Multi-modal MRI imaging in severe traumatic brain injury (TBI) patients to determine structural impact of DECRA craniectomy surgery, and early prognostication: Pilot studies

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Executive Summary

Key messages

- MRI-DTI scanning is an imaging tool that enables measurement of injury to brain fibres after traumatic brain injury.
- Scanning techniques have now been optimised at the Alfred to allow participation in an international collaborative project with 80 sites in Europe and Israel which aims to improve prognostication of outcome for patients with traumatic brain injury.
- Data from the MRI-DTI project suggests that frontal brain swelling after bilateral frontal craniectomy may lead to secondary injury due to the white matter stretch. These findings are preliminary due to sample size and do not allow us to rule out diffuse injury due to the severity of the initial brain insult.
- If these findings are confirmed with future research, they will transform neurosurgical thinking about unexpected brain injury after craniectomy

Purpose

This project aims to improve outcomes in TBI patients through two pilot studies. Specialized MRI brain imaging will (1) investigate patient brain structure after craniectomy and (2) enable early Prognostic algorithms to assist early decision making after severe TBI (contribute to an international collaboration NICER-WORLD led by Prof Louis Puybasset, Pitié-Salpêtrière Hospital, Paris).

Rationale

Our bi-national observational study(1) identified 485 patients with TBI in Australia and NZ over 6 months. The mortality, long term morbidity and cost of these patients is devastatingly high, and the costs have been quantified by ACCESS Economics for the Victorian Neurotrauma Initiative (VNI) at $5 billion lifetime costs to Australia, annually.(2)

MM-MRI provides the key to the next advances in clinical research in TBI patients. To date, limitations of technology and of clinical assessment tools have restricted progress. CT and standard MRI brain imaging has been invaluable for defining lesions that require immediate neurosurgical intervention. But these tools lack essential specificity to allow judgement on individual patient's functional outcomes in most cases. This may be due to insensitivity to detect subtle white matter injuries, including traumatic axonal injury (TAI). TAI or Diffuse axonal injury (DAI) is common following TBI,(3) which reflects damage to the tracts of white matter that connect vital structures of the brain. TAI has been shown to be associated with significant disability and poor outcome, including the majority of TBI related cognitive deficits.(4) TAI occurs when shearing forces act on neurons when the head is rapidly accelerated or decelerated, as frequently occurs in trauma. Damage to axons is poorly visualised by conventional imaging methods(4, 5) and is commonly missed. A simple analogy is that the brain is like a computer and conventional imaging cannot detect any damage to the wiring between important structures. Like a computer, the brain will not function when the wiring has been disrupted although all the key functional areas appear grossly intact. MM-MRI (Diffusion Tensor Imaging – DTI, Magnetic Resonance Spectroscopy

– MRS, and 3 Tesla scanners) are much more sensitive in identifying microstructural changes to the brain, which occur in TBI and are missed with routine scanning.

Diffusion Tensor Imaging: Diffusion Tensor Imaging (DTI) is a recently introduced modality of MRI scanning which has a much greater sensitivity to detect white matter micro-structural injuries in the TBI brain. DTI is a sophisticated technique which examines both the directionality and magnitude of diffusion of water molecules in structures in the brain.(6-10) It is based on the principle of Brownian motion, which is the random thermally driven movement of molecules. In an ideal solution without barriers this motion is equal in all directions (isotropic). However, where the molecules are restrained by physical barriers such as in a neuron, the motion tends to be greater along the axis of the neuron rather than across the breadth of the neuron (anisotropic). DTI utilises this property of neurons (brain white matter) to relate changes in anisotropy to the micro-architecture of the brain. Changes to the barriers of diffusion after injury, such as TAI, results in changes in the diffusion signal and thus it is a more sensitive measure of white matter injury, including TAI.

Clinical Studies of DTI in TBI: Clinical studies have demonstrated that DTI has improved sensitivity to detect white matter lesions not previously found using conventional imaging techniques(6) and that it is superior at detecting TAI.(11, 12) This has been confirmed in laboratory studies. It has also been observed that TBI patients with unfavourable outcomes have deep grey and white matter changes(9) and a greater number of brain stem lesions(13) *only* detected by DTI. A number of studies have identified correlations between DTI measures and outcome following TBI;(13) with some currently advocating that DTI may outperform current clinical measures.(11, 14, 15) A longitudinal study examined 30 adult patients at 8 weeks and 12 months after TBI(16) and reported a reduction in measures of anisotropy in TBI patients compared to healthy controls, and these DTI measures predicted dichotomised functional neurological outcome (extended Glasgow Outcome Scale GOSe) at 1 year. Other studies have suggested that DTI alone may have a sensitivity and specificity in determining functional outcome which approaches 90% following severe TBI.(17)

Recently predictive algorithms for TBI outcomes using clinical and CT parameters have been developed, made easily web-accessable, and provide prognostic guidance. They are good for groups, but are not sufficiently specific or precise to direct therapy decisions in individual patients. High specificity outcome prediction of long term severe disability in severe TBI and coma patients while they were still mechanically ventilated in ICU (7-10 days after injury) would transform clinicians' approaches to these patients. Rational palliative care in appropriate patients would become an early treatment option for those with devastating outcomes. MM-MRI combining metabolic (MRS) and anatomic (DTI) assessments, together with clinical parameters, will enable development of algorithms applicable for severe TBI patients.

Methods

- A 1.5T GE Signa MR Imaging System (General Electric Medical Systems, Milwaukee, WI) was used to acquire a contiguous AC-PC aligned axial SPGR T1-weighted sequence and diffusion tensor imaging data.

- All signals representing injury (excluding extra-dural) on each slice of the T2-FLAIR scans were manually outlined using Analyze 9.0® (Mayo Clinic, Rochester, MN) using the region of interest module.

- The length of craniectomy representing removed skull bone (in patients who underwent craniectomy) was manually outlined
- Midsagittal intracranial area (ICA) was manually segmented in order to normalize the brain injury volumes
- Color fractional anisotropy (FA; an index of white matter integrity) maps were produced (Figure 1)

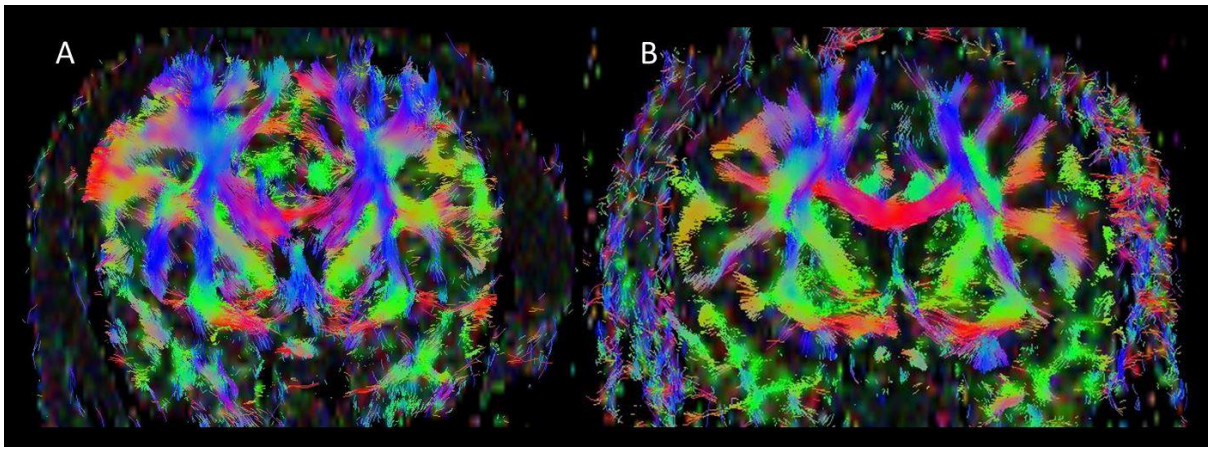

Figure 1. Example of color fractional anisotropy maps. Patient A=Bilateral decompressive craniectomy, Patient B= no craniectomy

- FA of the corpus callosum (CC), bilateral superior longitudinal fasciculi (SLFs) and posterior limb of the internal capsules (PLICs) were measured using DTIstudio (Figure 2)

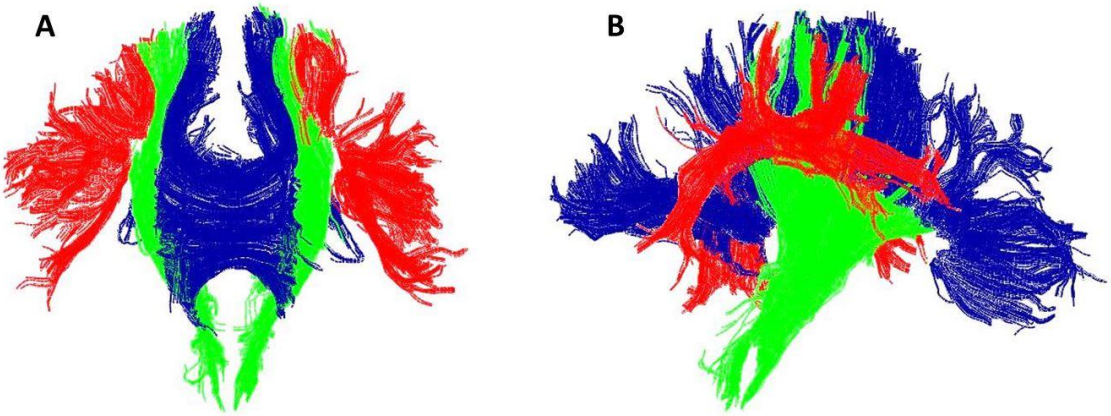

Figure 2. Example of manual tractography. Blue = Corpus callosum; Red = Longitudinal fasciculi; Green = Posterior limb of internal capsules. A = Anterior perspective, B = Right lateral perspective.

- All data were analysed using IBM SPSS 22.0 (IBM Corporation).

- Analysis of variance (ANOVA) was used to compare severity, volumetrics and DTI-derived FA values between the groups, and Pearson correlations were utilised to investigate further relationships between them.
- Injury volumes are presented as mm3/ICA.
- Families of the patients provided informed consent for the study.
- The study was approved by the Human Ethics Committee of The Alfred hospital

Research findings & implications

The complex technicalities required to obtain consistency with the NICER-WORLD collaboration were much greater than anticipated. Unfortunately because of these complexities despite scanning 10 patients we were unable to contribute to NICER-WORLD however 9 of these patients formed the basis of preliminary research into brain integrity post craniectomy.

Patient	Age	Sex	GCS	Motor Score	Mechanism of Injury	Group
01	19	F	5	3	High-speed motor vehicle accident	BFC
03	30	M	3	1	Assault – blunt trauma to head	BFC
04	53	M	3	1	Motorcycle accident	BFC
05	46	M	7	N/A	Fall while snowboarding	UTC
06	61	F	7	5	Assault – blunt trauma to head	UTC
07	60	M	3	1	Assault – blunt trauma to head	UTC
08	60	M	6	3	Motor vehicle accident	NC
09	30	F	5	2	Motor vehicle accident	NC
10	20	M	7	4	Motor vehicle accident	NC

BFC=Bifrontal craniectomy, UTC=Unilateral temporal craniectomy, NC=No craniectomy

*(Patient#2 excluded from analysis as they had evacuation of a subdural haematoma & extradural haematoma and bilfrontal decompressive craniectomy) .

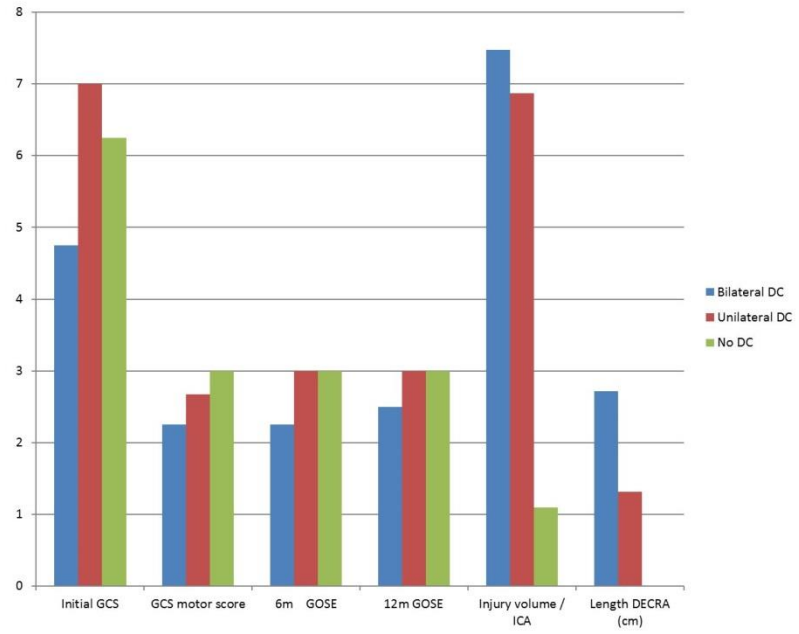

Figure 3. Differences between mean severity scores, injury volumes, and lengths of bone removed.

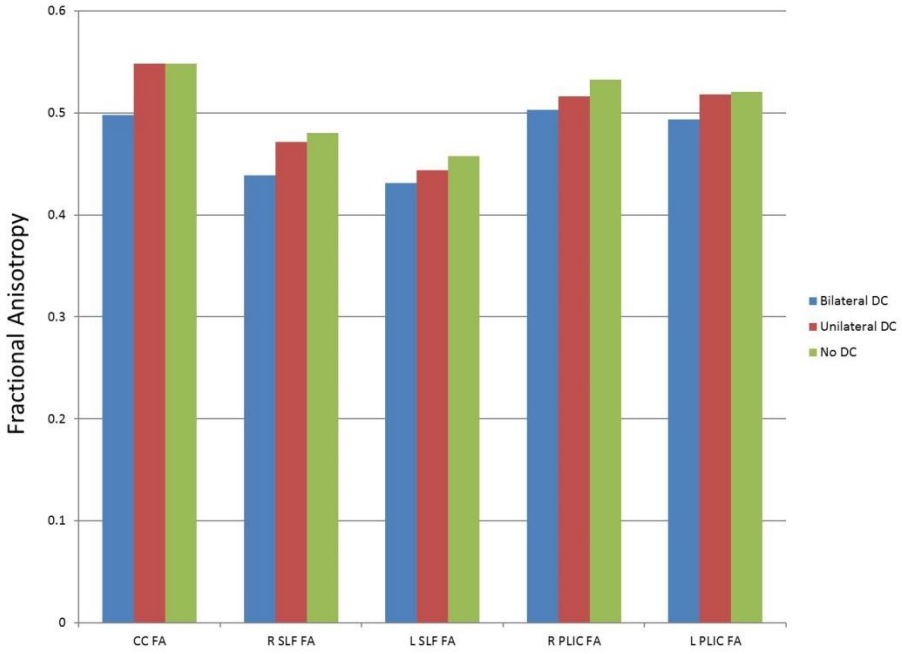

Figure 4. Differences between mean fractional anisotropy values.

Normalized injury volumes (T2-Flair) were not different between BFC and UTC patients but were higher compared to NC patients. A trend for lower mean fractional anisotropy (FA) values after BFC in the corpus callosum (CC) (0.497+/-0.07) and the frontal (0.422+/-0.02) areas was observed compared to UTC (CC:0.542+/-0.004; Frontal:0.434+/-0.02), and to NC (CC:0.552+/-0.02; Frontal:0.464+/-0.007).

In this pilot study we report for the first time that after BFC patients had greater injuries in the CC and frontal areas assessed by DTI. This difference was not seen in the temporal region

after UTC. Our data suggest that frontal brain swelling after BFC may lead to secondary injury due to the white matter stretch. These findings are preliminary due to sample size and do not allow us to rule out diffuse injury due to the severity of the initial brain insult.

Funding from ISCRR enabled us to scan an additional 10 control subjects which has refined the scanning protocol to ensure consistency with the NICER-WORLD collaborative. Future patients scanned under the refined protocol will contribute to data for NICER-WORLD.

Use of the research

Both studies in this project were pilot projects testing feasibility and as such there are no direct implications for TAC or work safe.

Potential impact of the research

This project illustrated the difficulties of performing research in a complex patient group using sophisticated techniques. Whilst no direct benefit to patient care has been found the preliminary work in this project will enable us to provide meaningful data to the NICER-WORLD collaboration and has stimulated interest in the use of DTI to further investigate brain integrity post decompression.

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