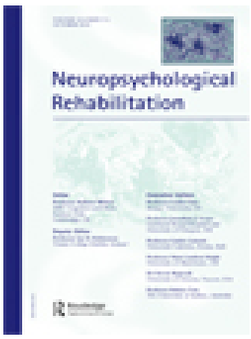

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Research Digest

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Research Digest

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UNDERSTANDING THE ORGANIC BASIS OF PERSISTENT COMPLAINTS IN MTBI: FINDINGS FROM FUNCTIONAL AND STRUCTURAL NEUROIMAGING

Introduction

Mild traumatic brain injury (mTBI; aka concussion) refers to a blow to the head or the exertion of forces to the brain that result in a brief alteration of consciousness (Alexander, 1995). This mild end of the TBI spectrum is typically defined by a loss of consciousness of less than 20 minutes (Esselman & Uomoto, 1995; Inglese et al., 2005; Lipton et al., 2008), less than an hour of post-traumatic amnesia (Lezak, Howieson, & Loring, 2004) or a Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974) score of 13 or greater. Mild TBI is a major public health issue. The estimated annual incidence ranges from 100 to 550 per 100,000 worldwide (Belanger, Vanderploeg, Curtiss, & Warden, 2007), and people who sustain mTBIs report a range of symptoms including headache, dizziness, memory and concentration difficulties, and mood changes (Lezak et al., 2004). These symptoms often resolve by three months post-injury (Iverson, 2005), but they sometimes endure (Middleboe, Andersen, Birket-Smith, & Friis, 1992) and often impede day-to-day functioning while present (King, 1997).

Although we scan a number of journals, finding good papers of relevance to neuropsychological rehabilitation is not always an easy task and we would be happy to be sent or pointed to any papers that readers of this journal consider useful, interesting, or even controversial. Contact details: Jonathan.Evans@clinmed.gla.ac.uk; andrew.bateman@ozc.nhs.uk; and levine@psych.utoronto.ca

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A particular challenge for clinicians is that traditional diagnostic tools such as neuropsychological assessment, CT scan and conventional MRI are insufficiently sensitive to reliably detect the mild, but nonetheless deleterious clinical symptoms of mTBI (Benson et al., 2007). In the absence of sensitive diagnostic measures, and in particular a reliable association between neuroimaging findings and the behavioural sequelae of mTBI, there has been a longstanding debate in the literature about whether the cause of clinical complaints – particularly persisting complaints – is truly organic (Macleod, 2010; Smith, Meaney, & Shull, 2003). Some have alternatively argued for a psychological explanation of ongoing clinical complaints (Barth, Diamond, & Errico, 1996; Hoge et al., 2008; Smith-Seemiller, Fow, Kant, & Franzen, 2003) and others have argued for a blend of organic and psychological (Bryant, 2001, 2008; Lishman, 1988). This research digest discusses two recent papers that speak to this debate (Kumar, Rao, Chandramouli, & Pillai, 2009 and Lo, Shifteh, Gold, Bello, & Lipton, 2009). Kumar et al. (2009) illustrate a novel approach to mTBI assessment, which they use to reveal a specific mapping between alterations in brain activation and changes in cognitive functioning. Lo et al. (2009) use diffusion tensor imaging (DTI) to illustrate neuropathology in chronic mTBI patients with persisting cognitive impairments.

Background

For many decades, the psychogenic explanation of chronic symptoms of mTBI has held sway in the research and clinical literature. For example, Lishman (1988) offered a "synthesis" model of post-concussive syndrome, suggesting that early organic symptoms could be converted into a psychogenic persisting disorder based on complex circumstances of injury, time and pre-morbid characteristics. Machulda, Bergquist, Ito and Chew (1998) found that the base rates of cognitive complaints in healthy individuals without concussion, but high "perceived stress" (referring to one's attitude towards stressors, i.e., whether one is inclined to inflate or minimise the significance of stressors) was comparable to that of chronic mTBI sufferers, and thus it was one's management of stress rather than actual brain injury that might explain the presence of *persisting* cognitive complaints after concussion. More recently, Hoge et al. (2008) examined a large cohort of soldiers 15–16 months following mTBI and found that aside from headache, mTBI did not significantly explain outcome variance on a range of health and functional outcome measures once post-traumatic stress disorder and clinical depression were controlled.

What is needed on the physiogenic side of the debate is a body of persuasive empirical findings linking positive neuroimaging to objective cognitive findings (Lee et al., 2008), particularly for chronic sufferers of mTBI. The first

paper that we review, by Kumar et al., (2009), links neurophysiological measures to cognitive impairments in a group of primarily sub-acute mTBI patients. In order to apply these findings clinically, what is further needed is a diagnostic test that permits a case-by-case understanding of the organic contributions to mTBI. DTI is an approach with the potential for single case diagnosis of mTBI. The second paper that we review, by Lo et al., (2009), provides data that underscore the potential clinical utility of DTI for chronic mTBI.

Research review

Kumar, S., Rao, S. L., Chandramouli, B. A., & Pillai, S. V. (2009). Reduction of functional brain connectivity in mild traumatic brain injury during working memory. *Journal of Neurotrauma, 26*(5), 665-675.

Kumar et al. (2009) compared 30 patients with mTBI to 30 group-matched controls. The study offers persuasive evidence of cognitive impairment that is linked to specific and predicted neurological underpinnings in a group of sub-acute patients with mTBI (2 months from injury on average; range 1–9 months). Kumar et al. (2009) examined coherence patterns of the brain on EEG (using spectral EEG analysis) as a measure of functional interactions of brain regions during the performance of a working memory task. Working memory involves the activation of fronto-parietal networks (Chuah, Maybery, & Fox, 2004; D'Esposito, et al., 1998), and a small number of previous studies have demonstrated that mTBI can disrupt the functional connectivity of these networks (e.g., Nuwer, Hovda, Schrader, & Vespa, 2005). The Kumar paper replicated these studies, and extended them by examining functional connectivity disruptions during each of the discrete stages of working memory (i.e., encoding, rehearsal, retrieval), and also by asking whether these alterations in functional networks were evident during a resting (i.e., task-free) condition.

Connectivity was examined between a number of regions: (1) intra-hemispherically at long range (frontal-parietal), mid-range (frontal-temporal; temporal-parietal) and short range (within the frontal, temporal, and parietal lobes separately) and (2) inter-hemispherically, across both frontal lobes, temporal lobes and parietal lobes. Verbal and visuospatial working memory were examined using a computerised Sternberg paradigm (Sternberg, 1966). The authors reported both brain and behavioural differences between the two groups. First, mTBI patients performed more poorly than control subjects on the tasks. Second, there were significant differences in the coherence of EEG recording patterns between the two groups during different stages of the two tasks. This was particularly significant in the case of frontal and temporal intra-hemispheric and inter-hemispheric connectivity, with significant compromise observed for the mTBI patients. On the other hand, there were no differences in coherence patterns between the

two groups during the resting state scan when subjects were simply asked to close their eyes and let their mind wander, consistent with findings of functional activation differences between TBI patients and controls under conditions of high cognitive demand only (Turner & Levine, 2008).

This research is important in that it provides powerful evidence that the patients in the study showed disrupted connectivity, and that this connectivity was associated with specific cognitive demands. As some of the sample was well beyond three months post-injury, the study also provides some support for an organic basis for chronic cognitive complaints. One limitation of the study was that the between-group design makes interpretation of differences in functional brain response less clear. For example, anxiety can alter patterns of EEG activity (Nuwer et al., 2005), raising the possibility that the functional brain differences reported here were secondary to task-related anxiety rather than reflecting altered neurocognitive patterns *per se*; this limitation is mitigated, though, by the absence of between-group differences in the resting condition. Perhaps a more significant limitation concerns the classification criteria for these mTBI patients. While described as mild on the basis of GCS score at the time of injury (mean of 14.57; range 13–5), 40% of the sample had known intra-cranial abnormalities including contusions and haematomas. They thus fall into the category of complicated mild.

Lo, C., Shifteh, K., Gold, T., Bello, J. A., & Lipton, M. L. (2009). Diffusion tensor imaging abnormalities in patients with mild traumatic brain injury and neurocognitive impairment. *Journal of Computer Assisted Tomography, 33*(2), 293–297.

Lo et al. (2009) examined diffusion tensor imaging (DTI) results in one complicated mTBI and nine uncomplicated. All had sustained mild TBIs, with GCS scores ranging from 13–15, and no neurological abnormalities in those with CT or MRI scans at the time of injury. MRI for the current study was acquired long after injury, ranging from 2.6–10.8 years from injury. Again, all MRI findings were normal, with the exception of one participant who showed evidence of lobar gliosis. All patients were referred for MRI because of persisting cognitive complaints. Neuropsychological assessments (completed anywhere from 1.2–9.3 years post-injury) had been completed prior to the MRI in all cases and assessments revealed mild to severe impairments in at least two domains of cognitive functioning in each patient. The purpose of the study was to compare the DTI findings of these patients with persisting cognitive complaints plus positive neuropsychological findings to a group of age- and sex-matched controls without brain injury.

DTI is an MRI technique with demonstrated sensitivity to the hallmark neuropathology of traumatic brain injury, namely diffuse axonal injury. DTI capitalises upon the directional diffusion of water molecules along white matter. In normal white matter, water movement is constrained and

runs parallel to fibres, with minimal perpendicular diffusion, but when the axons are disrupted, this pattern is disrupted, and diffusion becomes more random (or isotropic). DTI uses several different measures of diffusion (e.g., fractional anisotropy and mean diffusivity) to index the degree to which diffusion is less constrained than expected, reflecting tissue damage.

Lo et al. (2009) did find significant differences between the groups. The investigators identified loss of white matter integrity relative to controls in the genu of the corpus callosum on the left and in the internal capsule bilaterally. This study is very important, despite its small sample size. It is one of only a handful of studies, at the time of writing, to use DTI to assess patients with mTBI, and it is the only ROI study to date to examine DTI findings in patients with chronic cognitive complaints. The study demonstrated that DTI can detect persisting neurological injury years after mTBI in cognitively symptomatic patients. The Lo et al. (2009) paper provides evidence that mTBI can give rise to organically based persisting cognitive deficits.

Clinical implications

These papers illustrate the utility of experimental neuroimaging techniques for detecting mTBI and associated cognitive deficits. Kumar et al. (2009) illustrated a clear relationship between functional activation and working memory deficits; the findings suggest that attempts to confirm the presence of mTBI could focus on working memory in concert with imaging findings. There is debate as to whether or not EEG techniques have potential as a clinical diagnostic tool for mTBI (for discussion, see Nuwer et al., 2005). DTI, on the other hand, arguably has greater potential for the clinical diagnosis of mTBI, including chronic mTBI. However, for sensitive and specific clinical use, normative DTI data for healthy controls and mTBI patients would need to be collected, and this might need to be done separately for each respective MRI platform intended for this use. In addition, given the impact on DTI of demographic variables, normative data would need to be stratified according to those variables known to influence DTI values, such as age (Furutani, Harada, Minato, Morita, & Nishitani, 2005; Hasan, et al., 2007; Kennedy & Raz, 2009; Lee, Danielian, Thomasson, & Baker, 2009) and gender (Westerhausen et al., 2004).

Other experimental imaging techniques have shown potential for detecting abnormalities in mTBI patients who show normal results on conventional diagnostic neuroimaging (for summary, see Belanger et al., 2007 and Le & Gean, 2009). These techniques include functional MRI, magnetic resonance spectroscopy, which measures intracellular chemical ratios that are markers of neuronal integrity (e.g., *N*-acetyl aspartate to creatine or choline) and magnetic source imaging, which allows for assessment of regional dendritic electrical activity. However, these techniques are somewhat more remote from clinical application at this time.

Identification of mTBI is a significant concern for neurorehabilitation practitioners. Not only is the prevalence of mTBI high (Nuwer et al., 2005), but many individuals sustain a brain injury without awareness of its occurrence (Delaney, Abuzeyad, Correa, & Foxford, 2005), particularly when concomitant injuries are sustained that require immediate medical attention (e.g., crush injuries, spinal cord injury and burns; Lew, 2005). Here, in particular, the signs of mTBI (concentration problems, compromised memory, increased aggressiveness or apathy) may be misattributed to the emotional response to injury (Arzaga, Shaw, & Vasile, 2003) or to medication side effects (Davidoff, Roth, & Richards, 1992; Richards et al., 1991). Even if symptoms last only days, in the absence of a formal diagnosis, patients may return to prior activities like contact sports, driving and operation of other heavy machinery, leaving them at elevated risk of harm to themselves and others. Moreover, without a diagnosis and consequent vigilance against another mTBI, for which they are at increased risk (Nuwer et al., 2005), people with mTBI are also vulnerable to second impact syndrome (Saunders & Harbaugh, 1984) and the putative cumulative impact of multiple mTBIs (Nuwer et al., 2005).

Therefore, the diagnosis of mTBI is an important clinical need for society. The studies discussed in this paper provide compelling evidence that for some people, clinical complaints, including chronic ones, have organic underpinnings that are objectively measureable. At this time, DTI is arguably the most promising of the neuroimaging tools for the diagnosis of mTBI in individual patients. However, further work is needed before it will be ready for clinical application.

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