NeuroImage 61 (2012) 1067–1082

Contents lists available at SciVerse ScienceDirect

NeuroImage

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

An automatic MEG low-frequency source imaging approach for detecting injuries in mild and moderate TBI patients with blast and non-blast causes

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ARTICLE INFO

Article history:
Accepted 11 April 2012
Available online 20 April 2012

Keywords:
Magnetoencephalography
Traumatic brain injury
Slow-wave
Blast
Motor vehicle accident
Sport injury

ABSTRACT

Traumatic brain injury (TBI) is a leading cause of sustained impairment in military and civilian populations. However, mild (and some moderate) TBI can be difficult to diagnose because the injuries are often not detectable on conventional MRI or CT. Injured brain tissues in TBI patients generate abnormal low-frequency magnetic activity (ALFMA, peaked at 1–4 Hz) that can be measured and localized by magnetoencephalography (MEG). We developed a new automated MEG low-frequency source imaging method and applied this method in 45 mild TBI (23 from combat-related blasts, and 22 from non-blast causes) and 10 moderate TBI patients (non-blast causes). Seventeen of the patients with mild TBI from blasts had tertiary injuries resulting from the blast. The results show our method detected abnormalities at the rates of 87% for the mild TBI group (blast-induced plus non-blast causes) and 100% for the moderate group. Among the mild TBI patients, the rates of abnormalities were 96% and 77% for the blast and non-blast TBI groups, respectively. The spatial characteristics of abnormal slow-wave generation measured by Z scores in the mild blast TBI group significantly correlated with those in non-blast mild TBI group. Among 96 cortical regions, the likelihood of abnormal slow-wave generation was less in the mild TBI patients with blast than in the mild non-blast TBI patients, suggesting possible protective effects due to the military helmet and armor. Finally, the number of cortical regions that generated abnormal slow-waves correlated significantly with the total post-concussive symptom scores in TBI patients. This study provides a foundation for using MEG low-frequency source imaging to support the clinical diagnosis of TBI.

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Introduction

Traumatic brain injury (TBI) is a leading cause of sustained physical, cognitive, emotional, and behavioral deficits in the civilian population (due to motor vehicle accidents, sports, falls, and assaults) and military personnel (with blast injury as an additional cause). Annually, the Centers for Disease Control reports an estimated 1.7 million people sustain a TBI with 52,000 deaths, 275,000 hospitalizations, and 1.365 million, or nearly 80%, treated and released from an emergency department (Faul et al., 2010). The majority (75%) of the TBIs are in the "mild" range of severity (mTBI) (Centers for Disease Control and Prevention and National Center for Injury Prevention and Control, 2003). An estimated 5.3 million Americans live with disabilities associated with a TBI (Thurman et al., 1999). Blast-related TBI also represents one of the most significant health issues among surviving soldiers wounded in combat in Iraq and Afghanistan. These individuals often have residual impairments which have been attributed to central nervous system (CNS) damage either

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1053-8119/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.neuroimage.2012.04.029

as a direct result of the blast (e.g., blast-wave concussion or blunt trauma from impact) or as a secondary effect of damage to other organs such as the lungs.

Although post-concussive symptoms (PCS) in mTBI often resolve by three months after injury in the majority of individuals (Levin et al., 1987; Rutherford, 1989), about 20% (varying from 8 to 33%) of mTBI patients show persistent long-term cognitive and/or behavioral impairments (Alexander, 1995; Binder, 1986, 1997; Bohnen et al., 1992; Rimel et al., 1981; Rutherford, 1989). There have been few effective treatments for mTBI. Conventional neuroimaging techniques have limited sensitivity to detect physiological alterations caused by TBI and are usually not used to assess the efficacy of mTBI treatments. Mild (and some moderate) TBI can be difficult to detect because the injuries are often not visible on conventional acute MRI or CT (Bigler and Orrison, 2004; Johnston et al., 2001; Kirkwood et al., 2006). Approximately 80% of civilian patients with TBI do not show visible lesions using conventional MRI or CT (Alexander, 1995). For mTBI, intracranial lesions were detected with conventional neuroimaging techniques in only 4%, 16%, and 28% of patients with Glasgow Coma Scale scores (Teasdale and Jennett, 1974) of 15, 14, and 13, respectively (Culotta et al., 1996). Similarly, closed-brain injuries outnumbered penetrating injuries in more than 450 U.S. military TBI patients injured in Iraq and treated as inpatients between January 2003 and February 2007 at Walter Reed Army Medical Center. Of these closed-brain injuries, 56% were considered moderate or severe, and 44% were mild, with no visible lesion on clinical MRI or CT (Okie, 2005). A more recent combat-related TBI study in Operation Iraqi Freedom with 2074 participants showed that 89% of all TBIs were mild (MacGregor et al., 2010). The diagnosis of combat-related mTBI is based primarily on the characteristics of the acute clinical sequelae, following the injury and lesion(s) may be "subtle, scattered, varied,…, not detected on conventional brain CT" (Van Boven et al., 2009). These examples illustrate the limited diagnostic utility of standard neuroimaging techniques in this population. Furthermore, the absence of abnormalities on conventional neuroimaging techniques in the majority of mTBI patients even with post-concussive symptoms and cognitive and/or behavioral deficits illustrates the limited prognostic value of conventional neuroimaging techniques.

Usually, PCS and cognitive deficits in TBI patients cannot be explained solely by focal pathology; traumatic axonal injury (TAI) is another major contributor to these deficits. TAI is commonly induced by a sudden acceleration–deceleration or rotational forces. In a rodent TBI model, a silver staining technique reveals that axonal injury was the most prominent feature following blast exposure (Garman et al., 2011). In humans, the subsequent tissue injury is characterized by axonal stretching, inflammation, disruption, and separation of nerve fibers, although axotomy has been found to be relatively rare in even severe TBI (Adams et al., 1989; Basser and Pierpaoli, 1996; Gennarelli et al., 1982; Xu et al., 2007). Conventional CT and MRI are primarily sensitive to blood from nearby torn capillaries, and less sensitive to axonal damage itself, hence they underestimate the presence of TAI, especially in mTBI cases. The limited diagnostic value and poor predictive utility for long-term outcome of the conventional neuroimaging techniques underscore the urgent need for new neuroimaging methods for better diagnosis and longitudinal assessment of mTBI. The availability of neuroimaging techniques with greater sensitivity to the physiological alterations caused by TBI could promote the development of treatment interventions for mTBI through an improved understanding of brain mechanisms of injury.

Diffusion tensor imaging (DTI)

Diffusion tensor imaging (DTI) measures white-matter integrity in the brain by measuring the Brownian motion of water through tissues. Information obtained from DTI is representative of the local physical properties of tissue and may be used to estimate the location and orientation of white matter within the brain. Recently, DTI has also been used to examine potential axonal injury in mTBI patients with promising results. DTI has been successfully applied in mild, moderate, and severe TBI (Arfanakis et al., 2002; Gupta et al., 2005; Huisman et al., 2004; Inglese et al., 2005; Lee et al., 2006; Salmond et al., 2006; Xu et al., 2007), and the method has shown great potential in providing a better understanding and improved diagnosis of TAI. DTI studies in TBI patients have reported reduced fractional anisotropy (FA) in major white-matter tracts in central areas of the brain (Arfanakis et al., 2002; Gupta et al., 2005; Inglese et al., 2005; Salmond et al., 2006; Wilde et al., 2006; Xu et al., 2007), and the FA abnormality correlates with the GCS and post-traumatic amnesia (Benson et al., 2007). In mTBI patients (civilians and blast-injured military personnel), reduced FA values were found in anterior corona radiata, uncinate fasciculus, corpus callosum, inferior and superior longitudinal fasciculus, cingulum bundle, and middle cerebellar peduncles (Davenport et al., 2012; Mac Donald et al., 2011; Miles et al., 2008; Niogi et al., 2008; Rutgers et al., 2008; Smits et al., 2011). FA reduction is attributed to a change in the parenchymal structure, which may include misalignment of fibers, edema, fiber disruption, and axonal degeneration (Niogi et al., 2008; Rutgers et al., 2008). We also reported reduced FA in a multimodal MEG-DTI study of mTBI (Huang et al., 2009). However, increased FA (Bazarian et al., 2007; Henry et al., 2011; Mayer et al., 2011; Wilde et al., 2008) or no change in FA (Messe et al., 2011; Zhang et al., 2010) has also been reported in mTBI, indicating that more research is needed to delineate the relationships between DTI parameters and underlying neuropathological processes in mTBI.

With these considerations in mind, the present study examined the sensitivity of a new magnetoencephalography (MEG) source imaging approach for detecting pathology in mTBI. MEG demonstrates sensitivity to abnormal neuronal signals resulting from axonal injuries. Pioneering studies by Lewine and colleagues showed that the brains of mTBI patients generate abnormal low-frequency magnetic fields that can be measured and localized by MEG (Lewine et al., 1999; Lewine et al., 2007). They also showed that MEG was more sensitive than conventional MRI or EEG for detecting abnormalities in mTBI patients. Unlike normal spontaneous MEG data which is dominated by neuronal activity with frequencies above 8 Hz, injured neuronal tissues (due to head trauma, brain tumors, stroke, etc.) generate abnormal focal or multi-focal low-frequency neuronal magnetic signal (delta-band 1–4 Hz, or theta-band 5–7 Hz) that can be directly measured and localized using MEG (Baayen et al., 2003; de Jongh et al., 2003; Decker and Knott, 1972; Lewine and Orrison, 1995; Lewine et al., 1999; Nagata et al., 1985; Vieth et al., 1996). However, to make MEG low-frequency source imaging an effective clinical tool for assisting in the diagnosis of mTBI, one must address the following two key questions: 1) what is the neuronal mechanism of abnormal MEG slow-waves in TBI and how are the slow-waves related to axonal injuries? 2) Is it possible to develop an objective, automated, and operator-independent MEG low-frequency source imaging method for detecting and localizing the MEG slow-waves? The first question was addressed by our recent mTBI study using MEG and diffusion tensor imaging (DTI) (Huang et al., 2009), which examined the relationship between DTI abnormalities in white-matter fiber tracts and the generation of abnormal MEG slow-waves in mTBI. To appreciate the relationship between MEG slow-wave and DTI findings in mTBI, it is important to review the closely related animal studies.

Animal studies of delta-wave generation in gray matter and axonal injuries in white matter

Neurophysiological studies in animals have established a solid connection between pathological delta-wave generation in gray