Functional Changes Related to Episodic Memory in People with Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) has been shown to have a significant effect on every type of memory. Recently, Neuroscience literature on TBI deficits, and its behavioral effects, has increased. However, much of the research neglects considerations about the functional changes that occur after serious brain injuries. In relation to memory, specifically episodic memory, this study will analyze how those with a TBI handle for memory deficits, and identify what structures and systems are used. The current findings revealed an increase in the functional use of both hemispheres of the parietal lobe, the cerebellum, and the posterior parietal cortex in TBI participants. Continued work to clarify how the brain adapts to injury may positively influence the quality of neuro-rehabilitation services and drug therapies.

Introduction

Episodic memory enables human beings to remember specific moments in their lives in a way that is still being understood. Episodic memory is a type of long-term memory of events and is also the process of accessing those moments when the recall is necessary or triggered by association [1]. One important consequence of Traumatic Brain Injury (TBI) is a disruption in encoding and recognition of episodic memory [2, 3]. According to the Center for Disease Control (CDC), approximately 1.7 million people annually suffer from a TBI. In most cases, a patient cannot regain full memory function after his or her injury. Additionally, there are other consequences for those with an injury that negatively influences their employment and relationships. Those with moderate to severe injuries typically lose relationships and jobs due to behavioral and cognitive changes. Unfortunately, in contrast with working, semantic, or remote memory, few studies investigate the relationship between injury and episodic memory. There has been a significant change observed in cerebral mechanisms involved during episodic and other forms of memory in TBI subjects when compared to healthy controls. [4, 5]. The goal of this study is to research the question of how the brain adapts its networks after a TBI specifically in relation to the brain functions used in episodic memory that are not used in healthy controls. In order to improve rehabilitation, doctors and researchers need to better understand the brain systems and structures behind the mechanisms affected in episodic memory.

Brain Injury

TBI is damage sustained to the brain due to an external force impacting the head. It is classified as something that is acquired and is not progressive. Cognitive and physical impairment depends on the severity of the injury and the length of time unconscious after injury [6]. Quality and speed of recovery is dependent on age of injury. An injury to a prefrontal network is handled differently in terms of plasticity when you compare a developing network to an adult's established prefrontal system [7]. Coronado et al. mentions how prevalent this problem already is and that researchers may not even know how common this problem is because many of these cases do not lead to hospitalization. The injuries then go unreported so researchers may not even know how common this problem is. They mention gaps in TBI epidemiology as well as important steps that have been taken to decrease the incidence and suffering of TBI patients. This means TBI and TBI related problems will continue to be a major issue as the number of severe injuries continues to rise.

The severity of any brain injury is defined on a scale called the Glasgow Coma Scale (GSC). After analyzing a patient based on a number of criteria, he or she is usually placed into one of three levels of severity: mild, moderate, severe. Mild TBI typically has a GSC score between 13 and 15 at time of hospital admission. Moderate TBI patients score between 9 and 12 while severe patients score below 8 [6]. This score is intended to guide doctors towards the proper treatment but there has been controversy over misdiagnosed assessments and relying solely on this assessment [8-11]. Some common problems related to severe TBI include: increased aggression[12], decreased social skills as well as increased social anxiety, decreased educational performance and problem solving skills [13]. One of the most debilitating aspects for many TBI patients revolves around their tremendous memory issues, whether it is recalling old memories or forming new ones [14, 15]. It is important to understand the GSC when dealing with recovery from the injury and understanding the severity of the disability.

Episodic Memory

The current research will examine episodic memory deficit in moderate to severe TBI using functional MRI. Episodic memory can be divided into separable processes: encoding, retrieval, and consolidation as these different processes seem to involve different neuronal structures [1, 16-18]. The processes that will be assessed here are encoding and recognition. Recognition is a type of memory retrieval based on distinguishing previously encountered stimuli from stimuli that is new. Encoding is that actual action of memory formation into a construct that can be recalled later. Episodic memory as a whole relies heavily on the medial temporal lobe (MTL) system where the hippocampus is located and has been found to incorporate bilateral prefrontal areas for encoding and retrieval [1, 19]. When the brain is damaged it uses other areas to compensate for an injury. However, the work done focusing on the brain adapting to these other areas has mostly been done in relation to working memory and not nearly as much with episodic memory. Even with the growing literature in working memory, interpretations still vary on what is actually going on [20-22]. What remains to be determined is what is activated in the brain of control patients during an episodic memory task compared to that of TBI patients who are participating in the same task.

There is growing literature combining fMRI and behavioral methods for observing functional changes related to memory and other known TBI complications. FMRI is the most popular method of imaging used by research to infer and understand neurological changes [1].

However, only a few researchers have used fMRI to discuss where activation happens while the brain is using its episodic memory. One study in particular using fMRI in relation to episodic memory was conducted by Rugg et al (2002). The memory was tested with a simple yes or no recognition task and activation was observed in an fMRI scanner. This study distinguished some important processes that have not normally been seen as "different". For instance, when talking about episodic retrieval, or recollection, it is useful to distinguish between the processes that work off of retrieval cues while recovering information from memory, called the pre-retrieval processes. Those processes that are used during a retrieval attempt are called post-retrieval processes. This is noteworthy because researchers have understood that a many of the systems and structures that originally have been grouped together as the same really do have some important and different functions. These researchers found an overlap with activation in the left ventral prefrontal cortex and left anterior hippocampal formation for subsequent memory tasks.

The implications described by Rugg et al. suggest these findings offer no support for the idea that the neurology supporting episodic encoding is task sensitive, whether the task is an alphabetical task or one regarding animacy (is the word a living or nonliving entity). The researchers mention that in other studies the regions that consistently show more activity for old items than for new items suggests great significance for episodic over other memory forms. These areas are the left anterior prefrontal cortex and the lateral and medial parietal cortex. Findings from two other fMRI experiments suggest that these areas are important for recollection. This is different than 'Known' items as authors found that items judged as remembered over 'known' garnered greater hippocampal activation [23]. One issue that Rugg et al discovered is the need to develop methods to bring electrophysiological data (EEG) and haemodynamic data (neuronal blood flow aka fMRI data) together so that researchers can get good spatial as well as good temporal resolution under the same conditions and then use that measure to identify how different regions respond to memory tasks. Such a technique has been developed in recent years called EEG-fMRI or EEG-correlated fMRI where EEG and fMRI data are recorded simultaneously [24].

One of the stages involved in episodic memory is the "retrieval" of information. Rugg et al. suggested the model of memory as a "dual process" [18] in which one retrieval cue, for instance a vocabulary test item or a memory test word, will elicit two kinds of feedback. The first bit of feedback is a 'recollection signal' that provides detail information and context related to the cue and the other being a 'familiarity signal' that gives past experience with the number of times it has been encountered before. Knowing that the signal is split allows researchers to experiment in a way that separates these processes to see and understand everything that is happening on its own. The evidence so far has shown that this separation occurs in the medial temporal lobe (MTL) as well as just at the level of the outer frontal cerebral cortex. The MTL includes: the hippocampus, perirhinal cortex (BA 35 and 36), entorhinal and parahippocampal cortices. FMRI scans show that successful recollection is associated with activity in the hippocampus and parahippocampal cortex, however this has not been shown in all participants. In another study recall was associated by enhanced connectivity between the hippocampus and the perirhinal cortex as well, along with the parahippocampal cortex. The connectivity analysis also showed that the perirhinal cortex modulated the hippocampus during recognition but was then modulated itself by the hippocampus during recall [25]. These findings were different in two recent studies where items recognized as recollection elicited a greater hippocampal and parahippocampal activity than items matched for memory strength but stated to be "strongly familiar" [26, 27]. In summary what has been consistently associated with recollection-sensitive

fMRI effects are the following: the hippocampus, parahippocampal, posterior cingulate and lateral parietal cortices.

Imaging

One method gaining increased application in the study of cognitive deficits after TBI is functional magnetic resonance imaging (fMRI). FMRI will become incredibly relevant as each brain area that is activated will be looked at during certain episodic memory tasks and compared to non-TBI brains under the same task. An fMRI brain scanner can determine the level of and changes in blood flow in the brain. It uses what's called the blood-oxygen-level-dependent (BOLD) contrast to match structure and function. This imaging technique relies on the assumption that there is a direct relation between cerebral blood flow and neuronal activity [28]. There is little in the literature about how the brain reorganizes in relation to episodic memory even though every day millions of people struggle to remember simple things about what went on during their day. By focusing on changes seen in healthy brains vs TBI brains, it may be possible to improve rehabilitation techniques for post-injury patients.

It is important when relying on fMRI data and the research that has come from it to point out the arguments some have against how many researchers interpret what they're seeing. Cole et al. argue that there are too many issues, methodologically and interpretively, for researchers to fully understand the vastly complicated structures and systems that many of them claim to understand [21]. The researchers also note that while they have been very successful at separating the neuronal signals from other noise like cardiovascular signals using algorithms called ICA (independent Component Analysis); they have not been able to distinguish psychological noise from real neuronal components. Attempts to create an algorithm for this leads to many misclassifications by removing important evidence. The balance needs to be met between insuring the information being received is accurate and insuring that it does not contain too much extra noise.

In fMRI the unit of measurement used is called a *voxel* and can contain millions of neurons. The activities of these neurons are measured indirectly by their impact on the blood flow of the brain. To deal with the information from all these signals activity maps are created and each voxel is analyzed separate from the others to determine brain "activation" [22]. Some researchers see a problem in this, for this system only maps a large localized response where each voxel is compared to the stimulus, instead of relating it to other voxels in the brain. They state that a huge hurdle of systems neuroscience is to understand the parallel interactions at a deeper level in order to understand brain communication via connectivity of neurons [22].

Methods and Materials

To collect the functional data a new high-field (3T) head-dedicated scanner was used. This Siemens Allegra MR scanner is a state-of-the-art, head-dedicated, high-field (3T) MR scanner that is optimized for fMRI. It uses a pulse sequence-programming environment that provides full access to operating parameters via a C-like language. This instrument is sited at UMDNJ-New Jersey Medical School and is fully dedicated to research. Functional MRI data acquisition, pre-processing, analysis and visualization will be based on well-characterized methods that have been reported in the published literature and used extensively in our own research.

All data analysis is currently performed using the SPM8 for fMRI processing and SPSS for behavioral data analysis. The paradigms allowed us to collect both behavioral (i.e., response

accuracy and response latency) and fMRI (global and regional cerebral activation) data. Functional MRI data (i.e., change in hemodynamic response associated with cerebral activation) will be analyzed using the random effects procedure. This procedure is used to identify neuroanatomical regions of significant activation in each group, and to identify regions that are significantly more activated in one group versus the other. All raw scan data will undergo spatial realignment using the SPM8 six-parameter model to remove minor (subvoxel) motion-related signal change.

The data that will be analyzed was collected from 12 TBI participants and 8 non-TBI controls. The TBI patients range in severity from a 3 to a 13 on the GCS. The average age for these participants is 40 years old with a range of 21 to 58. The average number of months these participants have had their TBI before being scanned is just over 7 and a half years. The most common cause of TBI for these individuals is motor vehicle accidents (MVA). The average age for the healthy controls is just over 37. All subjects completed a consent form approved by an institutional review board at initiation of the testing session. This data was able to be analyzed using the SPM program.

The design for one run of the episodic memory task will yield fMRI scanning time of approximately 4.3 minutes (i.e., 256 seconds). There will be a total of four runs (see Table below) for a total scanning time of approximately 17 minutes (i.e., 1024 seconds).

Run	Condition	
1	Experimental	High Executive Control Word and Picture Encoding Task
2	Recognition	Recognition of High Executive Control Encoding Task
3	Experimental	Low Executive Control Word and Picture Encoding Task
4	Recognition	Recognition of Low Executive Control Encoding Task

High Executive Control Condition: Four categories of pictures and words, with four in each category were presented. Subjects were instructed to try and learn all the items. Subjects were then asked to judge whether each word/picture presented had pleasant or unpleasant associations and to press the corresponding button on a key pad placed under their right hand.
Low Executive Control Condition: Four categories of pictures and words, with four in each category were presented. Subjects during these runs were informed what the categories would be. They were further informed that all the words/pictures from one category will be presented together. Subjects were instructed to try and learn all the items and informed that keeping the list structure in mind would be helpful. Subjects were again asked to judge whether each word/picture presented had pleasant or unpleasant associations and to press the corresponding button on a key pad placed under their right hand.
Control Task: The control task for both the word high and low encoding conditions consisted of presentations of the letter "X".

For all of these conditions participants were asked to press the response button once each time the letter "X" appears. This condition controled for cerebral activations associated with seeing letters, subvocalizations, and making a simple button-press response.

Encoding

Prior to each stimulus presentation, a cross-hair fixation target was presented for 500 msec in order to prompt the participant to attend to the visual display. A stimulus (i.e., a word or picture) was then presented for 2 seconds, followed by a 2-second interstimulus interval (ISI). Participants were required to press the response button during the ISI if they have a "pleasant" association to the word. Cerebral activations were recorded in an event-related manner, with a total of 8 new words being presented during each 32 sec block of time (total of 16 words presented to each participant).

Recognition

Prior to each stimulus presentation, a cross-hair fixation target was presented for 500 msec in order to prompt the participant to attend to the visual display. A stimulus (i.e., a word or picture) was then presented for 2 seconds, followed by a 2-second interstimulus interval (ISI). Participants were required to press the left response button during the ISI if they recalled the word/picture as having been previously presented during the encoding task and the right response button if the word/picture was not presented during the encoding task. Of the 16 words/pictures from the original list, each participant was presented with 8 words/pictures of the target items from the original 16 interspersed with 8 novel words/pictures that will serve as foils. This is done in order to keep the recall session at the same length as encoding. Cerebral activations will be recorded in an event-related manner, with a total of 8 words/pictures being presented during each 32 second block of time (total of 16 words and 16 pictures presented to each participant).

Stimuli

WORDS

HIGH ENCODING CATEGORIES	LOW ENCODING CATEGORIES
VEGETABLES	INSECTS
SHAPES	COLORS
SPICES	MEAT
BABY ITEMS	APPLIANCES

PICTURES

HIGH ENCODING CATEGORIES	LOW ENCODING CATEGORIES
SPORTS	TOOLS
MUSICAL INSTRUMENTS	CLOTHING
ANIMALS	FRUIT
TRANSPORTATION	FURNITURE

Sample Design of Experimental Run

32 sec		*32 sec*		*32 sec*		*32 sec*	
Experimental Task (8 stimuli)	Control Task	Experimental Task (8 stimuli)	Control Task	Experimental Task (8 stimuli)	Control Task	Experimental Task (8 stimuli)	Control Task
32sec		*32sec*		*32sec*		*32sec*	

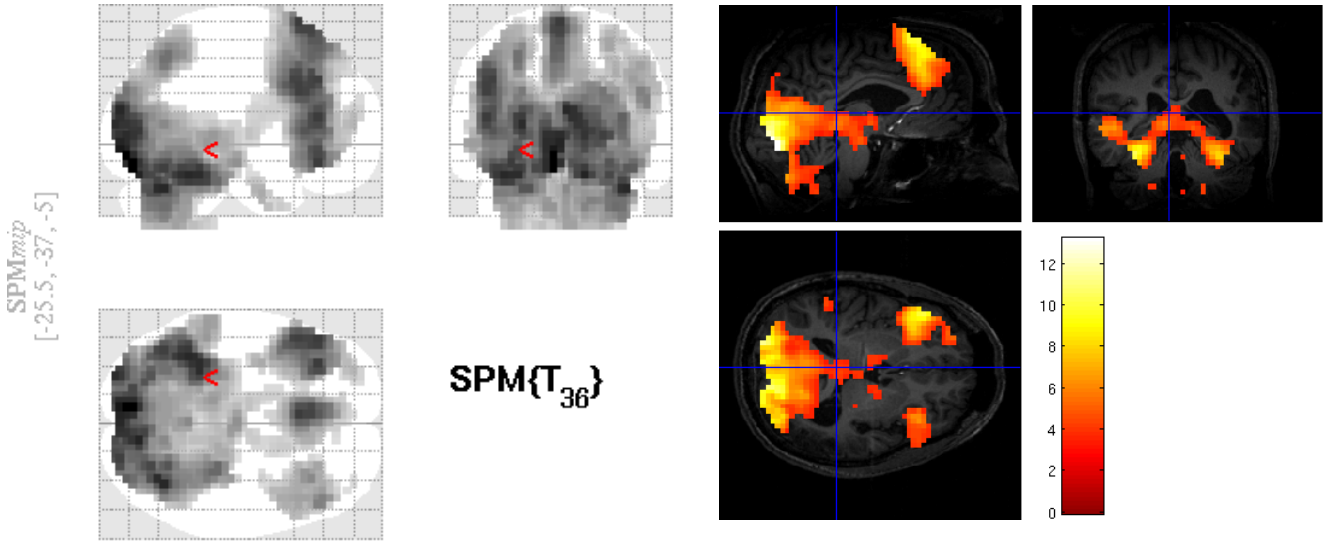
Results

The scans that were used at the time of writing this were of 12 TBI patients and 8 healthy controls (HC).We focused on the scans of the encoding step of the episodic memory process. The shared activation of the HC and TBI patients is consistent with the current episodic memory literature as well as the HC scans. This is activation in the visual cortex, medial temporal lobe, outer frontal cortex, and motor cortex. The scans of TBI patients showed significant activation in both hemispheres of the parietal lobe, the cerebellum, the posterior parietal cortex and the sub parietal sulcus as well as an increase in activation in the motor cortex, the somatosensory cortex and the lingual gyrus when compared to healthy controls.

<u>Areas used by both groups</u>:

Statistics: *p-values adjusted for search volume*

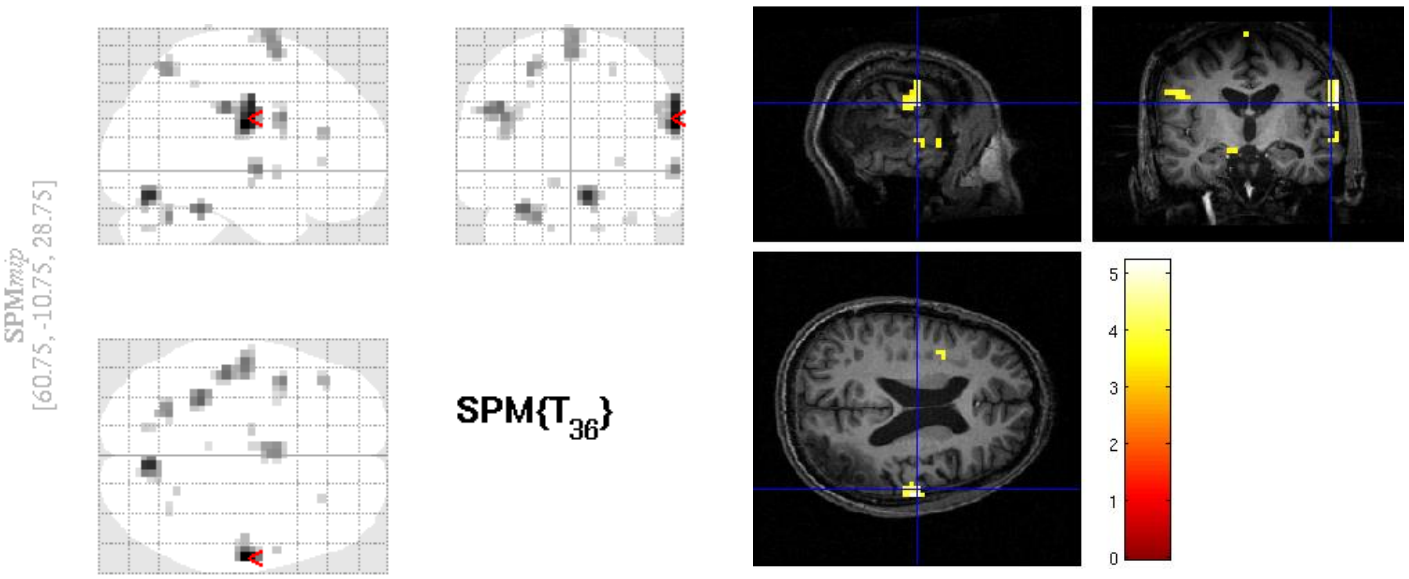
set-level		cluster-level				peak-level					mm mm mm		
p	c					$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_{\equiv})$	p_{uncorr}			
		0.000	**0.000**	**1483**	**0.000**	**0.000**	**0.000**	**10.41**	**7.03**	**0.000**	**-3**	**19**	**70**
						0.000	0.000	10.34	7.00	0.000	-48	30	14
						0.000	0.000	10.28	6.98	0.000	-33	30	-12
						0.000	0.000	10.15	6.93	0.000	-48	19	32
						0.000	0.000	10.08	6.90	0.000	-44	30	36
						0.000	0.000	10.05	6.89	0.000	-48	27	32
						0.000	0.000	9.30	6.60	0.000	-44	23	6
						0.000	0.000	7.73	5.90	0.000	-44	23	-9
						0.033	0.013	5.34	4.56	0.000	-29	23	59
						0.046	0.018	5.22	4.47	0.000	-29	53	10



TBI patients:

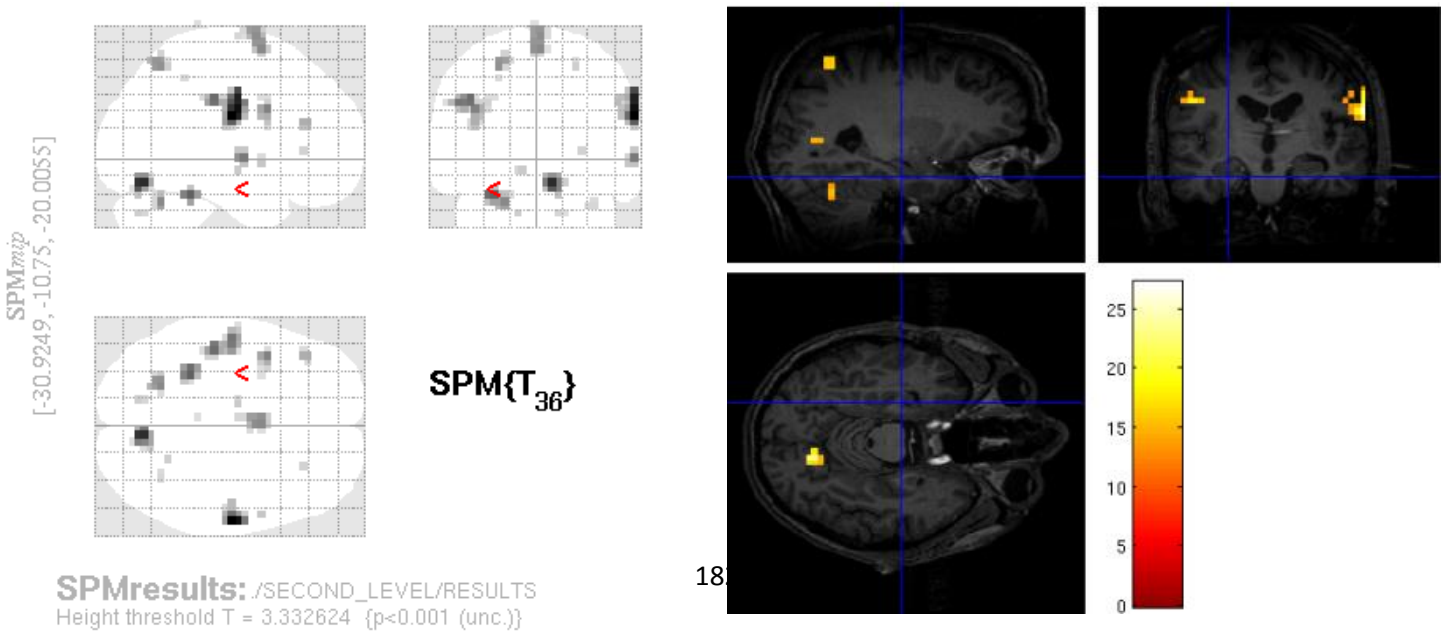
Statistics: *p-values adjusted for search volume*

set-level		cluster-level				peak-level					mm mm mm
p	c					$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_{\equiv})$	p_{uncorr}	
		0.104	**0.413**	**40**	**0.031**	**0.046**	**0.307**	**5.22**	**4.47**	**0.000**	**61 -14 25**
						0.098	0.307	4.90	4.26	0.000	61 -11 36
						0.852	0.958	3.64	3.33	0.000	50 -14 32



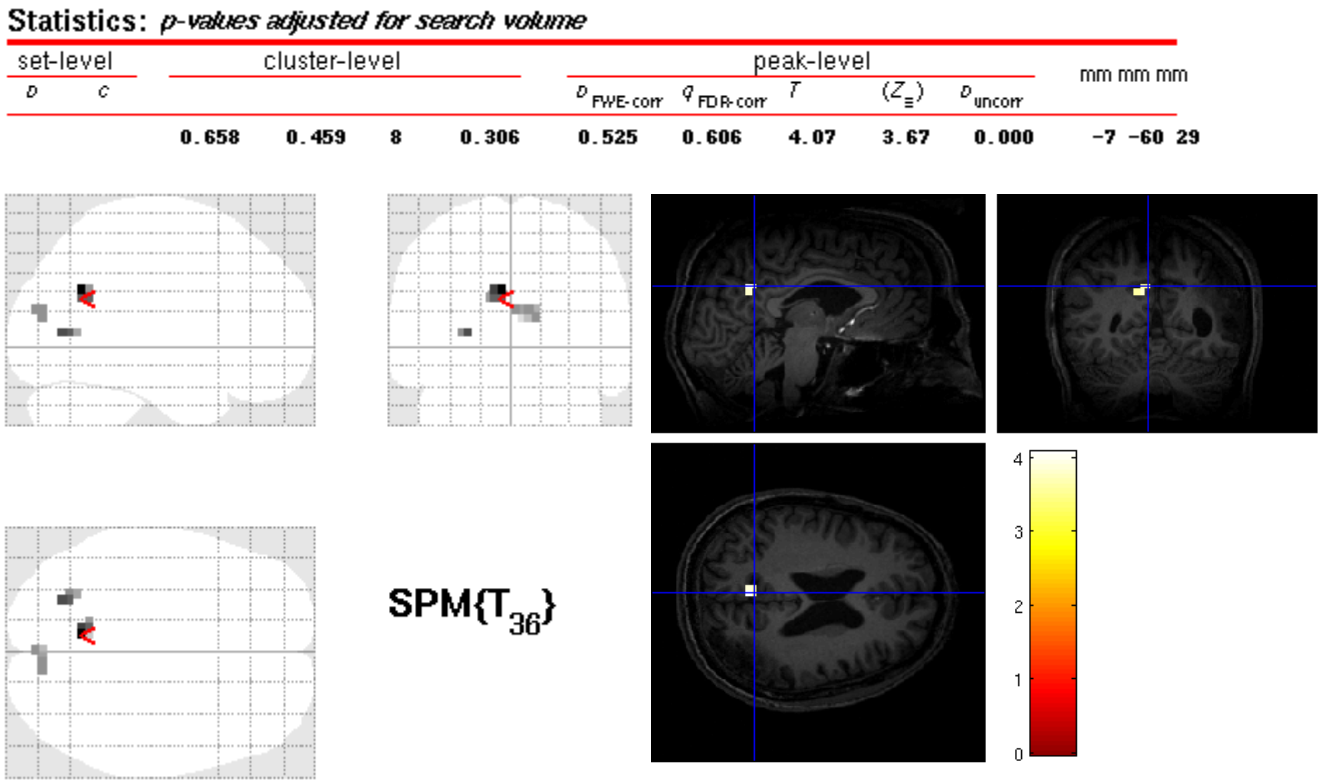
Statistics: *p-values adjusted for search volume*

set-level		cluster-level				peak-level					mm mm mm
p	c					$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_{\equiv})$	p_{uncorr}	
		0.888	**0.742**	**2**	**0.625**	**0.908**	**0.958**	**3.53**	**3.25**	**0.001**	**-10 -11 -9**



SPMresults: /SECOND_LEVEL/RESULTS
Height threshold T = 3.332624 {p<0.001 (unc.)}
Extent threshold k = 0 voxels

Healthy participants:



Discussion

The goal of this study is to examine episodic memory functioning after TBI using functional imaging. The primary finding was that in cases of TBI there is increased involvement, or "recruitment" of additional brain regions. Some of these results were consistent with the current literature while others were not.

Primary findings of episodic memory task, healthy controls and TBI:

These results show activation in the occipital lobe, the primary motor cortex, the medial temporal cortex (MTL), and the frontal lobe. These areas are consistent with the current neuroanatomical research relating to episodic memory encoding [4, 5]. These findings provide the basis for comparing the samples using this standard episodic memory task.

Activation of TBI greater than healthy controls:

The fMRI scans showed an increase in BOLD activation of TBI brains over healthy controls in the lingual gyrus, the precentral gyrus, and both hemispheres of the parietal lobe, the cerebellum, the somatosensory cortex and the motor cortex. These findings may reflect a change in strategy of encoding for TBI participants. Such an increase in the parietal lobe as well as other areas suggests an increase in "cerebral challenge" or demand. TBI participants must exert more energy and cognitive effort to complete the same task as healthy controls, as suggested by Ricker et al [4]. An increase was shown in the cerebellum during encoding for these participants, which is not concurrent with other research done in this area [5]. The cerebellum has been shown to have a role in memory possibly for the purposes of offsetting an increase in memory load [33]. The collected data shows that TBI patients use this area in an increased capacity which suggests

an adoption of different strategies used in the brain once a particular system is damaged or inactive in some way. This adoption of strategies is likely consistent and common in the TBI patients. This could be explained as an attempt for the brain to recruit areas local to the injury in a way to decrease memory load in other particular areas.

The increase in BOLD activation of the visual, motor, and somatosensory cortex could reflect a delay in reaction time by those with TBI. These participants had a longer reaction time and very likely spent more time looking at the stimuli as well as thinking about pressing the correct buttons.

Activation in healthy controls greater than TBI:

There is only one area that is active in HCs over TBI participants. This area appears to be the cuneus or the precuneus. The cuneus is a wedge shaped portion of the occipital lobe involved in basic visual processing. It is unclear why the HCs would be using this area while the TBI patients did not other than damage to that area. If it is the precuneus then it is hard to determine why it is used in healthy controls and not TBI patients since it has not received much attention in research due its location in the brain. It has been described as "one of the less accurately mapped areas of the whole cortical surface" due to its lack of study [29]. It has been speculated to have many roles linking to semantic processing but has been found to have some link to episodic memory [30-32]. Rarely the precuneus is attributed to motor vehicle accidents, the most common form of TBI, but it has been linked to gunshot wounds and acquired brain injuries such as strokes. It is not clear why this effect is being observed but it is possible that the HCs are engaging in greater semantic processing of the stimuli that is to be recalled.

Limitations

There are several constraints that were experienced during this research. One constraint was the sample size of my healthy controls which limited my analytical power. This can also impact reproducibility. Future work should integrate analysis of other parts of the episodic memory system including retrieval. Also long term episodic memory was not assessed as the participants only had to recognize pictures and words that they had recently been exposed to. Additional analysis is required of other aspects of episodic memory using more participants.

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