Progress Report to Brain Foundation
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Title of Project:
Pilot study: The return of memory following traumatic brain injury – The critical role of the medial temporal lobe, prefrontal cortex, and associated brain areas

Summary: (approximately 1,000 words)
Background:

Traumatic brain injury (TBI) remains the leading cause of death, disability, and hospitalisation 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 total cost of TBI is estimated to be $8.6 billion, annually.

For many individuals, difficulties with memory are observed almost immediately following a TBI, though impairments can persistent up to 10 years following the initial injury. In the acute period following injury, individuals initially experience a transient period of post-traumatic amnesia (PTA). Notable deficits in memory have been observed in this period of PTA. Specifically, declarative memory is shown to be impaired whilst procedural memory remains relatively intact. No study has explicitly investigated the impairments to specific stages of memory processing, the mechanisms responsible for initial memory disturbance, and the damage to underlying memory brain systems within the acute period following a TBI. Nor has there been an examination of the mechanisms responsible for the resumption of normal memory processes.

Brain regions and networks known to modulate normal memory processes are commonly damaged following TBI. Although brain pathology 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 lobe comprises a system of structures critical for transferring information from working to long-term memory.

The aims of the current study are to:

1. Identify the brain regions and networks implicated in impaired memory in patients with TBI during PTA using fMRI. This aim will also 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. To examine changes in activation in specific brain structures or networks that may modulate the recovery of memory. This aim will examine the change in memory functions 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).

Progress to date:

We have recruited six individuals with TBI into the study from consecutive admissions to the Head Injury Rehabilitation unit at Epworth HealthCare Rehabilitation, Melbourne, Victoria. The fMRI protocol was discontinued on only one occasion, where the participant became fatigued and mildly agitated. This participant was subsequently excluded from the study. Initial scans were conducted as soon a medically viable and when participants displayed low levels of agitation and sufficient cognitive capacity. This initial scan ranged from one day to a few weeks following post-emergence from PTA. One healthy control, matched for age, gender, and education has also been recruited.

Two notable barriers, however, have delayed our progress in this pilot study. Firstly, there was a significant decrease in patient admissions to the Epworth Hospital Acquired Brain Injury Unit between May-July 2015, which resulted in slow recruitment. Admission numbers have subsequently increased. Secondly, the Epworth MRI department unexpectedly changed medical imaging companies between August-September. The scanner used to scan our participants was dismantled, which meant a temporary inaccessibility to an MRI scanner. We have now secured a new scanner on which to scan our participants and scanning has recommenced.

Preliminary results:

This progress report presents preliminary findings pertaining to two aims:

1. To identify the brain regions associated with working memory following TBI.
2. To identify the brain regions associated with episodic memory encoding and consolidation following TBI.

Analyses included the six individuals with TBI recruited to date. 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.

Which brain regions are activated during working memory?

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 presents with a sequence of 6 letters prior to being shown the probe letter. Both the low and high memory load conditions were associated with activation in occipital regions (Figures 1a and 1b). Specific activation was observed in the lingual gyrus in both conditions. The lingual gyrus has shown to be heavily implicated in the processing of word and letter processing. There was also evidence that the high cognitive load working memory condition produced activity in frontal regions, which were not observed in the low cognitive load condition. The added recruitment of frontal regions during high cognitive load is consistent with the literature.

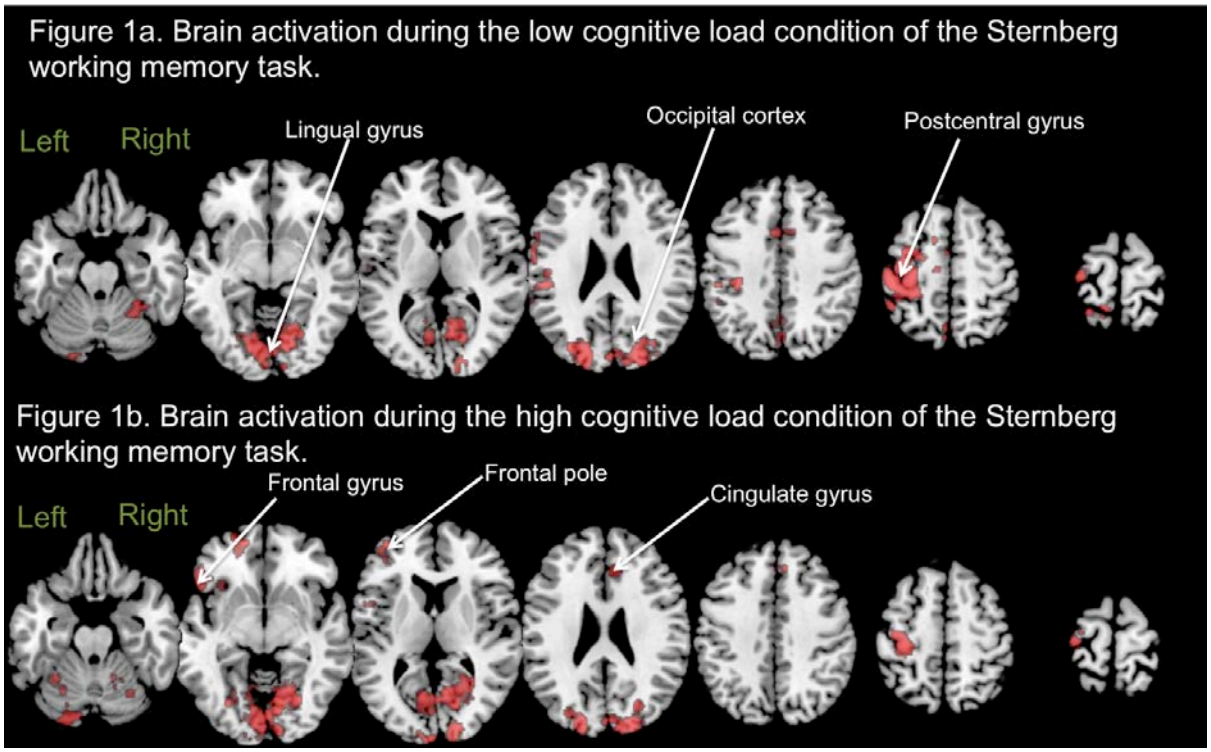


Figure 1a. Brain activation during the low cognitive load condition of the Sternberg working memory task.

Figure 1b. Brain activation during the high cognitive load condition of the Sternberg working memory task.

Which brain regions are activated during memory encoding and consolidation?

An episodic memory fMRI task was used to assess encoding, storage and consolidation of episodic memory. Participants were presented with images of animals, places, and faces. The occipital cortex was largely activated when participants viewed images of mammals (Figure 2a). Encoding and consolidation of scenes and faces, however, activated the precuneous cortex, which is a region associated with successful episodic memory retrieval (Figure 2b and 2c). Similarly,

the activation of the parahippocampal gyrus and fusiform cortex observed during scenes was expected, given their involvement in episodic memory encoding and retrieval. Interestingly, relatively more specific areas were recruited when processing faces. Although the cingulate gyrus, as well as other prefrontal areas, is associated with episodic memory retrieval, greater activation of hippocampal areas was also expected during encoding and consolidation of faces.

Figure 2a. Brain activation during the episodic memory task specific to processing mammals.

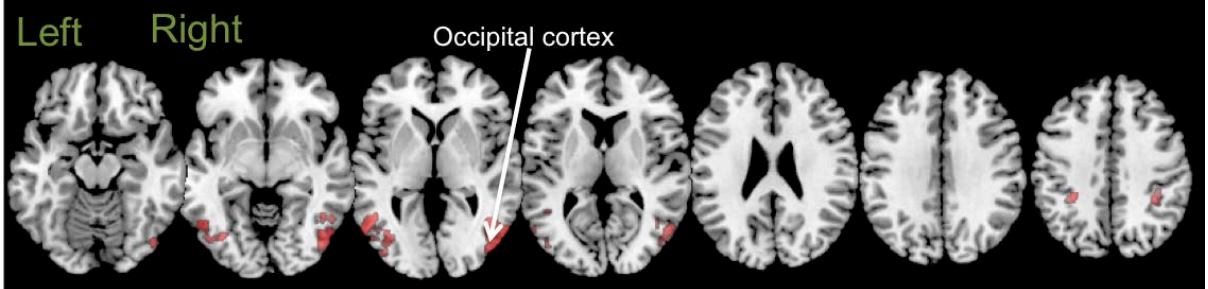


Figure 2b. Brain activation during the episodic memory task specific to processing scenes.

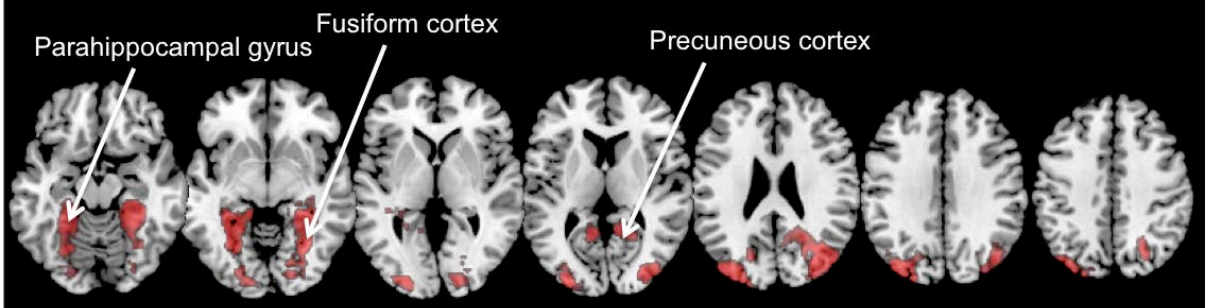
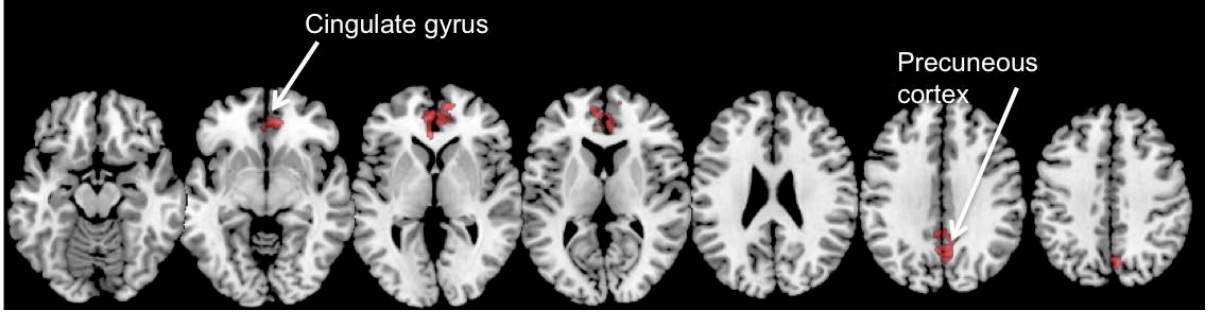


Figure 2c. Brain activation during the episodic memory task specific to processing faces.



Unanswered Questions

The preliminary results presented in this progress report form only the initial analyses that will be undertaken in this study. Several other important questions that will be answered in this project, will include:

1. Are similar brain regions recruited during working memory and episodic memory encoding/consolidation for individuals with TBI and healthy controls?
2. Does brain activation during encoding and consolidation of episodic memory predict successful retrieval at a later time?
3. Are improvements in working and episodic memory over time associated to specific regional changes in brain activity?

What these research outcomes mean

The outcomes presented in the current progress report suggest that tolerability of the study protocol is generally high. The results also demonstrate that the fMRI protocol is sufficiently sensitive to detect changes in BOLD activity in a heterogeneous sample of individuals with TBI. Statistically significant results were observed in brain regions expected to correlate with working and episodic memory in a sample comprising only six individuals.