ARTICLE IN PRESS

International Journal of Psychophysiology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Registered Reports

A review of the effects of physical activity and sports concussion on brain function and anatomy

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ARTICLE INFO

Keywords:
Sports concussions
Aerobic fitness
Physical exercise
Transcranial magnetic stimulation
Diffusion tensor imaging
Magnetic resonance spectroscopy

ABSTRACT

Physical activity has been associated with widespread anatomical and functional brain changes that occur following acute exercise or, in the case of athletes, throughout life. High levels of physical activity through the practice of sports also lead to better general health and increased cognitive function. Athletes are at risk, however, of suffering a concussion, the effects of which have been extensively described for brain function and anatomy. The level to which these effects are modulated by increased levels of fitness is not known. Here, we review literature describing the effects of physical activity and sports concussions on white matter, grey matter, neurochemistry and cortical excitability. We suggest that the effects of sports concussion can be coufounded by the effects of exercise. Indeed, available data show that the brain of athletes is different from that of healthy individuals with a non-active lifestyle. As a result, sports concussions take place in a context where structural/functional plasticity has occurred prior to the concussive event. The sports concussion literature does not permit, at present, to separate the effects of intense and repeated physical activity, and the abrupt removal from such activities, from those of concussion on brain structure and function.

1. Introduction

A sports concussion is a syndromic definition of symptoms following head exposure to biomechanical forces that occur in the context of a sporting activity. There is currently no consensus on the definition of a sports concussion or on the use of a classification or grading scheme. The most commonly used definition is that of the International Conference on Concussion in Sports, where a sports concussion is defined as a "complex pathophysiological process affecting the brain, induced by biomechanical forces" (McCrory et al., 2013). The diagnosis and management of a sports concussion is primarily based on self-reports of symptoms, such as headache, dizziness, nausea, and balance problems (McCrory et al., 2013). These symptoms usually disappear within weeks. However, in a small but notable proportion of individuals (up to 30% depending on studies), the symptoms can become chronic and turn into what is called post-concussion syndrome (PCS) (Williams et al., 2010). In addition, repeated sports-concussions have been associated with an increased risk of depression, cognitive impairment, early onset of Alzheimer's disease, dementia and neurodegenerative diseases such as chronic traumatic encephalopathy (Guskiewicz et al., 2005; Mez et al., 2013; Mendez et al., 2015). However, most of the studies detailing links between neurodegenerative disease and concussion have been retrospective, making strong causal associations difficult to establish (Meehan et al., 2015).

There exists a large body of literature describing the short- and long-term effects of sports concussions on brain structure and function (Dimou and Lagopoulos, 2014; Eierud et al., 2014; Gardner et al., 2012, 2014; Lefebvre et al., 2015). Neuroimaging studies have revealed a wide array of brain dysfunctions in the acute (hours), subacute (weeks) and chronic (years) phases of concussion, with some studies describing impaired brain function as late as 30 years post-concussion (De Beaumont et al., 2009). Brain dysfunction has also been repeatedly shown in asymptomatic athletes with a history of concussion (e.g. Churchill et al., 2017a), as well as in contact-sports athletes who never received a formal diagnosis of concussion (e.g. Koerte et al., 2012, 2015).

Reports describing brain abnormalities associated with a history of sports concussions have had tremendous impact on the way contact sports are viewed by the general public and the medical profession. However, some authors have argued that calls for severe restrictions on the practice of contact sports may be premature. For example, (Mannix et al., 2016) have argued that more data are needed before definitive

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http://dx.doi.org/10.1016/j.ijpsycho.2017.09.005
Received 5 December 2016; Received in revised form 2 August 2017; Accepted 7 September 2017
0167-8760/

Please cite this article as: Tremblay, S., International Journal of Psychophysiology (2017), http://dx.doi.org/10.1016/j.ijpsycho.2017.09.005

sweeping policy changes can be considered, especially since most studies have been conducted with athletes who were concussed before the current era of proactive concussion management, and causal relations between the identified abnormalities and the history of concussion remain lacking. Even more significantly, intensive physical activity, such as that which occurs in sports, has been shown to alter brain structure and function (see Nakata et al., 2010). Indeed, the brain of athletes has been consistently shown to differ from that of sedentary controls in terms of white and grey matter, neurochemistry, and neurophysiology, and sports-related brain modifications occur in parallel with significant positive health impacts (e.g. Pate et al., 2000) and cognitive enhancements (Voss et al., 2010). As a result, the study of the effects of sports concussion on brain function is often confounded by the effects of exercise and the abrupt removal from intense physical activity that accompanies the post-concussion period.

In the present paper, evidence showing that the brain of athletes is different from that of healthy individuals with a non-active lifestyle is reviewed and compared with data detailing the effects of sports concussions. Data of the brain at rest are reviewed, using two measures of anatomical (white matter microstructure and grey matter thickness/volume) and functional (metabolite concentration and cortical excitability) integrity. We show that the brain of physically active individuals has undergone significant anatomical and functional changes before the occurrence of a concussive event, and that concussion- and activity-related changes in brain function and anatomy often intersect.

2. Brain metabolism: magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is a MRI technique that allows in vivo quantification of brain metabolite concentration. The neurochemical profile of the acquired metabolites is typically displayed as a spectrum, with each metabolite generating a peak(s) at specific resonating frequencies (Puts and Edden, 2012). Approximately 25 metabolites can currently be quantified, the most common being *N*-acetylaspartate (NAA: marker of neural integrity and cell energy state), creatine (Cr: energy marker of neurons and astrocytes, thought to be stable and usually used as denominator for ratios), choline (Cho: membrane lipid synthesis and precursor of acetylcholine), glutamate (Glu: excitatory neurotransmission), glutamine (Gln: precursor of glutamine, GABA and glutathione), Myo-inositol (mI: marker of gliosis), lactacte (Lac: marker of energy metabolism), and gamma-Aminobutyric acid (GABA: inhibitory neurotransmission) (Puts and Edden, 2012).

2.1. *Physical exercise*

It is now well established that frequent physical activity leads to considerable benefits for general body functions, such as cardiovascular health, and is associated with a reduced risk of chronic disease and positive impacts on cognition (Cassidy et al., 2016; Morris et al., 2016). Physical exercise is also associated with changes in brain metabolism, such as a generalized increase in brain non-oxidative metabolism of carbohydrate (CHO) substrates (Rasmussen et al., 2011). These changes in brain metabolism are hypothesized to reflect modifications in specific neurotransmitter activity such as GABA, glutamate and lactate. Before the development of MRS methods, metabolic changes were measured via blood samples, and were therefore an indirect measure of metabolism, such as the oxygen-to-carbohydrate index and lactate consumption. The development of MRS offers a tool to study specific changes related to physical exercise.

Most studies to date have used an experimental paradigm whereby healthy non-athletes are required to perform graded aerobic exercise, and MRS scans are performed prior and after exercise. These studies assess the effects of acute exercise but fail to capture the effects of cumulative and sustained athletic training. Following aerobic exercise, increases in Lac/Cr levels (Dennis et al., 2015; Maddock et al., 2011) and GABA concentrations (Maddock et al., 2016) have been reported in the occipital cortex, while concentrations of glutamate and glutamine have been shown to be both increased (Maddock et al., 2011, 2016) or unchanged (Dennis et al., 2015; Gonzales et al., 2013).

Two studies investigated the impact of aerobic fitness on brain metabolism. Erickson et al. (2012) evaluated the effects of aerobic fitness in older adults by measuring NAA in frontal cortex. Compared to low fit individuals, those with high aerobic fitness showed a modulaion of age-related decreases in NAA. Moreover, NAA levels were positively correlated with both aerobic fitness (VO2 peak score) and performance in a working memory task. Similar results were found in a younger sample of middle-aged adults, where endurance training was associated with increased NAA levels in frontal areas and increased in NAA and Cho in occipitoparietal grey matter compared to sedentary individuals (Gonzales et al., 2013).

It is not yet clear how acute changes in brain metabolism following exercise translate into long-term changes in metabolite concentration. Increased NAA has been reported in the two studies that have addressed the issue of sustained physical activity effects on neurometabolism (Erickson et al., 2012; Gonzales et al., 2013). Interestingly, Erickson et al. (2012) and Maddock et al. (2016) have also reported *acute* increases in NAA concentration following vigorous exercise. It has been suggested that exercise-related increases in NAA could be related to BDNF-dependent neurogenesis or increased metabolic efficiency (Gonzales et al., 2013). Repeated physical activity could therefore induce long-lasting neurometabolic changes through either mechanisms. The limited number of studies, however, prevents conclusions on the topic to be drawn. Longitudinal studies are needed to determine how short-term, physical activity-dependent effects on brain metabolism transform into long-lasting changes on brain function.

2.2. *Sports concussions*

Animal studies have shown that traumatic brain injury is associated with a cascade of metabolic changes occurring in the first few days following injury (Giza and Hovda, 2001; Prins et al., 2013). In line with this, MRS has allowed a precise assessment of the acute and chronic effects of sports concussions on brain metabolism (for reviews: Chamard et al., 2012a; Dimou and Lagopoulos, 2014; Gardner et al., 2013; Henry et al., 2016).

NAA/Cr levels have been of particular interest in sports concussion research as this metabolite is considered a marker of neural integrity. Results from studies are variable. Vagnozzi et al. (2010) compared concussed athletes to healthy volunteers and showed decreased NAA/Cr in frontal lobes that resolved within 30 days. Reductions in NAA/Cr levels in frontal regions and primary motor cortex (M1), that persisted from the acute phase post-injury (< 1 week) to 6 months post-concussion, were also reported (Henry et al., 2010, 2011b). No changes in NAA/Cr levels were reported in the corpus callosum (CC) within 2 months post-concussion in another sample of concussed hockey players (Chamard et al., 2012b). Other studies investigated the long-term impact of sports concussion on NAA/Cr levels (> 6 months post-injury) and no changes were found in either female (Chamard et al., 2013) or male athletes with a history of concussion (Tremblay et al., 2014), up to 30 years post-concussion (De Beaumont et al., 2013; Tremblay et al., 2012). Interestingly, a study reported a significant decrease in NAA/Cr concentrations in the CC of female hockey players who did not sustain a concussion in pre- to post-season measurements (Chamard et al., 2012b).

With respect to glutamate levels, results have also been variable. In the acute phase, decreased Glx/Cr levels were found in motor cortex but resolved at 6 months post-concussion (Henry et al., 2011b), whereas no significant change was observed in another study (Chamard et al., 2012b). Other studies have assessed the long-term effects of concussions on glutamate levels (> 6 months) and found no significant abnormalities either in female (Chamard et al., 2013) or male athletes (Tremblay et al., 2014). Finally, two studies assessed glutamate levels in former athletes with a history of concussion: one reported decreased concentrations in the motor cortex (De Beaumont et al., 2013), while no difference was observed in the frontal cortex or hippocampus (Tremblay et al., 2012). GABA and lactate levels were also found to be similar to those of athletes without a history of concussion in two samples of athletes who were asymptomatic following a history of concussion (Tremblay et al., 2014; Wilke et al., 2016). Finally, some studies have reported increased levels of m-I/Cr in the chronic phase following a concussion in male athletes (Henry et al., 2011b), while decreases in concentrations were found in female athletes (Chamard et al., 2013). In older athletes with a history of concussion, one study reported increases in m-I/Cr in the hippocampus, as well as increased Cho/Cr levels in the prefrontal cortex and decreases in Cho/Cr levels in the hippocampus (Tremblay et al., 2012).

2.3. Summary

Studies using MRS to evaluate brain metabolite concentration show that it is possible to assess the effects of acute exercise on brain metabolism. However, results remain somewhat inconsistent and more work is needed to identify the main contributors to these effects. Whereas the effects of cumulative athletic training on brain metabolites are unknown, numerous studies have reported significant brain metabolic changes in athletes with a history of concussion. However, results have been inconsistent, both in terms of which specific metabolite is affected and in which direction the effects are expressed. Importantly, every study except that of Vagnozzi et al. (2010) compared athletes with a history of concussion to athletes without a history of concussion. This makes it difficult to determine how intensive, cumulative physical activity interacts with the effects of concussion on brain metabolite concentration if data are not compared to healthy individuals with a sedentary lifestyle.

3. Grey matter volume

In recent years, a number of objective methods for quantifying brain volumes in specific regions using structural magnetic resonance images have been developed, such as voxel-based morphometry (VBM) and cortical thickness measurement, allowing for accurate assessment of grey matter (GM) modification associated with health and disease. Voxel-based morphometry is a technique that is used to locate and quantify differences in grey matter anatomy between groups of participants (Ashburner and Friston, 2000; Whitwell, 2009). It is usually based on a T-1 weighted scan where statistical comparisons are made at each voxel of the MRI image. This allows an unbiased evaluation of volume differences between groups.

3.1. Physical activity

The effects of sports on GM have been widely studied. In judo athletes and world-class gymnasts, higher grey matter volumes were found in several regions of the frontal, parietal, occipital and temporal lobes (Huang et al., 2015; Jacini et al., 2009). Increases and decreases in GM volumes were also found in specific regions of the hippocampal formation in professional dancers (Hüfner et al., 2011). Changes in specific structures of the sensorimotor network have also been reported. In female ballet dancers, decreased GM volumes were observed in the left premotor cortex, supplementary motor area (SMA), putamen, and superior frontal gyrus, and decreased white matter (WM) volumes in both corticospinal tracts, both internal capsules, corpus callosum, and left anterior cingulum (Hänggi et al., 2010). Other studies have reported increases in GM volumes in similar structures, such as primary motor cortex, sensorimotor cortex, and bilateral SMA in female handball players (Hänggi et al., 2015), and thalamus and globus pallidus in professional divers (Zhang et al., 2013). Higher grey matter density in the thalamus and left precentral gyrus was also found in elite divers (Wei et al., 2009). Increased GM volumes have been reported in the cerebellum of badminton players (Di et al., 2012) and world-class mountain climbers (Di Paola et al., 2013). Moreover, Schlaffke et al. (2014) evaluated brain volumes in martial artists, endurance athletes and non-exercising men. Higher GM volumes were found in the SMA and dorsal premotor cortex in both athlete groups compared to controls, while endurance athletes showed higher GM volume in the medial temporal lobe. Peters et al. (2009) also showed in young healthy individuals that aerobic capacity was positively correlated with insula volume. Finally, Freund et al. (2012, 2014) conducted longitudinal studies in 15 ultramarathon runners assessing grey matter changes at three time-points during the race, as well as 4 and 8 months post-race. A global decrease of grey matter volume during the race that recovered 8 months post-race was found, in addition to transient GM volume reductions during the race in regionally distributed brain regions, such as posterior temporal and occipitotemporal cortices.

The impact of physical activity on brain morphology has also been extensively studied in older adults. The impact of long-term endurance training on brain morphology was assessed in older adults that had practiced high-level sports throughout their lives and revealed higher GM concentrations in regions related to visuospatial function, motor control, and working memory (Tseng et al., 2013). Also in older adults, the impact of a 6-month aerobic training program on brain volume was assessed and compared to a non-aerobic program (Colcombe et al., 2006). It was found that aerobic training significantly increased GM volume, most importantly in frontal areas. Another randomized controlled trial in older adults showed that moderate intensity aerobic training was associated with increases in hippocampal volume compared to stretching/toning exercises (Erickson et al., 2011). Importantly, Erickson et al. (2010) reported that physical activity in older adults was associated with cortical volume when brain scans were performed 9 years after baseline collection of physical activity data. Areas in prefrontal and temporal cortex showed increased grey matter volume related to the level of walking in a 1-week period at baseline. Most notably, increased grey matter volume linked to physical activity translated in reduced cognitive decline (Erickson et al., 2010).

Grey matter volume and its relationship with physical fitness has also been studied in children. In 9–10 years-old children, higher fit individuals presented larger hippocampal volumes compared to lower-fit participants (Chaddock et al., 2010a). Significantly, the volume of the hippocampus was related to memory function, where hippocampal volume correlated positively with relational memory accuracy. Moreover, results from the same group showed that basal ganglia volume was greater in physically fit children, and was correlated with cognitive control (Chaddock et al., 2010b).

3.2. Sports concussions

Few studies have assessed, or reported, GM modifications associated with sports concussions. Singh et al. (2014) assessed GM volumes in collegiate football players with a history of concussion and compared it to data collected in players without a history of concussion and healthy non-athletes. Athletes with and without a concussion showed smaller hippocampal volumes compared to healthy controls and hippocampal volume was smaller in athletes with a history of concussion compared to athletes without a history of concussion (Singh et al., 2014). A thinner cortex was also found in the anterior cingulate cortex, orbitofrontal cortex, and ventromedial frontal cortex of athletes with a history of concussion compared to non-athletes and central sulcus and precentral gyrus compared to athletes with no history of concussion (Meier et al., 2016a). Meier et al. (2016b) also compared college football players with a history of sports concussions to two control groups: football players without a history of concussion and non-athletes, and found that both athlete groups showed smaller dentate gyrus and CA2-3 volumes, but no difference was found between the two athlete groups. Finally, Churchill et al. (2017b) compared athletes with a history of concussion and athletes without a history of concussion. Volume reductions in athletes with a history of concussion were observed in cerebellum, temporal lobe, pre-central gyrus, SMA and superior frontal lobe. Increases in volume were also found in hippocampus, caudate nucleus and cuneus.

Importantly, studies of brain volume in athletes with a history of concussion have shown associations with GM modification and clinical factors. For example, cortical thickness in frontal, parietal and temporal areas has been shown to correlate negatively with self-reported symptoms (the thicker the cortex, the less reported symptoms) in hockey players with a history of concussion (Albaugh et al., 2015). Longer recovery times and number of previous concussions have also been associated with volumetric changes in a variety of brain areas, including temporal and frontal lobes as well as the hippocampus (Churchill et al., 2017b). Finally, Tremblay et al. (2012) found no difference in cortical thickness between older athletes with a remote history of concussion and those without such a history. However, the same study found that the association between cortical thickness thinning and episodic memory impairment was exacerbated in the group with a history of concussion.

3.3. Summary

Converging evidence suggests that physical activity in athletes, as well as in elderly and young individuals, is linked to structural brain changes. Described effects on GM volume are distributed throughout the brain, especially in sensorimotor areas (primary motor cortex, supplementary motor area, somatosensory cortex, cerebellum), frontal cortex, and hippocampal formation.

The pathophysiology of structural change associated with physical activity is not fully clear, but appears to be linked to cognitive benefits. Studies in athletes with a history of concussion are sparse but have revealed GM structural change in areas similar to those associated with physical activity, including pre-central gyrus, supplementary motor area and hippocampus. Two studies compared athletes with a history of concussion to athletes with no history of concussion and healthy non-athletes (Singh et al., 2014; Meier et al., 2016a). However, in all cases, athletes without a history of concussion were exposed to repeated contact to the head, which may have induced structural change. Here again, therefore, it is not possible to disentangle the relative contribution of concussion history and physical activity to patterns of GM volume and thickness modifications in athletes with a history of concussion.

4. White matter integrity: diffusion tensor imaging

Diffusion tensor imaging (DTI) is a non-invasive structural MRI method that allows in vivo quantification of white matter tract microstructure integrity. This technique uses diffusion of water molecules in white matter fibers of the brain to generate contrast maps in MR images. Several indices of white matter diffusion exist, the most frequently used being fractional anisotropy (FA: degree of anisotropy of the diffusion of water in fibers), mean diffusivity (MD: mean diffusion of water within a voxel), axial diffusivity (AD: mean diffusion parallel to the orientation of the principal axis), and radial diffusivity (RD: diffusion perpendicular to the orientation of the principal axis) (Alexander et al., 2007; Assaf and Pasternak, 2008).

4.1. Physical exercise

The link between physical exercise and white matter structure has been addressed to better understand plastic changes associated with sports participation and aerobic fitness. It has been hypothesized that the acquired skills of professional athletes could be related to changes in some important brain pathways. While some studies have compared professional or high-level athletes to healthy non-athletes, others have detailed the effects of prolonged training or high intensity aerobic training on white matter integrity.

The evaluation of white matter tracts in athletes has often focused on motor areas. In female professional ballet dancers, for example, decreased FA was observed in the white matter underlying the left and right premotor cortices compared to healthy non-athletes (Hänggi et al., 2010). Increased FA and AD was also reported in the right corticospinal tract of professional women handball players (Hänggi et al., 2015), while similar FA increases in the corticospinal tract of professional gymnasts were also found (Wang et al., 2013). Male elite professional runners displayed lower FA and marginally higher MD in the basal ganglia compared with healthy controls (Chang et al., 2015). In a study assessing whole-brain DTI in world-class gymnasts in comparison with healthy controls, decreased FA in several white matter tracts was observed, including the superior longitudinal fasciculus, inferior longitudinal fasciculus, and inferior occipito-frontal fascicle (Huang et al., 2015). In young non-athletes (15–18 years old) lower FA values in the left corticospinal tract were found to be related to higher VO2 peak. In children, similar patterns of results were observed. Chaddock-Heyman et al. (2014) found that FA was increased in high-fit children compared to low-fit children in the corpus callosum, corona radiata, and superior longitudinal fasciculus.

Some studies have also assessed the effect of aerobic fitness on white matter integrity in aging populations. Tseng et al. (2013) assessed whole-brain DTI in “master” athletes (mean age = 72 years, endurance training > 15 years) and compared data to age and education matched sedentary controls. They found increased FA values in many white matter tracts such as the superior longitudinal fasciculus and inferior occipito-frontal fascicle, as well as lower MD values in white matter tracts surrounding the thalamus and cingulum. Voss et al. (2013) assessed the effect of a 1-year training program in healthy individuals (mean: 65 years old) on white matter integrity. Results showed that greater aerobic fitness (VO2 max) as a result of the endurance training program was associated with changes in FA in prefrontal and temporal lobes, as well as cognitive improvement (short-term memory). In addition, another study showed a relationship between FA in the left middle cingulum and aerobic fitness in older adults (Marks et al., 2011).

4.2. Sports concussions

Diffuse axonal injuries can be observed following severe traumatic brain injury, suggesting that white matter tracts are vulnerable to mechanical forces applied to the head. In sports concussions, authors have hypothesized that microscopic alterations in white matter fibers may occur and may be observed via sensitive neuroimaging methods such as DTI (for reviews: Chamard et al., 2012a; Gardner et al., 2012; Henry et al., 2016). Several studies have focused on DTI measurements in the acute phase post-concussion; most studies found changes in FA or MD. Within 72 h to 1 month post-injury, persistent increases FA were found in several white matter tracts, including the internal capsule and the cerebellar peduncles (Meier et al., 2016c). It was also found that athletes following a concussion displayed increased RD 72 h post-injury, particularly in important tracts of the right hemisphere such as the internal capsule, and decreased FA at 72 h and 2 months post-injury in the same cluster of voxels (Murugavel et al., 2014). Within a month post-concussion, increased MD in the left hemisphere, including the inferior/superior longitudinal and fronto-occipital fasciculi, was observed in concussed athletes (Cubon et al., 2011), while decreased average diffusion was reported in the left DLPFC of athletes with a concussion (Zhang et al., 2010).

In the chronic phase after the concussion, no difference in FA was reported in female athletes, but higher levels of MD were found in large white matter tracts, including the corticospinal tract, the inferior/superior longitudinal fasciculi, and the cingulum (Chamard et al., 2013), as well as lower MD and radial diffusivity in the corpus callosum

(Chamard et al., 2015). Similarly, Henry et al. (2011a) reported higher FA and AD values, and lower MD values in the corticospinal tract and the corpus callosum of male athletes (American football) in the acute phase after a concussion, which persisted at least six months post-concussion. Increased FA in the left genu of the corpus callosum was also reported in ice hockey players with a history of concussion (Orr et al., 2016). Finally, increases in FA and AD, and significant decreases in RD in several areas, such as the internal capsule, the right corona radiata and the right temporal lobe, were also recently reported in ice-hockey male athletes with a concussion (Sasaki et al., 2015). Decreased FA, and increased MD and RD, were also found in brains of retired athletes with a history of sport concussions (> 30 years post-concussion) (Tremblay et al., 2013).

Finally, recent studies have focused on the impact of the accumulation of sub-concussive blows to the head sustained during a season of contact sports. Both in football and hockey players, Bazarian et al. (2012, 2014) reported increases in FA and decreases in MD in several tracts between pre- and post-season scans in athletes that were not diagnosed with a concussion. More recently, changes in FA were also observed pre- and post-season in American high school football players without a history of concussion (Chun et al., 2015). Increased AD and RD have also been found in numerous white matter tracts in soccer players without a history of concussion, compared to swimmers (Koerte et al., 2012).

4.3. Summary

White matter structure has been extensively studied in the context of physical activity, in young and elderly individuals. The most consistent result is that physical activity is associated with increased WM volume. Studies of WM microstructure have had mixed results, but increased FA in several WM tracts seems to be the most reliable finding. Alterations in FA is also one of the most consistently reported WM changes in athletes with a history of concussion. Most studies conducted during the chronic phase of concussion found decreased FA values in several WM tracts compared to control groups. Here again, athletes with a history of concussion were usually compared to teammates with no concussion history, or athletes taking part in a non-contact sport, and thus presumably at the same level of physical fitness. However, since following a concussion most athletes will stop sports activity, the effects of deconditioning would be important to consider. Indeed, although no study, to our knowledge, has assessed the effects of deconditioning on white matter integrity in concussed athletes, it has been suggested that extended periods of rest following concussion may be detrimental to recovery (Tan et al., 2014; DiFazio et al., 2016). Furthermore, it has been shown that controlled exercise in athletes with post-concussion syndrome can improve symptoms (e.g. Leddy et al., 2010). It is therefore important to consider how a sudden break in the physical activity routine of athletes following concussion can contribute to physical and mental health impairments, but also to plastic brain changes. More studies are needed to determine the effects of deconditioning on brain function and anatomy following a sports-related concussion.

5. Neurophysiology: transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that allows the stimulation of specific brain regions using brief time-varying magnetic pulses. Based on the principle of electromagnetic conduction, these pulses induce an electric current within the brain and consequently depolarize neurons that are underneath the stimulator (Rossini et al., 2015). Most studies have assessed the effect of TMS on the primary motor cortex (M1) because stimulation produces a motor response that is quantifiable through electromyography: the motor evoked potential (MEP). Changes in MEPs, such as in latency and amplitude, are thought to reflect the activity of M1. By varying stimulation parameters, it is possible to assess the integrity of several intracortical mechanisms, such as cortical inhibition mediated by GABAB receptors (LICI: long-interval intracortical inhibition, CSP: cortical silent period), cortical inhibition mediated by GABAA receptors (SICI: short-interval intracortical inhibition), general cortical excitability (MEP amplitude and latency, MT: motor threshold), and cortical facilitation (ICF: intracortical facilitation).

5.1. Physical exercise

Few studies have used TMS to assess motor neurophysiology associated with physical activity and sports participation. Pearce et al. (2000) first assessed corticospinal excitability in elite racquet players and compared results with a group of social players and non-playing control subjects. Results showed increased MEP amplitude and shifts in the motor maps for the playing hand in elite players. Authors interpreted these results as suggestive of functional reorganization in the motor cortex and corticomotor pathways in elite athletes. Similar enlargement of cortical representation of dominant muscles was reported in elite volleyball players (Boyadjian et al., 2005). In a study by Tyc et al. (2005), volleyball players were compared to runners to determine whether the extensive practice of motor skills in the context of sports participation could induce plastic changes in M1. Cortical map areas were compared between the two groups and significant differences were observed for proximal muscle representations, in line with previous studies (Pearce et al., 2000; Boyadjian et al., 2005). More than a decade later, Moscatelli et al. (2016a) assessed M1 excitability in male black-belt karate athletes and matched non-athletes. Karate athletes displayed lower resting motor threshold, shorter MEP latency and higher MEP amplitude (Moscatelli et al., 2016a, 2016b). Finally, Dai et al. (2016) studied M1 cortical excitability in elite badminton athletes and compared data with novices. Results showed increased corticospinal excitability, as revealed by steeper MEP input–output curves in athletes, and reduced inhibition, i.e. SICI and LICI. Authors concluded that the balance between excitation and inhibition is maintained in skill training and could be reflecting beneficial cortical plasticity within motor cortex.

5.2. Sports concussions

Several studies have assessed motor cortex integrity using TMS in athletes with a history of concussion. While results are variable, a trend toward persistent changes in cortical inhibition has been found (for reviews: Lefebvre et al., 2015; Major et al., 2015). In the acute phase following concussion, studies have reported decreased M1 excitability, revealed by decreased MEP amplitude, as well as prolonged MEP latency (Livingston et al., 2010, 2012). In addition, cortical hyperexcitability, specifically reduced ICF, was reported in American football athletes with a history of concussion (Powers et al., 2014), while another study reported significantly reduced inhibition, i.e. reduced CSP, in Australian football players with a history of concussion (Pearce et al., 2014).

Several studies have assessed long-term changes in cortical physiology in athletes with a history of concussion (all > 9 months). In a series of studies, increases in measures of cortical inhibition, such as CSP and LICI, were found in athletes with a history of multiple concussions (De Beaumont et al., 2007, 2009, 2011; Tremblay et al., 2011). However, one recent study found no change in the CSP, but altered transcallosal inhibition (Davidson and Tremblay, 2016), and another study found no change in measures of inhibition and excitation in the motor cortex of athletes with a history of concussion (Tremblay et al., 2014).

5.3. Summary

Reorganization of motor maps in primary motor cortex is a consistent finding in studies detailing the effects of physical activity, or skill training, on corticospinal excitability. Although the effects of concussions on muscle representation in primary motor cortex have not been reported, several studies have assessed the integrity of the excitation/inhibition balance in this area and results have been mixed and inconsistent. A pattern of increased intracortical inhibition in the chronic phase of concussion appears to be the most consistent finding. Here again, the interaction between the neurophysiological effects of physical activity and those associated with sports concussions has not been directly assessed.

6. Discussion

The literature on the effects of physical activity on brain structure and function clearly indicates that the brain of athletes is different from that of healthy individuals with a non-active lifestyle. Converging evidence shows that physical activity is associated with changes in metabolite concentration, grey and white matter structure, and corticospinal/intracortical excitability. These changes are distributed throughout the brain and are present in young, adult, and elderly populations. Physical activity-related modifications in brain structure and function can be observed after acute exercise sessions in non-athletes or throughout the lifespan in athletes. Significant modifications in brain structure and function have also been extensively described in athletes with a history of concussion. Here again, studies comparing athletes with a history of concussion to athletes without a history of concussion, or healthy non-athletes, have revealed widespread changes affecting brain areas and age groups very similar to those found for physical activity. In fact, numerous effects appear to be overlapping: physical activity and concussion have similar (or diverging) effects affecting similar structures.

A striking example of this can be seen in white matter microstructure. Changes in fractional anisotropy in athletes with a history of concussion and in individuals with high levels of fitness are well documented (Eierud et al., 2014; Hänggi et al., 2015). The corticospinal tract provides a prime example of these overlapping effects. Reduced FA in the CST has been consistently found in athletes with a history of concussion, especially during the chronic phase (Eierud et al., 2014). At the same time, *higher* FA in the CST has been reported in athletes practicing a non-contact sport (Wang et al., 2013; Hänggi et al., 2015), suggesting that the net effect of concussions on CST FA may be to offset the changes induced by higher levels of fitness seen in athletes.

Studies aiming at identifying specific and robust markers of sports concussions have yielded mixed results (see Eierud et al., 2014). Many factors can explain why some of the functional and structural results are sometimes conflicting, even contradictory (Eierud et al., 2014; Shultz et al., 2016). First, when a brain injury is present, it is unclear whether any lasting sequelae are present, as complete healing may be possible, event in an initially injured brain. A second factor is the important heterogeneity in participant characteristics (Shultz et al., 2016). Significant variability in factors such the number and severity of concussions, time elapsed since the last concussive event, pre-morbid conditions, sports and position played, and prospective or retrospective nature of the study design have contributed to the variability of results in terms of presence/absence and direction of significant brain effects. The presence of different control groups to which athletes with a history of concussion are compared may also contribute to conflicting findings. Three groups have usually been used as controls in the sports concussion literature: i) healthy non-athletes; ii) athletes with no history of concussion practicing a non-contact sport; and iii) athletes with no history of concussion practicing a contact sport. All three control groups, when taken in isolation, may confound some of the results and limit their generalizability. Athletes practicing a contact sport have been exposed to repeated head impacts for a number of years, which may lead to sub-concussive effects similar to those found in athletes with a history of concussion (Koerte et al., 2012, 2015), although recent studies suggest that these effects may not be as prevalent as originally thought (Kemp et al., 2016; Vann Jones et al., 2014). Athletes practicing a non-contact sport provide a better alternative as it controls for repeated blows to the head, but their increased level of fitness may render the data inadequate in generalizing to the general population.

Conversely, healthy non-athletes have not benefited from the effects of physical activity on brain structure and function and, as a result, significant differences with athletes with a history of concussion may be due to both physical activity and brain trauma. In this context, it is also important to remember that deconditioning, even short term effects of reduced or stopped sports activity in previously very active athletes, may lead to changes in brain structure and function (Tan et al., 2014; DiFazio et al., 2016). Such effects can further confound the effects of a concussion and warrant careful study.

As seen in the present review, another important question that has not been addressed in the literature is how elevated fitness levels in athletes may modulate the effects of concussions. It is clear from the reviewed studies that intense, long-term physical activity has a significant impact on brain function and anatomy (Nakata et al., 2010). Importantly, the effects of physical activity are not limited to the brain: repeated exercise is associated with better health outcomes (Reiner et al., 2013) as well as better cognition (Singh-Manoux et al., 2005). As a result, the effects of concussion in athletes may be modified by several factors such as better general health and structural/functional plasticity that occurred prior to and after the concussive event. This situation is well illustrated by the changes in white matter FA that are associated with physical activity and sports concussion. In older individuals, higher levels of physical activity have been linked to increased FA in WM tracts such as the superior longitudinal fasciculus and corpus callosum (Sexton et al., 2016). Strikingly, *decreased* FA has been reported in older ex-athletes with a history of concussion in the exact same WM tracts, compared to older ex-athletes with no history of concussion (Tremblay et al., 2014). These results suggest that concussions in athletes may, in some cases, reverse the plastic changes associated with physical activity. Whether such effects are related to the concussion itself or to the sudden transition from very active lifestyle to a period of inactivity and the resulting deconditioning is also unclear. In any case, this would become apparent when contrasting the brain of athletes following a concussion with that of athletes without a concussion, but could result in specific markers of brain integrity being indistinguishable from those of non-athletes. This stresses the importance of longitudinal studies. Furthermore, study designs that include healthy non-athletes *and* athletes without a history of concussion as controls can provide an important first step in determining if a history of physical activity, and its associated increased level of fitness, modulates the effects of sports concussions in athletes. Finally, it may also be beneficial to compare data to individuals with orthopedic injury, to account for the effect of injury pain and stress on physiological brain responses.

7. Conclusion

Intense physical activity is associated with structural and functional brain plasticity, which may interact with the effects of sports concussion. Without prospective studies and proper controls, it is difficult to determine to what degree the functional and anatomical changes associated with sports concussions result from injury, exercise, or abrupt cessation of physical activity. As a result, the brain dysfunctions that accompany concussions should be weighted against the modifications in brain structure and function that arise as a result of physical activity in the context of sports participation. As suggested elsewhere (Mannix et al., 2016), the health, psychological, and cognitive benefits associated with sports should be considered when discussing the risks associated with contact sports.

Acknowledgements

This work was supported by a grant from the Canadian Institutes of Health Research (311035). ST was supported by a Canadian Institute of Health Research postdoctoral fellowship. Dr. A. Pascual-Leone was partly supported by the Sidney R. Baer Jr. Foundation, the NIH (R01MH100186, R01HD069776, R01NS073601, R21 NS082870, R21 MH099196, R21 NS085491, R21 HD07616), the Football Players Health Study at Harvard University, and Harvard Catalyst/The Harvard Clinical and Translational Science Center (NCRR and the NCATS NIH, UL1 RR025758).

Disclosure

The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, the National Institutes of Health, or the Sidney R. Baer Jr. Foundation.

Dr. A. Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Axilum Robotics, Magstim Inc., and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging.

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