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Review

Functional magnetic resonance imaging of mild traumatic brain injury

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ABSTRACT

Functional magnetic resonance imaging (fMRI) offers great promise for elucidating the neuropathology associated with a single or repetitive mild traumatic brain injury (mTBI). The current review discusses the physiological underpinnings of the blood-oxygen level dependent response and how trauma affects the signal. Methodological challenges associated with fMRI data analyses are considered next, followed by a review of current mTBI findings. The majority of evoked studies have examined working memory and attentional functioning, with results suggesting a complex relationship between cognitive load/attentional demand and neuronal activation. Researchers have more recently investigated how brain trauma affects functional connectivity, and the benefits/drawbacks of evoked and functional connectivity studies are also discussed. The review concludes by discussing the major clinical challenges associated with fMRI studies of brain-injured patients, including patient heterogeneity and variations in scan-time post-injury. We conclude that the fMRI signal represents a complex filter through which researchers can measure the physiological correlates of concussive symptoms, an important goal for the burgeoning field of mTBI research.

Contents

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1. Introduction

Recently, there has been a dramatic change in thought regarding the physiological consequences of concussion, also referred to as mild traumatic brain injury (mTBI). It was initially believed that mTBI resulted in limited behavioral and no long-term neurological consequences (Pellman et al., 2004), except for in a small percentage of patients with pre-existing psychiatric conditions. Standard clinical neuroimaging methods (computed tomography scans; T_1- and T_2-weighted images) are typically negative for the majority of concussed patients (Hughes et al., 2004; Iverson, 2006), which helped propagate the view that mTBI did not lead to frank neuronal pathology. However, more recent studies suggest that the life-long effects of concussion, especially when repetitive, may be more severe than initially believed, predominantly a result of the dramatic increase in the diagnoses of chronic traumatic encephalopathy (CTE) amongst recently deceased athletes (McKee et al., 2013). A proliferation of neuroimaging studies of mTBI has also occurred, with different imaging modalities finding that neuronal pathology may be present long after traditional outcome measures (e.g., balance and neuropsychological testing) have returned to pre-morbid levels of functioning (Belanger et al., 2007; Bigler, 2013; Bigler and Maxwell, 2012; Mayer et al., 2011). As a result of these new lines of evidence, it has been suggested that a single concussion can result in lifetime impairment for some individuals. However, a more realistic assessment of the field suggests a nascent understanding of the neuronal and behavioral consequences of both single and repetitive mTBIs in humans, with several key challenges remaining to be resolved.

The goals of the current review are to provide the reader with a more thorough appreciation for the challenges of conducting functional magnetic resonance imaging (fMRI) studies in mTBI. We begin with a discussion of the physiological underpinnings of the blood-oxygen level dependent (BOLD) response, how mTBI may alter it, and the analytic strategies through which researchers attempt to non-invasively capture the effects of neuronal injury. The mTBI literature using both task-based (i.e., evoked) paradigms as well as resting state measurements (i.e., functional connectivity) is reviewed next. Finally, the many methodological challenges associated with fMRI studies of brain-injured patients are discussed from a clinical perspective. Although some groups have made a distinction between the terms concussion and mTBI based on injury severity (reviewed in Harmon et al., 2013), for the purpose of the current paper these terms are used inter-changeably.

2. fMRI physiology and putative effects of trauma

The relation between neuronal activity and the resultant hemodynamic response (i.e., neurovascular coupling) remains a topic of active investigation. The cerebral metabolic rate of glucose (CMR_{glu}), the cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral blood flow (CBF) are tightly coupled in the absence of evoked neuronal activity. There is an increase in metabolic demands/energy requirements following excitatory neuronal transmission, and excess glutamate must be rapidly removed from the synaptic cleft (Attwell et al., 2010; Logothetis, 2008). Astrocytes convert excess glutamate into glutamine and release vasoactive agents, with neurons concurrently releasing nitric oxide (Attwell et al., 2010). These events all contribute to vasodilation and an increase in CBF, followed by a concomitant decoupling between CBF and oxidative metabolism. All of these events ultimately culminate in an excess of oxygenated blood, a decrease in the ratio of deoxyhemoglobin relative to oxyhemoglobin, and a subsequent increase in MR signal due to differences in magnetic properties between the two forms of hemoglobin. Thus, the BOLD response during normal neurovascular coupling represents an amalgamation of signals derived primarily from the ratio of oxy- to deoxyhemoglobin, with contributions from CBF and cerebral blood volume (CBV).

The resultant shape of the BOLD response is similarly complex in nature. The canonical hemodynamic response function (HRF) consists of two primary components, a positive signal change that peaks approximately 4–6 s after stimulus onset, and a post-stimulus undershoot (PSU) that reaches maximum 6–10 s after stimulus end. As previously discussed, the positive phase of the BOLD response has been associated with an increase in CBF, and the resultant change in the ratio of oxy- to deoxyhemoglobin intravascularly (Buxton et al., 2004). The biophysical origins of the PSU are less well established. An early model attributed the PSU to differences in timing of the return of CBF (earlier response) and CBV (delayed response) to baseline levels (Buxton et al., 2004). However, other work indicates that the duration of the PSU extends beyond the time when CBV returns to baseline, leading others to suggest increased demands for $CMRO_2$ as a contributing factor (Schroeter et al., 2006).

Thus, there are several different mechanisms, as well as interactions between mechanisms, through which head trauma can affect the BOLD response (Barkhoudarian et al., 2011). When discussing pre-clinical studies of trauma, it is critical to consider that animal models that accurately represent the mechanical forces experienced in milder forms of human mTBI have only been recently developed (Angoa-Pérez et al., 2014; Chen et al., 2012; Kane et al., 2012; Viano et al., 2009; Xiong et al., 2013). Specifically, most animal models frequently require invasive neurosurgical procedures (i.e., opposed to a true closed-head injury) and induce cortical contusions or other parenchymal alterations of sufficient severity that they are visible with MR, suggestive of more severe injuries in human TBI (Hughes et al., 2004). Critically, these models do not include the rapid acceleration/deceleration and loading factors on the brain that are more typical in human mTBI (Kane et al., 2012; Viano et al., 2009). In addition, non-specific effects of trauma (e.g., pain and fatigue), as well as the presence of prescribed medications (e.g., narcotics or sedatives), can also alter neurovascular coupling following mTBI in both human and animal models of injury.

Principally, trauma can cause frank neuronal dysfunction (e.g., alterations in synchronous excitatory neuronal activity), resulting in down-stream effects on BOLD-based activity through changes in the amount of glutamate in the synaptic cleft and the energetic needs of cells following neurotransmission. Reports of neuronal loss in animal models of fluid percussion injury (Lowenstein et al., 1992) and abnormal cell signaling (Alwis et al., 2012) directly support this hypothesis. Indirect support comes from magnetic resonance spectroscopy findings of altered glutamate and glutamine concentrations in the semi-acute stage (i.e., first few months of injury) of mTBI, as well as through more invasive measures during severe injury models (Hartley et al., 2008; Henry et al., 2011; Yeo et al., 2011).

The structural integrity of the microvasculature can also be directly affected by trauma. Fluid percussion studies in animal models indicate a semi-acute reduction in capillary number and diameter both at the injury site and distally (Park et al., 2009), with several other studies indicating a reduction in cerebral vascular reactivity (Metting et al., 2009). Similarly, hemosiderin depositions, secondary to microhemorrhages and inflammation, have been noted in human cases of mTBI using both non-invasive neuroimaging as well as at autopsy (Bigler and Maxwell, 2012). TBI also directly affects CBF transit time as well as cerebral perfusion (Soustiel and Sviri, 2007). Researchers may capitalize on TBI-related changes in CBF through the use of both static and dynamic arterial spin labeling (ASL). Static ASL can be used to both directly measure CBF and calibrate the BOLD signal for CBF changes (Liau and Liu, 2009), although the measurements must be made in a quantitative