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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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

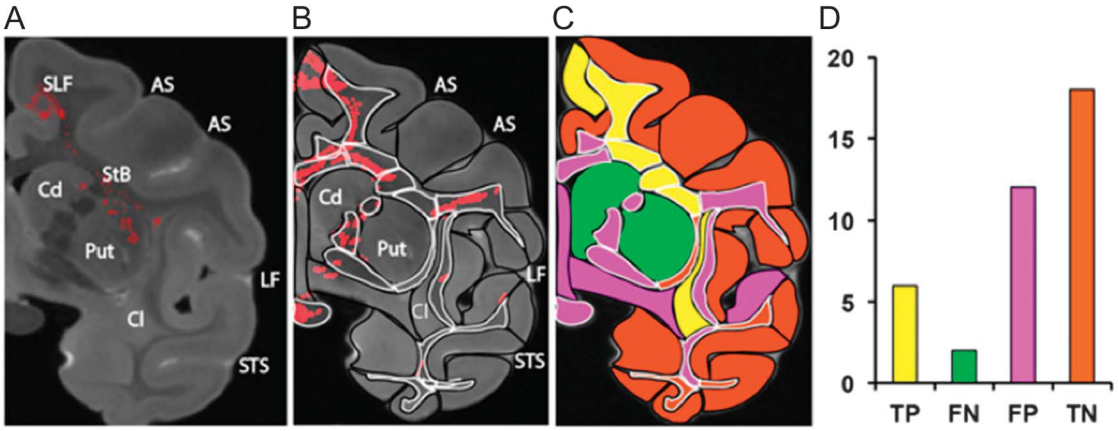

Figure. Representative illustration of the procedure used for assessing the anatomic accuracy of various diffusion tractography approaches. **A**, *the red dots indicate the topography of axonal pathways after the injection of an anterograde tracer in the left PCG.* **B**, *for each diffusion-weighted imaging slice that was anatomically matched with the histology slice from the reference atlas, the gray matter (black lines) and white matter (white lines) regions were manually segmented and parcellated into discrete regions of interest. The red dots in* **B** *represent the location of axonal pathways as determined with the Q-ball tractography method based on the left PCG as the seed region and an angular threshold of 80°.* **C**, *agreement between tracer and tractography results was computed for each slice. The colors indicate regions of interest that were categorized as true positive (TP), false negative (FN), false positive (FP), and true negative (TN).* **D**, *histogram showing the TP, FN, FP, and TN for the specific slice.* From Thomas et al.[4]

anatomy is the combined use of magnetic diffusion histology and microtractography to reveal mesoscale features of human brain.[6] The spatial resolution used in this technique is orders of magnitude more than that in DTI, allowing the disentangling of connections that might have been grouped together in a single window with DTI. In the meantime, it is important to recognize the subjective nature of tractography results, especially at the resolution required for addressing fundamental questions in neuroscience.

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Progesterone Is Not Effective in the Treatment of Traumatic Brain Injury

Read the introduction of any given traumatic brain injury (TBI) study, and the staggering impact of the condition will be clear. The statistics paint a bleak picture of the effect of TBI on individuals, families, and society as a whole. Neurosurgeons and neurologists are intimately familiar with the effects of TBI, and many have dedicated their careers to improving outcomes. One principal goal of this research has been to identify a pharmacological intervention that will mitigate the effects of TBI. Thus far, a multitude of compounds and studies have failed. Early animal studies using progesterone, however, have demonstrated a neuroprotective effect. Translation to humans showed improved outcomes in phase I and II trials in progesterone-treated acute TBI patients, but unfortunately, the phase III trial produced negative results.

The Neurologic Emergencies Treatment Trials (NETT) Group has recently published in *The New England Journal of Medicine* a multicenter, double-blind, placebo-controlled phase III trial titled "Very Early Administration of Progesterone for Acute Traumatic Brain Injury," which did not show an improvement in TBI outcome after treatment with progesterone compared with placebo.[1] Also known as the Progesterone for the Treatment of Traumatic Brain Injury (PROTECT III), the trial was conducted at 49 trauma centers in the United States. The study enrolled adult patients with a Glasgow Coma Scale (GCS) score of 4 to 12. Exclusion criteria included a nonsurvivable injury; bilateral dilated, unresponsive pupils; the need for cardiopulmonary resuscitation or physiological findings of hypoxemia, hypotension, active myocardial infarction, ischemic stroke, pulmonary embolism, deep vein thrombosis, spinal cord injury, or status epilepticus; pregnancy; status as a prisoner or ward of the state; severe intoxication (ethanol level, >249 mg/dL); history of reproductive cancer; allergy to progesterone or a fat-emulsion vehicle; and a blood-clotting disorder.

Patients were randomly assigned to either the progesterone group or the placebo group. In both groups, the TBI was managed according to standardized protocols, and adherence to these protocols was monitored on a daily basis in all centers. The progesterone group received an initial loading dose (progesterone 0.05 mg/kg body weight), a maintenance dose (14.3 mL/h for 1 hour, then 10 mL/h for 71 hours), and a tapering dose (tapered by 2.5 mL every 8 hours). This resulted in a total treatment duration of 96 hours, and treatment was initiated within 4 hours of injury. The primary outcome was functional recovery determined by the Extended Glasgow