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Mean cortical curvature reflects cytoarchitecture restructuring in mild traumatic brain injury

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ABSTRACT

In the United States alone, the number of persons living with the enduring consequences of traumatic brain injuries is estimated to be between 3.2 and 5 million. This number does not include individuals serving in the United States military or seeking care at Veterans Affairs hospitals. The importance of understanding the neurobiological consequences of mild traumatic brain injury (mTBI) has increased with the return of veterans from conflicts overseas, many of who have suffered this type of brain injury. However, identifying the neuroanatomical regions most affected by mTBI continues to prove challenging. The aim of this study was to assess the use of mean cortical curvature as a potential indicator of progressive tissue loss in a cross-sectional sample of 54 veterans with mTBI compared to 31 controls evaluated with MRI. It was hypothesized that mean cortical curvature would be increased in veterans with mTBI, relative to controls, due in part to cortical restructuring related to tissue volume loss. Mean cortical curvature was assessed in 60 bilateral regions (31 sulcal, 29 gyral). Of the 120 regions investigated, nearly 50% demonstrated significantly increased mean cortical curvature in mTBI relative to controls with 25% remaining significant following multiple comparison correction (all, pFDR < .05). These differences were most prominent in deep gray matter regions of the cortex. Additionally, significant relationships were found between mean cortical curvature and gray and white matter volumes (all, $p < .05$). These findings suggest potentially unique patterns of atrophy by region and indicate that changes in brain microstructure due to mTBI are sensitive to measures of mean curvature.

1. Introduction

The number of persons living with the enduring consequences of traumatic brain injuries (TBI) is estimated to be between 3.2 and 5 million people in the United States alone (Coronado et al., 2012). In 2010, the Centers for Disease Control and Prevention estimated that 2.5 million emergency department visits were TBI related (Centers for Disease Control and Prevention, 2014). However, individuals serving in the United States military or seeking care at Veterans Affairs hospitals are not accounted for in those estimates suggesting the true incidence of TBI is widely underestimated (Centers for Disease Control and Prevention, 2014). With the recent return of veterans from conflicts overseas, increasing pressure is being placed on the medical community to better understand the neurobiological consequences of mild traumatic brain injury (mTBI). However, identifying the regions of the brain most affected by mTBI continues to prove challenging due primarily to the heterogeneous nature of these injuries (Irimia et al., 2014) and diagnostic complexities (Buck, 2011; Shenton et al., 2012; Amyot et al., 2015). Cortical contusions, which involve gray matter and contiguous subcortical white matter, and diffuse axonal injury are two of the most common types of nonpenetrating TBI, which often result in focal damage to the inferior, lateral and anterior aspects of the frontal and temporal lobes and at the gray–white matter junction respectively (Osborn, 2010). Additionally, rapid acceleration or deceleration can lead to focal shear injuries, which are caused by rotational forces, shear, and/or strain on the axon typically at the gray–white matter junction (Bigler, 2001). It has also been suggested that sulcal regions may be biomechanically vulnerable to the dynamic forces associated with the injury which may explain why neurofibrillary tangles are often associated with sulci in chronic traumatic encephalopathy (Smith et al., 2013). Furthermore, recent evidence suggests that tissue pathology related to TBI can be progressive and chronic (Ding et al., 2008; Cole et al., 2015).

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Numerous neuroimaging techniques have been used to investigate changes to brain integrity related to TBI including structural magnetic resonance imaging (MRI), functional MRI (fMRI), diffusion tensor imaging (DTI), magnetoencephalography, positron emission tomography, and macromolecular proton fraction (Huang et al., 2009; Bigler et al., 2010; Yurgelun-Todd et al., 2011; Lopez-Larson et al., 2013; Han et al., 2014; Petrie et al., 2014). Despite the many limitations inherent in studying TBI, progress has been made as emerging technologies allow for novel uses of neuroimaging data to study the effects of TBI. For example, Palacios et al. (2013) examined the contrast between gray and white matter signal intensities between 26 subjects with traumatic axonal injury and 22 controls. They found a pattern of white matter/gray matter contrast reduction in widespread regions of the brain in the TBI group relative to controls. Functional connectivity, a measure of voxel to voxel synchrony based on BOLD fMRI signal, is more frequently being applied to investigate the neuropathology associated with mTBI. Recent advances with this approach are highlighted in Mayer et al. (2015) in a review of the current state of research related to fMRI findings in mTBI populations. In one recent example, Iraji et al. (2015) measured functional connectivity in 358 dense individualized common connectivity based cortical landmarks in 16 mTBI patients compared to 24 controls and found regions of functional hyperconnectivity in the mTBI group. The authors suggest that mTBI may result in connectome-scale brain network connectivity changes resulting in hyper-activation to compensate for the physiological disturbance. Maudsley et al. (2015) used magnetic resonance diffusion and spectroscopy measures to investigate altered metabolism and axonal injury in 40 subjects with a range of TBI severities compared to controls. They found widespread alteration of tissue metabolites in the TBI group relative to controls characterized primarily by increased choline in the cerebellum and cerebrum. A between-group voxel-based analysis using DTI measures revealed few regions with altered fractional anisotropy or mean diffusivity in the TBI group compared to controls. In another example, Trivedi et al. (2007) used SIENA, a package included in the FSL imaging suite, to investigate longitudinal changes to global brain volumes in 37 patients with mild to severe TBI scanned on average of 79 and 409 days post-injury. Longitudinal data from the TBI group were also compared to a control group scanned approximately 6 months apart. Significantly greater percent brain volume change was reported in the TBI group relative to controls. Greater percent brain volume changes were also associated with a longer post-injury coma durations suggesting a relationship between TBI severity and cerebral atrophy. Despite the wide range of TBI severities, many recent neuroimaging studies have begun to focus on mTBI as it is one of the most common types of head injury as well as one of the most difficult to diagnose (Amyot et al., 2015).

As the technology and methods associated with MR acquisition and processing advance, so does the ability to detect finer microstructural alterations to the cortex. Recent advances in the reconstruction of the cortex allow for separate calculation of mean cortical curvature in brain's gyri and sulci. Curvature provides a function of how a point on the surface of the cortex is embedded in space. Mean cortical curvature is made up of the average of principal curvatures derived from the inverse of the radius of the osculating circles at each point on the surface on the gray–white matter junction. Thus, mean cortical curvature values provide a quantitative illustration of the folding of the cortex with convex areas indicating gyral regions and concave areas designating sulcal regions. Increased mean curvature denotes areas with sharper cortical folds than regions with decreased mean curvature. As such, increased cortical curvature in gyri leads to a more “pointed” or “peaked” appearance while increased cortical curvature in sulci indicates a sharper downward trajectory.

It has been suggested that increased cortical curvature may be a biomarker for white matter atrophy (Deppe et al., 2014). Furthermore, cortical curvature has been used to investigate sex differences in gyrification (Luders et al., 2006) and changes to cortical morphology as part of normal cortical development and aging (Pienaar et al., 2008; Operto et al., 2012; Wang et al., 2014). Cortical curvature has also been measured to study cortical malformations and/or atrophy related to developmental (Schaer et al., 2008), neurodegenerative (Im et al., 2008), neurological (Ronan et al., 2011; Deppe et al., 2014), and psychiatric disorders (Ronan et al., 2012).

The aim of the current study was to evaluate the use of extrinsic mean cortical curvature as a potential indicator of progressive tissue loss in a cross-sectional sample of veterans with mTBI as compared to controls. It was hypothesized that mean cortical curvature would be increased in veterans with mTBI, relative to controls, due in part to cortical restructuring related to tissue volume loss and that this increase in curvature would be more robust in deeper regions (sulci) of the cortex as opposed to more superficial regions (gyri). Furthermore, it was predicted that increases in mean cortical curvature would be associated with irregularities in both gray and white matter volumes.

2. Methods and materials

2.1. Subjects

The Institutional Review Boards at the University of Utah and the George E. Whalen Department of Veterans Affairs (VA) Medical Center approved this study. All subjects provided written informed consent prior to study participation. A total of 62 males with mTBI and 40 male controls were recruited from the George E. Whalen VA Medical Center and the community via local advertisements and by word of mouth. Inclusion criteria for all participants in this analysis were: ages 18–55 years old. The Ohio State University-TBI Identification Method (OSU-TBI) was used to determine presence, number, and severity of lifetime TBI injuries (Corrigan and Bogner, 2007). Participants were considered to have a mTBI if they reported an injury event to the head followed by an alteration or loss of consciousness (LOC) (Belanger et al., 2009). Mild brain injury events were defined as a LOC for 30 min or less. Only participants with mTBI that occurred after the age of 12 were considered for inclusion in this study.

Control comparison participants were required to be free from having a current major DSM-IV Axis I diagnosis based on clinical interviews. Exclusion criteria for all subjects included major sensorimotor handicaps (e.g., deafness, blindness, paralysis), estimated full scale IQ < 80, history of claustrophobia, autism, schizophrenia, anorexia nervosa or bulimia, active medical or neurological disease other than mTBI that would impact neurobiology or brain function, history of electroconvulsive therapy; and metal fragments or implants that would be contraindicated in an MRI.

All participants, including controls, completed the Structured Clinical Interview for DSM-IV Patient Version (SCID-I/P) (First et al., 1996) administered by trained clinicians. Diagnoses of mTBI and any DSM-IV diagnosis/diagnoses were confirmed via clinician consensus. The DSM-IV-TR Global Assessment of Functioning (GAF) (American Psychiatric Association, 2000) was used to subjectively rate occupational, social, and psychological functioning on a scale of 1 (worst) to 100 (best).

2.2. Data acquisition and processing

2.2.1. MRI data acquisition

Acquisition of imaging data was performed at the Utah Center for Advanced Imaging Research (UCAIR) using a 3.0-T Siemens Trio scanner. Structural data was acquired using a T1-weighted 3D MPRAGE GRAPPA sequence acquired sagittally using a 12-channel head coil with TE/TR/TI = 3.38 ms/2.0 s/1.1 s, 8° flip, 256 × 256 acquisition matrix, 256 mm^2 FOV, 160 slices, 1.0 mm slice thickness. Original images were transferred from the scanner in DICOM format and coded. Participants' MRI scans were reviewed by a board-certified CAQ neuroradiologist to rule out gross pathology.