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Neuroimaging after mild traumatic brain injury: Review and meta-analysis ☆

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ABSTRACT

This paper broadly reviews the study of mild traumatic brain injury (mTBI), across the spectrum of neuroimaging modalities. Among the range of imaging methods, however, magnetic resonance imaging (MRI) is unique in its applicability to studying both structure and function. Thus we additionally performed meta-analyses of MRI results to examine 1) the issue of anatomical variability and consistency for functional MRI (fMRI) findings, 2) the analogous issue of anatomical consistency for white-matter findings, and 3) the importance of accounting for the time post injury in diffusion weighted imaging reports. As we discuss, the human neuroimaging literature consists of both small and large studies spanning acute to chronic time points that have examined both structural and functional changes with mTBI, using virtually every available medical imaging modality. Two key commonalities have been used across the majority of imaging studies. The first is the comparison between mTBI and control populations. The second is the attempt to link imaging results with neuropsychological assessments. Our fMRI meta-analysis demonstrates a frontal vulnerability to mTBI, demonstrated by decreased signal in prefrontal cortex compared to controls. This vulnerability is further highlighted by examining the frequency of reported mTBI white matter anisotropy, in which we show a strong anterior-to-posterior gradient (with anterior regions being more frequently reported in mTBI). Our final DTI meta-analysis examines a debated topic arising from inconsistent anisotropy findings across studies. Our results support the hypothesis that acute mTBI is associated with elevated anisotropy values and chronic mTBI complaints are correlated with depressed anisotropy. Thus, this review and set of meta-analyses demonstrate several important points about the ongoing use of neuroimaging to understand the functional and structural changes that occur throughout the time course of mTBI recovery. Based on the complexity of mTBI, however, much more work in this area is required to characterize injury mechanisms and recovery factors and to achieve clinically-relevant capabilities for diagnosis.

1. Introduction

Two important points about today's neuroimaging clinical standard of care of mTBI may be surprising. First, even though MRI is a premier modality for imaging the brain, when used in conventional clinical modes (e.g. T2- and T1-weighted structural scans) it adds little to clinical diagnoses beyond what is provided by CT (computed tomography). Thus CTs, which are faster and more cost-effective (Holmes et al., 2012; Stein et al., 2006), are routinely used by the emergency department, while MRIs, which do not pose a health risk from repeated ionizing radiation exposure, are virtually never utilized for mTBIs. Second, imaging is not used to diagnose mTBI itself, but to test for hematomas as well as to rule out head injury complications from more severe trauma. Various guidelines for diagnosing mTBI exist, most of which rely on the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) and details of the injury (such as self and witness reported descriptions of the accident, loss of consciousness, and evaluation of sustained trauma) (Ruff et al., 2009). The GCS assesses motor, verbal and eye responses; while there is some variability in the categories, a GCS

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from 13 to 15 is often designated as mild TBI, 8 or below is considered severe, and 9 to 12 is considered a moderate TBI (Jennett, 1998; Parikh et al., 2007). Ultimately, the diagnosis of TBI and its severity is made by a clinician. Approximately 1.4 million Americans receive TBI (Langlois et al., 2004), with most of these categorized as mTBIs (Cassidy et al., 2004).

Although mTBI has long been considered a noncritical injury, serious short and long term effects have been documented. Additionally, there is broad acceptance that multiple mTBIs can have serious long-term consequences (Guskiewicz et al., 2003). There are two common conjectures regarding the etiology of mTBI. The first is that the frontal and anterior cortices are vulnerable to neural contusion (Adams et al., 1980; Beaumont and Gennarelli, 2006; Brandstack et al., 2006; Levin et al., 1992). The second is that linear and rotational forces act on axon bundles, leading to axonal injury (Buki and Povlishock, 2006; Gennarelli et al., 1982; Meythaler et al., 2001; Povlishock et al., 1992). After initial injury, secondary mechanisms elicit biochemical, metabolic, and cellular changes in the time frame of minutes, days and months (Giza and Hovda, 2001; Loane and Faden, 2010; Xiong et al., 1997). Within the first fifteen minute post-injury, there is an extreme dip in neuropsychological performance (McCrea et al., 2002) and deficits can often linger for a week or longer (McCrea et al., 2003). The definition of the acute time frame varies across publications and some studies report acute periods of up to 1 month post-injury (Landre et al., 2006). Our study uses the term acute mTBI up to two weeks post-injury. Using the term acute or "semi-acute" for time periods up to 2 weeks post-injury is common in the literature (Gasparovic et al., 2009; Mac Donald et al., 2011; Mayer et al., 2010; Messe et al., 2011). Most mTBI patients recover, but a substantial minority have persistent disabling problems (Alexander, 1995; Kushner, 1998), known as post-concussion syndrome (PCS). Although criteria have been established by the Diagnostic and Statistical Manual of Mental Disorders IV (American Psychiatric Association, 2000) and International Statistical Classification of Diseases and Related Health Problems (ICD-10), PCS is difficult to diagnose and its symptoms are nonspecific. PCS also manifests symptoms similar to other disorders such as major depression (Iverson, 2006; Iverson and Lange, 2003), chronic pain (Smith-Seemiller et al., 2003) and other diseases such as somatization disorder. Indeed, neuropsychological testing in chronic stages of mTBI (even on the time scale of months) has been criticized as non-specific and insensitive (Iverson, 2005; McCrea and American Academy of Clinical Neuropsychology, 2008), and several studies have questioned the ecological validity of these assessments (Satz et al., 1999; Silver, 2000) and proposed improved approaches for detecting persisting cognitive deficits and linking these to neuroimaging results (Geary et al., 2010).

Heterogeneity of injury and current limitations in the sensitivity of imaging are challenges to developing diagnostic tools as well as predictors of recovery. Some of the major complicating factors include: 1) the fact that mTBI is a heterogeneous injury, with complicated dependencies on the mechanism of injury (e.g. an automobile accident vs. a military blast exposure) and the directional and temporal profiles of the forces impacting the skull and body; 2) mTBI lesions are diffuse and microscopic; and 3) the expected outcome of most patients is an eventual recovery. Thus, the physical size and heterogeneous distribution of injury in the brain make detection in an individual challenging and further make reliance on group averages problematic. In addition, since the time course of the injury leads to lingering post-concussive symptoms in a small number or injuries (Alexander, 1995; Kushner, 1998), it is a statistically challenging goal to try to predict which individuals will not recover fully. Finally, longitudinally, the presence or absence of CT findings does not correlate with long-term outcomes such as PCS (Hanlon et al., 1999; Huynh et al., 2006; Kurca et al., 2006; Lee et al., 2008; McCullagh et al., 2001; Tellier et al., 2009). To summarize, imaging is challenging at both acute and chronic stages of mTBI, and attempting to characterize the full time course compounds the level of complexity.

Despite the challenges, there has been a growing research effort to characterize structural and functional effects of mTBI. As shown in this paper, the full range of neuroimaging technologies have been brought to bear on this issue, including CT, positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetoencephalography (MEG), electroencencephalography (EEG), and 12 subtypes of MRI, such as diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), arterial spin labeling (ASL) and functional magnetic resonance imaging (fMRI). Moreover, collectively, these studies have examined mTBI at both acute and chronic stages of the injury. In reviewing the literature, it is important to note that the time post-injury of a study can affect its participant exclusion criterion, leading to prospective and symptomatic mTBI groups (Dikmen et al., 1992). In prospective mTBI studies, the exclusion criteria are independent from mTBI (e.g. specific age ranges or drug dependences). Symptomatic mTBI studies recruit chronic participants. Based on estimated recovery rates, this corresponds to effectively excluding the majority of those who sustain mTBIs. In other words, studies of symptomatic groups enroll participants because they have lingering complaints caused (presumably) by their head injury, whereas prospective studies recruit based on mTBI records at the time of concussion (before any chronic mTBI is known).

This paper broadly reviews mTBI neuroimaging studies of structure and function to highlight the tremendous effort that has taken place to investigate the spectrum of acute to chronic time scales. We additionally provide meta-analyses to examine the current utility of MRI for studying both structure and function. In terms of structure, some reports claim that MRI is more sensitive to detect complicated mTBI than CT (Mittl et al., 1994). Similar to other authors, we use complicated mTBI to include the broad range of abnormalities that lead to non-negative imaging results (Arciniegas et al., 2005; Iverson, 2005; Williams et al., 1990). It should be pointed out that definitions of 'mild' vary widely among both clinicians and researchers. Thus while many studies exclude participants with imaging findings, this is not universally the case. Among the other neuroimaging methods, it is also unique in that it can be used to study both structure and function. Many physical parameters provide MRI with a wide range of contrast mechanisms, enabling "traditional" T1- and T2-weighted structural scans, neural correlates of brain function using fMRI, white-matter microstructure by diffusion MRI, and biochemistry through MR spectroscopy. Thus our meta-analyses focus on three areas of MRI study. The first meta-analysis is motivated by the heterogeneity of fMRI findings and focuses on the question of anatomical consistency for fMRI. Similarly, the second analysis examines the issue of white matter vulnerability to mTBI. Looking at anatomically localized findings, previous neuroimaging data suggest that anterior regions of the brain are more vulnerable to abnormalities (Hashimoto and Abo, 2009; Lipton et al., 2009; McAllister et al., 1999; Niogi et al., 2008a). However, published reports are highly heterogeneous in their findings of regional white matter changes. Thus we examined whether anatomical consistency in mTBI lesions exists in the literature.

Our third meta-analysis examines the apparent inconsistency in diffusion-based anisotropy findings across studies that has led to debates about whether or not anisotropy values increase, decrease, or even change at all after mTBI (Lange et al., 2012) as well as whether anisotropy levels positively or negatively correlate with performance levels in neuropsychological assessments (FitzGerald and Crosson, 2011). Recent reports suggest that it is important to consider the time post injury in diffusion weighted imaging (Mayer et al., 2011; Niogi and Mukherjee, 2010). For example, Niogi and Mukherjee (2010) suggest that anisotropy is increased in the acute phase and decreased in the chronic phase in symptomatic TBI patients. Similarly Mayer et al. (2011) note that anisotropy values can be either reduced or increased in semi-acute time points, but tend to be decreased in later, chronic stages of symptomatic mTBI. Based on these considerations, we tested the hypotheses that anisotropy is increased in the acute phase and