FMRI Hypoactivation During Verbal Learning and Memory in Former High School Football Players with Multiple Concussions

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Abstract

Multiple concussions before the age of 18 may be associated with late-life memory deficits. This study examined neural activation associated with verbal encoding and memory retrieval in former athletes ages 40–65 who received at least two concussions (median = 3; range = 2–15) playing high school football and a group of former high school football players with no reported history of concussions matched on age, education, and pre-morbid IQ. Functional magnetic resonance imaging data collected during a modified verbal paired associates paradigm indicated that those with concussive histories had hypoactivation in left hemispheric language regions, including the inferior/middle frontal gyri and angular gyrus compared with controls. However, concussive history was not associated with worse memory functioning on neuropsychological tests or worse behavioral performance during the paradigm, suggesting that multiple early-life concussions may be associated with subtle changes in the verbal encoding system that limits one from accessing higher-order semantic networks, but this difference does not translate into measurable cognitive performance deficits.

Keywords: Childhood brain insult; Head injury, traumatic brain injury; Learning and memory; Neuroimaging (functional); Language and language disorders

Introduction

Reports from the Centers for Disease Control and Prevention indicate ~207,000 concussions, or mild traumatic brain injuries (mTBIs), occur in America each year (Centers for Disease Control and Prevention, 2007). This is likely an underestimate for several reasons, such as differing definitions of concussions related to loss of consciousness, lack of understanding about concussive symptoms, unwillingness to report symptoms in athletic situations, and lack of available medical care (Guskiewicz, Weaver, Padua, & Garrett, 2000; Macciocchi, Barth, Alves, Rimel, & Jane, 1996). Other estimates suggest 1.6–3.8 million sports-related concussions occur each year (Langlois, Rutland-Brown, & Wald, 2006). Concordances cause a variety of acute symptoms and may cause more long-term cognitive changes. Acute symptoms frequently include headaches, dizziness, and fatigue (McCrorry et al., 2009), irritability, anxiety, and cognitive difficulties such as reduced attention and memory problems (Arciniegas et al., 2000; Hall, Hall, & Chapman, 2005). These symptoms most often resolve within hours, days, or months (Frencham, Fox, & Mayberry, 2005; Guskiewicz et al., 2003; McCrorry et al., 2009; Schretlen & Shapiro, 2003), but in some cases, may persist at 1-year follow-up (Dikmen, McLean, & Temkin, 1986; Jacobson, 1995; Rutherford, Merrett, & McDonald, 1978). Further, studies suggest that concussions may be associated with long-term cognitive deficits. While some studies have only cited subtle cognitive differences several years post-injury in the attention and working memory domains (Bernstein, 2002; Segalowitz, Bernstein, & Lawson, 2001; Vanderploeg, Curtiss, & Belanger, 2005; Vanderploeg, Curtiss, Luis, & Salazar 2007), others have found larger effects sizes when comparing concussed to non-concussed groups several years after the injury across several cognitive domains (Konrad et al., 2010). Other studies have not yielded these
long-term cognitive differences in people with mTBI (Dikmen, Ross, Machamer, & Temkin, 1995; Echemendia, Putukian, Macklin, Julian, & Shoss, 2001; Ettenhofer & Abeles, 2009; Macciocchi and colleagues, 1996; for review see Carroll et al., 2004). Given that those with a history of mTBI is at a greater risk for having a second concussion (Guskiewicz et al., 2003; Hollis et al., 2009), investigators have examined the cognitive effects of multiple concussions. History of at least two concussions has been associated with poorer performance on tests measuring executive functioning and processing speed (Collins et al., 1999; Gardner, Shores, & Batchelor, 2010), attention and concentration (Moser, Schatz, & Jordan, 2005), verbal memory and reaction time (Covassin, Moran, & Wilhelm, 2013), and overall neuropsychological functioning (Moser & Schatz, 2002). Athletes with two concussions in the same season showed declines in visuomotor speed, decreased visual learning, and increased errors on visual processing tasks (Pedersen, Ferraro, Himle, Schultz, & Poolman, 2014). Middle-aged athletes with multiple concussions sustained in early adulthood had lower performance across several cognitive domains, suggestive of chronic of chronic changes related to concussion (De Beaumont et al., 2009), while only subtle cognitive effects have been shown post-acute in young adult athletes with multiple concussions (Terry et al., 2012). Other studies have failed to find differences between athletes who sustained multiple concussions and controls (Gaetz, Goodman, & Weinberg, 2000; Iverson, Brooks, Collins, & Lovell, 2006; Iverson, Brooks, Lovell, & Collins, 2006; Macciocchi, Barth, Littlefield, & Cantu, 2001).

Due to these potential long-term effects, mTBIs have been studied using functional MRI (fMRI) to examine the functional sequela associated with these injuries, as fMRI has a temporal resolution that allows one to examine transient cognitive events that may be able to reveal the subtle changes in brain functioning (McAllister, Sparling Flashman, & Saykin, 2001; Ptito, Chen, & Johnston, 2007). Concussed individuals within 1-month of injury exhibited hyperactivation in the dorsolateral prefrontal cortex (DLPFC) and in right parietal regions during a working memory task despite comparable behavioral performance (2-back; McAllister et al., 1999). In a follow-up study with a substantial overlap of participants, both groups exhibited less activation during a more difficult condition (i.e. 3-back; McAllister, Sparling, Flashman, Guerin, Mamourian, & Saykin, 2001). However, the concussed group showed a greater, but statistically non-significant, decrease in activation than the control group, suggesting a complex and non-linear relationship between extent of activation and working memory load. Other 2-back paradigms demonstrated that hyperactivation in young adult athletes with a concussion 1 week post-injury was associated with a longer clinical recovery compared with athletes who did not demonstrate hyperactivation (Lovell et al., 2007). This activation pattern was shown to persist longitudinally for at least 2 months in young adults at acute and sub-acute phases of recovery (Dettwiler et al., 2014). Acute hyperactivation was also evident during motor programming and spatial memory fMRI tasks in young athletes (Jantzen, Anderson, Steinberg, & Scott-Kelso, 2004; Slobounov et al., 2010; Zhang et al., 2010), suggesting that patients with an acute mTBI require more cognitive resources to perform a task despite comparable behavioral performance, which manifests as an increased BOLD response.

However, some studies show task-related hypoactivation compared with control participants. Kontos et al. (2014) revealed that college athletes showed hypoactivation in multiple brain regions across a battery of functional tasks at 3 weeks post-injury. Paradigms assessing working memory have also shown hypoactivation compared with controls in adolescent and young adult samples, both acutely and sub-acutely (Chen et al., 2004; Chen, Johnston, Collie, McCrory, & Ptito, 2007; Keightley et al., 2014). Task-related hypoactivation may indicate several processes, such as increased difficulty allocating attention during the cognitive tasks, impaired neuronal functioning, or reduced neuro-vascular coupling due to the metabolic changes associated with concussions (Giza & Hovda, 2001).

Studies assessing the long-term brain activation differences of mTBI have yielded mixed findings. A symptomatic concussed group at 6 months post-injury showed hypoactivation in several regions during a working memory task (Gosselin et al., 2011). Similarly, a group of symptomatic mTBI participants 2 years post-injury showed reduced regional cerebral blood flow bilaterally in the thalamus using arterial spin labeling, which was significantly correlated with neurocognitive dysfunction in several domains (Ge et al., 2009). However, in a sample that included symptomatic and asymptomatic college athletes, there were no statistically significant fMRI activation differences across motor, response inhibition, and working memory paradigms (Terry et al., 2012). In a recent paper, middle-aged individuals with a history of one or more concussions before the age of 25 had worse memory performance, smaller hippocampi, and reduced neural activity during memory performance in cortical regions important for memory retrieval (Monti et al., 2013). Further, former NFL players who reported three or more concussions exhibited hyperactivation in the PFC compared with players with zero, one, or two concussions (Ford, Giovanello, & Guskiewicz, 2013). However, the “high” concussion group showed hypoactivation in memory-related regions such as the parahippocampal gyrus and inferior parietal cortex.

The present study examined verbal memory in individuals who sustained at least two football-related concussions, but have not received a concussion in at least 15 years, in hopes to better understand the long-term effects of multiple head injuries. This is the first study to our knowledge to examine the chronic effects of multiple concussions in former high school football players using fMRI methodologies. Authors expected participants who suffered from multiple concussions to have lower neuropsychological performances on tasks related to delayed memory, but have similar behavioral scores on the fMRI paradigm when compared with
the control group based on the lack of significant group differences during previous fMRI paradigms (e.g., Ford et al., 2013; Jantzen et al., 2004; McAllister et al., 2001). Additionally, participants with a history of multiple concussions were hypothesized to show hyperactivation compared with controls in an attempt to appropriately complete the tasks.

Method

Participants

Former high school football players were recruited from a suburban southeastern community though newspaper advertisements, online advertisements, and news articles about the study, or were contacted by researchers using emails and phone calls based on information gained though public records and football alumni listservs. Participants were included if they were right-handed, male, and age 40–65 years. This age range was selected to maximize the number of participants who may have sustained a concussion in their remote history, but limit the frequency of people who, by virtue of their age, may be experiencing symptoms of MCI or dementia as this would be a confounding factor. Participants were excluded if they were incompatible with the magnetic resonance imaging (MRI) environment, younger than 40 years, or older than 65 years. They were also excluded if they reported being illiterate, left-handed, learning English as a second language, a history of alcohol or drug abuse/dependency within the past 5 years, a history of significant neurological disorder (e.g., seizures, epilepsy), a history of a developmental learning disorder (e.g., learning disability, and ADHD), current use of any psychotropic medications, bipolar disorder, or schizophrenia. Participants were provided with a small monetary compensation for their time.

Forty-one participants were ultimately enrolled in the study. However, imaging data are only available for 36 participants due to claustrophobia during the task (n = 4) and late identified MRI incompatibility (n = 1). Participants were divided into two groups: one with a history of two or greater concussions and whose most recent concussion was > 15 years prior to examination (n = 25); and one without any concussive history (n = 16). Concussions were identified using a two-step processes that included a self-report questionnaire followed by an in-depth, empirically based semi-structured interview. A self-report questionnaire was developed to identify concussive history based on criteria set by American Congress of Rehabilitation Medicine (1993), where an mTBI is diagnosed when at least one of the following criteria is met after an injury involving the head: first, any period of loss of consciousness; second, any loss of memory for events immediately before or after the accident; third, any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and fourth, focal neurological deficit(s) that may or may not be transient (American Congress of Rehabilitation Medicine, 1993; Cassidy et al., 2004). If loss of consciousness was reported, it was for < 30 min. Participants were then administered the Acute Concussion Evaluation (ACE; Gioia & Collins, 2006), a systematic evidence-based clinical protocol designed to assess first, the specific characteristic of the injury including the details of the blow to the head; second, a full array of 22 symptoms and 5 signs associated with mTBI; and third, risk factors that might predict a prolonged recovery shown to have moderate-to-high internal consistence (α = 0.82) and adequate content, predictive, and convergent validity when compared with other concussion assessments (Gioia, Collins, & Isquith, 2008). Other studies using retrospective reporting showed adequate recall with high 1-month test–retest reliability (Kendler, Jacobson, Myers, & Eaves, 2008; Moffitt et al., 2007). People with exactly one concussion were not included in the study. Groups were matched on age (t[39] = 1.01, p = .28), education (t[39] = 0.28, p = .78), and pre-morbid IQ level (t[39] = −0.63, p = .53) based on independent samples t-test analyses (Table 1). Exposure to high school football, measured in seasons played, was also equivalent across groups (concussed group: M = 3.49, SD = 0.94; control group: M = 3.36, SD = 1.02, t[39] = 0.56, p = n.s.).

Procedures

After determining eligibility via a phone screen, participants were scheduled for either one or two research sessions depending on their personal preference. The commitment totaled 4–5 h and encompassed informed consent, concussion interview, self-report measures, neuropsychological testing, MRI safety screening, and MRI scanning. Before engaging in the fMRI task, participants learned how to complete the task using a computer outside of the MRI environment. Participants were in the MRI scanner for ~55 min, during which structural, functional, and phase/magnitude images were collected among other scan sequences not relevant for this study.
Measures

Symptom Assessment Scale. A 22-item concussion symptom checklist to index current, if any, post-concussive symptoms. The participant ranked both the duration and the severity of each system over the past 24 h using a Likert scale (0–6); the maximum total score is 132 on each of the two sub-scales (Broglio, Macciocchi, & Ferrara, 2007). The severity sub-scale is anchored with not severe at all and as severe as possible, and the duration scale is anchored with briefly and always.

Green’s Medical Symptom Validity Test. This short, computerized verbal memory test was used to quantify each participant’s memory and symptom validity based on level of performance on each trial and consistency of responding over trials to assess for adequate task engagement (Green, 2004). Participants must have achieved a score considered to show effortful participation (85%) to continue the study. All participants (n = 41) met or exceeded this threshold on the four main indices (immediate recognition, delayed recognition, consistency, and paired associates).

Wechsler Test of Adult Reading. This 50-item word reading test estimates pre-morbid intellectual ability by incorporating participants’ performance with demographic variables (Green et al., 2008). Participants pronounced words of increasing difficulty. This was used to control for the potential confound of pre-morbid intellectual functioning differences between the concussed and control group. Raw scores are converted to standard scores that account for age, gender, race, education, and word reading performance.

California Verbal Learning Test—Second Edition. California Verbal Learning Test—Second Edition (CVLT-II) was used to assess verbal learning and memory over immediate and delayed memory trials. Participants listened to word lists read orally and then repeated as many words from the list as they can remember. Recall of the initial list of words occurred following each of the five list presentations, after hearing a new list of words, and after a 20-min delay. Recognition of the list is also tested. Split-half reliability for total trial scores (trail 1 + 3 vs. trails 2 + 4, etc.) was high for the normative sample (r = .82) and for a mixed clinical sample (r = .83) (Delis, Kramer, Kaplan, & Ober, 2000). Raw scores are converted to normed scores that account for age and gender.

Logical Memory I/II, Wechsler Memory Scales-4th Edition. To assess contextual memory, participants listened to two short story narratives and immediately repeated as many details from the story as possible (Wechsler 2009). Participants were also asked to recall the stories after a longer delay and to answer forced-choice recognition questions that pertain to the stories. Logical Memory

Table 1. Group demographics

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 16)</th>
<th>Concussed (n = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.1 (8.3)</td>
<td>52.0 (8.05)</td>
<td>.28</td>
</tr>
<tr>
<td>Years of education</td>
<td>15.0 (2.2)</td>
<td>15.2 (2.3)</td>
<td>.78</td>
</tr>
<tr>
<td>WTAR</td>
<td>108.3 (12.5)</td>
<td>110.6 (11.1)</td>
<td>.53</td>
</tr>
<tr>
<td>Number of concussions</td>
<td>–</td>
<td>4.3 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Concussions with LOC</td>
<td>–</td>
<td>29.0%</td>
<td></td>
</tr>
<tr>
<td>Concussions with medical attention</td>
<td>–</td>
<td>29.0%</td>
<td></td>
</tr>
<tr>
<td>Concussions with memory lapse</td>
<td>–</td>
<td>43.0%</td>
<td></td>
</tr>
<tr>
<td>SAS number of symptoms</td>
<td>3.4 (3.0)</td>
<td>4.8 (4.3)</td>
<td>.24</td>
</tr>
<tr>
<td>SAS average duration</td>
<td>2.0 (1.7)</td>
<td>2.1 (1.4)</td>
<td>.85</td>
</tr>
<tr>
<td>SAS average severity</td>
<td>1.6 (1.1)</td>
<td>1.9 (1.3)</td>
<td>.39</td>
</tr>
<tr>
<td>CVLT-II Trials 1–5 T-score</td>
<td>57.0 (11.6)</td>
<td>55.7 (10.4)</td>
<td>.72</td>
</tr>
<tr>
<td>CVLT-II Short Delay Z score</td>
<td>0.41 (1.39)</td>
<td>0.36 (1.12)</td>
<td>.91</td>
</tr>
<tr>
<td>CVLT-II Long Delay Z score</td>
<td>0.43 (1.25)</td>
<td>0.32 (0.76)</td>
<td>.71</td>
</tr>
<tr>
<td>WMS-IV LM I Scaled Score</td>
<td>10.6 (2.5)</td>
<td>10.7 (2.9)</td>
<td>.90</td>
</tr>
<tr>
<td>WMS-IV LM II Scaled Score</td>
<td>10.3 (3.1)</td>
<td>10.5 (2.7)</td>
<td>.83</td>
</tr>
</tbody>
</table>

Notes: The T-score distribution has a mean of 50 and an SD of 10. The Z-score distribution has a mean of 0 and an SD of 1.0. The scaled score distribution has a mean of 10 and an SD of 3.

Values are mean and (SD). The median number of concussions for the concussion group was 3. When two extreme values in the number of reported concussions were reduced to 2 SD above the mean, the average number of concussions was 3.9. WTAR = Wechsler Test of Adult Reading; LOC = loss of consciousness; SAS = Symptom Assessment Scale; CVLT-II = California Verbal Learning Test-II; WMS-IV = Wechsler Memory Scale-IV; LM I = Logical Memory Immediate Recall; LM II = Logical Memory Delayed Recall.
I and II were both shown to have high split-half reliability coefficients, thus demonstrating internal consistency ($r = .82$ and $r = .85$, respectively). Raw scores are converted to normed scores that account for age and gender. Participants in this study also completed several additional measures that will not be examined in the current analysis.

**Neuroimaging**

**Task.** While in the MRI scanner, subjects performed a learning and recall-based task involving unrelated pairs of words that is particularly sensitive for the identification of damage to the medial temporal lobe (Rausch & Babb, 1993) and shown to engage memory systems maximally, as adopted by Bookheimer and colleagues (2000) and Braskie, Small, and Bookheimer (2009). There were three parts to this task (i.e. encoding, distractor, and recall) that repeated in the same order a total of 10 times (Fig. 1). During the encoding epochs, participants viewed pairs of words (e.g., UP and FOOT) and were instructed to remember that the two words went together. This occurred a total of 10 times, each epoch lasting 19.5 s. There were a total of 10 word-pairs in the paradigm. Each encoding epoch contained five of the word-pairs. All words were presented in white on a black screen. Initially, the first word of the word-pair was presented alone (1 s) and then accompanied by the second word of the word-pair (2 s). Participants pressed a button on the response pad with their right index finger when they saw the second word of the word-pair appear on screen to validate that they were attending to the stimuli. This also served to control for motor activity in other conditions. A black screen (0.9 s) followed each word-pair. The five word-pairs in each encoding epoch were pseudo-randomly selected in a pre-determined manner such that all of the words were presented one time during epochs 1 + 2, one time during epochs 3 + 4, etc. Therefore, each of the 10 word-pairs was presented a total of five times. The word-pairs were presented in a fixed order across participants. The list contained 6 two-syllable words and 14 one-syllable words, randomly combined into 10 pairs. Thirteen of the 20 words in the list were nouns and 7 were adjectives. No word in the list was a common associate of any other word in the list, based on word association norms (Nelson, McEvoy, & Schreiber, 2004).

Each encoding block was followed by a distracter epoch (19.5 s), where participants attended to a series of letters (i.e., “XXXX—YYYY”) to mimic the active stimulus. This was included to discourage rehearsal. Participants pressed with their right index finger when they saw the letters to control for motor activity in the other conditions. Immediately after each distracter epoch was a 19.5 s recall epoch, during which participants saw the first word of each pair from the encoding epoch that preceded it (e.g., UP - ???), attempted to recall the second word silently (3 s), and viewed a black screen (0.9 s). Subjects indicated perceived success at recalling the second word with a right index finger response and perceived failure with a left index finger response. After each recall epoch, participants focused on a crosshair (6 s) to allow for brain activity to return to its baseline. The sequence of encoding epoch, distractor epoch, and recall epoch repeated ten times. Before each new epoch began, there was a 3 s prompt to inform the participant which task they would need to perform. The full presentation of the task lasted 12 m and 24 s. The total number of perceived successful recalls for each subject was summed across the 10 recall epochs, where participants achieved scores between 0 and 50. Additionally, immediately after scanning, participants were asked to freely recall as many words as they could from the paradigm. They received credit each time they verbalized a “second word” from the word-pair (post-task free recall, maximum score = 10). Then, participants were prompted to say the second word from each word-pair after the experimenter orally read the first word of the pair (post-task cued recall, maximum score = 10). To ensure participants...
performed this task correctly in the scanner, participants were trained on this task by the lead author using a desktop computer and alternate word-pairs until they obtained 80% accuracy on the recall epoch.

MRI acquisition. A 3.0T General Electric (GE) Signa HDx magnetic resonance system was used to collect anatomical and functional images. This scanner was equipped with 16 RF receiver channels with TQ Engine gradients (amplitude, 45 mT/m [z-axis], 40 mT/m [x, y axes]; slew rate, 200 T/m/s) and an 8-channel head coil. Functional scans were acquired axially along the AC-PC line using a T2*-weighted single shot echo planar imaging sequence (4 mm slice thickness, 30 interleaved axial slices, TR = 1500 ms, TE = 25 ms, 90° RF pulse, matrix size = 64 × 64, FOV = 220 × 220 mm, in-plane resolution: 220 × 64 mm). Four dummy sample images were recorded and discarded at the beginning of each run to allow longitudinal magnetization to reach equilibrium. A high-resolution 3D T1-weighted fast spoiled gradient recalled echo scan was also acquired to be used in the post-processing of BOLD fMRI images (TR = 7.5 ms; TE = min full; FOV = 256 × 256 mm matrix; flip angle = 20°; slice thickness = 1.2 mm; 154 axial slices); acquisition lasted 6 m 20 s.

Functional MRI data reduction and analysis. Data were processed and analyzed using Statistical Parametric Mapping (SPM12b, Wellcome Department of Cognitive Neurology, London, UK). Images were converted from GE DICOM format to NIFTI using the dcm2nii conversion tool (Rorden, 2007). Each subject’s data was slice time corrected to account for the interleaved acquisition. Data then underwent realignment and unwarping procedures to adjust for any distortion that may have resulted from magnetic field inhomogeneities and movement during the scan. The anatomical scan was co-registered to the functional images through a transformation process, and then was segmented into gray matter, white matter, and cerebrospinal fluid, which aided the normalization of functional images into normal space. Functional images were normalized to the Montreal Neurological Institute (MNI) template using a non-linear, 12-parameter affine transformation registration, and smoothed with a 6.75 × 6.75 × 8 mm FWHM Gaussian filter to de-emphasize random noise and increase the signal-to-noise ratio.

For the verbal memory task, activation maps were generated using the General Linear Model (SPM12b) including the following contrasts for each subject: encoding versus baseline; retrieval versus baseline. Contrasts were subjected to 2nd level, random effect analysis on the group level. Another set of random effects analyses compared these contrasts between groups. Whole-brain activation maps of control and mTBI subjects were subtracted from each other using two-sample t-tests to identify differential activation at the statistical threshold of p < .005, uncorrected with a minimum of 20 contiguous voxels, as this has been shown to be equivalent to a false discovery rate of p < .05 and achieve a more desirable balance between Type 1 and Type 2 error rates in fMRI data than more conservative approaches (Lieberman & Cunningham, 2009). Similar thresholds have been used in recent literature examining memory and concussive injuries (Ford et al., 2013; Jacques, Rubin, & Cabeza, 2012).

Region of interest (ROI) analyses (WFUPickAtlas; Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Burdette, & Kraft 2003) were performed for the verbal memory task using the cluster level interference method (statistical threshold p < .005, 20 contiguous voxels). ROIs were identified a priori based on previous literature (Dobbins & Wagner, 2005; Mitchell, Johnson, Raye, & D’Esposito, 2000; Mitchell, Johnson, Raye, Mather, & D’Esposito, 2000; Wagner et al., 1998), and included first, hippocampus/parahippocampal gyri; second, middle temporal gyrus; third, inferior temporal gyrus; fourth, fusiform gyrus; fifth, DLPFC; and sixth, ventromedial prefrontal cortex.

Behavioral Data Analysis

To analyze accuracy during the verbal memory task, a between-groups t-test was conducted using SPSS version 16.0 (SPSS, Chicago) to identify group differences in total accuracy scores (range: 0–50) from data obtained during the fMRI scanning session as well as post-task free recall (range: 0–10) and post-task cued recall (range: 0–10). Neuropsychological data were compared across groups with assess differences in cognitive functioning. p-values were set to ≤.01 to correct for multiple comparisons.

Results

Concussion Symptomatology and Neuropsychological Measures

Those in the concussion group reported a median of three concussions (M = 4.3, SD = 3.7, range = 0–15 concussions). When two extreme values in number of reported concussions were reduced to the value of 2 SD above the mean, the average number of concussions was 3.9. LOC was accompanied with 29% of the concussions, while 43% of the concussions were associated with either anterograde or retrograde amnesia (Table 1). Medical attention was reportedly sought following 29% of the concussions. Both groups endorsed several current symptoms associated with concussion (control group M = 3.4, SD = 3.0; concussion group
M = 4.8, SD = 4.3). t-Test analyses failed to find group differences between the total number of current symptoms endorsed (t(39) = −1.18, p = .24), the average duration of these symptoms (t(39) = −0.19, p = .85), and the average severity of these symptoms (t(39) = −0.87, p = .39) (Table 1).

Independent samples t-tests failed to reveal group differences on several neuropsychological measures (Table 1). The concussion group was not statistically different from the control group when learning a list of words across repeated trials (CVLT-II Trials 1–5 T-score: t(39) = 0.37, p = .72), recalling the list of words after a short delay (CVLT-II Short Delay Z-score: t(39) = 0.12, p = .91), and recalling the list of words after a 20-min delay (CVLT-II Long Delay Z-score: t(39) = 0.38, p = .71). Similarly, recall of two stories was comparable between groups both immediately after the story was read and after a 20-min delay (WMS-IV LM I scaled score: t(39) = −0.13, p = .90; WMS-IV LM II scaled score: t(39) = −0.23, p = .83). Significance levels did not change when the five participants who did not undergo MRI scanning were excluded from the analyses.

**FMRI Task Performance**

Bivariate correlation between subjective correct responses during the scanning paradigm (maximum raw score = 50) and post-task cued recall of the word-pairs (maximum raw score = 10) for all participants showed a strong association (r = .52, p < .001), suggesting that the participants’ responses in the scanner were accurate in estimating memory performance. Independent t-test analyses showed no differences in accuracy between groups for subjective memory during the paradigm (t(34) = 0.54, p = .59), for post-task free recall (t(34) = 1.23, p = .23), or for post-task cued recalled (t(34) = 0.97, p = .34) (Table 2).

**Functional Imaging**

For the encoding-view contrast, within group analyses of concussion group yielded widespread activation at the threshold of p < .05, family-wise error (FWE) corrected and a minimum of eight contiguous voxels. Of the 11 significant clusters, the largest area of activation was in the left inferior frontal gyrus, pars opercularis (BA44), which spread into the precentral gyrus (Peak T = 11.56). The left paracingulate and left fusiform cortices also showed activation. Other areas of activation included the bilateral paracingulate gyrus (Peak T = 3.40), the left orbitofrontal cortex (maxima at MNI 54, 38, 12; k = 46, Peak T = 3.34), planum temporale (Wernicke’s area)/the left supramarginal gyrus (maxima at MNI −50, −44, 18; k = 69, Peak T = 3.40), and the left orbitofrontal cortex (maxima at MNI −50, −24, −6; k = 49, Peak T = 3.34). Exploratory post hoc analyses of the a priori ROIs revealed hyperactivation in the control group compared with the concussion group during the encoding task in the left orbitofrontal cortex (maxima at MNI −50, 26, 6; k = 49, Peak T = 3.32) and the left middle temporal gyrus (maxima at MNI −50, −64, 12; k = 34, Peak T = 3.10) at uncorrected p < .005, 20 contiguous voxels. There were no areas of hyperactivation in the concussed group over the control group in the ROI analyses.

The recall-view condition also revealed diffuse activation. The concussed group showed activation in 12 clusters, the largest in magnitude being in the bilateral paracingulate gyrus (Peak T = 12.15) at a threshold of FWE corrected p < .05, eight contiguous voxels (Table 4 and Fig. 3). Other areas of activation include the bilateral orbitofrontal cortex, left inferior frontal gyrus

<table>
<thead>
<tr>
<th>Condition</th>
<th>Controls (n = 16)</th>
<th>Concussed (n = 20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective correct responses (%)</td>
<td>77.6 (13.0)</td>
<td>74.6 (18.9)</td>
<td>.59</td>
</tr>
<tr>
<td>Post-task free recall (%)</td>
<td>53.0 (25.8)</td>
<td>45.0 (17.3)</td>
<td>.22</td>
</tr>
<tr>
<td>Post-task cued recall (%)</td>
<td>76.8 (23.0)</td>
<td>68.5 (28.1)</td>
<td>.34</td>
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</tbody>
</table>

Note: Values are mean and (SD).
Widespread activation was similarly seen in the control group during the recall-view condition, which also yielded 12 clusters of significant activation at a threshold of FWE corrected $p < .05$, eight contiguous voxels. Areas of activation included the bilateral paracingulate gyrus, the bilateral insula, left inferior frontal gyrus, bilateral middle frontal gyri, the right insula, the left angular gyrus, the left lateral occipital cortex, the right thalamus, and the right cerebellum.

At the threshold of $p < .005$, 20 contiguous voxels, the concussion group did not show any areas of increased activation compared with the control group. However, the control group showed more activation during recall-view in the left middle frontal gyrus compared with the concussed group (maxima at MNI $-34, 12, 28$; $k = 26$, Peak $T = 3.38$). Exploratory post hoc ROI analyses failed to show any activation related to the recall contrast.
Discussion

The purpose of this study was to examine BOLD activation in middle-aged former high school football players reporting a history of multiple concussions compared with non-concussed players in response to a verbal memory paradigm. In addition,
we compared verbal memory functioning as measured by standard neuropsychological tests given the literature’s previous discrepant findings. Overall, we found similar patterns of activation between the two groups, with modest but notable differences in neural recruitment evident. These data suggest that sustaining multiple mTBIs as an adolescent may be associated with modest long-term alterations in brain activity during memory encoding and retrieval later in life.

These subtle differences are meaningful given the nature of the two participant groups. The experimental group was matched to the control group on age, education, estimated pre-morbid IQ, and, importantly, on the type, period, and general duration of sport (high school football) activity at the time of concussion. Further, differences in verbal learning and recall were not evident on traditional neuropsychological measures nor were there differences in the behavioral performance on the task during the functional imaging. Given that both perceived and objective accuracy on the memory paradigm were equivalent between the concussed and

<table>
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<tr>
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<th>R/L</th>
<th>Region Extent</th>
<th>Peak T</th>
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<tr>
<td></td>
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Notes: Threshold for each group was \( p < .05 \), FWE corrected, with a minimum count of eight contiguous voxels. Regions were identified using the AAL and Harvard Cortical/Subcortical Atlases. Coordinates are in MNI space.
non-concussed participants, the ability to attribute potential differences in brain activation during the encoding and retrieval processes were not confounded by differences in behavioral performance.

Overall, participants in both groups recruited similar brain regions during encoding and retrieval. After subtracting out the distractor (i.e. “View”) condition from the encoding blocks, both groups showed activation in left fronto-parietal areas such as the inferior frontal gyrus, middle temporal, and right supramarginal regions. These regions have previously been implicated in the “levels-of-processing” model of language functioning (Craik & Lockhart 1972), which suggests that encoding more complex information requires additional cortical resources and therefore increases retention. The encoding of more complex verbal information has previously been associated with increased BOLD signal in the left inferior frontal, left prefrontal, and right orbitofrontal cortices (Bonner-Jackson, Csernansky, & Barch, 2007; Henson, Hornberger, & Rugg, 2005). Our results suggest that concussed individuals may have subtle underlying changes in their verbal memory encoding system that limits them from accessing higher-order semantic networks. For instance, the control group may have used verbally mediated encoding strategies to a greater extent than the concussed group.

The recall condition also showed similar activation patterns for both groups. Consistent areas of activation included the paracingulate gyrus, the left inferior frontal gyrus, the right orbitofrontal cortex, the left precentral gyrus, the right thalamus, the left lateral occipital cortex, and the bilateral cerebellum. However, the concussion group showed hypoactivation compared with the control group in the left middle frontal cortex, an area associated with memory recall that becomes progressively more activated during the retrieval of perceptually detailed information that was previously encoded (Ranganath, Johnson, & D’Esposito, 2000). Given the complexity of the verbal paired associates task, this suggests that those with concussive histories may have alterations in both encoding and retrieval networks associated with higher-order verbal processing. Further, this pattern of hypoactivation related to concussive history is consistent with other functional imaging studies that similarly examined the long-term effects of concussions several years after the injury (Ford et al., 2013; Ge et al., 2009; Monti et al., 2013). However, this is the first study to find these effects in a cohort of former athletes who did not play for a college or professional team.

Despite a lack of statistically significant differences in behavioral performance on the verbal memory paradigm according to independent samples t-tests, effect size analyses may help explain the differences in neural activation. Effect size analyses show that the control group outperformed the concussed group by approximately one third of a standard deviation (post-task free recall, Cohen’s $d = 0.36$; post-task cued recall, Cohen’s $d = 0.32$). This difference was not statistically significant likely due to the small sample size, but the magnitude of effect size suggests that the concussed group may have a subtle memory disturbance that helps to explain their pattern of hypoactivation in the fMRI paradigm compared with controls. A strong association between worse behavioral performance and decreased brain activity has been shown in other patient populations, which may be due to dysfunctional cortical networks (e.g., worse memory functioning) or other methodological factors (e.g., divergent cognitive processes, differential motivational effects; Manouch, 2003).

These differences on a paired associate learning paradigm may have important theoretical implications. This task, which requires one to quickly form and remember novel relationships between items, is related to theories of medial temporal lobe functioning, which posit the hippocampus receives and encodes personally relevant information by binding it to existing percepts (Cohen et al., 1999; Henke, Buck, Weber, & Wieser, 1997). Paired associate tasks have been implicated in medial temporal lobe dysfunction (Cohen & Eichenbaum, 1993) and have been shown to be sensitive in characterizing the preclinical stage of Alzheimer’s disease (Fowler, Saling, Conway, Semple, & Louis, 2002; Swainson et al., 2001). Our results may help explicate the subtle behavioral differences related to episodic memory functioning those with multiple mTBIs experience as well as describe the neural manifestations of these cognitive differences.

Findings do not appear to be affected by current concussion symptomatology. The SAS has previously discriminated between a group of athletes who had a history of multiple concussions and a group of non-concussed athletes (Terry et al., 2012). However, given the relatively common nature of these symptoms (e.g., headache, fatigue, and sleep disturbance), both groups endorsed experiencing several symptoms over the 24 h prior to testing. Therefore, the hypoactivation exhibited by the concussed group is likely not an artifact of their symptomatology. The implications of these activation differences are yet to be determined. They could potentially be related to a reorganization of neural networks following multiple sports-related concussive injuries. Alternatively, they could be indicative of a subtle insult that has yet to manifest as a measurable functional deficit. Longitudinal studies will be helpful in clarifying the course of these changes and implications of these findings.
There are some caveats to acknowledge in this study. History of concussions was remote (i.e., >15 years prior) and measured in a retrospective way. Memory ability and nonspecific factors (e.g., personality, interest in football, and knowledge of concussions) may have influenced participants’ self-report. Further, two participants (8% of the concussion group) reported a history of >10 concussions. Several of these concussions were confirmed by an examiner using the ACE, thus validating membership to the multiple concussion group. However, accuracy of all concussions was unable to be documented due to the participants’ difficulty recalling the events. Validating concussions by examining medical records may be useful, but many concussions would be excluded due to the underreporting of symptoms (McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004). This study was also cross-sectional. Although the previously concussed group and the non-concussed controls were matched on several variables thought to influence our findings, it is possible that the groups differed on factors other than their history of head injuries. Longitudinal studies would more accurately show the chronic effects of mTBIs as a product of aging. Like other studies in this field, the sample size was small due to the specialized nature of the participants. This can lead to a reduced ability to detect true differences on some conditions. Additionally, this highly specialized sample limits the generalizability of these findings. Future studies need to replicate the current findings and help clarify the nature of concussions in other samples across other age groups. Finally, research has showed that people over the age of 60 may have reduced BOLD signal in areas related to verbal memory encoding (Park, Kennedy, Rodrigue, Hebrank, & Park, 2013). Although very few participants in the current sample were over 60 (i.e., \(n = 2\) in the control group, \(n = 3\) in the concussion group), this potential confound should be taken into account in studies examining aging.

Despite these limitations, this study had many strengths. Unlike several previous studies, we used an empirically based assessment tool to confirm the presence of concussions and to screen out concussive histories in the control group. This study also employed a measure of task engagement, on which all participants performed adequately. This suggests the participants were putting forth sufficient effort during testing and were not trying to exaggerate or mangle symptoms as previous studies have warned (**Green et al., 1999).**

Conclusions

The current study is the first to our knowledge to examine the long-term consequences of sports-related concussions in former high school athletes using functional imaging. Results on formal memory tests suggest that players with a history of multiple concussions perform just as well as a group of matched, non-concussed teammates. Further, history of concussions did not appear to have an effect on the behavioral performance on a verbal memory task during functional imaging. However, the concussion group had a modestly different pattern of neural activity associated with both verbal encoding and memory retrieval such that they showed several clusters of hypoactivation in brain regions traditionally associated with language and memory functioning. Such differences suggest that multiple concussions sustained early in life may lead to differential recruitment of neural regions. Future research is needed to examine the longitudinal pattern of these differences as well as how they may affect players later in older adulthood, particularly as to how this may or may not influence later functional ability.

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Conflict of Interest

None declared.

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References


