects of concussion. Nevertheless, because of the involvement of frontal and temporal brain regions, and the susceptibility of these areas to pathologic change with advancing age, the heightened degeneration and functional abnormalities seen at first visit may make these individuals more vulnerable to dysfunction in the future. We will continue to follow these participants to further investigate the incidence of age-related neurodegenerative diseases in this sample.

Acknowledgments

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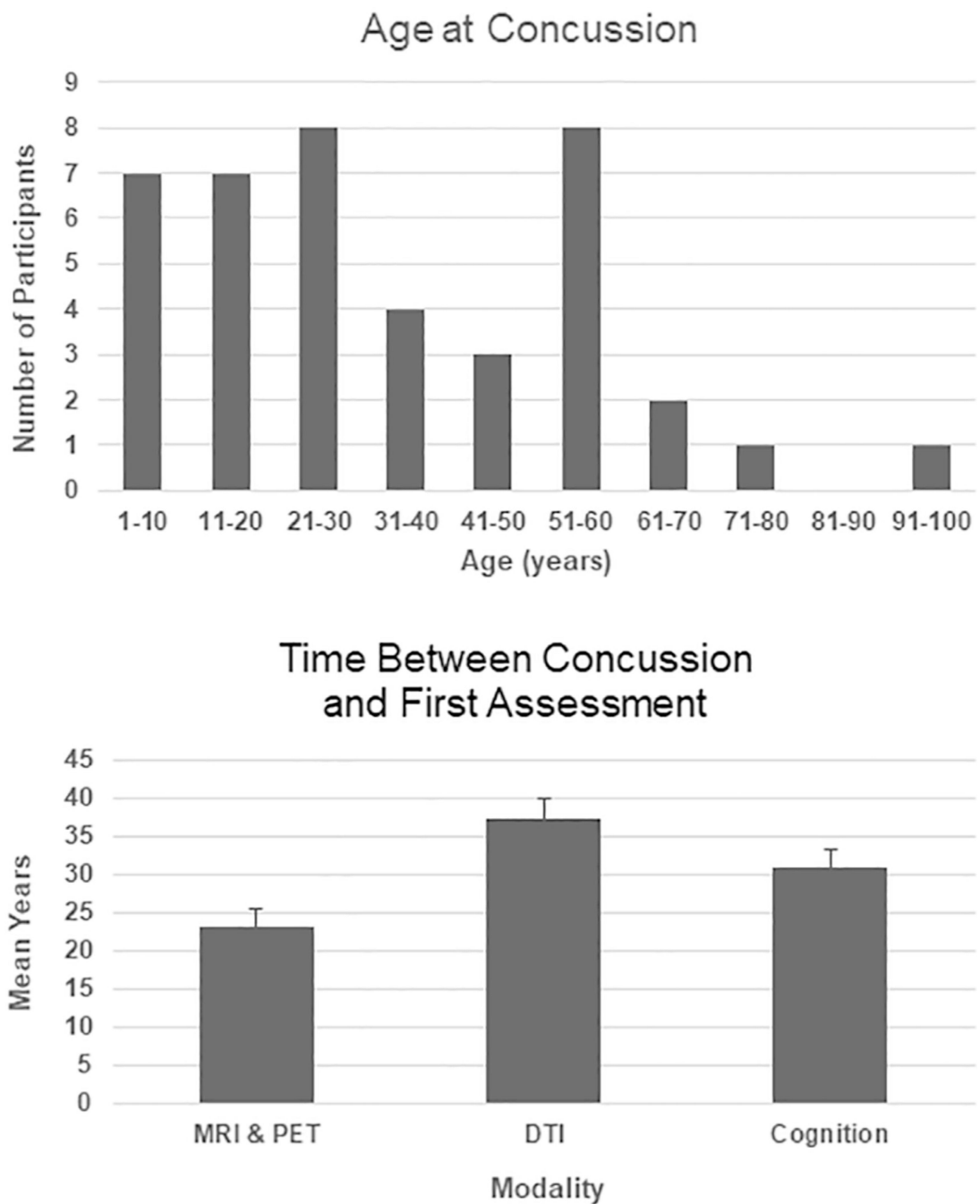
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Fig. 1.

Age at concussion.

The top graph shows the age distribution is shown for the 40 participants who reported age at concussive event. The bottom graph shows the average time between concussion and the first assessment for each modality examined in the study.

Fig. 2.
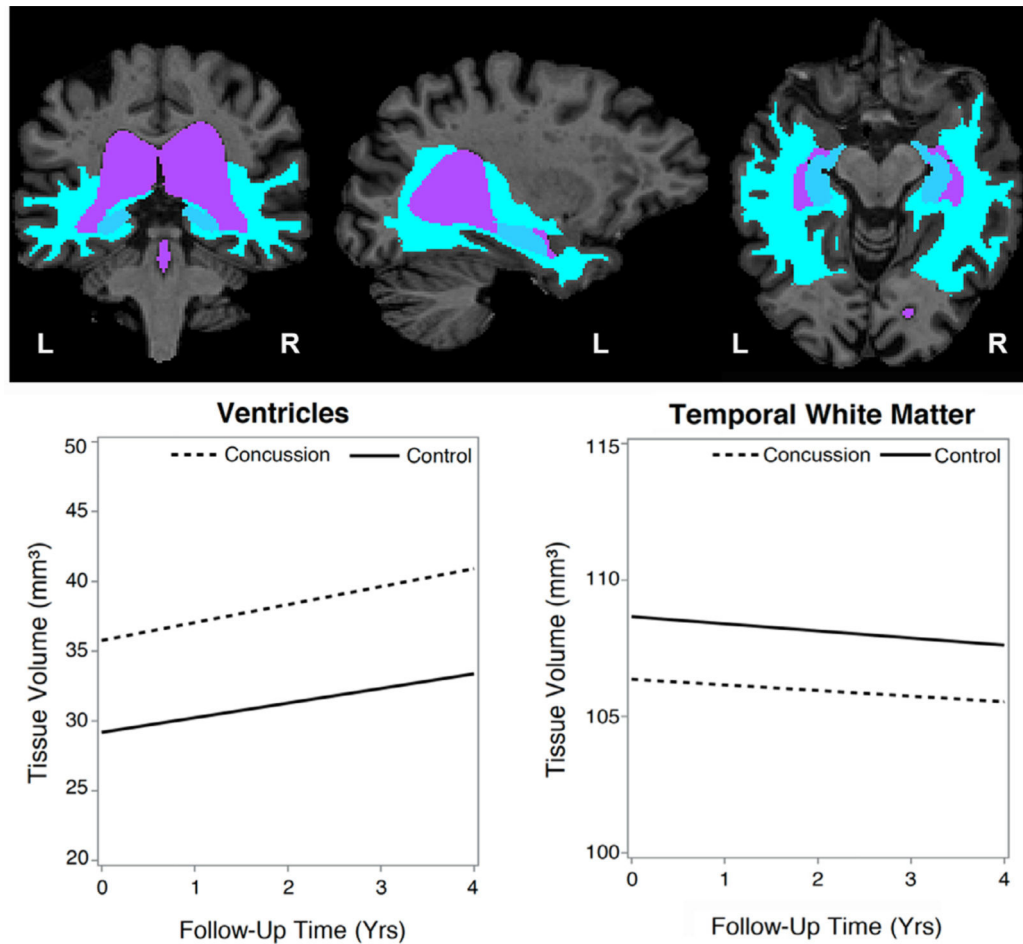Concussion and brain volume.

Regions where brain volume differences are seen in the concussion group relative to the control group at first imaging visit ($p<0.05$). Larger brain volume is indicated in purple, and smaller in blue. As illustrated in the graphs, differences observed at first imaging visit remained stable when examining the slope of longitudinal volume change in these regions.
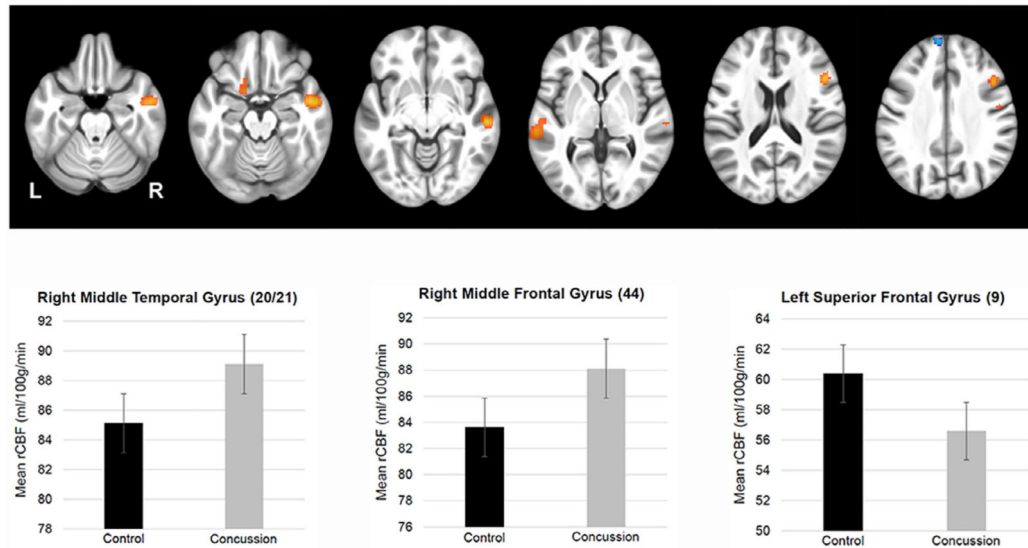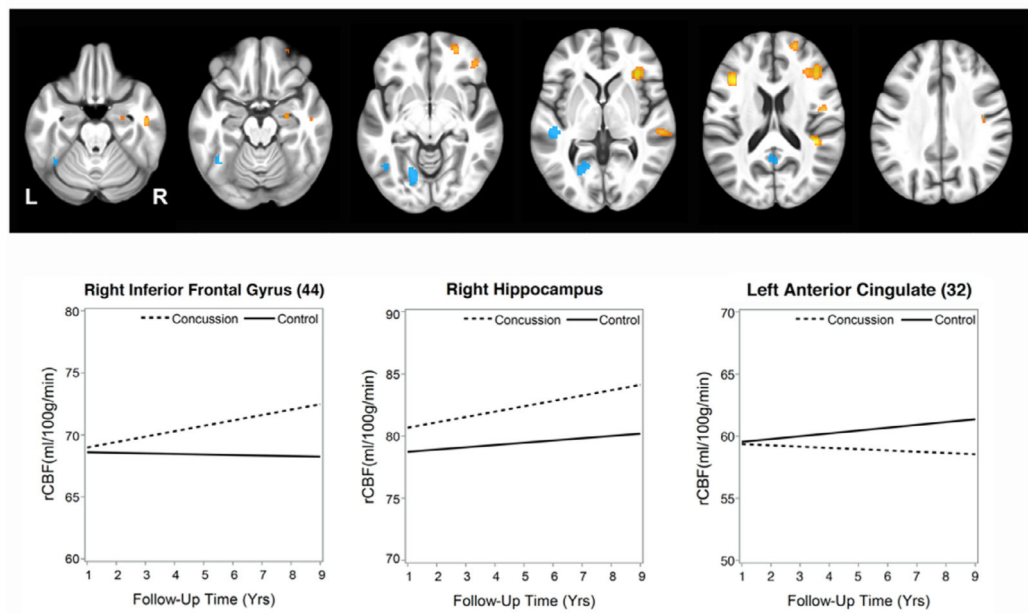
Fig. 3.
Regional differences in brain activity.

Regions where differences in brain activity are seen in the concussion group relative to the control group as measured by rCBF ($p < 0.005$, 50 voxels). **A)** Axial slices beginning at the base of the brain and moving upward illustrate regional differences in brain activity at the first imaging visit. Lower activity is indicated in blue and higher activity is indicated in orange. Graphs illustrate group differences in regional CBF. **B)** Differences in rCBF rate of change over an average of 6.33years. Decreased activity over time is indicated in blue and

increased activity is indicated in orange. Graphs illustrate the longitudinal slope of rCBF change in these regions.

Table 1

Participant demographics.

	CONTROL	CONCUSSION
PARTICIPANT POOL (n)	**150**	**51**
Age at first imaging visit (yrs), mean (SD)	66.64 (10.97)	65.14 (11.23)
Male, n (%)	90 (60)	29 (56.9)
White, n (%)	131 (87.3)	44 (86.3)
Age at first concussion (yrs), mean (SD)	...	33.05 (22.25)
MRI SAMPLE (n)	**102**	**51**
Age at first imaging visit (yrs), mean (SD)	65.2 (11.25)	65.14 (11.23)
Male, n (%)	58 (56.9)	29 (56.9)
White, n (%)	88 (86.3)	44 (86.3)
Longitudinal MRI (%)	63 (61.8)	37 (72.6)
Follow-up duration (yrs), mean (SD)	4.45 (5.78)	5.17 (6.14)
No. Visits, mean (SD)	3.85 (4.07)	4.1 (4.25)
DTI SAMPLE (n)	**76**	**40**
Age at first imaging visit (yrs), mean (SD)	65.63 (12.37)	64.45 (12.125)
Male, n (%)	40 (52.6)	20 (60)
White, n (%)	64 (84.2)	34 (85)
Longitudinal DTI (%)	51 (67)	28 (70)
Follow-up duration (yrs), mean (SD)	2.54 (2.20)	2.92 (2.22)
No. Visits, mean (SD)	2.30 (1.47)	2.15 (1.05)
^{15}O SAMPLE (n)	**30**	**15**
Age at first imaging visit (yrs), mean (SD)	67.64 (7.00)	66.92 (7.47)
Male, n (%)	20 (67)	10 (67)
White, n (%)	28 (93.3)	14 (93.3)
Longitudinal ^{15}O (%)	29 (96.6)	12 (80)
Follow-up duration (yrs), mean (SD)	6.77 (2.25)	6.33 (2.19)
No. Visits, mean (SD)	7.27 (2.27)	5.93 (3.13)
COGNITION SAMPLE	102	51
Age at first imaging visit (yrs), mean (SD)	66.67 (10.89)	60.08 (9.43)
Male, n (%)	58 (56.9)	29 (56.9)
White, n (%)	88 (86.3)	44 (86.3)
Longitudinal Cognition (%)	88 (86.3)	46 (90.2)
Follow-up duration (yrs), mean (SD)	9.44 (6.62)	11.62 (7.41)
No. Visits, mean (SD)	6.08 (4.98)	7.04 (5.25)

Table 2

Effects of concussion on brain volume.

Region	β	SE	t-value	p-value
Group Differences at First Imaging Visit				
Ventricles	6.58	2.69	2.45	0.016
Temporal White Matter	−2.29	0.95	−2.42	0.017
Hippocampus	−0.30	0.12	−2.53	0.013

Effects of Concussion on Brain Volume. Significant differences in brain volume (mm3) between the concussion and control groups at first imaging visit.

Table 3

Effects of concussion on white matter microstructure.

Region	Measure	β	SE	t-value	p-value
Group Differences at First Imaging Visit					
Fornix/Stria terminalis	RD	3.75e-05	1.79e-05	2.09	0.039[*]
Superior longitudinal fasciculus	AD	1.68e-05	8.37e-06	2.00	0.048
Anterior corona radiata	AD	3.07e-05	1.27e-05	2.43	0.017

Effects of Concussion on White Matter Microstructure. Significant differences in white matter measures between the concussion and control groups at first imaging visit. Axial diffusivity (AD) and radial diffusivity (RD) measures were different between the groups.

[*] No longer significant if participants with more than one concussion are excluded from the analysis.

Table 4

Effects of concussion on brain activity.

Region	Side	Coordinate x	y	z	p value	voxels
Lower Activity at First Imaging Visit (Conc < Ctl)						
Superior Frontal Gyrus (9)	L	−6	60	30	<0.001	89
Higher Activity at First Imaging Visit (Conc > Ctl)						
Orbitofrontal Cortex (47)	L	−16	10	−16	0.001	110
Mid Frontal Gyrus (44)	R	48	18	26	<0.001	273
Precentral Gyrus (4)	R	52	−10	38	0.001	85
Mid Temporal Gyrus (21)	R	50	−2	−18	<0.001	280
Mid Temporal Gyrus (20/21)	R	58	−22	−6	<0.001	200
Middle Temporal Gyrus (22)	L	−62	−32	4	<0.001	255
Decreased Activity Over Time (Conc < Ctl)						
Anterior Cingulate (32)	L	−18	32	24	<0.001	60
Posterior Cingulate (30)	R	2	−56	14	0.001	132
Superior Temporal Gyrus (22)	L	−48	−30	2	<0.001	163
Fusiform Gyrus (37)	L	−42	−60	−10	0.001	106
Lingual Gyrus (19)	L	−20	−62	6	<0.001	416
Increased Activity Over Time (Conc > Ctl)						
Superior Frontal Gyrus (10)	R	20	56	22	<0.001	124
Superior Frontal Gyrus (11)	R	26	54	−10	0.001	96
Inferior Frontal Gyrus (44)	R	34	28	2	<0.001	603
Inferior Frontal Gyrus (45)	L	−40	24	16	<0.001	161
Anterior Insula	R	48	−4	14	<0.001	181
Posterior Insula	R	40	−36	18	<0.001	95
Middle Temporal Gyrus (21)	R	60	−30	−2	<0.001	113
Temporal Pole (20)	R	54	−26	−32	<0.001	152
Temporal Pole (20)	R	50	−12	−24	0.001	78
Hippocampus	R	26	−12	−12	0.001	55

Effects of Concussion on Brain Activity. Differences in resting state regional cerebral blood flow (rCBF) between the concussion and control groups at first imaging visit and longitudinal follow-up over an average of 6.33 years. Stereotaxic coordinates are listed, Brodmann Areas (BA) are indicated in parentheses.