EDITORIAL

Uncovering Subclinical Neural Alterations in Sport-Related Concussion

The Added Value of Longitudinal Neuroimaging

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It is now widely admitted that mild traumatic brain injury, or concussion, represents an important societal burden, and it is, therefore, crucial to strengthen our efforts to enhance its diagnosis and management. This is especially true in the context of sport-related concussion (SRC), which primarily affects children and young adults and can lead to persisting symptoms potentially affecting cognitive, emotional, and somatic domains. Important initiatives toward detection and management of SRC shaped the field over the past decades, including the International Consensus of Concussion in Sport, which led to the development of standardized detection tools (e.g., SCAT6[1] and return to learn and sport protocols[2]). However, these tools are highly dependent on the athletes' subjective reports and clinical examination, which has been a controversial approach and continues to pose daily challenges for team physicians because it can lead to underreporting and unsafe return-to-play decisions.[3] Validating objective metrics to guide clinical decisions surrounding removal from and return to play (RTP) is of special importance. In this issue of *Neurology*®, Churchill et al. [4] report a prospective longitudinal study in a cohort of concussed athletes and noninjured controls, using complementary MRI metrics, assessing microstructural white matter and perfusion changes by means of diffusion tensor imaging and cerebral blood flow (CBF), at baseline, time of injury, RTP, 1–3 months, and 1-year follow-up. The study's strength lies in its longitudinal and prospective design, which includes a control group of non–brain-injured athletes scanned at 2 time points. This design enables to (1) disentangle brain alterations due to the concussion from possible physiological neural changes throughout the sport season and (2) address the issue of individual baseline differences.

The authors observed that the athletes who experienced a concussion exhibited increased white matter mean diffusivity (MD), reduced fractional anisotropy (FA), and decreased CBF. However, when compared with matched controls (i.e., injury-free athletes), the most sensitive MRI marker was the alteration in CBF, which demonstrated a statistically significant difference from baseline, beyond the range of "natural" variability. By contrast, longitudinal changes in MD and FA observed in SRC did not significantly differ from those observed in the control group, which underscores the importance of longitudinal study designs with baseline assessments. In addition, the authors found a significant correlation between CBF alterations (abnormally elevated perfusion in medial temporal regions) and time to RTP. Altered CBF reveals microvascular injury and has been associated with impaired neural function that could contribute to the neurometabolic cascade of concussion.[5] Such alterations are undetectable with standard medical assessment where clearance for RTP is given. Notably, this study highlights an apparent—and concerning—mismatch between the absence of clinical symptoms of concussion (e.g., physical, psychological or cognitive impairments) at RTP (similar to baseline) and the MRI findings. The latter revealed a significant decrease in CBF not only at return to play but also 1–3 months later and at 1-year follow-up (i.e., symptoms-free). This finding points out that (neuro)physiological recovery persists longer than clinical recovery after concussion, stressing the need to develop objective tools to detect subclinical neural alterations.[6] Therefore, altered CBF could be used to complement concussion assessments, but its access (MRI) is limited and expensive, preventing its clinical translation. In this context, advanced electrophysiology technologies (such as transcranial

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magnetic stimulation and electroencephalography) represent an alternative of choice for the diagnosis and prognosis of concussion.[6]

One limitation of this study is that it based its group categorization on clinically diagnosed concussion only, ignoring the potential influence of subconcussive impacts, which are especially important in contact sports. Subconcussive head impacts do not lead to clinical signs and symptoms of concussion, but their repetition can affect brain functioning, as demonstrated by decreased motor control or memory performance.[7] A recent study underlined the relationship between higher head impact exposure and decreased primary motor cortex excitability measured through transcranial magnetic stimulation, in football athletes.[8] This further emphasizes the importance of detecting subclinical brain alterations in athletes to better promote safety and health in sport. Besides such neurophysiological tools, evaluating subtle cognitive-motor changes could represent a valuable avenue to overcome the abovementioned limitations. For example, motor learning, which reflects synaptic plasticity supported by excitatory and inhibitory mechanisms, has been shown to be altered in patients and athletes after concussion compared with healthy controls, outlasting the recovery of other cognitive functions.[9]

In conclusion, in their well-designed longitudinal controlled study, Churchill et al. described the short-term and long-term neural alterations of athletes who had suffered from a concussion compared with baseline and a group of noninjured athletes. They highlighted the sensitivity of CBF to detect subclinical changes after SRC and its correlation with time to RTP. This is crucial because early RTP and incomplete recovery could have serious short-term and long-term consequences, especially in youth. It is important that they found that some neural changes after concussion did not significantly differ from changes observed in noninjured athletes, stressing the importance of longitudinal controlled studies. It is worth mentioning that, unlike most SRC studies, the authors achieved an appropriate gender balance. This addresses a significant issue, as women seem to be at higher risk of sustaining concussions and experiencing more severe symptoms.[10] Following these findings, alternatives to facilitate clinical implementation of subclinical detection of neural alteration should be developed, considering the representativity of study samples regarding sex but also geographic origin and sport levels, among others.

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