EPWORTH RESEARCH INSTITUTE

Final Report 2017

Authors: Dr Gershon Spitz, Ms Abbie Taing, Professor Jennie Ponsford, Dr Matthew Mundy,
Affiliations: Epworth Research Foundation and Monash University

Title of Project: The return of memory following traumatic brain injury – The critical role of the medial temporal lobe, prefrontal cortex, and associated brain areas.

Background:

Traumatic brain injury (TBI) remains the leading cause of death, disability, and hospitalization worldwide. TBI incidence is estimated to be 100-386 per 100,000. Moderate and severe TBI accounts for 30% of injuries, often resulting in ongoing adverse cognitive, behavioural and psychiatric outcomes. In Australia, the annual cost of TBI is estimated to be $8.6 billion.

For many individuals, difficulties with memory are observed almost immediately following a TBI, and may persist for 10 or more years following injury. In the acute period following injury, individuals initially experience a transient period of post-traumatic amnesia (PTA), characterised by severe confusion and memory impairment. Although most individuals emerge from this period of PTA, many experience residual memory deficits. No study has explicitly investigated these residual deficits in terms of the nature of impairments to specific stages of memory processing, the mechanisms responsible for memory disturbance, and the damage to underlying memory-related brain systems within the acute period following a TBI.

Brain regions and networks known to modulate normal memory processes are commonly damaged following TBI. Although brain pathology following TBI is generally heterogeneous, frontal and temporal lobes are frequently affected. Anatomical structures within these regions are essential for attending to, encoding, consolidating, storing, and retrieving information. The prefrontal cortex is critical for processing information in short-term or working memory. Information in short-term memory is then selectively transferred into long-term memory. It is now evident that the medial temporal lobes comprise a system of structures critical for transferring information from working to long-term memory.

Overall, this study aimed to:

1. Identify the brain regions and networks implicated in impaired memory in patients with TBI during PTA using fMRI. The study also aimed to characterise the impairments to specific aspects of memory experienced by individuals during the acute period (i.e. working memory, encoding, consolidation, storage, and retrieval).
2. Examine changes in activation in specific brain structures or networks that may modulate the recovery of memory. The change in memory functions was examined in relation to neural activity in specific brain regions and networks known to modulate normal memory processing (i.e. prefrontal cortex, medial temporal lobe, parietal cortex, default mode network, and attention network).

This interim study update includes preliminary findings pertaining to the following aims:

1. To compare working and episodic memory behavioural performance between TBI participants and healthy controls.
2. To identify differences in brain activity between TBI and healthy control participants during a working memory task.
3. To identify differences in brain activity between TBI and healthy control participants during an episodic memory task.

Methods

The current analyses are based on 9 individuals with TBI recruited from consecutive admissions to the Head Injury Rehabilitation unit at Epworth HealthCare Rehabilitation, Melbourne, Victoria. Initial scans were conducted as soon as medically viable and when participants displayed low levels of agitation and sufficient cognitive capacity to cope with the scan. In addition, 3 healthy controls, matched for age, gender, and education have also been recruited.

Working memory was assessed using a low and high conditions of the Sternberg working memory task. Participants were required to correctly indicate whether a 'probe' letter was shown in the preceding two-letter sequence (low cognitive load condition) or six-letter sequence (high cognitive load condition). Episodic memory was assessed by presenting images of places, animals, and human faces while participants were in the scanner. Participants were required to correctly recognise the images in an out-of-scanner behavioural task.

FSL (FMRIB Software Library) was used for analysis of fMRI data. Pre-processing and statistical analysis will was carried out using FEAT (FMRI Expert Analysis Tool). Echo-planar imaging (EPI) data as registered to high resolution 3D anatomical T1 scans (per participant) and to a standard Montreal Neurological Institute template image (for group average). FSL was used to examine BOLD signal in relation to high and low working memory conditions as assessed on the Sternberg Working Memory Task. BOLD activations were also examined during an Episodic fMRI Task to detect cortical regions activated during memory encoding of mammals, scenes and faces.

Working memory behavioural performance and fMRI findings

The Sternberg working memory task was used to examine brain activity under low and high cognitive load. In the low condition participants were presented with a sequences of two letters followed by a probe letter. During the high cognitive load condition participants were presented with a sequence of 6 letters prior to being shown the probe letter. That is, during the high cognitive load condition, participants were required to hold a greater informational load to achieve a correct response. Individuals with TBI displayed statistically equivalent working memory performance during the low cognitive load condition (Figure 1). However, they displayed significantly lower performance during the high cognitive load condition.

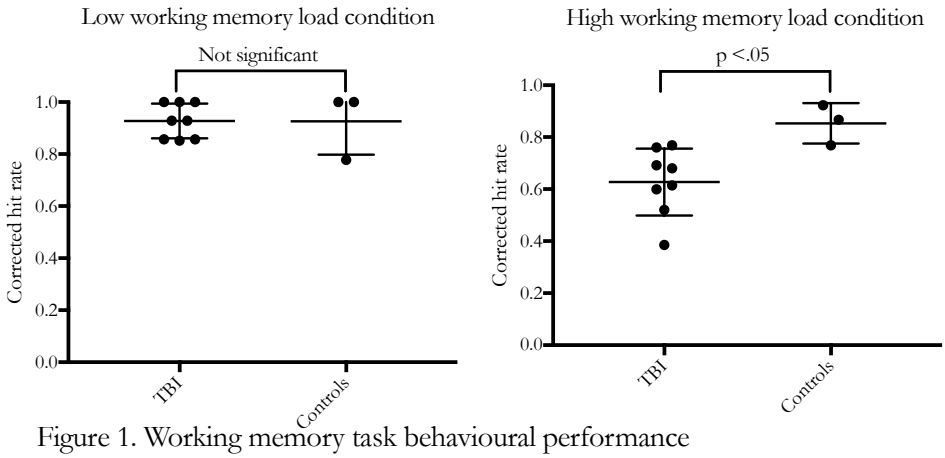

Figure 1. Working memory task behavioural performance

Activation during the low cognitive load working memory condition

TBI participants showed greater fMRI BOLD activity in the low WM condition compared to healthy controls (Figure 2). As indicated in figure 2, TBI participants displayed a more widely distributed brain activity profile, including frontal, parietal, and temporal brain regions. Brain activity for healthy participants was mostly isolated to visual brain regions.

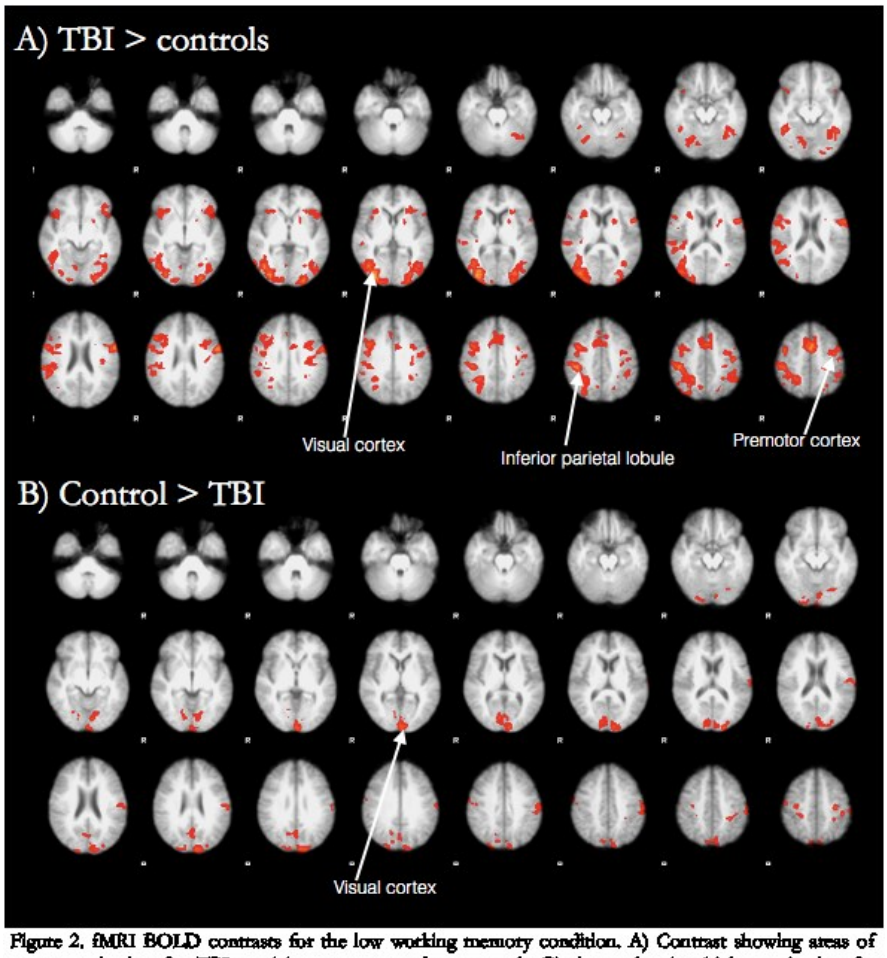

Figure 2. fMRI BOLD contrasts for the low working memory condition. A) Contrast showing areas of greater activation for TBI participants, compared to controls. B) Areas showing higher activation for controls compared to TBI participants.

Activation during the high cognitive load working memory condition

Similar to the low cognitive load condition, TBI participants showed greater fMRI BOLD activity in the high WM condition compared to healthy controls (Figure 3). TBI participants displayed significantly greater activation of frontal brain regions compared to healthy individuals.

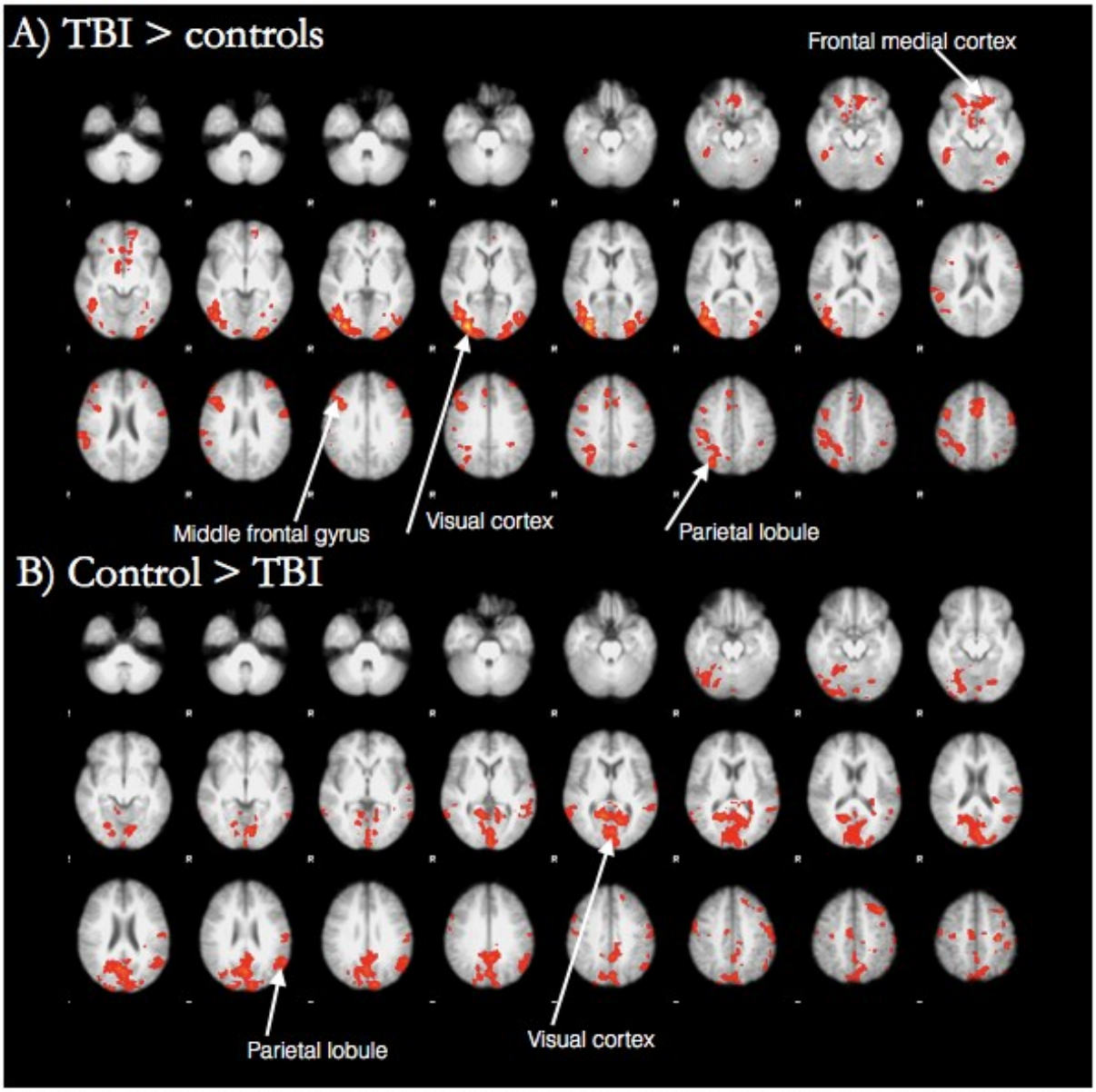

Figure 3. fMRI BOLD contrasts for the high working memory condition. A) Contrast showing areas of greater activation for TBI participants, compared to controls. B) Areas showing higher activation for controls compared to TBI participants.

Group differences in activation between the low and high cognitive load working memory condition

We also investigated changes in brain activation between the low and high working memory conditions, and whether the magnitude of these changes differed between TBI participants and healthy controls (Figure 4). TBI participants did not display any changes between the low

and high cognitive load working memory condition that were greater than the changes experienced by controls. However, we found that healthy individuals displayed significantly greater activation between the low and high conditions of several brain regions, such as the orbitofrontal cortex.

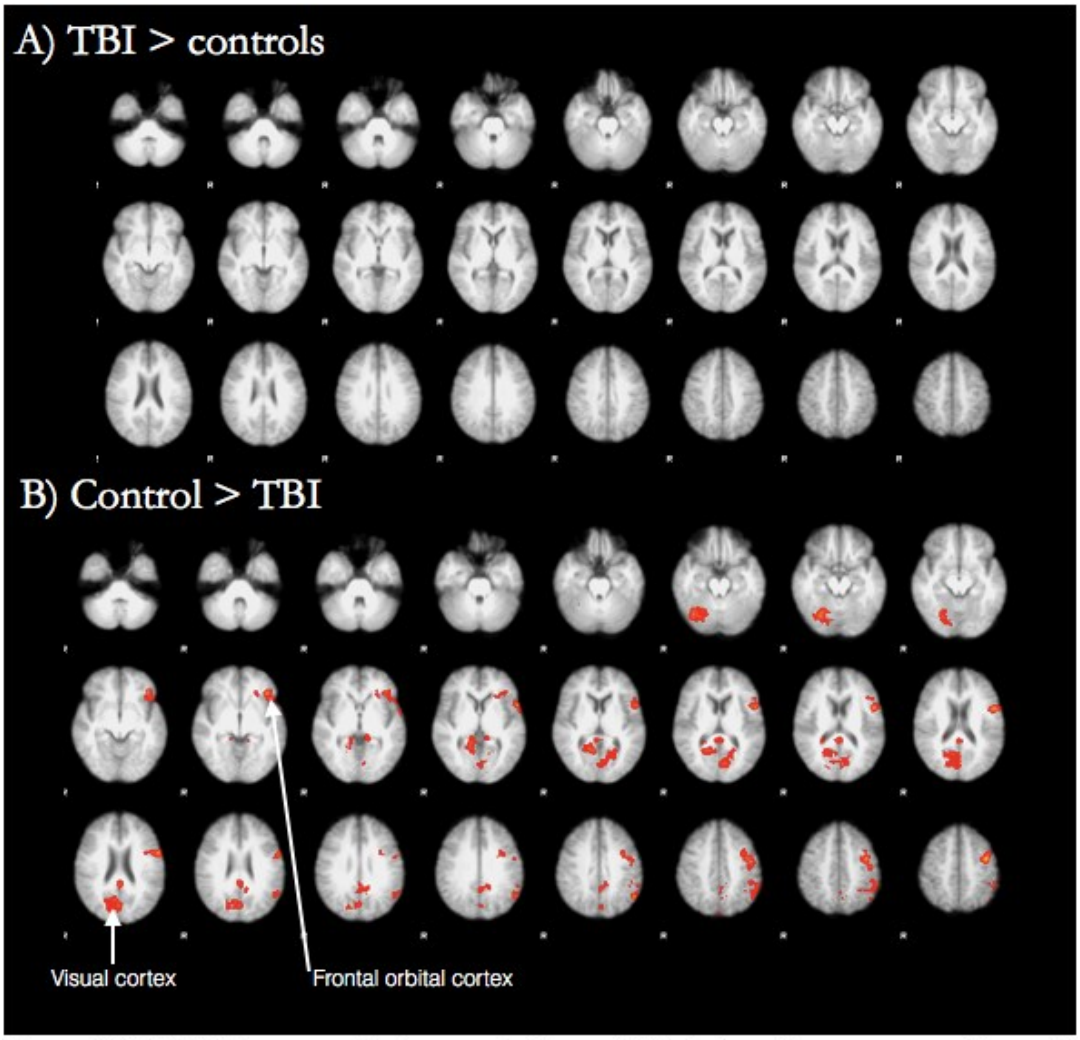

Figure 4. fMRI BOLD contrasts for between the low and high load working memory conditions. A) Contrast showing areas of greater activation for TBI participants, compared to controls for the high vs low working condition. B) Areas showing higher activation for controls compared to TBI participants, for the high vs low working memory condition.

Episodic memory behavioural performance and fMRI findings

An episodic memory task was used to examine brain activity during the encoding of mammals, scenes, and faces as well as the ability of participants to recognise these pictures at a later time. Participants attended to pictures of mammals, scenes, and faces in the scanner. Following the MRI scan, participants were presented with pictures and asked to indicate whether these were presented previously. Recognition of mammals, scenes, and faces did not statistically differ between TBI and healthy control participants (Figure 5).

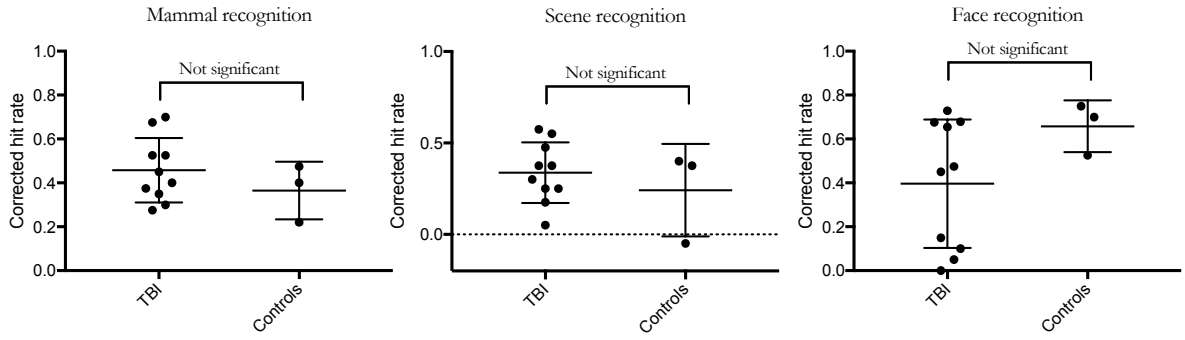

Figure 5. Episodic memory task behavioural performance

Brain activation during the visual encoding

We investigated whether brain activation when participants first saw pictures in the scanner were associated with their capacity to accurately recognise the pictures at a later time. There was no relationship between BOLD activity and the recognition of mammals or faces. However, greater activation of the precuneus when participants viewed scenes was associated with more accurate recognition of these same pictures at a later time-point. Activation of the precuneus has previously linked to episodic memory retrieval.

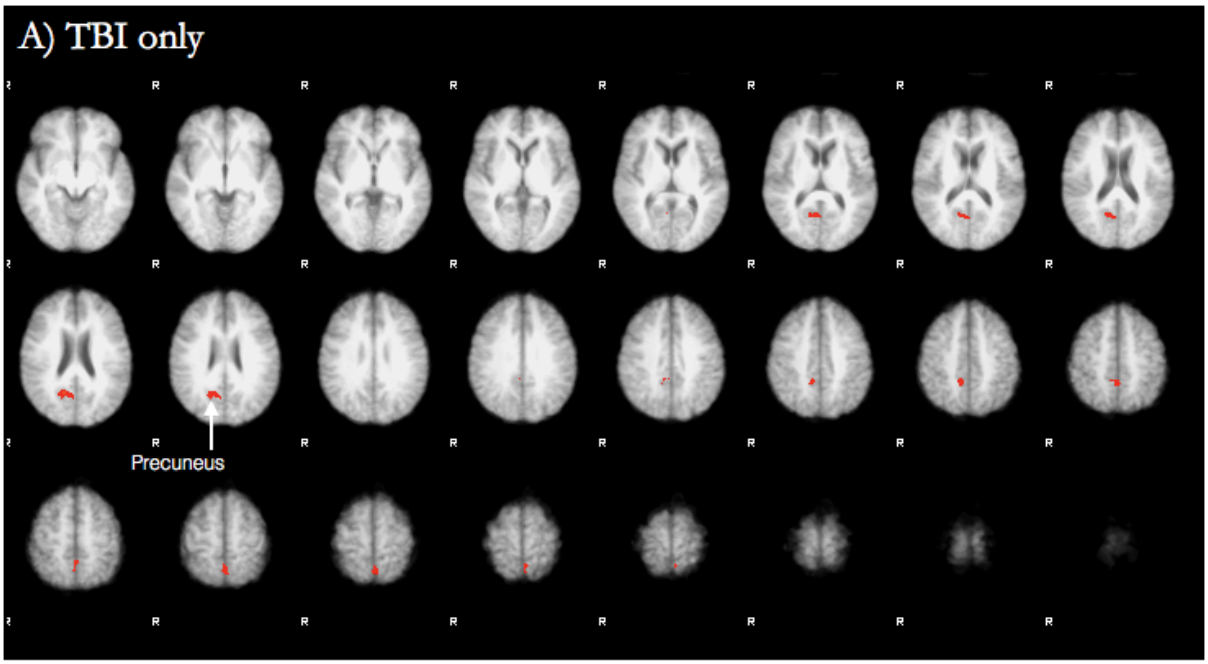

Figure 6. fMRI BOLD contrasts showing brain region activity associated with better scene recognition.

Conclusions

These interim results begin to describe the neural correlates of memory impairment following TBI. A greater number of participants, both TBI and healthy controls are required to more adequately resolve our intended aims. Nevertheless, these results trend towards our initial hypotheses, suggesting altered neural processing underlies overt behavioural impairment following TBI.

Individuals with TBI displayed similar working memory performance during the low cognitive load condition, but impaired performance during the more difficult high load condition. Despite these results, TBI participants showed greater neural activity in both working memory conditions compared to healthy individuals. Interestingly, healthy individuals demonstrated a greater change in neural activation between the low and high cognitive load conditions compared to TBI participants. These results indicate TBI individuals may require greater effort during low condition, to achieve similar behavioural results. During the high WM load condition, healthy individuals may be able to boost their brain activity to achieve behavioural performance equivalent with that witnessed in the lower WM load condition. Individuals with TBI may not be able to accomplish this, subsequently leading to impaired performance. Preliminary evidence suggested that activation in certain parts of the brain may support recognition memory. However, a greater sample size is required to elucidate whether the regions that support better recognition differ between TBI and control participants.