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SPECIAL ISSUE ARTICLE

Loss of consciousness, but not etiology, predicts better working memory performance years after concussion

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ABSTRACT

Background: Patients with uncomplicated cases of concussion are thought to fully recover within several months as symptoms resolve. However, at the group level, undergraduates reporting a history of concussion (mean: 4.14 years post-injury) show lasting deficits in visual working memory performance. To clarify what predicts long-term visual working memory outcomes given heterogeneous performance across group members, we investigated factors surrounding the injury, including gender, number of mild traumatic brain injuries, time since mild traumatic brain injury (mTBI), loss of consciousness (LOC) (yes, no), and mTBI etiology (non-sport, team sport, high impact sport, and individual sport). We also collected low-density resting state electroencephalogram to test whether spectral power was correlated with performance.
Aim: The purpose of this study was to identify predictors for poor visual working memory outcomes in current undergraduates with a history of concussion.
Methods: Participants provided a brief history of their injury and symptoms. Participants also completed an experimental visual working memory task. Finally, low-density resting-state electroencephalogram was collected.
Results: The key observation was that LOC at the time of injury predicted superior visual working memory years later. In contrast, visual working memory performance was not predicted by other factors, including etiology, high impact sports, or electroencephalogram spectral power.
Conclusions: Visual working memory deficits are apparent at the group level in current undergraduates with a history of concussion. LOC at the time of concussion predicts less impaired visual working memory performance, whereas no significant links were associated with other factors. One interpretation is that after LOC, patients are more likely to seek medical advice than without LOC.
Relevance for patients: Concussion is a head injury associated with future cognitive changes in some people. Concussion should be taken seriously, and medical treatment sought whenever a head injury occurs.

1. Introduction

There is growing interest in concussion, generally considered a mild traumatic brain injury (mTBI) [1,2]. The sheer prevalence of mTBI makes it worthy of attention. For example, in the United States there are an estimated >3 million yearly pediatric cases of mTBI [3]. Symptoms usually resolve over several weeks and patients gradually return to activities without lasting cognitive

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consequences [4] in pediatric [5] and adult [6] populations. There are now widespread and effective "when in doubt, sit it out" public health policies guiding return-to-play decisions [7,8] and clinicians' groups regularly publish updated assessment and management guidelines [1,9-12]. Despite the efforts, there is no standard in care when treating a concussion.

Although full cognitive recovery is expected within ~3 months of a mTBI, subsets of mTBI cohorts exhibit long-lasting cognitive changes. In particular, executive functions such as working memory (WM) can show impairment when tested [13,14]. It is also known that there is insufficient data following up mTBI patients over time to comprehensively understand the range of cognitive outcomes [15]. Despite the emerging evidence identifying the possibility of lasting cognitive changes long after mTBI, there is still a lack of research in understanding the long-term sequelae associated with a history of mTBI [e.g. 16]. One explanation for lasting cognitive impairment is that mTBI causes heterogeneous diffuse axonal injury due to shearing forces [17-25]. This damage can disrupt connectivity and impact behavior [26-28]. There is also growing concern that lasting anatomical and behavior changes are particularly associated with high impact sports such as football and hockey [29-32]. However, a major challenge in assessing mTBI is the need for a reliable biomarker in the form of a laboratory test [33] and for advanced neuroimaging scanning techniques to be able to detect mTBI [22,34,35]. Given this challenge, it is worth noting that recent research shows that atypical neural network activity can be detected using resting-state electroencephalogram (rs-EEG) data [36-38].

One overlooked population that may shed light on the lasting consequences of mTBI are current undergraduates with a history of mTBI. It is a conservative experimental approach, because students must rely on cognition to be successful in an academic environment. However, if deficits are identified it suggests that lasting deficits are likely more prevalent than previously believed. In the previous research, undergraduates with a history of mTBI were found to be significantly impaired at visual WM tasks [39]. More specifically, undergraduates with a history of mTBI were significantly impaired at maintaining three-items for 900 ms in change detection tasks using color patch or oriented line stimuli (Figure 1). Subsequent experiments showed that extending encoding times or shortening maintenance durations did not benefit the mTBI group, and neither did providing performance feedback. However, in the heterogeneous mTBI population, these group level comparisons could not shed light on which factors predicted later cognitive performance. Our goal in this analysis was to identify the predictors of later visual WM deficits in undergraduates with a history of mTBI. Again, the participants are undergraduates with a self-reported history of mTBI (>3 months post-injury) and their peers without a history of mTBI. WM is a key executive function that allows us to temporarily store and actively manipulate information unavailable to perception. WM is capacity limited and draws from frontoparietal networks that may be impacted by frontal coup and/or contrecoup torsional impact [22]. WM more generally allows us to perform upper level cognitive tasks such as reading [40-42], learning [43,44], multitasking [45], language comprehension [46,47], and problem

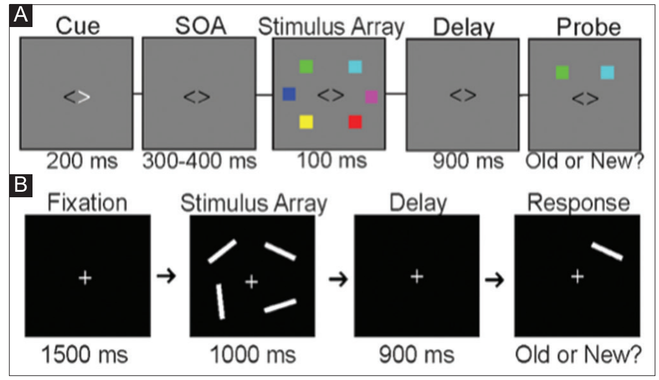

Figure 1. Visual WM task paradigms and stimulus configurations. Trial sequence and timing for the two WM change detection tasks: **(A)** Color patch stimuli, in which the white cue indicated the hemifield to covertly attend, and the **(B)** oriented line segment stimuli. For both tasks, a WM recognition probe appeared at the end of the trial and participants made a key press response indicating whether the probe was identical to what was shown during encoding (old) or whether it was a new stimulus item (new).

solving [48-50]. In addition, WM is significantly correlated with fluid intelligence [51,52]. In essence, WM is an important executive function that is heavily involved in the upper level cognition and may be affected by damage to multiple brain regions.

The prior work could not address the heterogeneity of outcomes in a highly heterogeneous population. Here, we sought to better understand what predicts WM performance years after mTBI. We examined etiology of mTBI (non-sport, individual sport, team sport, and high-impact sport), and loss of consciousness (LOC) on visual WM performance. We included factors that commonly show a relationship with cognitive performance, such as gender, time since mTBI, and number of mTBIs. We also collected low-density rs-EEG data from three frontal electrodes sites to evaluate if changes in power spectral densities can predict later visual WM performance. The previous findings using rs-EEG in mTBI participants report abnormalities following injury [36-38,53-55]. We were primarily interested in power spectral densities differences not only in mTBI but also in evaluating if our portable low-density EEG system can detect neural changes commonly picked up by conventional EEG systems. Thus, the focus of this work is to better understand why some people are impaired years after mTBI and others are indistinguishable from those who have never had a mTBI. We anticipated that team sports and high impact etiologies would be associated with worse outcomes, as would LOC. We predicted that spectral power derived from rs-EEG might begin to clarify the underlying mechanism (s) accounting for behavioral performance. To answer these questions, we re-analyzed previously publish data and included newly collected data from mTBI and control participants.

2. Materials and Methods

2.1. Participants

Data from a total of 93 undergraduates with a history of mTBI were analyzed. Data came from two sources. First, we re-analyzed

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data from participants who had provided mTBI etiology in the color change detection task (Experiment 3: N=21 mTBI) and the line orientation change detection task (Experiment 4: N=22 mTBI) from the publication described above [39]. Second, we included recently collected data from controls and undergraduates with a history of mTBI who have not been previously reported (N=50) in a replication of the color change-detection task (Figure 1A). To evaluate the interaction across different experimental tasks collected from these samples, we converted performance into z-scores computed from the appropriate control group data (N=93).

The mTBI participants were divided into four groups as a function of mTBI etiology: Non-sports (N=35), team sports (N=13), high-impact sport (N=27), and individual sports (N=18); Table 1. High-impact sports were classified using National Collegiate Athletic Association (NCAA) outcome measures using the annual national estimate rates during the 2009-10 to 2013-14 academic years. All mTBIs were closed-head injuries. The non-sports group included: Twelve falls, eight head bangs, five car accidents, three being hit by a car, one blast, one trampoline, one fight, one aerial dancing, and three did not report specific etiology but indicated it was not sport related. The team sports group consisted of the following injuries: Three cheer, three basketball, two rugby, one men's soccer, one lacrosse, one softball, one tennis, and one volleyball. The high-impact sport contained injuries from the following causes: Thirteen football, 11 women's soccer, two wrestling, and one hockey. The individual sports group included the following causes: Six snowboarding, four skiing, two motocross, one biking, one para vaulting, one skateboarding, one surfing, one wakeboarding, and one weightlifting. The history of mTBI group (N=93 total, M: 21.3 years, 51 females) was compared to an age- and education- matched control group (N=93 total, M: 22.9 years, 62 females); Table 1 for demographics breakdown. The University IRB approved all protocols. Participants provided written consent and received $15/hour or course bonus credit, their choice.

2.2. Apparatus

Experiments were coded in MatLab (The Mathworks, Natick, MA) using the Psychophysics Toolbox 3.0 extension [56]. For each experiment, a single monitor was used and found significant group differences. Across experiments three different monitor sizes were used (19" NEC MultiSync CRT, 16" MGC CRT, 15" MacBook Pro). CRT monitors ran at 75 Hz with 1024×768 resolution and MacBook ran at 1440×900 with participants seated at a distance of 57 cm.

2.3. Stimuli and procedure

2.3.1. Color Patch Stimuli (Figure 1A)

Seventy-one mTBI and control participants completed this task across three experimental manipulations. The experiments all found a significant deficit in the mTBI group at a set size 3, 900 ms delay. Trials began with fixation (0.4°×0.4°, 300 ms), followed by a spatial cue (white arrowhead: 2.1°×0.4°, 200 ms) directing covert attention to one hemifield. In our condition of interest, three colored squares appeared (0.7°×0.7°; cyan, white, red, blue, yellow, green, and magenta, 100 ms). Stimuli appeared within 2 rectangular areas (7.1°×12.2°) at 4.6° from fixation. After a delay (900 ms), a single probe item appeared (3 s). Participants indicated whether the stimulus and probe item matched what was shown at encoding ("o" key, 50%) or not ("n" key). Self-paced trials included three breaks. Participants completed 24 practice trials to acclimatize them to the task. Across experiments, participants completed 120 or 192 trials of the set size 3, 900 ms delay condition. Participants were instructed to maintain fixation and eye movements were monitored by eye movement artifacts collected using HD-EEG (data not discussed).

2.3.2. Oriented Line Stimuli (Figure 1B)

Twenty-two mTBI and control participants participated in the task (Experiment 4) [39]. Participants were instructed to remember the orientations of 4 lines (7.5°×1.5°) displayed equidistantly (6.5°) from fixation. Trials began with a fixation cross (1500 ms), followed by a longer encoding period (1000 ms) to facilitate performance. The maintenance delay was consistent with the first task (900 ms). A recognition probe item appeared, and participants reported ("o" match, "n" mismatch, 50% chance) whether the probe item matched the orientation of the original line segment. There were 200 trials.

2.4. Analysis

In both of the WM change detection tasks (Figure 1A, B for diagrams of the color patch and line orientation versions of the

Table 1. Participant demographics.

	Age (SD)	# (# F)	# mTBI	Range #	Years (SD)	Time range	LOC
Non-sport	22 (4.1)	35 (23)	2.23	1-8	5 (5.4)	0.25-25.25 y	16
Team-sport	20.4 (2.4)	13 (8)	1.76	1-3	3.66 (2.9)	0.25-8 y	5
Individual-sport	20.6 (2.9)	18 (5)	2.61	1-7	2.3 (2.1)	0.25-9y	6
High-impact sport	21.3 (2.6)	27 (15)	3.26	1-12	4.28 (4.1)	0.42-16 y	11
Task 1 controls	23.1 (4.3)	71 (46)	-	-	-	-	-
Task 2 controls	22.4 (3.5)	22 (15)	-	-	-	-	-
All controls	22.9 (4.1)	93 (62)	-	-	-	-	-

Each row reports the demographic data from each history of mTBI group (top to bottom: Non-sport, team sport, individual sport, high-impact sports, control group 1, control group 2, and combined control groups). The column labels refer to the following: Age: Current age in years, # (#F): Number in the cohort and the number who are female; # mTBI: Mean number of mTBIs reported for that group, Range #: The range in reported numbers of mTBIs in that group, Years (SD): Mean time (standard deviation) in years (y) since the most recent mTBI, Time Range: The range in reported time since the most recent mTBI, LOC: Number of participants in each group reporting loss of consciousness (LOC).

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task), the primary behavioral performance measure was WM capacity: K = Set size*(Hit rate – False alarm rate) [57,58]. These K values were converted to standardized z-scores using the appropriate control sample (color patch stimuli, N=71; oriented line stimuli, N=22 control). Z-score values were used to compare performance across experiments using different retrieval probes.

2.5. Low-density resting-state EEG collection and analysis

2.5.1. EEG Data Collection

We used a wireless three-electrode B-Alert SleepProfiler system (Advanced Brain Monitoring, ABM, Carlsbad, CA) to make EEG measurements. The system was controlled by a tablet computer and used ABM software. The three electrodes were located on the subject's forehead in positions AF7, FpZ, and AF8. The sampling rate was 256 Hz and electrode impedance was kept to below 40 kΩ. Resting state measurements were collected in two successive 2-min periods.

2.5.2. Artifact Removal and Feature Extraction

The EEG signals were bandpass filtered to record frequencies in the range 0.1 Hz-100 Hz. Signal artifacts from muscle movement (EMG), eye blinks, excursions, saturations, and spikes as well as regions with excursions and saturated signals were marked and eliminated from the analysis. EMG artifacts were flagged by monitoring high-frequency EEG power in the 70-128 Hz band and low-frequency EMG in the 35-40 Hz band. A small number of blink-like artifacts were detected and removed using the algorithm described in Chang *et al*.[59].

Matlab software version R2018a (The Mathworks, Natick) was used to perform feature extraction and data analysis. Power spectral densities (PSD) were calculated from 1 to 40 Hz in 1-Hz frequency and 1-s time bins. The conventional EEG bands (delta 1-3 Hz, theta 3-7 Hz, alpha 8-13 Hz, beta 13-30 Hz, sigma 12-15 Hz, and gamma 25-40 Hz) were obtained by combining the 1-Hz frequency bins. The feature variables used in the analysis were the PSD base-10 logarithm of these EEG bands averaged over the full testing period.

The same analysis as performed on the behavioral data was applied to each of the EEG power bands. This included a series of forward regressions including gender, number of mTBIs, time since TBI, LOC, and mTBI etiology.

3. Results

3.1. Behavioral Results: mTBI versus Control Participants

The first question is to demonstrate that there was a group difference in these pooled data. The majority of the mTBI participants (N=71) completed the color patch change detection task (Figure 1A) in which the condition held in common across experiments was the set size 3, and maintenance delay duration of 900 ms condition. If we pool these data and compare the history of mTBI data to performance in N=71 control participants, there is a significant impairment in the mTBI group ($t(70)=5.55, p<0.00001$, Cohen's d=0.94). The remaining N=22 participants completed the line orientation task using a set size of 4 and a maintenance delay of 900 ms and compared performance to 22 control participants ($t(21)=2.21$, $p=0.03$, Cohen's d=1.26). To collectively evaluate performance across tasks, we converted the data to z-scores using the appropriate task-specific control group and conducted a one-sample t-test that showed the mTBI group performed significantly worse than did the control group ($t(92)=-6.90$ $p<0.00001$, Cohen's d=0.70; Figure 2A).

3.2. Regression Analysis: Predicting WM Performance

The purpose of this analysis was to identify any factors that predict WM performance in undergraduates with a history of mTBI. Toward this end, we conducted a forward regression including the factors of: gender (male, and female), number of mTBI's, time since mTBI, LOC (yes, no), and mTBI etiology (non-sport, team sport, high impact sport, and individual sport). Of these factors, LOC was the only significant predictor of later visual WM performance ($R^2=0.05$, $F_{1,91}=4.72$, $p=0.03$). The nature of this relationship was unexpected. Participants reporting LOC at the time of their mTBI were less impaired on the WM task ($\beta=0.7$, $p=0.03$; Figure 2B and C). None of the other predictors reached significance (all p's>0.26). When we compared task performance between the mTBI groups reporting LOC (N=38) and No LOC (N=55), there is a significant difference (z-score data: $t(91)=-2.22$, $p=0.03$, Hedge's g=0.46) such that participants who reported LOC performed better on the WM task; Figure 2B.

3.3. Low-Density Resting-State EEG Analyses

To determine whether there were readily detectible differences in anterior power, the rs-EEG data were subjected to the same analysis as the behavioral data. More specifically, EEG power bands (delta 1-3 Hz, theta 3-7 Hz, alpha 8-13 Hz, beta 13-30 Hz, sigma 12-15 Hz, and gamma 25-40 Hz) were subjected to a series of forward regressions with the factors of gender, number of mTBIs, time since TBI, LOC, and mTBI etiology. However, there was no significant effect of LOC in any of the spectra bands.

4. Discussion

At the group level, undergraduates at a large state university show impairment at visual WM tasks even years after mTBI [39]. The goal of the current paper was to better understand what factors predict their overall lower, but heterogeneous visual WM performance. Specifically, we evaluated whether factors, including etiology, LOC, gender, or spectral power were predictors for later WM performance. We observed no significant difference in visual WM outcomes across any of these factors except for LOC. The presence of LOC at the time of the mTBI predicts less severely impaired visual WM in undergraduates long after mTBI.

4.1. Implications

These data add to the accumulating evidence indicating that mTBI should be taken seriously, and that findings are not always intuitive. The implication of these data is that regardless of the cause

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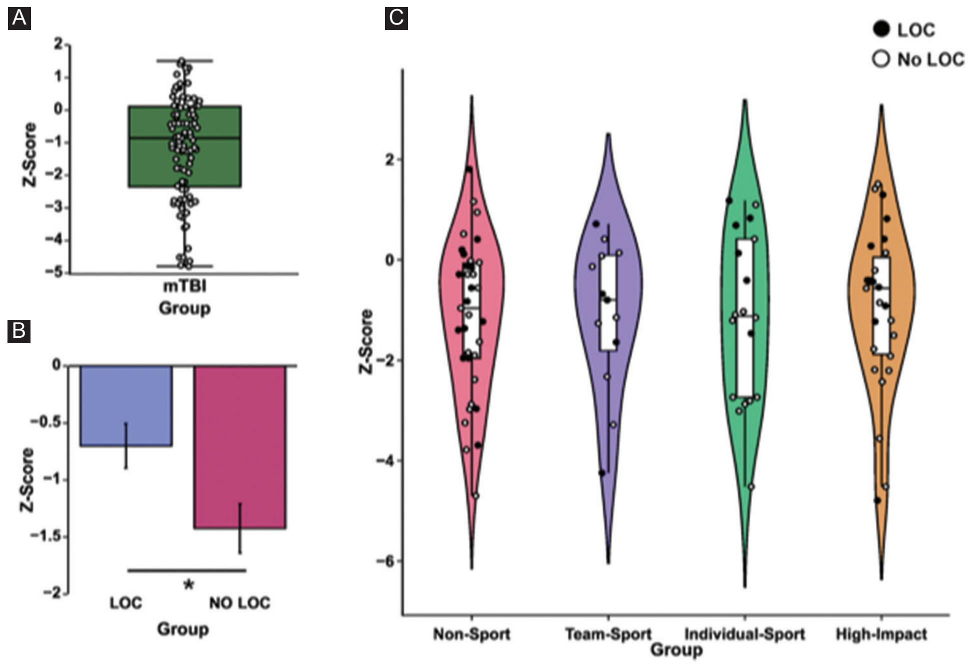

Figure 2. Loss of consciousness (LOC), but not etiology, predicts later visual WM performance in undergraduates with a history of mTBI. **(A)** Bar plot including z-score data for control (N=93) and mTBI (N=93) participants for the visual WM tasks. **(B)** Bar plot showing behavioral performance (z-scores) showing the significant difference (*) between groups defined by LOC (N=38) and No LOC (N=55). The data reveal that mTBI participants who reported LOC at the time of their mTBI performed better on the visual WM task than those who reported no LOC. **(C)** The violin plot includes embedded box plots indicating the median and quartile (q1, and q3) range of visual WM performance with whiskers noting the range of values (minimum, maximum, and excluding outliers). The violin plot shows the smoothed probability density of the empirical data for non-sport (N=35, LOC=16), team-sport (N=13, LOC=5), individual-sport (N=18, LOC=6), and high-impact sport (N=27, LOC=11). Data are spatially jittered to show data from each participant (open symbol: No LOC; closed symbols: LOC). The data reveal no clear link between etiology and visual WM, but along the orthogonal dimension of LOC at time of injury reveal better visual WM outcomes in those whose mTBI included LOC.

of the mTBI, the consequences of mTBI may not be self-limiting, even after physical symptoms resolve. In other words, in some people, there appears to be lasting cognitive consequences of mTBI. Although there are emerging links between high impact sports and chronic traumatic encephalopathy [reviewed in: 20]; in the current sample, the etiology of the mTBI was not associated with later visual WM performance despite the significant overall deficits in visual WM. A recent paper examining similar factors in retired NFL players revealed no significant linear relationships between number of concussions, LOC, and years played and later cognitive performance [60]. What remains unsatisfactory is that there is no way to predict whether someone who has just experienced a mTBI will have lasting cognitive consequences. Furthermore, there are no evidence-based interventions that would effectively restore any performance deficits even if vulnerable individuals could be identified.

The group-difference visual WM deficit for the mTBI group suggests an alternative interpretation that merits further comment. Although we interpret the data to show that mTBI leads to worse visual WM, it is possible that it is the other way around. People who are poor at executive function tasks such as WM may get more mTBIs. This perspective is supported by research showing that impulsive individuals, especially during adolescence, take more risks and have worse executive function [reviewed in: 61]. It is worth the reminder that the bulk of our mTBI group experienced their mTBI while teenagers. Other findings do point toward pre-injury aggression and mood disorders [62]. Furthermore, several populations show significantly higher incidence of mTBI in their medical histories, including individuals with serious behavioral disorders such as intermittent explosive disorder and suicidal ideation [63], juvenile offenders in detention [64], and perpetrators of partner abuse [65]. In short, the distribution of who is likely to have had a mTBI is not uniform. Yet, because we were testing undergraduates who have to maintain an elevated level of executive functioning and emotional regulation for academic success, we may be sampling from the most highly-functioning subset of the pool.

4.2. Why Does LOC Predict Less Impaired Visual WM in Undergraduates?

Of particular interest is that LOC is not required for diagnosis of mTBI [66]. Yet, LOC during mTBI is typically associated with greater white matter damage [67-69], and with impaired performance on prospective memory [70], and executive function [71]. Of particular relevance here, children who have detectible brain abnormalities visible on CT scan show lasting cognitive deficits for at least 1 year [72]. In other words, LOC is usually associated with more severe mTBI that can lead to visible white matter abnormalities and lasting cognitive changes.

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These findings contrast with our observation that LOC predicted less impaired visual WM in undergraduates with a history of mTBI. We speculate that in our sample, the presence of LOC ensured that the mTBI was taken more seriously and medical treatment was sought and followed. In contrast, we suspect that in many mTBI without LOC, no medical treatment was sought, and this may mean that the person returned to play or did not take the opportunity to rest post-injury. Evidence supporting this perspective comes from estimates suggesting that most mTBI go untreated by medical professionals. Unfortunately, we did not collect descriptions of medical treatment or compliance at the time of their mTBI.

4.3. Open Questions

By demonstrating that LOC paired with mTBI predicts less impaired WM in undergraduates, the current paper raises new questions. Undergraduates provided self-report of mTBI that was not verified by medical documentation. Because undergraduates could participate as controls, there was no incentive to deceive researchers. Our view was that accepting self-report would only work against a positive finding showing group differences. The heterogeneity of outcomes, though, does raise questions regarding the relationship between compliance with medical advice – if it was sought in the first place. As we used a convenience sample it is also possible that there were undetected differences between the control and mTBI groups. Prospective work is needed to confirm that the observed patterns were not pre-existing in these samples. Furthermore, we only tested visual WM in these participants. Ongoing data collection includes a more comprehensive neuropsychological assessment. For an undergraduate population, these data raise questions regarding the impact a history of mTBI has on student outcomes, study habits, time to graduation, and realization of academic goals. It may be the case that some students with a history of mTBI study longer, drop more courses, change their majors, but we simply do not know. Future work is needed to identify and mitigate the consequences of mTBI in the undergraduate population.

5. Conclusions

Undergraduates with a history of mTBI perform worse on visual WM tasks, but the degree of impairment is not predicted by mTBI etiology, gender, number of mTBI, time since mTBI, nor rs-EEG power. Surprisingly, the presence of LOC at the time of the injury predicted less impaired visual WM in these undergraduates. Further research is needed to clarify whether there was greater medical attention and compliance with medical advice when mTBI was accompanied by LOC.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

References

[1] Sharp DJ, Jenkins PO. Concussion is Confusing us All. Pract Neurol 2015;15:172-86.

[2] West GL, Drisdelle BL, Konishi K, Jackson J, Jolicoeur P, Bohbot VD. Habitual Action Video Game Playing is Associated with Caudate Nucleus-dependent Navigational Strategies. Proc Biol Sci 2015;282:20142952.

[3] Centers for Disease Control and Prevention. Rates of TBI-related Emergency Department Visits by Age Group United States, 2001-2010. Atlanta, Georgia: Centers for Disease Control and Prevention; 2016.

[4] Lumba-Brown A, Yeates KO, Sarmiento K, Breiding MJ, Haegerich TM, Gioia GA, *et al*. Diagnosis and Management of Mild Traumatic Brain Injury in Children: A Systematic Review. JAMA Pediatr 2018;172:e182847.

[5] Carroll LJ, Cassidy JD, Peloso PM, Borg J, von Holst H, Holm L, *et al*. Prognosis for Mild Traumatic Brain Injury: Results of the who Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2004; 43:84-105.

[6] Carroll LJ, Cassidy JD, Cancelliere C, Cote P, Hincapie CA, Kristman VL, *et al*. Systematic Review of the Prognosis after Mild Traumatic Brain Injury in Adults: Cognitive, Psychiatric, and Mortality Outcomes: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 2014;95:S152-73.

[7] Kerrigan JM, Giza CC. When in Doubt, Sit it Out! Pediatric Concussion-an Update. Childs Nerv Syst 2017;33:1669-1675.

[8] Shanley E, Thigpen C, Kissenberth M, Gilliland RG, Thorpe J, Nance D, Register-Mihalik JK, *et al*. Heads up Football Training Decreases Concussion Rates in High School Football Players. Clin J Sport Med 2019. https:/doi.org/10.1097/JSM.0000000000000711.

[9] Broglio SP, Baldwin G, Castellani RJ, Chrisman SP, Duma S, Hainline B, *et al*. Summary of the 2015 University of Michigan Sport Concussion Summit. Concussion 2016;1:CNC23.

[10] McCrory P, Meeuwisse W, Dvorak J, Aubry M, Bailes J, Broglio S, *et al*. Consensus Statement on Concussion in Sport-the 5th International Conference on Concussion in Sport Held in Berlin, October 2016. Br J Sports Med 2017;51:838-47.

[11] Patricios JS, Ardern CL, Hislop MD, Aubry M,

Bloomfield P, Broderick C, *et al*. Implementation of the 2017 Berlin Concussion in Sport Group Consensus Statement in Contact and Collision Sports: A Joint Position Statement from 11 National and International Sports Organisations. Br J Sports Med 2018;52:635-41.

[12] Balasundaram AP, Schneiders AG, Sullivan SJ. Rest and Return-to-sport Recommendations Following Sport-related Concussion (Pedro Synthesis). Br J Sports Med 2018;52:616-7.

[13] Kumar S, Rao SL, Chandramouli BA, Pillai S. Reduced Contribution of Executive Functions in Impaired Working Memory Performance in Mild Traumatic Brain Injury Patients. Clin Neurol Neurosurg 2013;115:1326-32.

[14] Iverson GL, Karr JE, Gardner AJ, Silverberg ND, Terry DP. Results of Scoping Review do not Support Mild Traumatic Brain Injury being Associated with a High Incidence of Chronic Cognitive Impairment: Commentary on Mcinnes *et al*. 2017. PLoS One 2019;14:e0218997.

[15] Kristman VL, Borg J, Godbolt AK, Salmi LR, Cancelliere C, Carroll LJ, *et al*. Methodological Issues and Research Recommendations for Prognosis after Mild Traumatic Brain Injury: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 2014;95:S265-77.

[16] Levin HS, Diaz-Arrastia RR. Diagnosis, Prognosis, and Clinical Management of Mild Traumatic Brain Injury. Lancet Neurol 2015;14:506-17.

[17] Sharp DJ, Ham TE. Investigating white Matter Injury after Mild Traumatic Brain Injury. Curr Opin Neurol 2011;24:558-63.

[18] Ham TE, Bonnelle V, Hellyer P, Jilka S, Robertson IH, Leech R, *et al*. The Neural Basis of Impaired Self-awareness After Traumatic Brain Injury. Brain 2014;137:586-97.

[19] Sharp DJ, Scott G, Leech R. Network Dysfunction after Traumatic Brain Injury. Nat Rev Neurol 2014;10:156-66.

[20] Pan J, Connolly ID, Dangelmajer S, Kintzing J, Ho AL, Grant G. Sports-related Brain Injuries: Connecting Pathology to Diagnosis. Neurosurg Focus 2016;40:E14.

[21] Eierud C, Craddock RC, Fletcher S, Aulakh M, King-Casas B, Kuehl D, *et al*. Neuroimaging after Mild Traumatic Brain Injury: Review and Meta-analysis. Neuroimage Clin 2014;4:283-94.

[22] Shenton ME, Hamoda HM, Schneiderman JS, Bouix S, Pasternak O, Rathi Y, *et al*. A Review of Magnetic Resonance Imaging and Diffusion Tensor Imaging Findings in Mild Traumatic Brain Injury. Brain Imaging Behav 2012;6:137-92.

[23] Tate DF, Shenton ME, Bigler ED. Introduction to the Brain Imaging and Behavior Special Issue on Neuroimaging Findings in Mild Traumatic Brain Injury. Brain Imaging Behav 2012;6:103-7.

[24] Bajaj S, Dailey NS, Rosso IM, Rauch SL, Killgore WD. Time-dependent Differences in Cortical Measures and their Associations with Behavioral Measures Following Mild Traumatic Brain Injury. Hum Brain Mapp 2018;39:1886-97.

[25] Dall'Acqua P, Johannes S, Mica L, Simmen HP, Glaab R, Fandino J, *et al*. Prefrontal Cortical Thickening after Mild Traumatic Brain Injury: A One-year Magnetic Resonance Imaging Study. J Neurotrauma 2017;34:3270-9.

[26] Hotiu A. Diffusion Tensor Imaging in Mild Traumatic Brain Injuries. ProQuest Inform Learn 2010;71:2895-5.

[27] Cubon VA, Putukian M, Boyer C, Dettwiler A. A Diffusion Tensor Imaging Study on the White Matter Skeleton in Individuals with Sports-related Concussion. J Neurotrauma 2011;28:189-201.

[28] Henry LC, Tremblay J, Tremblay S, Lee A, Brun C, Lepore N, *et al*. Acute and Chronic Changes in Diffusivity Measures after Sports Concussion. J Neurotrauma 2011;28:2049-59.

[29] Niogi SN, Mukherjee P, Ghajar J, Johnson CE, Kolster R, Lee H, *et al*. Structural Dissociation of Attentional Control and Memory in Adults with and without mild Traumatic Brain Injury. Brain 2008;131:3209-21.

[30] Lipton ML, Gellella E, Lo C, Gold T, Ardekani BA, Shifteh K, *et al*. Multifocal white Matter Ultrastructural Abnormalities in Mild Traumatic Brain Injury with Cognitive Disability: A Voxel-wise Analysis of Diffusion Tensor Imaging. J Neurotrauma 2008;25:1335-42.

[31] Wilde EA, McCauley SR, Hunter JV, Bigler ED, Chu Z, Wang ZJ, *et al*. Diffusion Tensor Imaging of Acute Mild Traumatic Brain Injury in Adolescents. Neurology 2008;70:948-55.

[32] Hirad AA, Bazarian JJ, Merchant-Borna K, Garcea FE, Heilbronner S, Paul D, *et al*. A Common Neural Signature of Brain Injury in Concussion and Subconcussion. Sci Adv 2019;5:eaau3460.

[33] Jeter CB, Hergenroeder GW, Hylin MJ, Redell JB, Moore AN, Dash PK. Biomarkers for the Diagnosis and Prognosis of Mild Traumatic Brain Injury/Concussion. J Neurotrauma 2013;30:657-70.

[34] Bigler ED, Abildskov TJ, Eggleston B, Taylor BA, Tate DF, Petrie JA, *et al*. Structural Neuroimaging in Mild Traumatic Brain Injury: A Chronic Effects of Neurotrauma Consortium Study. Int J Methods Psychiatr Res 2019;28:e1781.

[35] Koerte IK, Hufschmidt J, Muehlmann M, Lin AP, Shenton ME. Advanced Neuroimaging of Mild Traumatic Brain Injury. In: Laskowitz D, Grant G, eds. *Translational Research in Traumatic Brain Injury*. Boca Raton (FL): CRC Press/Taylor and Francis Group; 2016.

[36] McCrea M, Guskiewicz KM, Marshall SW, Barr W, Randolph C, Cantu RC, *et al*. Acute Effects and Recovery Time Following Concussion in Collegiate Football Players: The NCAA Concussion Study. JAMA 2003;290:2556-63.

 DOI: http://dx.doi.org/10.18053/jctres.05.202004.003

[37] Barr WB, Prichep LS, Chabot R, Powell MR, McCrea M. Measuring Brain Electrical Activity to Track Recovery from Sport-related Concussion. Brain Injury 2012;26: 58-66.

[38] Slobounov S, Gay M, Johnson B, Zhang K. Concussion in Athletics: Ongoing Clinical and Brain Imaging Research Controversies. Brain Imaging Behav 2012;6:224-43.

[39] Arciniega H, Kilgore-Gomez A, Harris A, Peterson DJ, McBride J, Fox E, *et al*. Visual Working Memory Deficits in Undergraduates with a History of Mild Traumatic Brain Injury. Atten Percept Psychophys 2019;81:2597-603.

[40] Lee YB, Lee J, Tak S, Lee K, Na DL, Seo SW, *et al*. Sparse SPM: Group Sparse-dictionary Learning in SPM Framework for Resting-state Functional Connectivity MRI Analysis. NeuroImage 2016;125:1032-45.

[41] Peng P, Barnes M, Wang C, Wang W, Li S, Swanson HL, *et al*. A Meta-Analysis on the Relation between Reading and Working Memory. Psychol Bull 2018;144:48-76.

[42] Hahnel C, Goldhammer F, Kröhne U, Naumann J. Reading Digital Text Involves Working Memory Updating Based on Task Characteristics and Reader Behavior. Learn Individ Dif 2017;59:149-57.

[43] Neumann N, Lotze M, Eickhoff SB. Cognitive Expertise: An ALE Meta-analysis. Hum Brain Mapp 2016;37:262-72.

[44] Collins AG, Frank MJ. Within and Across-trial Dynamics of Human EEG Reveal Cooperative Interplay between Reinforcement Learning and Working Memory. Proc Natl Acad Sci U S A 2018;115:2502-7.

[45] Barrett LF, Tugade MM, Engle RW. Individual Differences in Working Memory Capacity and Dual-process Theories of the Mind. Psychol Bull 2004;130:553-73.

[46] Baddeley A. Working Memory and Language: An Overview. J Commun Disord 2003;36:189-208.

[47] Just MA, Carpenter PA. A Capacity Theory of Comprehension: Individual Differences in Working Memory. Psychol Rev 1992;99:122-49.

[48] Conway AR, Kane MJ, Engle RW. Working Memory Capacity and its Relation to General Intelligence. Trends Cogn Sci 2003;7:547-52.

[49] Chuderski A, Jastrzębski J. Much ado about aha!: Insight Problem Solving is Strongly Related to Working Memory Capacity and Reasoning Ability. J Exp Psychol 2018;147:257-81.

[50] Swanson HL, McMurran M. The Impact of Working Memory Training on Near and Far Transfer Measures: Is it all about Fluid Intelligence? Child Neuropsychol 2018;24:370-95.

[51] Kane MJ, Hambrick DZ, Tuholski SW, Wilhelm O, Payne TW, Engle RW. The Generality of Working Memory Capacity: A Latent-variable Approach to Verbal and Visuospatial Memory Span and Reasoning. J Exp Psychol Gen 2004;133:189-217.

[52] Engle RW, Tuholski SW, Laughlin JE, Conway AR. Working Memory, Short-Term Memory, and General Fluid Intelligence: A Latent-variable Approach. J Exp Psychol Gen 1999;128:309-31.

[53] Lewine JD, Plis S, Ulloa A, Williams C, Spitz M, Foley J, *et al*. Quantitative EEG Biomarkers for Mild Traumatic Brain Injury. J Clin Neurophysiol 2019;36:298-305.

[54] McNerney MW, Hobday T, Cole B, Ganong R, Winans N, Matthews D, *et al*. Objective Classification of MTBI Using Machine Learning on a Combination of Frontopolar Electroencephalography Measurements and Self-reported Symptoms. Sports Med Open 2019;5:14.

[55] Conley AC, Cooper PS, Karayanidis F, Gardner AJ, Levi CR, Stanwell P, *et al*. Resting State Electroencephalography and Sports-Related Concussion: A Systematic Review. J Neurotrauma 2018. https://doi.org/10.1089/neu.2018.5761.

[56] Brainard DH. The Psychophysics Toolbox. Spatial Vision 1997;10:443-6.

[57] Cowan N. The Magical Number 4 in Short-term Memory: A Reconsideration of Mental Storage Capacity. Behav Brain Sci 2001;24:87-185.

[58] Pashler H. Familiarity and Visual Change Detection. Percept Psychophys 1988;44:369-78.

[59] Chang WD, Cha HS, Kim K, Im CH. Detection of Eye Blink Artifacts from Single Prefrontal Channel Electroencephalogram. Comput Methods Programs Biomed 2016;124:19-30.

[60] Fields L, Didehbani N, Hart J, Cullum CM. No Linear Association between Number of Concussions or Years Played and Cognitive Outcomes in Retired NFL Players. Arch Clin Neuropsychol 2020;35:233-9.

[61] Romer D. Adolescent Risk Taking, Impulsivity, and Brain Development: Implications for Prevention. Dev Psychobiol 2010;52:263-76.

[62] Tateno A, Jorge RE, Robinson RG. Clinical Correlates of Aggressive Behavior after Traumatic Brain Injury. J Neuropsychiatry Clin Neurosci 2003;15:155-60.

[63] Mosti C, Coccaro EF. Mild Traumatic Brain Injury and Aggression, Impulsivity, and History of Other and Self-directed Aggression. J Neuropsychiatry Clin Neurosci 2018;30:220-7.

[64] Farrer TJ, Frost RB, Hedges DW. Prevalence of Traumatic Brain Injury in Juvenile Offenders: A Meta-analysis. Child Neuropsychol 2013;19:225-34.

[65] Farrer TJ, Frost RB, Hedges DW. Prevalence of Traumatic Brain Injury in Intimate Partner Violence Offenders Compared to the General Population: A Meta-analysis. Trauma Violence Abuse 2012;13:77-82.

[66] Jordan BD. The Clinical Spectrum of Sport-related Traumatic Brain Injury. Nat Rev Neurol 2013;9:222-30.

[67] Wilde EA, Li X, Hunter JV, Narayana PA, Hasan K, Biekman B, *et al*. Loss of Consciousness is Related to

 DOI: http://dx.doi.org/10.18053/jctres.05.202004.003

White Matter Injury in Mild Traumatic Brain Injury. J Neurotrauma 2016;33:2000-10.

[68] Hayes JP, Miller DR, Lafleche G, Salat DH, Verfaellie M. The Nature of White Matter Abnormalities in Blast-related Mild Traumatic Brain Injury. Neuroimage Clin 2015;8:148-56.

[69] Delano-Wood L, Bangen KJ, Sorg SF, Clark AL, Schiehser DM, Luc N, *et al*. Brainstem White Matter Integrity is Related to Loss of Consciousness and Postconcussive Symptomatology in Veterans with Chronic Mild to Moderate Traumatic Brain Injury. Brain Imaging Behav 2015;9:500-12.

[70] Bedard M, Taler V, Steffener J. Long-term Prospective Memory Impairment Following Mild Traumatic Brain Injury with Loss of Consciousness: Findings from the Canadian Longitudinal Study on Aging. Clin Neuropsychol 2018;32:1002-18.

[71] Sorg SF, Delano-Wood L, Luc N, Schiehser DM, Hanson KL, Nation DA, *et al*. White Matter Integrity in Veterans with Mild Traumatic Brain Injury: Associations with Executive Function and Loss of Consciousness. J Head Trauma Rehabil 2014;29:21-32.

[72] Levin HS, Hanten G, Roberson G, Li X, Ewing-Cobbs L, Dennis M, *et al*. Prediction of Cognitive Sequelae Based on Abnormal Computed Tomography Findings in Children Following Mild Traumatic Brain Injury. J Neurosurg Pediatr 2008;1:461-70.

 DOI: http://dx.doi.org/10.18053/jctres.05.202004.003