Concussion Related to White Matter Abnormalities and Cognitive Dysfunction in Aging Athletes

The incidence and consequences of concussion among athletes have come under intense scrutiny in the setting of the untimely deaths of several notable professional athletes. Brain injury in its most severe forms has been exhaustively studied, but we have only begun to scratch the surface of our understanding of milder injuries. Historically, these types of injuries have been difficult to study because patients did not frequently come to medical attention and there were no meaningful imaging correlates that confirmed the diagnosis. The acute and subacute side effects of concussion in young athletes include cognitive and psychiatric disorders, and concussive injuries have been linked to pathological findings of the white matter of the brain associated with aging and neurodegenerative conditions. Recently, advanced magnetic resonance imaging techniques like diffusion tensor imaging (DTI) have been used to detect white matter abnormalities after concussive injuries. Tremblay et al[1] used these techniques to explore one of the more vexing questions in concussion research: What are the long-term consequences in older individuals with a history of concussion?

To examine for even the subtlest of abnormalities, the investigators recruited 15 clinically normal, former university-level football and hockey players with a mean age of 60 who had a history of sports-related concussion. None of these individuals had other meaningful medical or psychiatric problems, and they had suffered

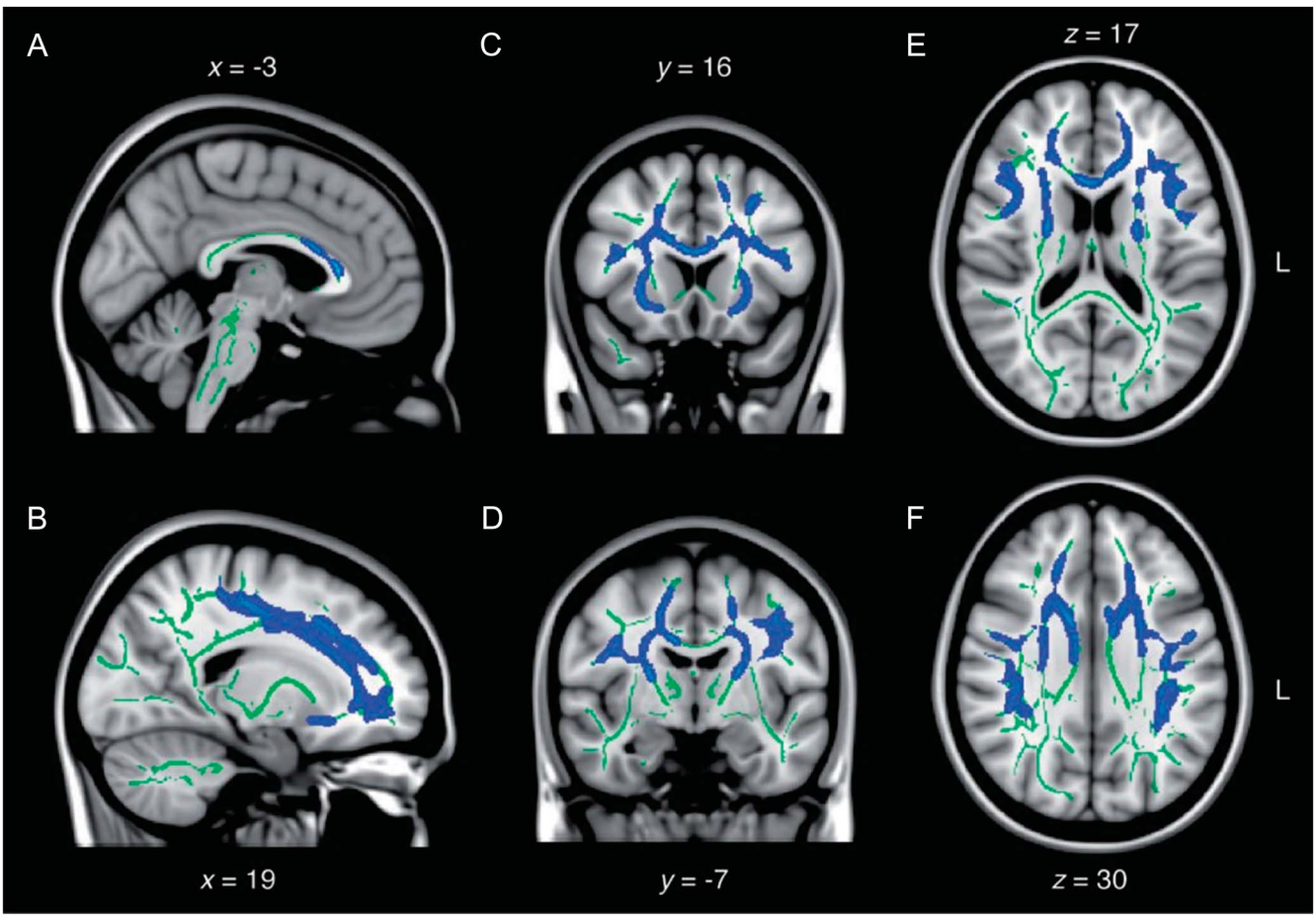

*Figure. Diffuse increase in mean diffusivity after remote concussions. Sagittal (**A** and **B**), coronal (**C** and **D**), and axial (**E** and **F**) slices of the tract-based spatial statistics group contrast on mean diffusivity maps (controls vs concussed in blue). The contrasts are overlaid on the mean fractional anisotropy skeleton (in green) and the standard MNI152 T_1 1-mm brain template. The results are thresholded at* $P \geq .05$*, corrected for multiple comparisons. Reprinted with permission from Oxford University Press: Tremblay S, Henry LC, Bedetti C, et al. Diffuse white matter tract abnormalities in clinically normal ageing retired athletes with a history of sports-related concussions. Brain. 2014;137:(11) 2997-3011.*

a mean of 2 sports-related concussions in their youth. These individuals were compared with a control cohort of athletes with similar ages and educational levels who had never sustained a concussion. Each individual was administered an exhaustive neuropsychological test battery to identify neurocognitive dysfunction. Patients then underwent magnetic resonance imaging examinations, including DTI, determinations of fractional anisotropy, and mean, radial, and axial diffusivity. Using these data, the authors carried out a novel computational technique called tract-based spatial statistics. This technique allows the correlation between white matter integrity metrics and neurocognitive measurements via the performance of statistics on every voxel from a 3-dimensional network of coregistered fiber tracts from every study participant.

What these authors discovered is concerning but not shocking. Neuropsychological testing revealed that the cohort of retired athletes, many years removed from their concussions, demonstrated cognitive dysfunction in the domains of memory and executive functioning compared with the control subjects. It is notable that this is a population of individuals having suffered only a mean of 2 known concussions as discerned by a standardized concussion questionnaire. Conventional magnetic resonance imaging identified typical alterations in the brain tissue usually associated with aging and did not reveal significant differences between groups. Structural imaging analysis revealed that the older concussed athletes demonstrated significantly enlarged lateral ventricles compared with control subjects. This was statistically correlated with delayed recall and recognition testing. There were no meaningful differences in gray matter between the 2 cohorts. However, this was not the case for white matter. Tract-based spatial statistics identified widespread abnormalities in the aging, previously concussed brains compared with the controls (Figure). Numerous areas of the brain, including the interhemispheric fibers of the corpus callosum, the anterior limb of the internal capsule, the corona radiate involving the corticospinal tracts, and the superior and inferior longitudinal fasciculi, all demonstrated DTI evidence of damage. A regression analysis was performed to correlate these findings with the abnormal results of the neuropsychological testing batteries. Importantly, extensive correlations were identified. For example, dysfunction of visual episodic memory function correlated with abnormal DTI metrics and predicted delayed recall on the Taylor Complex Figure Test. Disruption of the anterior body and genu of the corpus callosum was associated with disturbances in episodic memory. Injury to left hemispheric tracts was associated with dysfunction in sequential motor learning in the contralateral hand. No similar structure-function relationships were identified in the control cohort.

As the authors indicate, this is the first study of its kind to demonstrate persistent white matter abnormalities in clinically normal, aged, retired athletes. This research has profound implications for the worlds of amateur and professional athletics. First, although a questionnaire administered years after an injury has the potential to underestimate the incidence of concussions, the low incidence in the concussed cohort suggests that even a single concussion can lead to lifelong consequences and may work in concert with the negative effects of normal aging on cognitive function. Moreover, sequelae of such injuries is now detectable on both imaging and neurocognitive testing. Such knowledge calls into question any participation in sports in which concussion is common. Now that we are identifying these structure-function relationships in concussed athletes, what will the culpability be of athletic organizing bodies and professional leagues for the consequences of these injuries going forward? Previously, there was deniability for these matters. Demonstration of the power of DTI techniques to uncover white matter injuries begs the question as to when such techniques will be applied on a routine clinical basis for athletes. Data such as these are already affecting the billion-dollar sports industry and will change the current sports landscape as we know it from the youth level to the professional level.

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REFERENCE

1. Tremblay S, Henry LC, Bedetti C, et al. Diffuse white matter tract abnormalities in clinically normal ageing retired athletes with a history of sports-related concussions. *Brain*. 2014;137(pt 11):2997-3011.

Inherent Limitations of Tractography for Accurate Connectivity Maps

The injection of viral tracers to map the axonal connections of the brain is a gold standard in neuroscience research but cannot be applied in humans. Thus, since the advent of diffusion-weighted magnetic resonance imaging (DWI),[1,2] massive efforts have been undertaken to produce maps of the connectional neuroanatomy of the human brain using this imaging technology. Since its introduction in the 1980s, DWI has gained utility in a number of clinical settings. Despite the leaps this technology has taken over the years, its exact relationship to actual physical connections in the brain is still not clear. Nonetheless, DWI is now one of the cornerstone modalities used in the ambitious 5-year collaborative Human Connectome Project to create a map of human brain connectivity.[3]

Thomas and colleagues[4] recently challenged the assumption underlying many recent initiatives for mapping structural brain connectivity from DWI data that high-resolution image data and sophisticated diffusion modeling approaches will result in anatomically accurate maps of white matter connections. They began by imaging an ex vivo rhesus monkey brain with a 7-T scanner. This paradigm allowed the acquisition of imaging data free from artifacts caused by cardiac pulsation and patient motion that typically reduce the quality of data acquired from subjects in vivo. The data were then processed by implementing a battery of tractography algorithms that represent the current state of the art in the technology (DTI, Q-ball, constrained spherical, and ball and stick) under a wide range of parameters. The results were then compared with the connectivity defined by a well-known atlas based on anterograde axonal tracer results from a series of rhesus monkeys (Figure).

The clear trend encountered across all tractography methods was that, as the sensitivity for detecting true anatomic connections increased, the specificity decreased, specifically as a function of increasing the angular threshold, the maximum bending angle allowed for a tract trajectory. Maneuvers to reach the ideal tradeoff point between sensitivity and specificity were highly variable across the combination of parameters used and the different pathways being traced. Even after allowances were made for the potential increased false-positive rate encountered by the use of an anterograde-only axonal tracer atlas, tractography still demonstrated suboptimal anatomic accuracy.

Clinically, tractography has a potential role in the diagnosis and treatment of traumatic brain injury[5] and is increasingly used in tumor resection planning, although even these uses have not been fully validated. The comparison with anatomic tracing results in rhesus monkeys provided by Thomas et al[4] is a key contribution that highlights the inherent limitations of DWI for mapping human brain connectivity. One potential source for improving our understanding of the relationship between tractography and