Final Report

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Date: 18 October 2022

Title of Project: Using advanced MRI to detect mild traumatic brain injury in individual patients

Summary:

Sports-related concussion is a growing public health concern in Australia. The detection and management of concussion is highly important, as mismanagement can lead to persistent or long-term problems. Unfortunately, we still do not have any device that medical practitioners can use to diagnose concussion in an individual. The goal of this project is to determine if we can detect a concussion in an individual's brain using specialised neuroimaging tools.

Recently, a specialised type of brain imaging tool, known as diffusion MRI, has been shown to detect subtle changes to the brain's wiring following a concussion. Our research group at the Florey specialise in advanced diffusion MRI technologies, and in this project, we apply these technologies to explore it's potential as a diagnostic tool in concussion.

Hypothesis vs Findings:

The major hypotheses of our work were that:

1. Advanced diffusion MRI measurement of white matter (fibre density and cross-section) can detect concussion in an individual, when compared to a reference control group
2. The fibre density and cross-section (FDC) measure will relate to signs and symptoms of concussion in an individual.

One of the key elements in being able to detect individual-level changes is to build a reference 'template' image. This reference template can then be used to compare individuals with an acute concussion (mild traumatic brain injury or mTBI) to detect any individual differences or abnormalities. For this study, we built a large healthy reference template image, using diffusion MRI data from 90 healthy volunteers scanned at our site.

A substantial portion of this project was dedicated to constructing this reference healthy template, and developing a pipeline for individual participant differences, so that we could detect white matter changes in individuals following concussion. The analysis pipeline includes the following steps:

1. Constructing a template using diffusion MR images from healthy individuals, and computing the FDC measure at each white matter element (known as a ‘fixel’) within this template
2. Extracting key white matter fibre tracts, and computing the average FDC within the fibre tract across all healthy individuals (and individuals with concussion)
3. Performing data harmonization to remove any potential biases due to scanner differences
4. Computing the distribution of mean FDC across each tract in the healthy control cohort. Non-normal distributions were normalised using rank-based inverse normal transformation.
5. Mean FDC was computed across the healthy control cohort for each key fibre tract
6. Z-scores were computed for each individual participant with concussion

We tested this pipeline on individual patients with neurological conditions in whom ground truth was available, and expected tract-specific abnormalities were observed for these patients.

In individuals with an acute sports-related concussion, we did not observe any significant abnormalities in selected tracts. Our preliminary findings also demonstrate that is a high level of individual heterogeneity in tract-level changes in acute concussion.

Unanswered Questions:
At the tract-level, we may not be sensitive to subtle white matter abnormalities in acute concussion. There may still be subtle abnormalities within these fibre tracts; however, by examining changes across the entire tract, these subtle changes may go undetected. To this end, we have recently begun to develop a similar pipeline to investigate ‘fixel’-level (specific ***fi***bre populations within a brain imaging vo***xel***) changes within white matter in acute concussion. Here, our preliminary data suggests that there are small areas of abnormality within white matter in participants with a recent concussion; however, these are heterogeneously distributed in the white matter; that is, each individual exhibits a different pattern of white matter abnormality.

What these research outcomes mean:
Our findings, both at the tract-level and fixel-level, suggest that white matter changes in acute concussion are likely to be highly individualized. When we performed group-level comparisons, we found common regions of white matter to exhibit abnormality in acute concussion (Mito et al., 2022, *Brain Communications*). However, these regions may not necessarily be the most abnormal area of white matter in a given individual, so we may not be able to use these specific white matter tracts as biomarkers of concussion. To detect subtle brain white matter abnormalities in concussion, it is likely that we will require large reference data sets in future.