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Research report

Volumetrics relate to the development of depression after traumatic brain injury

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HIGHLIGHTS

- Development of depression after brain injury investigated with brain volumetrics.
- Fully-automated brain imaging analysis software was utilised.
- Temporal, parietal, occipital and cingulated regions were the most significant findings.
- Regional volumetric reduction relates to developing depression after brain injury.

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ABSTRACT

Previous research suggests that many people who sustain a traumatic brain injury (TBI), even of the mild form, will develop major depression (MD). We previously reported white matter integrity differences between those who did and did not develop MD after mild TBI. In this current paper, we aimed to investigate whether there were also volumetric differences between these groups, as suggested by previous volumetric studies in mild TBI populations. A sample of TBI-with-MD subjects ($N = 14$), TBI-without-MD subjects ($N = 12$), MD-without-TBI ($N = 26$) and control subjects (no TBI or MD, $N = 23$), received structural MRI brain scans. T1-weighted data were analysed using the Freesurfer software package which produces automated volumetric results. The findings of this study indicate that (1) TBI patients who develop MD have reduced volume in temporal, parietal and lingual regions compared to TBI patients who do not develop MD, and (2) MD patients with a history of TBI have decreased volume in the temporal region compared to those who had MD but without a history of TBI. We also found that more severe MD in those with TBI-with-MD significantly correlated with reduced volume in anterior cingulate, temporal lobe and insula. These findings suggest that volumetric reduction to specific regions, including parietal, temporal and occipital lobes, after a mild TBI may underlie the susceptibility of these patients developing major depression, in addition to altered white matter integrity.

1. Introduction

There are many studies investigating volumetric differences in brain regions between patient groups with mild traumatic brain injury (mTBI/concussion) and control subjects. Findings suggest widespread regions of compromise, including frontal, temporal, parietal, and occipital regions, as well as the corpus callosum (CC; [1–3]). In the past few years the focus has turned to areas related to the onset of mood disorders after head injury, specifically major depression (MD). mTBI cases constitute approximately 85% of reported TBI cases [4], and the incidence of MD after mTBI is reported to range from 10% to 77% [17]. Our group and others have found that white matter integrity was compromised in a number of regions in patients who developed MD after mTBI [5–8]. Those regions included the dorsolateral prefrontal cortex (DLPFC), CC, nucleus accumbens, and temporo-parietal regions [5]. In the current study we examine the structural data of these subjects to investigate whether there are also reductions in grey matter.

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Previous investigations of patients with MD have revealed volume reductions compared to controls in areas such as the hippocampus, frontal lobe, cingulate and corpus callosum (CC; [9–11]), as well as occipital and parietal regions (e.g.[3,12]. Similar regions have also been found to be reduced in volume in patients who have sustained a mild to moderate TBI [2,13], as a result of brain rotation or impact against the inside of the skull, leading to a stretching and thinning of the white matter referred to as diffuse axonal injury (DAI; [14,15]). Noteworthy is the variation throughout the literature with regards to brain regions affected; this may be the result of demographic differences, variations in imaging protocols that could influence volume estimates [16], or the elapsed time since injury. Such inconsistencies could also result from not taking into account behavioural conditions such as MD which has been reported in up to 77% of patients post-TBI [17–20].

Despite the high rates of TBI–MD, there has been a dearth of research into the pathophysiology of TBI–MD. Research that has been conducted has typically utilised magnetic resonance imaging (MRI) to examine the relationship between lesion location and MD. Some studies have found lesion location to relate to MD [21–23], while other studies have not [24,25]. However, these studies offer no information about changes in volume in general. Mild TBI in particular is unlikely to result in lesions detectable via MRI, but may result in smaller changes that effect volumetric MRI measures, and may predict the development of MD, which has been shown to have a negative impact on outcomes following TBI.

The few volumetric studies that have considered post-TBI MD found reduced volume in a variety of structures including the DLPFC and orbitofrontal cortex, cingulate gyrus, occipital, parietal and temporal lobes (e.g. [26–29]), when compared to TBI-no-MD or controls. The studies that have focused on lesions or spectroscopic analysis (e.g. [6,21,30]) have reported ACC, thalamic, frontal, temporal, parietal and posterior cerebral areas to relate to the development of MD. However, there is inconsistency in severity of the TBI subjects across the studies and the techniques that were utilised to measure regional brain volumes.

Additionally, no studies have included a group with MD and no TBI, and some did not have control (no MD and no TBI) subjects. We hypothesized that patients with post-TBI MD will display significantly reduced volume in widespread brain regions compared to patients post-TBI who have no MD, patients with post-TBI MD will display significantly reduced volume compared to patients with MD not related to TBI, patients with MD not related to TBI will display significantly reduced volume compared to healthy controls with no history of TBI or MD, and there will be a correlation between volume and depressive symptoms in patients with post-TBI MD.

2. Methods and materials

2.1. Subjects

A total of 78 subjects were recruited. Twenty-six patients with MD without a history of TBI (MD-no-TBI), 15 patients with a history of mTBI who developed MD (TBI–MD), 12 patients with a history of mTBI who did not develop MD (TBI-no-MD), and 25 controls were included in this study. All participants underwent psychiatric and MRI assessments. Patients were recruited through public notices and through the clinical services of the Alfred Hospital, Melbourne, Victoria, MD patients were required to have no history of TBI, while TBI patients were required to have no history of pre-TBI depression and TBI–MD patients were required to have developed MD between 6 weeks and 12 months post-TBI. All subjects with TBI were required to have a Glasgow Coma Sale score of 13 or 14 on ambulance arrival at the accident scene. Loss of consciousness among mTBI subjects ranged from 15 min to 2 h, and post-traumatic amnesia ranged from 10 min to 48 h, according to formal hospital records (and some patients had no post-traumatic amnesia). Time since injury varied from 6 weeks to 10 years. The number of medications that each MD subject had tried was between three and eight, and length of depression ranged from 1 year to 50 years. One TBI–MD patient had a very large head whose whole brain could not fit into the MRI Field Of View, hence their data were excluded from analyses (reducing the number of TBI–MD subjects to 14). Another TBI-no-MD participant had a low volume subarachnoid haemorrhage over the left parietal lobe. Their data were included as their data registered well during the Freesurfer processing steps with no misalignments in the region of the haemorrhage. No participants had destructive white matter lesions on FLAIR images. All patients underwent CT scanning in the acute phase with all but one patient having no abnormality detected (as described above).

All MD patients (the MD only and TBI–MD groups) were required to have a diagnosis of major depressive disorders made by a treating psychiatrist and confirmed with the Mini-International Neuropsychiatric Interview (MINI; [31] and a score of at least 16 on the Montgomery–Åsberg depression rating scale (MADRS; [32]).

Twenty-five controls were recruited from notices and word of mouth. Exclusion criteria for controls included a current or previous DSM-IV (SCID; [33]) axis I diagnoses, current active medical problem, and subjects were required to have no known neurological disease or a contraindication to MRI scanning. In addition, control subjects were required to have no history of psychiatric illness. Two control scans were discarded due to incidental abnormalities, hence control sample size was 23 (9 males) and total sample size was 75 (Table 1). All subjects provided written informed consent on a form approved by the Alfred Human Subjects Research and Ethics Committee.

Table 1
Descriptive statistics for control, TBI and MD participants.

Variable	Group			
	TBI–MD	TBI-no-MD	MD-no-TBI	Control
Number (M:F)	14 (6:8)	12 (10:2)	26 (17:9)	23 (9:14)
Age mean (SD)	48.00 (9.92)	33.08 (12.69)	44.08 (12.99)	38.35 (13.00)
MADRS mean (SD)	28.77 (7.68) Range: 16–43	2.25 (2.38) Range: 0–6	32.27 (4.11) Range: 25–39	N/A
Total GM (L)	0.6143 ± 0.0485	0.6826 ± 0.0438	0.6311 ± 0862	0.6691 ± 0757
Total WM (L)	0.4866 ± 0.0494	0.5495 ± 0.0402	0.5020 ± 0.0720	0.5373 ± 0.0660
CSF (L)	0.2057 ± 0105	0.2066 ± 0.0932	0.2314 ± 0.0115	0.1838 ± 0.0852
TBV (L)	1.1009 ± 0.0973	1.2321 ± 0.0830	1.1330 ± 0.1571	1.2063 ± 1400
TIV (L)	1.6066 ± 0.1394	1.759 ± 0.1665	1.6467 ± 0.1720	1.6945 ± 0.1833

Note: CSF is the Cerebrospinal fluid; F is the Females; GM is the Grey matter; L is the Litres; M is the Males; MADRS is the Montgomery-Åsberg depression rating scale; MD is the Major depression; N/A is the not applicable; SD is the Standard deviation; WM is the White matter; TBI is the Traumatic brain injury; TBV is the Total brain volume; TIV is the Total intracranial volume.