Brain Imaging and Behavior (2012) 6:224–243
DOI 10.1007/s11682-012-9167-2

MTBI SPECIAL ISSUE

Concussion in athletics: ongoing clinical and brain imaging research controversies

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Published online: 5 June 2012

Abstract Concussion, the most common form of traumatic brain injury, proves to be increasingly complex and not mild in nature as its synonymous term mild traumatic brain injury (mTBI) would imply. Despite the increasing occurrence and prevalence of mTBI there is no universally accepted definition and conventional brain imaging techniques lack the sensitivity to detect subtle changes it causes. Moreover, clinical management of sports induced mild traumatic brain injury has not changed much over the past decade. Advances in neuroimaging that include electroencephalography (EEG), functional magnetic resonance imaging (fMRI), resting-state functional connectivity, diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS) offer promise in aiding research into understanding the complexities and nuances of mTBI which may ultimately influence clinical management of the condition. In this paper the authors review the major findings from these advanced neuroimaging methods along with current controversy within this field of research. As mTBI is frequently associated with youth and sports injury this review focuses on sports-related mTBI in the younger population.

Keywords Mild TBI · Neuroimaging · Clinical outcome

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Current clinical research of mild TBI in athletics

Mild traumatic brain injury (mTBI), commonly known as concussion, is gaining significant attention within the clinical research community. With some researchers reporting 1.6 to 3.8 million concussions occurring in sports (Langlois et al. 2006), mTBI accounts for 80 % of all reported traumatic brain injuries (Ruff 2011). The annual rate of diagnosed concussions over the past 10 years in high school sports demonstrated an increase of 16.5 % annually (Lincoln et al. 2011). With such high rates of sport related brain injury occurring during adolescence and young adulthood an emphasis has to be placed on fully understanding the short and long term consequences of this complex and still most puzzling neurological disorder (Cantu et al. 2006).

The aim of this review article is to provide empirical evidence from neuroimaging and behavioral studies that go against the conventional wisdom that *typical* recovery following a sport-related mTBI is rapid and full with no residual deficits. There is growing evidence that *atypical evolution* of mild TBI may be more prevalent due to the fact that physical, neurocognitive, emotional symptoms and underlying neural alterations persist months or even years post-injury. Specifically, the findings of recent brain imaging studies challenge the conventional wisdom based upon clinical assessment of mTBI.

The acute effects of concussion are typically short lived in the majority of athletes suffering a sport related mild TBI.

Concussed athletes can experience a variety of symptoms including headache, dizziness, nausea, confusion, abnormal balance and postural instability, cognitive deficits, sleep disruption, sensitivity to light and noise among others. These symptoms may be a product of physiologic damage to neural tissues and its neurometabolic sequelae (Henry et al. 2010), and/or gross indicators that reflect underlying brain trauma induced neuropathology at the cellular level (Bigler and Maxwell 2012). Short term effects of mild TBI have been linked to several neurologic and mental health disorders later in life crossing the spectrum from Alzheimer's disease (Uryu et al. 2002), chronic traumatic encephalopathy (CTE) (Gavett et al. 2010; Blaylock and Maroon 2011), Post-Traumatic Stress Disorder (Hoge et al. 2008; Barnes et al. 2012a), substance abuse, (Helgeson 2011), anxiety and depression leading to suicide (Teasdale and Engberg 2001; Barnes et al. 2012b). Interestingly, these findings are similar to those reported by Max et al., (2011), indicating possibility of both non-anxious and anxious depression both after adult and childhood TBI 6 months post-injury with respect to lesion laterality, genetic factor, age of injury, and more generalized affective dysregulation. In fact, the 2010 death of a University of Pennsylvania Football player has unearthed the reality that repetitive trauma may have contributed to his depression and suicide through early onset CTE or dementia (Schwarz 2010).

Allied health professionals treating concussed young people have been using the same approach to treatment for nearly two decades. Initially, focused on classification systems, clinicians would choose a system based on their general preference. With 41 different and most often controversial classification systems (Anderson et al. 2006) and a return to play protocol based on a clinical construct (CAoSMC 2000), practitioners have been held to management and return to play standards that were based less on well researched physiologic data and more on clinical intuition and consensus statements from leaders in the field of neuropsychology (Aubry et al. 2002). Serial testing of patients' cognitive status was first recommended in the early 1980's as a mechanism to help the clinician determine when an athlete could safely return to athletic participation (Hugenholtz and Richard 1982). Contributing to the early treatment approach was the formation of neuropsychological assessment batteries (Alves et al. 1987; Barth et al. 1989), which are still in clinical use today as the cornerstone of clinical management for sporst-related concussion (Moser et al. 2007; McCrory et al. 2009). These testing batteries primarily measure a patient's cognitive status. Initially performed with paper and pencil, cognitive test batteries designed for managing athletes recovering from sporst-related concussion have now almost fully evolved to computer-based online batteries of tests which can be interpreted by many health care professionals (McCrory et al. 2005)

Even with increased awareness of concussion and an increased presence of trained allied health professionals like athletic trainers monitoring high schools and college sports, concussion is still commonly misunderstood by some clinicians and can be over simplified in terms of its diagnosis and recovery (Bazarian et al. 2001; Chrisman et al. 2011). Athletes typically present clinically with a variety of physical and cognitive symptoms which can be reasonably detected with a thorough clinical evaluation both on the field and in the clinic or athletic training room (McCrea et al. 1997). One common tool that has been endorsed for sideline assessment or clinical use is the Sport Concussion Assessment Tool (SCAT-2) (McCrory et al. 2009). This clinical assessment tool has been endorsed in one form or another in the proceedings and consensus statements of the 2nd and 3rd International Conference on concussion for use on athletes recovering from mTBI. The use of which mandates the inclusion of a baseline measure taken when the athlete is asymptomatic. The SCAT-2 is designed to evaluate the patient using a composite score generated from: the Self-Reported Symptoms Score; Physical Signs Score; the Glasgow Coma Scale; Sideline Assessment—Maddock's Score; Cognitive Assessment (SAC); and Coordination Examination Scores. The athlete's overall score is recorded and then compared to the athlete's premorbid level of function on their pre-season baseline measure. This basic clinical assessment tool score along with other clinical findings on exam are used to determine when an athlete may be ready to progress back into exercise and athletic participation.

However, once physical symptoms resolve and their SCAT-2 scores return to baseline, clinicians lean heavily on efforts to measure any residual cognitive deficits using a more rigorous neuropsychological testing battery like immediate post-concussion assessment and cognitive testing (ImPact), automated neuropsychological assessment metrics (ANAM), Headminder, and CNS Vital Signs, among others. These computer-based testing batteries are designed to measure patient cognitive status and can assist the clinician when combined with a good clinical evaluation. These computer-based neuropsychological test batteries evaluate patients across many cognitive domains including verbal memory, visual memory, executive function, reaction time, cognitive flexibility or fluency. Although neuropsychological evaluation is used to determine current cognitive status, the recovery of cognitive decrements and patient self-reported symptoms scores is accepted as a measure of clinical recovery from injury as opposed to functional recovery of cognitive status. This viewpoint is widely accepted across clinical research in sports-related mTBI. (Moser et al. 2007)

There is still a lack in belief among neuropsychological and clinical researchers that concussion results in long lasting structural injury to the neuron. This idea is reflected in the sentiment of nearly every consensus statement on

concussion (Aubry et al. 2002; McCrory et al. 2005; Moser et al. 2007; McCrory et al. 2009) and is frequently repeated in these statements. The authors of these statements frequently repeat that; "Concussion may result in neuropathologic changes, but the clinical symptoms largely reflect a functional disturbance *rather than a structural injury*". This clinical sentiment is repeated and re-examined in clinical research in which neuropsychologists and other clinical concussion researchers continue to promote the idea of cognitive functional recovery being representative of clinical recovery (Moser et al. 2007). Moreover, this basic statement represents a construct flaw in their hypothesis. All of the supportive data are mainly based on the restoration of cognitive functioning measured by neuropsychological testing and not based on the healing of the microstructural lesion. For example, the detection of residual abnormalities in single and multiple concussed subjects is a current topic of debate among neuropsychological researchers and other clinical researchers. In a large sample study by (Bruce and Echemendia 2009) the authors report no differences across baseline neuropsychological scores of subjects with previous history of single or multiple concussion and normal volunteers without history of concussion. Thus, the authors claim that there are no long or short term measureable effects of single or multiple concussions on individuals despite other neuropsychological testing data to the contrary.

Further and in contrast to the Bruce study other clinical researchers using neuropsychological testing batteries have reported abnormalities across multiply concussed groups on measures of verbal and visual memory (Covassin et al. 2010), delayed recall, executive function (Belanger et al. 2010) and processing speed (Gardner et al. 2010). In the field of pediatric mTBI, the clinical return to play picture is even cloudier as adolescents undergo several rapid cognitive growth periods that would impact their overall cognitive abilities. In a study by Daniel et al., the authors find that 'return to baseline' measures are therefore not a good indicator of resolution of injury due to the cognitive maturation that happens in the 14–17 y/o age range (Daniel et al. 1999). Moreover, Wilde et al. (2012) have reported longitudinal changes in cortical thickness in children suffering from moderate-to-severe TBI and their relations to behavioral regulation and emotional control. Clearly, decreased cortical thickness bilaterally in aspects of the superior frontal, dorsolateral frontal, orbital frontal and ACC regions 3 months post-injury compared to normal controls may also be present in mild form of TBI, leading to residual behavioral alteration of pediatric patients later in life.

Aforementioned controversies exaggerated even more by the fact that conventional MRI and CT scans are often negative due to the absence of macrostructural alterations. Over the past 10 years, animal studies and physiological reviews have demonstrated a complex series of neurometabolic cascades, neurovascular compromise and neurophysiologic impairment (Giza and Hovda 2001; Barkhoudarian et al. 2011; Kan et al. 2012) stemming from the mechanical forces of sport-related concussion. The mechanical stretch of axons produces injury to the cytoarchitecture of the axon (Goetz et al. 2004; Browne et al. 2011) and surface architecture of the axon (Yuen et al. 2009) which significantly impairs normal neurologic function (Creed et al. 2011) and leaves the neuron vulnerable to more significant insult repeatedly (Yuen et al. 2009). These forces are also capable of inducing short term and lasting vascular changes (Flamm et al. 1966; Grundl et al. 1994; Lewine et al. 2007). For more detailed review, please see the article by Bigler and Maxwell of nueropathology in this special issue. These are findings that the neurobiological research community and neuroimaging community have paid particular attention to in recent years, but have been identified for decades (Chason et al. 1958; Nevin 1967; Faas and Ommaya 1968). However, these findings are largely overlooked and underappreciated in the clinical management of sports-related concussion. Inclusion of these findings into the clinical management of concussion must be considered, combining advanced neuroimaging techniques with data driven neuropsychological and neurological assessments.

The neuroimaging community has seen an exponential increase in imaging findings with the use of functional MRI. There are increasing numbers of articles which demonstrate alterations in brain activation through blood oxygen level dependent (BOLD) signal alterations, resting state functional connectivity (Slobounov et al. 2010; Mayer et al. 2011), magnetic resonance spectroscopy (Vagnozzi et al. 2010), diffusion tensor imaging (Cubon et al. 2011) and SPECT imaging (Harch et al. 2012). In addition, contributions from the field of clinical electroencephalography (EEG) have long been used to analyze pediatric and young athletes recovering from sports related concussion (Daniel et al. 1999). Specifically, EEG decrements have been demonstrated in the presence and/or absence of self-reported symptoms and neuropsychological performance in single or multiply concussed individuals (Gosselin et al. 2006; Broglio et al. 2009; Theriault et al. 2009, 2011; Barr et al. 2012). These decrements may be attributable to persistent neurologic dysfunctions that may to be measureable through more rigorous analyses. The application of EEG indices to the management of concussion should be considered (see elaboration of these thoughts in the following section of the paper). The major goal of the following discussion is to explore current findings of EEG and advanced neuroimaging research (fMRI, MRS, DTI) in the examination of subjects recovering from sport-related mild TBI.

EEG research in mild TBI

Electroencephalography (EEG) is a graphic representation of the difference in the voltage between two different brain

locations plotted over time. The scalp signal generated by cerebral neurons is modified by electrical conductive properties of the tissues between the electrical source and the recording electrode, conductive properties of the electrode itself, and the orientation of the cortical generator to the recording electrode (Olejniczak 2006). Current views suggest that EEG originates in the depolarization of the dendritic trees of pyramidal cells (Lutzenberger et al. 1987; Dasilva 1991). Specifically, graded postsynaptic potentials of the cell body and dendrites of vertically oriented pyramidal cells in cortical layers III and V give rise to the EEG recorded on the scalp. The unique ability to record the relatively small voltage at the scalp from these actions results from the fact that pyramidal cells tend to share a similar orientation and polarity and to be synchroneously fired.

Considering the high temporal resolution of EEG signal, EEG is highly suitable for examining fast sensori-motor and cognitive functions succeptable to concussive impacts. Not surprisingly, historically, electroencephalography (EEG) was the first monitoring assessment tool to demonstrate the alteration of brain functions in subjects suffering from TBI (Glaser and Sjaardema 1940; Jasper et al. 1940; Williams 1941). Since then, considerable empirical evidence was accumulated indicating both (a) clinical value of EEG in terms of the accuracy of assessement of mTBI, and (b) conceptual significance of EEG in enabling the examination of neural substrates underlying neurological, behavioral and neuropsychological alterations in mild TBI (Arciniegas 2011).

Early EEG research in 300 patients clearly demonstrated the slowing of major frequency bands and focal abnormalities within 48 h post-injury (Geets and Louette 1985). A study by McClelland et al. has shown that EEG recordings performed during the immediate post-concussion period demonstrated a large amount of "diffusely distributed slow-wave potentials," which were markedly reduced when recordings were performed 6 weeks after injury (McClelland et al. 1994). A shift in the mean frequency in the alpha (8–10 Hz) band toward lower power and an overall decrease of beta (14–18 Hz) power in patients suffering from mTBI was observed by Tebano et al. (Tebano et al. 1988). The reduction of theta power (Montgomery et al. 1991) accompanying a transient increase of alpha-theta ratios (Pratapchand et al. 1988; Watson et al. 1995) was identified as residual symptoms in mTBI patients.

The most comprehensive EEG study using a database of 608 mTBI subjects up to 8 years post-injury revealed: (a) increased coherence in frontal-temporal regions; (b) decreased power differences between anterior and posterior cortical regions; and (c) reduced alpha power in the posterior cortical region, which was attributed to mechanical head injury (Thatcher et al. 1989). A study by Thornton has shown a similar data trend in addition to demonstrating the attenuation of EEG within the high frequency gamma cluster (32–64 Hz) in mTBI patients (Thornton 1999). Also, the usefulness and high sensitivity of EEG in the assessment of concussion have been demonstrated (Duff 2004).

More recently, Barr et al. followed the recovery from concussion in a sample of athletes using quantitative EEG (qEEG) in conjunction with clinical assessment, postural stability and cognitive functioning measures (Barr et al. 2012). They reported clinical abnormalities in mTBI subjects only at the time of injury. Also, qEEG based abnormalities were observed at day 8 post-injury. However, EEG measures returned to normal at 45 days post-injury. Similar qEEG findings were reported by McCrea et al., suggesting the clinical utility of qEEG in detecting abnormal brain functioning in the acute phase of sport-related concussion (McCrea et al. 2010).

There is also a line of recent research indicating the efficacy of EEG based ERP (event-related potentials) in detecting subtle and pervasive alterations of cognition-related waveforms in athletes suffering from mild TBI, including multiple concussions (Gosselin et al. 2006; Broglio et al. 2009; Davis et al. 2009; Theriault et al. 2011). It appeared that the athletes with the history of previous mTBI exhibited significantly attenuated amplitude of posterior contralateral negativity (SPCN) compared to normal volunteers in absence of working memory abnormalities (Theriault et al. 2009). Similarly, Broglio et al. reported significant decrement in the N2 and P3b amplitude of the stimulus-locked ERP in athletes with a history of concussion on average of 3.4 years post-injury (Broglio et al. 2009). Most importantly, no significant alterations were observed based on commonly used ImPACT tests. Overall, these findings strongly support the notion that sport-related mild TBI can no longer be considered as a *transient* injury.

A number of reports from our research group clearly indicate that advanced tools of EEG feature extraction may indeed detect subtle brain functional abnormalities in absence of any clinical mTBI symptoms. Specifically, we applied advanced *EEG-wavelet entropy* measures to detect brain functional deficits in mTBI subjects. These EEG measures were significantly reduced primarily after the first and especially after the second mTBI far beyond 7 days post-injury. Most importantly, the rate of recovery of EEG entropy measures was significantly slower after second mTBI compared to those after the first concussion (Slobounov et al. 2009). In fact, we have recently reported the alteration of EEG signals in mTBI subjects detected by a novel measure of nonstationarity, named Shannon entropy of the peak frequency shifting (Cao and Slobounov 2011). These findings are complementary to our previously published concussion report indicating the presence of residual deficits in mTBI subjects detected by the multi-channel EEG signals classifier using a support vector machine (Cao et al. 2008).

Our research group also conducted an EEG resting state study and reported the alteration of cortical functional

connectivity in mTBI subjects revealed by graph theory, independent component analysis (ICA) and low resolution brain electromagnetic tomography (LORETA) analyses (shown in Fig. 1). Overall, a clear departure from *small world like network* was observed in mTBI subjects (Cao and Slobounov 2010).

Moreover, clear departure from small world like network configuration was observed in subjects after mTBI (Cao and Slobounov 2010). We observed a reduction in the clustering coefficient (C_p) and a enhancement of the mean-shortest path length (L_p)as a result of concussion, which indicated an impaired small-world-like structure of the whole brain network. These results seem to be in agreement with the "network randomization" hypothesis, as a general framework of abnormal brain functions commonly observed in neurological subjects, including those suffering from low-grade tumor and/or epilepsy. It is worth noting that these patients commonly experience disturbed cognition similarly to our mTBI athletes at least in acute stage of injury. Also, the alterations of vertex degrees, as an index of functional cortical connectivity in concussed subjects were consistently observed in ROIs centered at frontal, occipital, and parietal sites.

Recently Arciniegas outlined the major limiting factors contributing to the limited capacity of EEG measures in clinical assessment of mTBI, including: (a) the lack of control for subjects' homogeneity, (b) lack of research when EEG assessment was performed immediately after and serially over the first year of injury; (c) poor experimental designs when EEG data are collected independently from performance-based assessment of patients' functional status; (d) different time frame since injury when EEG measures were obtained (Arciniegas 2011). Our research team partially addressed these limitations by obtaining further EEG evidence of a residual disturbance of the neuronal network that is involved in execution of postural movement in mTBI subjects. This was done by incorporating EEG and Virtual Reality (VR) induced measures (Slobounov et al. 2011a). We designed an EEG study using a virtual reality (VR) graphics system aimed to examine the brain activation patterns preceding the loss of postural stability induced by a "Moving Room" experimental paradigm. VR experimental set-up is shown in Fig. 2.

As shown in Fig. 3 (NV), there was a significant increase of *theta* power during the progression of a balance task. Specifically, this *theta* increment was obvious initially at central areas with further diffusion to frontal electrode sites bilaterally. Interestingly, no significant *theta* power was present in concussed subjects at either phases of postural task progression (see Fig. 3, mTBI). These EEG findings are complementary to our brain imaging studies demonstrating the neural underpinning of postural responses to visual field motion, that maybe impaired as a result of mTBI (Slobounov et al. 2005, 2006a, b, 2012). The presence of visual-kinesthetic disintegration induced by visual field motion and associated alterations of brain functions could potentially be considered within the scope of existing grading scales of concussion.

Similar to *typical* course of clinical recovery after mTBI, abnormalities on conventional EEG recording tend to resolve during the first several months post-injury (Nuwer et al. 2005). EEG assessment could contribute to the development and refinement of differential diagnostic information

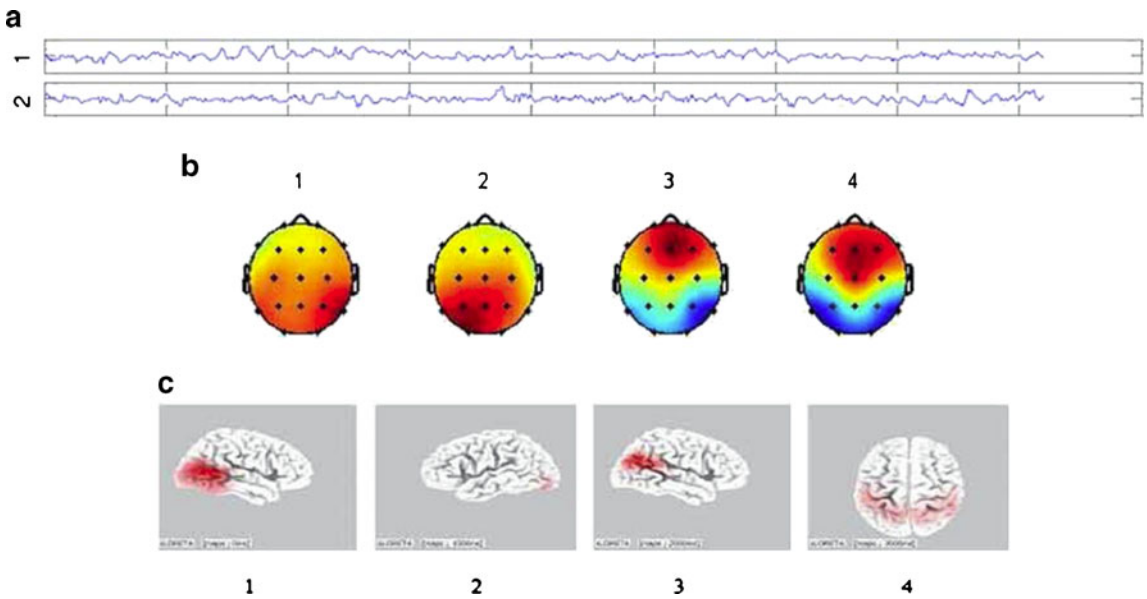

Fig. 1 The time series of the ICs extracted from a single EEG epoch. (b) The topographies of these ICs. (c) The respective source distributions of the ICs obtained from sLORETA. The ICs, the associated topographies and source distributions are labeled by numbers. It is shown in (c) that some of the ICs, such as 4, 5, 6, 9, 13, and 16, have truly distributed sources

Fig. 2 AMTI force platform and 6 ° of freedoms ultra-sound IS-900 micro motion tracking technology from "InterSense Inc" was used to control the head and body kinematics and postural responses to visual manipulations of VR scenes. Courtesy of HeadRehab LLC

among subjects with atypical clinical recovery following mTBI. That said, it is important to note that the differences in EEG profiles in subjects showing the *typica*l and *atypical* functional recovery after mTBI may serve as a starting point from which to begin more fully investigating the neural substrates for differential recovery after traumatic brain injury (Arciniegas 2011). With this in mind our research group combined EEG (alpha power difference during sittting versus standing upright postures) and balance measures (standing still with eyes open and closed) in subjects prior to injury (baseline testing, n=380) and serially over 1 year post-injury (n=49) to further examine the neural substrates of cerebral brain dysfunctions in mTBI subjects as injury evolves over time.

The major findings in our study are the following: (a) Percent alpha power suppression from sitting to standing postural conditions significantly increased in mTBI subjects shortly after the injury (p<0.01); (b) Percent alpha power suppression significantly correlated with increased area of COP during standing posture with eye closed (r^2=0.53, p< 0.01); (c) The magnitude of alpha power suppression predicted the rate of recovery of this measure in sub-acute and chronic phases of injury (r^2=0.609, p<0.01); Finally, 85 % of mTBI subjects who showed more than 20 % of alpha power suppression in the acute phase of injury did not return to pre-injury status up to 12 months post-injury (see also Figs. 4, 5, 6).

Overall, the efficacy of serially implemented EEG measures in conjunction with balance assessement over the course of mTBI evolution to document residual cerebral dysfunction was clearly demonstrated. Specifically, alteration of EEG alpha power dynamics in conjunction with balance data in the acute phase of injury with respect to baseline measures may predict the rate of recovery from a single concussive blow. As such, EEG measures (if properly executed in conjunction with other behavioral variables) are excellent tools to assess the status and prognosis of patients with mTBI.

Functional magnetic resonance imaging & mild TBI

Blood oxygen level-dependent MR

One of the more recent and popular advancements in neuroimaging, fMRI, has become a widely used research tool in probing the complexities of the brain (Logothetis 2008). fMRI uses the principal of BOLD contrast as an index of neuronal activity (Ogawa et al. 1990). The BOLD signal in fMRI is sensitive to blood-based properties, specifically the local magnetic susceptibility produced by deoxyhemoglobin which cause a reduction in signal. The assumption in BOLD fMRI is that an increase in neuronal activity within a brain region results in an increase in local blood flow, leading to reduced concentrations of deoxyhemoglobin in nearby vessels (Ogawa et al. 1993). Therefore, the higher concentrations of oxyhemoglobin associated with neuronal activity results in higher signal intensities due to a reduction in local field inhomogeneities and signal dephasing caused by

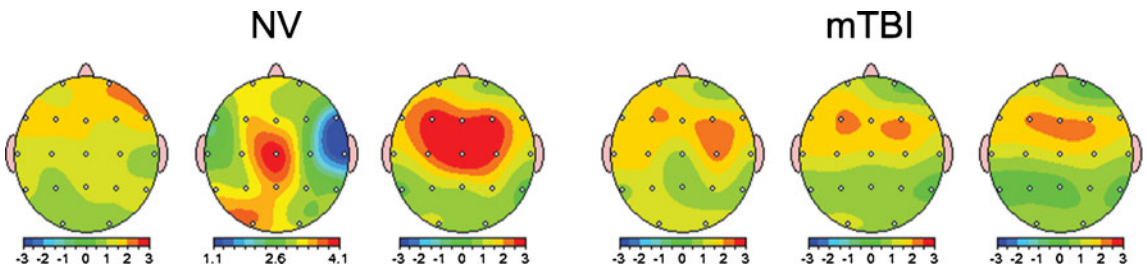

Fig. 3 2D plots grand-average of *theta* power as the postural task progressed at 10, 15 and 27 s before and after mTBI. EEG data included during the VR "Roll" condition. Note a significant enhancement of theta power over frontal-central electrode sites as trial progressed during baseline (p<.01), but not in concussed subjects. Courtesy of Elsevier (Barwick et al., 2012)

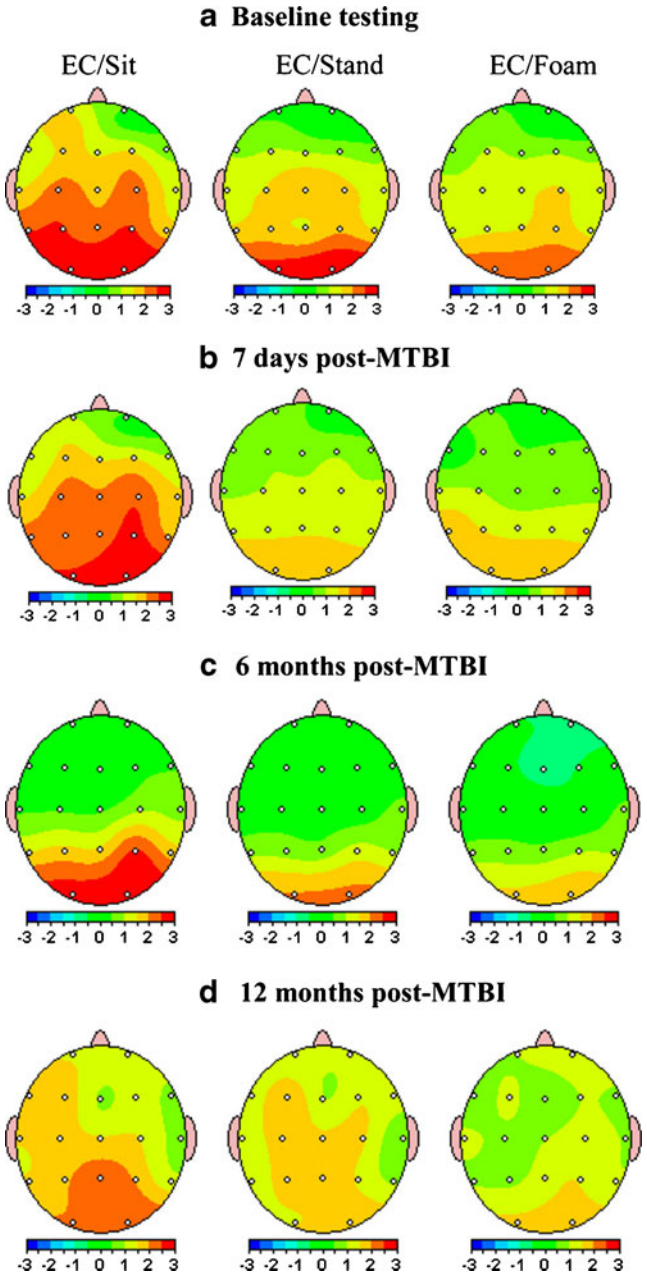

Fig. 4 2D plots grand-average of alpha power at baseline (**a**) and pre-post injury [7 days (**b**), 6 months (**c**) and 12 months (**d**) post-mTBI] during sitting, standing on the force plate and standing on the foam conditions. Note a significant suppression of alpha power at occipital and parietal ROI during standing posture both on force plate and on the foam after mTBI on day 7th post-injury. Also note (**c** & **d**) mTBI subjects who showed more than 20 % of alpha power suppression in the acute phase of injury did not return to pre-injury status up to 12 months post-injury. Visually, no significant differences in alpha power were noticed after mTBI while standing on the force plate or on the foam on day 7th, 6 months and 12 months post-injury. Courtesy of Elsevier (Slobounov et al. 2012)

deoxyhemoglobin. For a more detailed review of MR physics or fMRI methodological and conceptual pitfalls see Horowitz (1995) and Hillary et al. (2002) respectively. The currently accepted notion is that BOLD fMRI most likely detects secondary effects of neuronal firing due to the *hemodynamic response*, allowing *indirect* assessment of the neuronal responses to cognitive and/or sensory-motor task demands (Jueptner and Weiller 1995).

fMRI research of mild TBI

There is hope that advanced brain imaging techniques like fMRI will be a valuable tool in the assessment of mTBI due to the limited ability of conventional brain imaging and current neuropsychological tests (Ptito et al. 2007). Recent brain imaging research, particularly fMRI, revealed alteration of the BOLD signal in concussed individuals while performing working memory, attention, sensory-motor and other neurocognitive tasks. Empirical findings have suggested that task-related fMRI studies may be a robust and more sensitive tool for assessment of residual functional motor and cognitive deficits, especially in the sub-acute phase of mTBI (Ptito et al. 2007). However, there is still debate in the literature regarding the values of advanced brain imaging data (e.g., fMRI, DTI, MRS) in a clinical assessment of concussion, at least as it pertains to athletics (McCrory et al. 2009). For additional information, please see the reviews by McDonald et al. and Stevens et al. in this special issue.

Since working memory (WM) deficits are nearly universal following most of the neurological disruption (including mTBI), the functional imaging clinical literature has focused on examining these deficits with respect to basic information processing. In functional imaging studies of mTBI, specifically, there have been more or less similarities in the findings, with most results (see however, Chen et al., below) pointing to increased neural activity in several brain regions, but most consistently in the prefrontal cortex (PFC), and especially the dorsolateral prefrontal cortex (DLPFC). For example, McAllister et al. (1999, 2001, 2006) have shown enhanced and more widespread BOLD signal in concussed subjects performing a series of cognitive tasks (McAllister et al. 1999, 2001, 2006) In these fMRI studies mTBI subjects within 1 month post-injury and age-matched normal controls performed the 'n-back' working memory task. Significant differences between the two groups' brain activation patterns were shown in response to increasing working memory processing loads. The primary finding from McAllister's team was an increased activation in DLPFC in concussed subjects who successfully performed the 'n-back' working memory task. Another interesting finding of this research group is that mTBI patients showed disproportionately increased activation during the moderate processing load condition (McAllister et al. 2001). Similarly, Jantzen et al. showed increased activation in the parietal, lateral frontal, and cerebellar regions in concussed subjects when compared with pre-injury in absence of changes in cognitive performance (Jantzen 2010). The hyper-

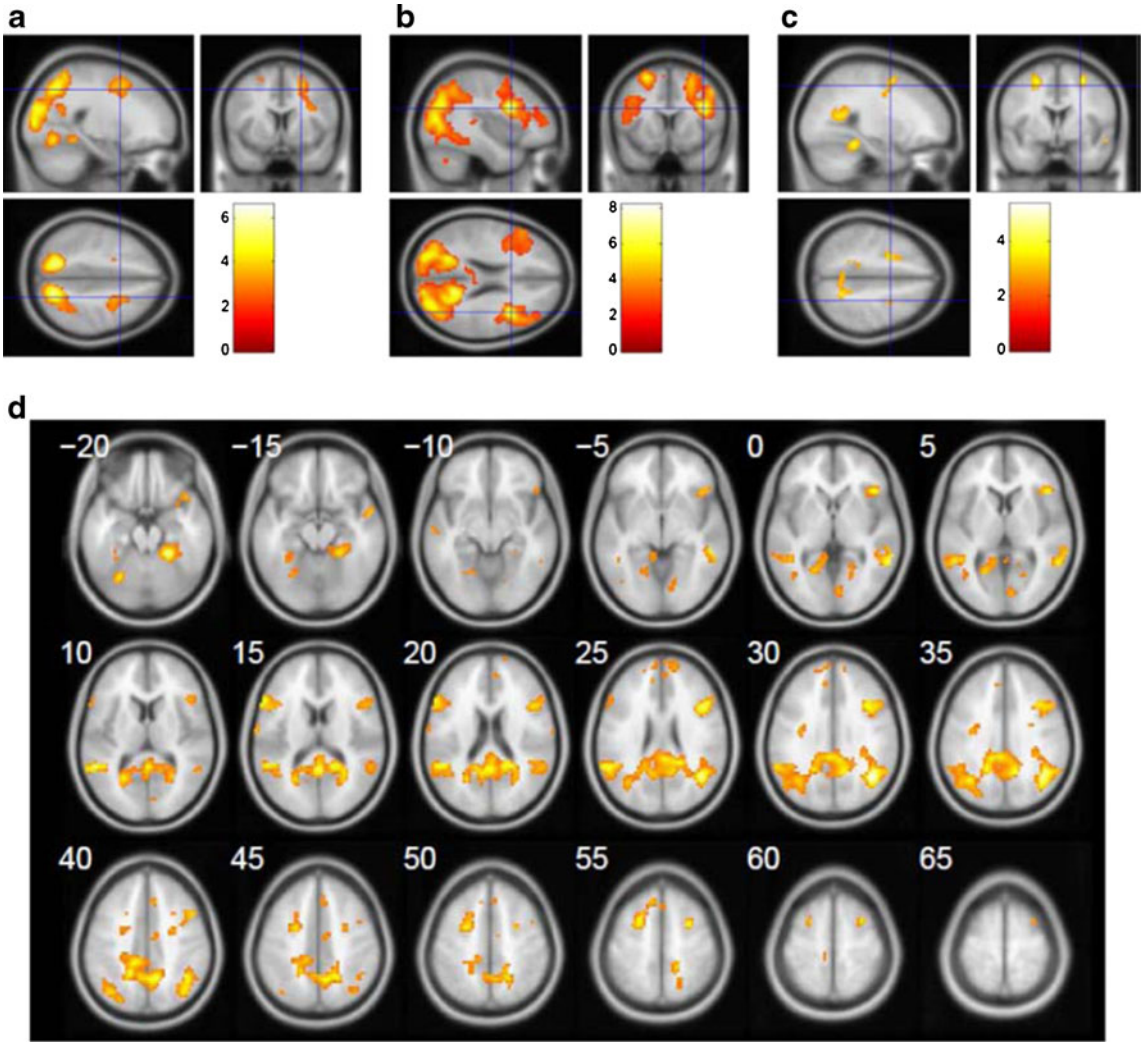

Fig. 5 Sagittal, coronal and axial sections showing activation patterns during (**a**) encoding (*E*–BL) versus retrieval (*R*–RN) contrast, normal controls; (**b**) encoding (*E*–BL) versus retrieval (*R*–RN), contrast, mTBI subjects; (**c**) encoding mTBI–normal controls contrast. (**d**) Transversal images series of the contrast in (c). Note, significantly larger activation at several regions including the lateral extrastriate visual cortex V3 (33, −76, 19), extending to V2 (−21, −85, 22); premotor cortex bilaterally (−24, 5, 58 and 30, 2, 55); and right DL-PFC (45, 38, 22) during encoding in both groups. Also note additional activation during encoding in cerebellum (33, −64, ¡29) and left DL-PFC (−51, 23, 22) in mTBI subjects (c). These identified peaks were not present in the normal control group. The regions shown are threshold at $p<0.001$, uncorrected to show subthreshold extent of the activated regions. The *color bar* indicates the *t* statistic associated with each voxel and *z* score equivalent. Courtesy of Elsevier (Slobounov et al. 2010)

activation of PFC and possibly other regions of interest (ROI) in mTBI may represent a "neural inefficiency" concept that has been linked to neurological patients' diminished performance of cognitive tasks (Hillary et al. 2003; Chang et al. 2004; Perlstein et al. 2004; Chiaravalloti et al. 2005).

Our research team has recently reported fMRI data on the performance of spatial memory navigation tasks in a virtual reality (VR) environment in 15 athletes suffering from mTBI and 15 neurologically normal, athletically active age matched controls. No differences in performance were observed between these two groups of subjects in terms of success rate (94 % and 92 %) along with time to complete the spatial memory navigation tasks (mean=19.5 s and 19.7 s). Whole brain analysis revealed that similar brain activation patterns were observed during both encoding and retrieval among the groups. However, similar to the aforementioned imaging studies, concussed athletes showed larger cortical networks with additional increases in activity outside of the shared ROIs during encoding. Quantitative analysis of the BOLD signal revealed that concussed individuals had a significantly larger cluster size during encoding in the parietal cortex, right DLPFC, and right hippocampus. In addition, there was a significantly larger BOLD signal percent change in the right hippocampus. Additionally we observed bilateral recruitment of DLPFC in concussed subjects during encoding that was not present in normal volunteers.

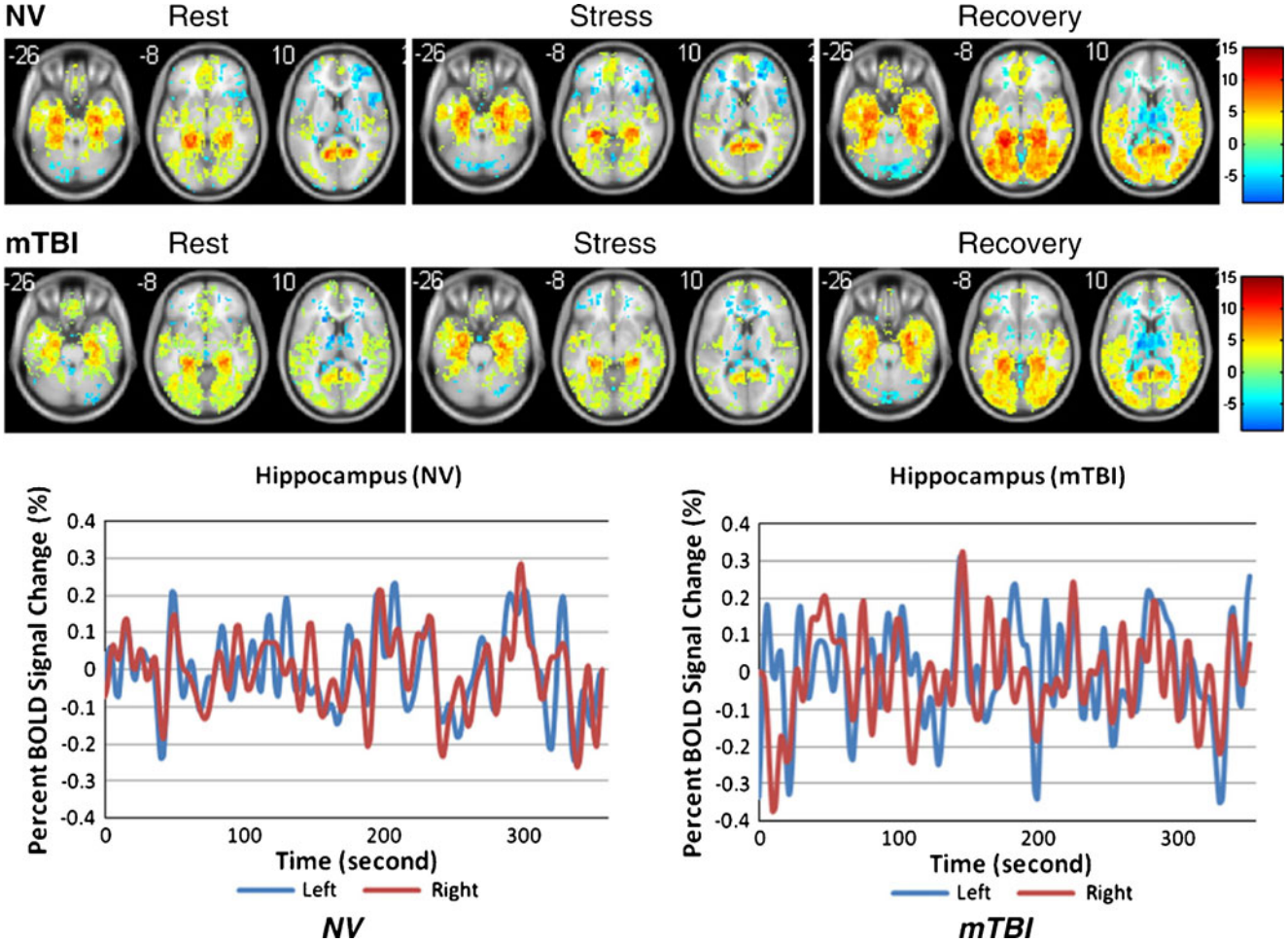

Fig. 6 **a** Functional connectivity maps of the hippocampal network pooled across all subjects indicating correlations between right and left hippocampi as well as with other voxels in the brain (k=100, <0.05, FDR corrected). Positive correlations are depicted in warm colors and their overlap is depicted in red in the conjunction analysis. Negative correlations are depicted in cool colors and their overlap is depicted in blue in the conjunction analysis. Resting state functional connectivity revealed correlations within the hippocampal network (specifically interhemispheric hippocampal connectivity), which were observed in normal volunteers (NVs) and subjects suffering from mild traumatic brain injury (mTBI). This pattern of hippocampal network qualitatively was preserved in response to physical stress and during recovery. **b** BOLD signal percent change for the right and left hippocampi is plotted over time. Visually, the BOLD signal fluctuates more synchronously in NVs as opposed to mTBI subjects. Time course of a single run shown for the seed region (right hippocampus is highly correlated with the left hippocampus (r=0.78, pb0.05) for NVs and mTBI subjects (r=0.56, pb0.05). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.) Courtesy of Elsevier (Slobounov et al., 2011b)

There are at least three possible explanations that may account for additional neuronal recruitment observed in studies of WM dysfunction in mTBI. *First*, "brain reorganization", supposes that additional DLPFC recruitment reflects underlying changes in the neural substrate and/or changes in the functional network associated with WM tasks (Audoin et al. 2003; Levin 2003; Chang et al. 2004; Forn et al. 2006; Mainero et al. 2006; Pantano et al. 2006; Sanchez-Carrion et al. 2008a, b). This change is presumed to be permanent, and the neural resources that are recruited are in charge to maintain a positive relationship with performance. The *second* explanatory construct, most often used interchangeably with the "brain reorganization" concept, is "neural compensation". "Neural compensation" is thought to operate similarly to "brain reorganization" in that it implies transient alteration of brain functions to bolster task performance without permanent alterations in the underlying neural substrate (McAllister et al. 1999, 2001; Maruishi et al. 2007; Turner and Levine 2008; Scheibel et al. 2009). The *third* explanation which has been recently proposed by Hillary et al. (2010) posits that extensive neural recruitment in PFC largely represents a natural support mechanism operating in response to degraded performance. This notion was proposed based on their major fMRI findings and formalized as the "latent support hypothesis" neural recruitment is neither permanent, nor operating to bolster cognitive functioning (Hillary 2008; Hillary et al. 2010). Rather, the hyper-activation of PFC and occasional anterior cingulate

cortex (ACC) recruitment observed in TBI and other neurological disorders represents the engagement of cognitive control and attentional resources (Courtney 2004; Weissman et al. 2006) in order to meet task demands in a "challenged" neural system (Hillary 2008). This position argues that the PFC is subserving an identical support function as has been observed in healthy adults during task load manipulations (Braver et al. 1997; Rypma and D'Esposito 1999; Jaeggi et al. 2003; Landau et al. 2004). Also, an additional region often shown to be recruited in the mTBI population, the inferior parietal cortex (IPC), is an important region subserving WM function, as was revealed by Owen's fMRI study (Owen et al. 2005).

It should be noted however, that Chen et al. reported opposite findings suggesting a reduction (hypo-activation) of fMRI BOLD in the mid-DLPFC in symptomatic concussed subjects in conjunction with poorer performance on the WM tasks (Chen et al. 2004). Later on, this group reported additional activation in concussed subjects in the posterior brain regions including the left temporal lobe that were not present in the normal controls (Chen et al. 2007). Most recently, Chen et al. reported reduced activation in DLPFC and striatum in concussed athletes with depression who have no performance difference compared to patients without depression and healthy controls (Chen et al. 2008). In a more recent Mayer et al. (2009) study, mTBI individuals also reported hypo-activation within several cortical and subcortical areas along with poor performance of auditory orientation and attention inhibition tasks. Another study of mTBI patients within 6 weeks post-injury reported no significant difference in the brain activation patterns compared to normal volunteers, but there was an inverse correlation between medial temporal lobe activation and injury severity (Stulemeijer et al. 2010). Clearly, whether research methodology pitfalls (i.e., differential time of scanning since injury, susceptibility artifact, SNR especially when dealing with group analysis), conceptual biases (e.g., selecting primarily frontal and anterior temporal ROIs as the common site for the brain damage after TBI) or inhomogeneity of the mTBI subjects (differential severity of acute brain injury and/or lack of control for the history of multiple concussive and sub-concussive blows) may cause controversial fMRI finding obtained in different research laboratories and requires further analysis.

Resting-state functional connectivity from fMRI

There has been recent focus in studies using BOLD fMRI to approximate brain activation patterns, specifically to incorporate baseline or "resting state" measurement of the BOLD signal. Conceptually, the human brain has two contradictory properties: (1) "segregation", which means localization of specific functions; and (2) "integration", which means combining all the information and functions at a global level within the conceptual framework of a "global integrated network" (Varela et al. 2001; Reijneveld et al. 2007). Consistent with this conceptual framework, Biswal et al. were the first to document the spontaneous fluctuations within the motor system and high potential for functional connectivity in resting state fMRI (rs-fMRI) using intrinsic activity correlations (Biswal et al. 1995). Since this discovery of coherent spontaneous fluctuations, many studies have shown that several brain regions engaged during various cognitive tasks also form coherent large-scale brain networks that can be identified using rs-fMRI (Smith et al. 2009). For more information, please visit the review by Stevens et al. in this special issue.

The recent advances in brain imaging technologies offer promise for improving clinical applicability of fMRI examining spontaneous modulations in the BOLD signal that occur during resting state (Fox and Raichle 2007). In contrast to the traditional task-related approach, rs-fMRI has thus provided unique information about the behavior of networks in the absence of direct task and/or stimulation. In this approach, subjects generally are asked to lie quietly with eyes closed or while fixating on a crosshair. One of the reasons to use resting state functional connectivity for clinical applications is that the task-related increases in neuronal metabolism are usually small (5 %) when compared to the larger resting energy consumption (20 % of the body's energy, most of which supports ongoing neuronal signaling) (Raichle and Mintun 2006) and eliminates differences based upon performance. Overall, ongoing spontaneous activity provides a window into the neural processing that appears to consume the vast majority of the brain resources, which might provide a more accurate and richer source of disease-related BOLD signal change (Fox and Greicius 2010).

Recent fMRI reports have indicated alterations of resting state functional connectivity in neurological populations, including mTBI and have brought new insight into better understanding the pathophysiology of these disorders. Nakamura et al. examined neural network properties at separate time points during recovery from TBI (Nakamura et al. 2009). They reported that the strength but not the number of network connections diminished during the acute phase of TBI indicating the disruption of the neural system. Marguez de la Plata also reported a deficit in the functional connectivity of the hippocampus and frontal lobe circuits 6 months after traumatic diffuse axonal injury (DAI) (de la Plata et al. 2011). In our own recent study, we focused on alterations of several interhemispheric brain functional networks at rest and in response to the YMCA physical stress test in subjects suffering from sports-related mTBI (Slobounov et al. 2011b).

Overall, we found that interhemispheric connectivity was significantly reduced in the primary visual cortex, hippocampal and dorsolateral prefrontal cortex networks in mTBI subjects. However, the YMCA physical stress induced non-specific and similar changes in brain network connectivity patterns in both the mTBI and normal control groups. Considering the fact that all mTBI subjects were clinically asymptomatic at the time of scanning, our findings clearly indicate that functional brain alterations in the acute phase of injury are overlooked when conventional clinical and neuropsychological examinations are used.

In fact, similar rs-fMRI data were earlier reported by Nakamura et al. indicating such a change in the context of "sparsity", meaning that the magnitude of the cortical connections between nodes within the whole brain is reduced in TBI patients (Nakamura et al. 2009). They hypothesized that alterations in the neural connections observed during recovery may not signify formal brain reorganization (e.g., creation of novel connections). Instead these changes represent utilization of existing support resources early after neural disruption and this demand on auxiliary resources diminishes later, thereby resulting in a less costly network with greater neural efficiency.

Default mode network (DMN)

The existence of a "default mode network" in the brain during the resting state was reported by Greicius et al. (Greicius et al. 2003). Both functional and structural connectivity between brain regions were examined to detect whether there are orderly sets of regions that have particularly high local connections (forming families of clusters) as well as limited number of regions that serve as relay stations or hubs (Sporns et al. 2007). It was suggested that the neural network of the brain has a small-world structure, namely, high-cluster coefficients and low average path length allowing optimization of information processing (Reijneveld et al. 2007). Overall, network analysis is necessary to explore the integration phenomena observed in both resting states and in response to high-level information processing in the brain induced by cognitive and/or motor tasks. As one of the resting state networks (RSN) of the brain, the DMN includes the precuneus/posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), and medial, lateral, and inferior parietal cortex (Broyd et al. 2009). Although the DMN is active during rest it is not actively involved in attention or goal-oriented tasks (Raichle et al. 2001). Despite the fact that the DMN is deactivated during specific tasks, the presence of the DMN during rs-fMRI has been reported and validated in several studies (Greicius et al. 2003; Beckmann et al. 2005; Damoiseaux et al. 2006; De Luca et al. 2006).

Up-to-date, there are few reports focusing on alteration of DMN in mild TBI. Mayer et al. (2011) investigated the resting state DMN of sub-acute mTBI and showed that these subjects displayed decreased BOLD connectivity within the DMN and hyper-connectivity between the right prefrontal and posterior parietal cortices involved in the fronto-parietal task-related network (TRN). However, inhomogeneities such as: (a) differential diagnosis of mTBI including the presence or absence of loss of consciousness (LOC); (b) time since injury; and (c) detailed subject's medical history that includes information on past head injuries influence fMRI data. In our own recent study (Johnson et al. 2012) we examined DMN in mTBI athletes using resting state fMRI with specific focus on recruiting a homogeneous subject population and controlling for the number of previous concussions. We have reported three major findings. *First*, there were disruptions in the connections that make up the DMN in mTBI subjects. Specifically, the mTBI resting state DMN showed no connections in the PCC with both left and right DLPFC and parahippocampal gyri, as well as a reduced number of overall connections and strength of connections. Left and right lateral parietal cortex connectivity in mTBI subjects has shown only ipsilateral connections with DLPFC as compared to bilateral DLPFC connectivity in NV groups. *Second*, we documented an overall reduction in the number and strength of connections in the mTBI group within the left and right parietal cortex ROI seed. That is said, an increased number of connections and strength of connections were seen in the MPFC in mTBI subjects. *Third*, connections between the left DLPFC and left lateral parietal cortex were significantly reduced in magnitude as the number of episodes of mTBI increased as well as an overall downward trend suggesting a larger departure from the DMN as the number of episodes of mTBI increased.

In our most recent rs-fMRI study we focused on the functional integrity and strength of the brain functional connections that make up the DMN in sub-acutely concussed individuals (Zhang et al. 2012). Our expectation that DMN may be jeopardized as a result of mild TBI was not confirmed. In fact, the functional integrity within the DMN (PCC, LLP, RLP, and DLPFC) lateral parietal ROI, remained resilient to a single episode of concussive blow. The major ROIs constituting the DMN and the connectivity within these four ROIs were similar between NVs and mTBI subjects. However, the YMCA Bike Test disrupted the DMN, significantly reducing magnitude of connection between PCC and left lateral parietal ROI, PCC and right lateral parietal ROI, as well as between PCC and MPFC in mTBI subjects. Thus, while the DMN remained resilient to a single mTBI without exertion at 10 days post injury, it was altered in response to the light intensity of physical stress. This may explain some clinical features of mTBI and gives some insight into its pathology. This important and novel finding should be considered by clinical practitioners when making the decision regarding the recovery and return to play for athletes with mTBI (see also Fig. 7).

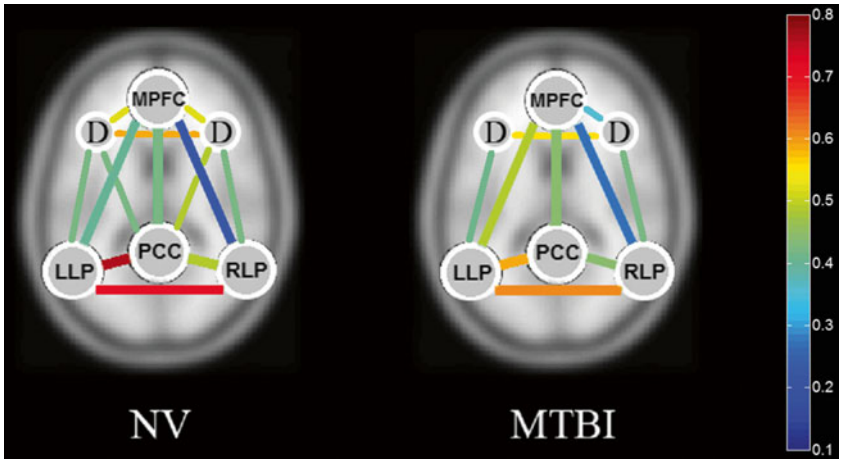

Fig. 7 Graphic representation of the DMN and its connections to dorsolateral prefrontal cortex (D). The strength of connectivity is reflected by color in terms of correlation coefficients (r). Usually $r>0.3$ is used as a threshold of valid connection. False Detection Rate (FDR) correction is used for multiple comparisons

Diffusion tensor imaging (DTI)

Diffusion tensor imaging (DTI) is an advanced imaging technique that exploits the molecular diffusion or Brownian motion of water due to thermal energy. Due to this random diffusion the displacement and motion of molecules can be used to gain information on microscopic tissue structures and characteristics that are beyond the basic resolution of MRI (Le Bihan 2001). Brownian motion is random and this free diffusion is described as being isotropic yet the direction and mobility of water molecules can be restricted by certain tissue characteristics and structures that result in anisotropy (Snook 2005). In the white matter of the brain this diffusion anisotropy becomes ever apparent as myelinated axonal fibers organized into bundles and tracts allow for quicker diffusion along axonal fibers as compared to diffusion oriented perpendicular to the fiber (Le Bihan 2001). As the name implies a tensor model is fitted in order to obtain certain indices, λ_1, λ_2, and λ_3 that allow for a quantitative description of this anisotropic diffusion, where λ_1 is the axial diffusivity, and λ_2 and $\lambda_3$are combined together to form the radial diffusivity (Sharp 2011). Another important scalar measure reported in the literature is the fractional anisotropy (FA). The FA value is between 0 and 1, with 0 representing free diffusion in all directions and 1 representing diffusion confined to only one direction. More precisely the FA value is the ratio of the direction of maximal diffusion to the diffusion that is perpendicular to that main direction (Sharp 2011). Further metrics include the apparent diffusion coefficient (ADC) which tries to correct image contrasts due to relaxation effects or diffusion, and the mean diffusivity (MD) which is an averaged value of diffusion. See also graphical representation of the DTI tractography in the following Fig. 8. For more detailed clarification of DTI, please refer to Shenton et al. in this special issue.

As is the nature of mTBI shearing forces cause diffuse axonal injury (DAI) and initiate a complex pathophysiological response that can alter the cellular environment and brain function (Bryant 1999). DAI in the highly vulnerable white matter is known to produce microscopic lesions, myelin loss, axonal degeneration and axonal swelling all of which can affect diffusion (Maruta et al. 2010). Due to its sensitivity DTI offers a promising tool in assessing and investigating alterations in the brain following injury (Chu et al. 2009).

Clearly, feasibility of DTI in isolation (Wilde, et al., 2012) and in conjunction with volumetric analysis (Shah et al., 2012) to monitor the evolution of moderate-to-severe TBI have been recently documented both in adult and pediatric patients. DTI studies are also gaining popularity in mild TBI research and a recent review of the literature by Sharp and Ham (2011) reported that DTI studies in the subacute and chronic stages the major findings are either a decrease in FA and an increase in MD or both; compared to the opposite findings during the acute phase of injury. As the injury and subsequent recovery from mTBI evolves, many cellular processes are taking place and changing the diffusion properties measured by DTI. These results suggest that even though DTI is sensitive to detect changes in the diffusion patterns, especially in the white matter, work still needs to be done to optimize the effectiveness and use of DTI. Also adding to the confusion in the literature is the lack of uniformity in DTI protocols and the ability to standardize the data, with multiple parameters that can be adjusted along

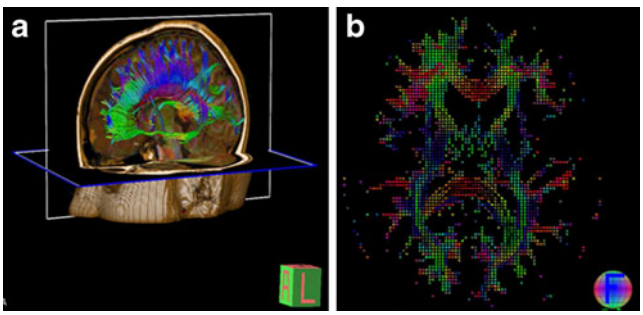

Fig. 8 Examples of DTI tractography (**a**) and tensor (**b**) images allowing for visualization of orientation and direction of white matter bundles

with the number of different vendor platforms on which DTI is performed (Zhu et al. 2011).

There are a few mTBI studies that use DTI and direct their focus on the pediatric to young adult population (Bazarian et al. 2007; Wilde et al. 2008; Chu et al. 2009; Zhang et al. 2010; Cubon 2011; Henry et al. 2011; Maugans et al. 2012) with a majority falling into either adolescent or collegiate age groups. Similar to the DTI studies in adults during the acute phase of injury, studies report an increase in FA values and a reduction in ADC and radial diffusivity. An acute study by Chu et al. (2009) of mTBI in adolescents with a mean age of 15.7 years old used both voxel based and region of interest (ROI) based analysis of DTI. Voxel based analysis revealed 6 areas with a reduction in ADC values and increased FA values, which is reflective of acute injury and resulting cytotoxic edema. Another acute stubby by Wilde et al. (2008) took 10 adolescents aging from 14 to 17 years old and performed DTI scans 1–6 days after mTBI. Statistical analysis found a significant increase in FA as well as a decrease in ADC and radial diffusivity in the corpus callosum. Surprisingly though, a 2012 study by Maugans et al. of 12 children between the ages of 11–15 showed no differences in any DTI metrics from age matched controls and from scans acquired at 3, 14, and 30 days post injury. Although in another study that recruited 18 collegiate male football players (mean age 22.08) who had suffered a concussion performed DTI scans within 5 days of injury and then follow-up scans at 6 months post injury (Henry et al. 2011) there were contradictory results found in the chronic phase of injury. FA values were elevated in the 6 month scan from both the control group and the acute scan. Overall ANOVA revealed site-specific main group effects of FA and axial diffusivity with FA increasing in the dorsal regions of the corpus callosum and corticospinal tract and axial diffusivity elevated in the right corticospinal tract. MD values were also found to be decreased in the concussed group.

It seems that time from injury is an important element when utilizing DTI. As scanning takes place further away from the initial insult the majority of studies have shown some inconsistent results. In a subacute study of collegiate athletes (mean age 21.3) scanned at 30 days post injury by Zhang et al. (2010) no differences in FA values between the mTBI group and controls were observed with both voxel and ROI based analysis methods. However, a larger variability of FA values in the corpus callosum was observed for the mTBI group and a significant reduction of ADC in both the left and right dorsolateral prefrontal cortex. A recent voxel based analysis of DTI study of high school athletes by Bazarian et al. (2012) performed DTI within a 3 month interval pre and postseason. Despite the small sample size 1 athlete received a concussion during the season and had the largest number of affected voxels in the white matter. Specifically, this athlete showed significant changes of FA values in 3.19 % and mean diffusivity in 3.44 % of white matter voxels from the preseason to post season scan with an overall increase in FA and decrease in mean diffusivity values. Another investigation into collegiate concussion took 10 concussed athletes (mean age 19.7) and scanned them with DTI at least 1 month post injury (Cubon 2011). Again a voxel based analysis was implemented and revealed significant increases in mean diffusivity only in the left hemisphere. It is also important to note that in this study a majority of subjects had a prior history of concussion. This highlights the importance in taking into consideration when analyzing data the history of previous mTBI or concussion. Another concern when using DTI in younger patients is the fact that there are differences between pediatric and adult brains. As the brain develops there are many changes seen in the grey and white matter that are associated with the changing microstructures of the tissues that coincide with process of myelination, synaptogenesis and dendritc arborization (Neil et al. 2002). Consequently ADC values are higher in pediatric populations and decrease with age and are associated with changes in brain water content (Neil et al. 2002) and FA has been shown to increase sharply from childhood to adolescence and a continued increase at a slower rate from adolescence to adult (Asato 2010).

Overall DTI studies of mTBI in the younger age ranges have seen time from injury to testing dependent results, with an increase in FA and a decrease in ADC the closer DTI is performed to the time of insult. Conversely it appears as DTI is acquired later and later after concussion the findings become more varied and unpredictable. DTI offers valuable structural and molecular information and insight into the brain and as it becomes more commonplace in neuroimaging studies, work needs to be done to optimize its effectiveness. This being said it is also important to keep this in mind as newer and more advanced techniques that try to improve on some of the limitations of DTI like: diffusion spectrum imaging (DSI), Hybrid Diffusion Imaging (HYDI), q-ball imaging (QBI), and High Angular Resolution Diffusion Imaging (HARDI) are implemented in mTBI research.

Magnetic resonance spectroscopy (MRS)

Magnetic resonance spectroscopy (MRS) is a useful tool that allows for identification and quantification of cellular metabolites in vivo (Shekdar 2011). As with many MRI applications there are a number of different parameters and pulse sequences that can be used in order to acquire MRS data, all of which have their advantages and disadvantages and can make comparisons between studies difficult. The metabolites in the brain that are most often studied are N-acetylaspartate (NAA), choline (Cho), and creatine-phosphocreatine (Cr) (Cecil 1998; Belanger 2007; Govind 2010). NAA is used as an indicator of neuronal and axonal integrity as decreased levels are seen after injury and associated with neuronal loss,

metabolic dysfunction, or myelin repair (Gasparovic et al. 2009). The second most common MRS finding after head trauma behind decreases in NAA are increases in Cho levels (Ross 1998) which are a marker of cell membrane turnover (Shekdar 2011). The Cr peak, which is a combination of the two creatine-containing compounds (creatine and creatine phosphate), is an accepted indicator of cell energy metabolism (Signoretti et al. 2009). Despite the information MRS can yield about the metabolic response of the brain to injury there are limited numbers of studies that utilize it to evaluate mTBI in the childhood to young adult age ranges (Walz 2008; Johnson 2012; Maugans et al. 2012). Most MRS studies that do look at this younger age population focus on the moderate to severe TBI spectrum (Babikian 2010) or have an age range that does not allow for clear delineation of the younger age group (Kirov 2007; Babikian 2010; Govind 2010; Vagnozzi et al. 2010). For further information on metabolic imaging including MRS, single photon emission tomography (SPECT) and positron emission tomography (PET), please see the article by Lin et al. in this special issue.

A recent study of collegiate athletes recovering from mTBI used MRS to assess the sub-acute phase of injury (Johnson 2012). All subjects were clinically asymptomatic at the time MRS evaluation was performed and analysis was focused on the genu and splenium of the corpus callosum. The main finding was a reduction in NAA/Cr and NNA/Cho levels in both ROIs as compared to controls. A 2008 study by Walz et al., used MRS to look at children ages 3–11 that received a TBI whether it be a mild to severe case. In this study, 3 of the children were classified as having mild TBI but no direct mention or separation of these 3 individuals was done. Overall they found a trend that NAA levels in the medial frontal gray matter were lower and that Glasgow Coma Scale score was significantly correlated in this area to NAA and Cr levels. Similar to their DTI results Maugans et al. (2012) found contradictory MRS results with no significant differences between children and controls. Specifically they reported that mean NAA values and NAA/Cr ratio in the frontal gray matter, left frontal white matter, and left thalamus were comparable between the two groups and did not change significantly over time.

It is apparent that despite the current literature, it is hard to find advanced neuroimaging studies like MRS that fit the criteria of strictly childhood to young adult patients who have suffered only from a mild form of TBI. This lack of specificity in the mTBI research is understandable due to its inherent complexities, but should be taken into consideration so more directed investigations can be designed to help uncover the subtle abnormalities seen after a concussion. As seen with DTI it is important to understand the changes that the brain is undergoing during development and maturity as these might influence and change MRS results. NAA levels in the brain increase rapidly during maturation and peak around 10–15 years of age and then begin a slow decline as the number of neurons decreases (Shekdar 2011). After approximately age 2, Cho has reached normal levels and after the first year of birth Cr concentrations remain stable and is therefore sometimes used as an

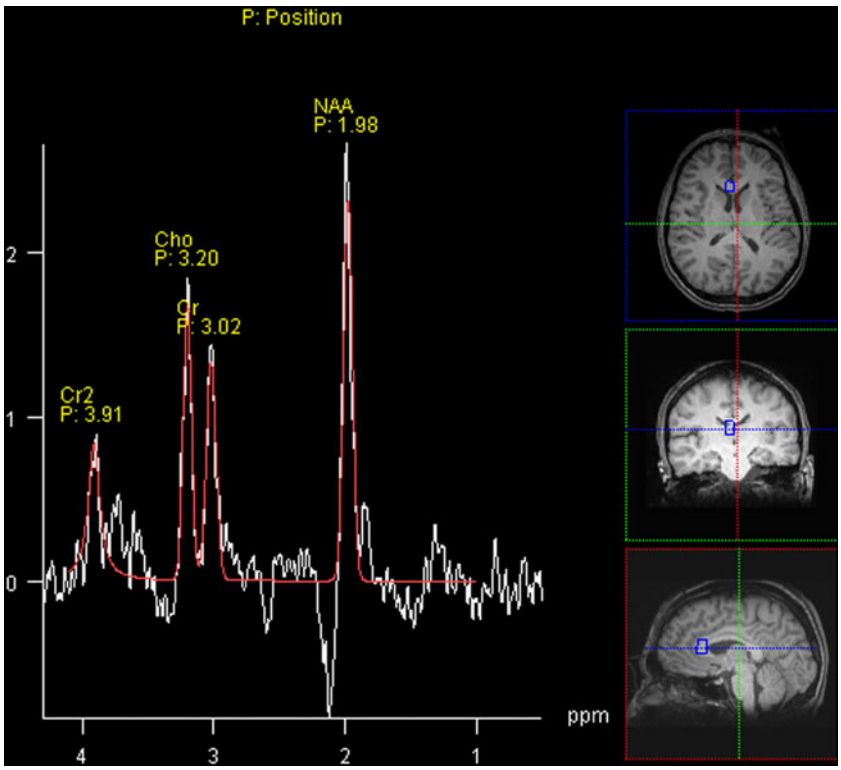

Fig. 9 Example of ^{1}H-MRS spectrum obtained from a voxel outlined in blue on the three reference images on the right and where P denotes the position of the peak in parts per million (ppm)

internal control when using ratios to evaluate certain metabolites (Shekdar 2011).

The general findings in MRS studies of mild TBI have been a reduction in NAA and an increase in Cho with Cr remaining stable (see Fig. 9). However, recent studies by Gasparovic et al. (2009) imply that Cr may not be as stable as once thought and the sheer lack of numbers of MRS studies focused directly on the pediatric to young adult population makes interpretation of the results difficult.

Concluding statement

With this aforementioned information in mind, it becomes clear that the proposed solution for existing controversies in sport-concussion research needs to result in a combination of multiple modalities that will be able to concurrently record performance (functional) variables as well as structural brain imaging (fMRI, DTI, MRS, EEG) variables. Clinicians should be interested not only in the restoration of successful functional performance (memory, balance, executive functions) as well as the structural (neural) underpinnings of that performance. Numerous multimodal findings obtained in our research laboratory are indicative of the types of results to which clinicians should be attentive. These studies seek to find a behavioral resolution and its structural underpinnings. How does a subject recovering from mild TBI perform and does the subject cognitive recruitment match that of a cohort of normal controls with no history of head injury? Is there ever ultimate restoration of a normal structural components and functional integrity, or permanent "brain reorganization"? With combined modality longitudinal studies, we can come closer to answering that question.

And the final thought Conventional wisdom holds that *typical* recovery following a sport-related mTBI is rapid, with most acute clinical symptoms resolving within hours, so that a person is symptom-free by around 10 days post-injury. However, there is growing evidence of an *atypical evolution* of mild TBI whereby physical, neurocognitive, emotional symptoms and underlying neural alterations persist months or even years post-injury. The findings of recent brain imaging studies challenge the conventional wisdom that is based on clinical research of mTBI. The discrepancies and controversies may be attributable to several possible factors including: (a) lack of sensitivity and specificity of conventional assessment tools currently used in clinical practice; (b) inhomogeneity of subject studies; (c) differential sensitivity of various brain imaging modalities as injury evolves; and (d) different time frame of assessment since injury. In order to resolve this controversy it is necessary to conduct systematic research using a homogeneous subject population and advanced research tools with a specific focus on examining the neural mechanisms underlying the consequences of mTBI.

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