Psychiatry Research: Neuroimaging 191 (2011) 160–165

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Brain morphometry changes and depressive symptoms after traumatic brain injury

Anne Hudak [a,*], Matthew Warner [b], Carlos Marquez de la Plata [c], Carol Moore [b], Caryn Harper [b], Ramon Diaz-Arrastia [b]

[a] Dept. of Physical Medicine and Rehabilitation, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX, 75390-9055, USA
[b] Dept. of Neurology, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX, 75390-9036, USA
[c] University of Texas at Dallas, Center for Brain Health, Frances and Mildred Goad Bldg., 2200 West Mockingbird Lane, Rm. 3.252, Dallas, TX 75235, USA

ARTICLE INFO

Article history:
Received 21 April 2010
Received in revised form 6 October 2010
Accepted 7 October 2010

Keywords:
MRI
BDI-II
Cerebral atrophy

ABSTRACT

Traumatic brain injury (TBI) is associated with an increased risk of depressive symptoms. Recent imaging studies on spontaneous depression have implicated several brain structures; however, few studies have done the same for post-TBI depression. We report on a pilot observational study correlating atrophy of brain regions of interest in subjects after TBI with depressive symptoms measured by the Beck Depression Inventory-II. Regional brain volumes were calculated on both acute and 6-month MRI using an automated segmentation algorithm (FreeSurfer). Percent volume changes in brain regions were correlated with BDI-II scores using Spearman's rank order correlation coefficient. Correction for multiple comparisons was performed using the false discovery rate (FDR). Three regions of interest (left rostral anterior cingulate and bilateral orbitofrontal cortex) were found to be significantly correlated with depressive symptoms (FDR 0.05). With FDR 0.1, six regions were significantly correlated. The use of volumetric analysis of brain regions of interest to study post-TBI depression is worthy of further study. Regions associated with depressive symptoms in this pilot study were similar to those implicated in study of spontaneous depression.

1. Introduction

Approximately 1.5 million U.S. civilians per year sustain a traumatic brain injury (TBI) (Langlois et al., 2006). Rates of major depressive disorder determined by diagnostic interview within the first 12 months are reported to be between 20 and 30% for most studies (Jorge et al., 1993; Fann et al., 1995; van Reekum et al., 1996; Gomez-Hernandez et al., 1997; Rapoport et al., 2006; Ashman et al., 2009) and, more recently, up to 53.1% (Bombardier et al., 2010). In contrast, the 12-month rate of major depression in the general population is 6.7% (Kessler et al., 2005). Rates of suicide after TBI are known to be elevated up to three-(Harrison-Felix et al., 2009; number of suicides 10, expected 3, standardized mortality ratio 2.95, 95% SMR interval 1.42–5.43) to four-fold (Teasdale and Engberg, 2001; contusion or intracranial hemorrhage: number of suicides 99 of 11,766 = 0.84%). The current estimate of suicide rate in the general population is 11 per 100,000 (National Institute of Mental Health, 2009). Development of depression after TBI worsens outcomes in the functional and psychosocial arenas (Fann et al., 1995; Satz et al., 1998; Deb et al., 1999; Levin et al., 2001; Rapoport et al., 2003; Underhill et al., 2003; Franulic et al., 2004; Jorge et al., 2004). While progress has been made in understanding the pathophysiology of spontaneous depression, much less is understood regarding the pathophysiology of depression following TBI.

Spontaneous depression has been linked to atrophy in specific brain regions, including the limbic system, prefrontal cortex, anterior cingulate gyrus (Theberge, 2008; Yucel et al., 2008; Kronenberg et al., 2009; Mak et al., 2009), and gray matter volume (Drevets et al., 1997). The limbic–frontal model of depression (Mayberg, 1997; Seminowicz, et al., 2004) is supported by atrophy in these regions. Koolschijn et al. (2009) reported a meta-analysis on structural MRI and depression, noting significant correlation of depression with decreased volumes in the anterior cingulate gyrus (P value for Cohen's d: left $P = 0.005$, right $P < 0.001$), hippocampus (P value for Cohen's d: left $P < 0.001$, right $P < 0.001$), orbitofrontal cortex (P value for Cohen's d: left $P = 0.002$, right $P = 0.004$) and prefrontal cortex (P value for d: right $P = 0.053$, left $P = 0.045$). With no restrictions on the brain regions included, the Koolschijn et al. meta-analysis included 64 studies with 130 brain regions from 2418 subjects and 1974 controls.

There is a paucity of published information delving into the pathophysiology of post-TBI depression. Previously reported work has shown an association between post-TBI depression and atrophy in the prefrontal cortex (Jorge et al., 2004), hippocampus (Jorge et al., 2007), anterior cingulate, and dorsolateral prefrontal cortex, among others (Chen et al., 2008). Jorge et al. in 2004 reported an association between outcome (GOS-E) and hippocampal volumes. What is not yet clear is if post-TBI depression is definitively linked to the limbic–frontal model of depression.

* Corresponding author. Tel.: +1 214 648 7878; fax: +1 214 648 2324.
E-mail address: Anne.Hudak@utsouthwestern.edu (A. Hudak).

0925-4927/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2010.10.003

In both general (Douglas and Porter, 2009) and TBI populations, depressive symptoms have been reported to impair cognitive function. In the TBI population, depression has been reported to impair working memory (Rapoport et al., 2005), processing speed (Rapoport et al., 2005), executive function (Jorge et al., 2004; Rapoport et al., 2005), and verbal memory (Rapoport et al., 2005).

In this study we report data from a pilot study examining the relation between volumetric changes after TBI for various brain regions and scores on the Beck Depression Inventory-II (BDI-II) (Beck, et al., 1996). This is a convenience sample consisting of subjects enrolled in a prospective neuroimaging study (Warner et al., 2010). For the regions of interest analysis, we selected brain regions that have shown the strongest link between depression and brain atrophy in the non-TBI population (Drevets et al., 1997; Theberge, 2008; Yucel et al., 2008; Kronenberg et al., 2009; Mak et al., 2009; Koolschijn et al., 2009) and have been linked with post-TBI depression in previous work, including superior frontal and middle frontal regions, hippocampus, and rostral anterior cingulate. We also selected areas functionally related to the above-mentioned structures. We explore the relationships between regional brain atrophy and depressive symptom severity as measured by the BDI-II. Further, we explore the relation between depressive symptoms and the impact on neuropsychological data.

2. Methods

2.1. Subjects

We undertook a pilot study on a convenience sample of TBI subjects previously recruited for an imaging study (Warner et al., 2010). Subjects were recruited between September 2005 and October 2008. Inclusion criteria were as follows: age between 16 and 65 years, required admission to hospital for TBI. Consent was obtained from either the patient or a legally authorized representative. Subjects were excluded if they were found to have 1) pre-existing neurological or psychiatric disorders, conditions that may have resulted in abnormal MRI findings and/or compromised cognitive functions, including prior history of TBI, in an attempt to eliminate any other cause other than the current TBI for alterations in imaging, consciousness or cognition. This information was gathered by experienced research assistants, who utilized the patient, family and medical chart as sources of information. By history, these subjects had no history of suicide attempts, psychiatric hospitalization and were not under the active care of a psychiatrist; 2) presence of focal lesions (including contusions, extra-axial hematoma, and/or intraparenchymal hemorrhages) with volume greater than 10 ml on cranial CT which could provide an alternative explanation for the decline in cognition or consciousness; 3) contraindications to MRI; and 4) prisoners, homeless patients, and pregnant women. Prisoners and homeless patients were excluded because of the difficulties in contacting and arranging the follow-up scan after hospital discharge; pregnant women were excluded due to the potential risk to the fetus. Fifty-eight subjects were enrolled; 14 additional patients were enrolled but were never scanned for a variety of reasons, including death, inability to lie still in the scanner, or MRI incompatible brace or incompatible implanted medical device. Of the 58 subjects recruited, we excluded subjects with only one scan and selected only those subjects with both an acute and chronic scans and who had a scored BDI-II at the time of follow-up MRI. The final sample size consisted of 25 subjects with paired imaging and follow-up data. For a particular subject, the same scanner was used for both the acute and chronic scans. Data on the neuropsychological testing were compared with population normative data available for the tests administered. This study was approved by the institutional review board at the University of Texas Southwestern Medical Center. Analyses for this report were performed using de-identified data.

2.2. Imaging methods

Acute and 6-month MRI scans were performed on a GE Signa Excite 3T scanner (15 subjects) (General Electric Healthcare, Milwaukee, Wisconsin) or Siemens 3T (10 subjects) (Siemens Medical Solutions, Erlangen, Germany). For the GE scanner, three-dimensional (3D) T1-weighted structural images were obtained using fast spoiled gradient-recalled acquisition in the steady state (GRASS) sequences with a 256×192 matrix size, 240 mm field of view, 130 slices, 1.3/0 slice thickness/gap ratio, 2.4 ms echo time, 25° flip angle, 2 excitations, and a 6 min acquisition time. For the Siemens scanner, 3D T1-weighted structural MPRAGE images were obtained with a 240 mm field of view, 1.0/0 slice thickness/gap ratio, 4.0 ms echo time, 900 ms inversion time, 2250 ms repetition time, and 5 min 36 s acquisition time. No major scanner upgrades were performed during the study period and protocols remained consistent. All images were analyzed using FreeSurfer (v4.5.0) software (Arhinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, 2009) on a Macintosh workstation to derive regional subcortical and cortical brain volumes. FreeSurfer has been described in detail in previous publications (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 1999, 2002). To address the potential variability due to the use of two different scanners, five control subjects were scanned on both scanners. Volume measurements for these control subjects had a net intraclass correlation coefficient of 0.996, and there were no significant differences between scanners after correction for multiple comparisons.

2.3. Outcome measures

The Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) is a 21-question self-report tool measuring symptoms of depression with an ordinal scale. Previously used in the TBI population (Glenn, et al., 2001; Seel and Kreutzer, 2003; Rowland et al., 2005; Chen, et al., 2008), the BDI-II can be administered through self-report or by oral presentation (Beck, et al., 1996). It has test–retest reliability of 0.93 (Beck, et al., 1996).

The Glasgow Outcome Scale-Extended (GOS-E) (Teasdale et al., 1998) is a 1–8 categorical scale measuring outcome after TBI. It has a test–retest reliability of 0.78 (Wilson et al., 1998). Administered via a structured interview, it is widely used in the TBI literature (Wilson et al., 1998).

The Functional Status Examination (FSE) (Dikmen et al., 2001) is a 10-domain functional outcome measure designed to describe outcomes in the TBI population. The information provided is more descriptive of functional abilities than the standard GOS-E. It has a test–retest reliability of 0.8 (Dikmen et al., 2001; Kirkness et al., 2002).

Neuropsychological testing was administered by a trained neuropsychologist. To investigate associations between depression, cerebral atrophy and cognitive outcome, we used a standard neuropsychological battery assessing learning and memory, processing speed, and executive functions. The neurocognitive outcome battery included the WAIS-III (Wechsler, 1997) digit symbol coding, symbol search and digit span backwards from the digit span subtest, Trail Making Tests A and B (Reitan, 1992), controlled oral word association test (COWAT) (Benton and Hamsher, 1983), Dodrill Stroop (Dodrill, 1978), and California Verbal Learning Test-II (CVLT-II) (Delis et al., 2000) (total learning, short delay and long delay recalls). This targeted battery was subjected to a factor analysis with varimax rotation to reduce the data to the three domains the battery purports to assess. The resulting three-factor structure accounts for 77% of the variance, and comprises learning and memory (CVLT total learning, CVLT short delay, CVLT long delay (51% of variance)), executive function (COWAT, Digit span, Stroop word reading Stroop color naming (10% of variance)), and processing speed (Trails A and B, digit symbol coding, symbol search (16% of variance)).

Participants' performance on these cognitive tasks was corrected for demographic variables (where available). The result is a