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Verbal Episodic Memory Alterations and Hippocampal Atrophy in Acute Mild Traumatic Brain Injury

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Abstract

Episodic memory deficit is a symptom frequently observed after a mild traumatic brain injury (mTBI). However, few studies have investigated the impact of a single and acute mTBI on episodic memory and structural cerebral changes. To do so, we conducted two experiments. In the first, we evaluated verbal episodic memory by using a word recall test, in 52 patients (mean age 33.1 (12.2) years) 2-4 weeks after a first mTBI, compared to 54 healthy controls (31.3 (9.2) years) and followed both groups up for six months. In the second, we measured hippocampal volume in a subset of 40 participants (20 mTBI patients, 20 controls) from Experiment 1 using magnetic resonance imaging (T1-weighted images) and correlated memory performance scores to hippocampal volume.

Experiment 1 showed significantly reduced verbal episodic memory within the first month after a mTBI and a tendency for a reduction 6 months later, more pronounced for men. In Experiment 2, patients with mTBI exhibited a generally reduced hippocampal volume; however, we did not observe any linear correlation between hippocampal volume and memory scores.

These results suggest that one single mTBI is associated with both episodic memory alteration and reduced volume of the hippocampus in the acute phase. Future studies are needed to elucidate the link between both measures.

Keywords: Mild Traumatic Brain Injury, MRI, Hippocampus, Volumetry, Memory, HVLT

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Introduction

Traumatic Brain Injuries (TBI) impact cognition as well as other aspect of daily life and are associated with high costs for both the patient and the society as a whole [1]. In Western societies such as the US, they have an annual incidence of approximately 500/ 100,000 individuals [2]. Approximately 80 % of TBI are classified as mild TBI (mTBI) [3]. Although the term “mild” implies a less severe head trauma, even mTBI can have an important impact on the patients’ health. In fact, 10-15% of the victims of mTBI continue to suffer persistent symptoms for months or years, leading to employment, economic and social issues [4, 5]. One of the most frequent symptoms is the impairment of episodic memory, i.e., the ability to recall and mentally reexperience specific episodes from one's personal past [6-9]. In fact, deficits in patients with mTBI were found in many tasks that assess episodic memory such as immediate recall, delayed recall and recognition [10-12]. However, most of the studies on the topic are conducted on special populations such as veterans or athletes with particular characteristics. Indeed, participants may have suffered multiple mTBI and studies are typically carried out years after the trauma. These factors make it hard to discern the impact of a single mTBI on episodic memory. Nevertheless, a recent study on the general population observed poorer verbal episodic memory scores 1 month and 12 months after a single mTBI. However, participants from the mTBI group were significantly older than controls [13] limiting the interpretation, given the known effect of age on episodic memory performance [14]. Therefore, age and similar epidemiological variables have to be well matched to help drawing conclusions.

The hippocampus in the mesial temporal lobe is a brain structure that is central to episodic memory. Indeed, this region is mostly known for its implication in the memory of past events [15-17]. Moreover, impairment of the hippocampus, typically associated with atrophy, is linked to episodic memory deficits, such as those reported in Alzheimer’s disease [18, 19]. One study using automated segmentation and T1-weighted images on a general population, focussed on neuroanatomical changes in the hippocampus after mTBI several years or even decades after the trauma and found bilateral atrophy of the hippocampus [20]. The impact of a single mTBI on the hippocampus in the acute phase and a possible

association between episodic memory and hippocampus volume are however still unknown.

To elucidate the points raised in the previous paragraphs, we designed Experiment 1 in which we evaluated verbal episodic memory 2 to 4 weeks after a mTBI and at a follow up period of six months after the trauma. We hypothesized (1a) verbal episodic memory to be impaired in a group of patients with mTBI compared to controls within first weeks after the trauma; (1b) the impairment to remain present six months after the trauma. Further, we designed Experiment 2 in which we measured MRI-derived hippocampal volume in a subgroup of participants from Experiment 1. We hypothesized (2a) patients with mTBI to exhibit a volumetric reduction of hippocampus compared to controls; and (2b) hippocampal volume to be correlated to memory performance in mTBI.

EXPERIMENT 1

Material and methods

Both experiments were conducted in accordance with the Declaration of Helsinki on biomedical research involving human subjects and approved by the local Ethics Committee of the *Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'Île-de-Montréal – Hôpital du Sacré-Coeur de Montréal (CIUSS-NÎM – HSCM)* (#2014-1016) and by the *Comité mixte d'éthique de la recherche* of the Regroupement Neuroimagerie Québec. After a detailed explanation of the study, all participants gave their written consent prior to inclusion.

Participants

We recruited a total of 53 patients (29 men) with mTBI. between 2 and 4 weeks after the trauma over a period of 1 year—May 2017 to May 2018. All 53 patients were referred and diagnosed by a medical team at the emergency room of CIUSS-NÎM – HSCM using the following criteria: head trauma with (1) confusion, disorientation, and/or loss of consciousness for 30 min or less, (2) posttraumatic amnesia for less than 24h, and (3) Glasgow Coma Scale (GCS) between 13 and 15, observed within the first 30 min after the

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trauma or upon presentation at the emergency room. None were admitted to the hospital. One of the 53 patients with mTBI did not complete all tests and had to be excluded, resulting in the inclusion a total of 52 patients with mTBI. The causes of mTBI were (1) falls (n=20, 38%), (2) sport accident (29%, n=15), (3) car accident (19%, n=10), (4) assaults (6%, n=3), and unknown (8%, n=4). None of the patients suffered from a polytrauma. In line with Canadian CT head rules[21],34 of the 52 mTBI patients had a CT scan done within the first hours following their arrival in the ER. Identification of any cranial or intracranial injury on radiological imaging was used to confirm the presence of complicated mTBI, which was the case in 8 of the 34 patients. Of them, five had right cerebral lesions (sub-epidural bleeding, signs of petechiae) while three had occipital lesions with unspecified laterality. Because of the small sample size, we did not analyze the CT-positive group separately. We compared their results to those of 54 (27 men) healthy controls recruited through ads posted at the hospital and online. We collected information such as age, gender, manual dominance and years of education for all participants. Patients and controls were matched with regards to sex, age, and education (See Table 1). Certain data from these participants have been presented in another publication [22].

For both groups, we applied the following exclusion criteria: (1) past history of TBI independent of severity (2) history of psychiatric or neurological disorders (3) excessive use of recreational drugs (cannabis: >1 consumption/day; alcohol: >3 consumptions/day; Canadian Center on Substance Use and Addiction 2012) (4) intoxication during the testing, and (5) use of any medication known to interfere with cognitive abilities (antidepressants, benzodiazepines, and hypnotics).

Procedure

First, we carried out semi-structured phone interviews to verify the presence of inclusion and exclusion criteria in participants from both groups. Then, participants were invited to the laboratory within 2 to 4 weeks after the trauma where they provided free and informed consent. Next, we carried out the baseline memory assessment.

Six months after this first evaluation, all participants were invited to the follow-up examination, where we carried out a second memory evaluation using the same

procedure as baseline. From the total of 106 participants at baseline, 70 (66%) accepted to return to the laboratory for the follow-up (31 patients and 39 controls).

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Memory Assessment

Memory assessment: We used the Hopkins Verbal Learning Test - Revised (HVLT-R) to measure different component of verbal episodic learning and memory; this tool is especially useful in repeated measurements of memory [23]. The test begins with a learning phase of three trials to recall a list of 12 words. At each trial, we asked the participant to recall as many words as possible (immediate recall 1, 2, 3). The 3 sub-scores were then summed up to an overall score (total immediate recall). After a 25 minutes interval filled with unrelated tasks (which did not contain any memory, reading, or verbal fluency aspect), we asked the participant again to recall the words on the list (delayed recall). Following that fourth trial, we read another list of 24 words (12 target words and 12 nontarget words, 6 semantically related to the targets, 6 unrelated to the targets) to the participant. Next, we asked them to identify which words were on the original list (recognition). With this task, we were able to evaluate (1) learning (total immediate recall), (2) long-term memory (delayed recall) and (3) recognition.

Analysis

We used SPSS (23.0; IBM Inc., Chicago IL) for the statistical analysis. First, we compared HVLT recall scores between groups at baseline by computing a Multivariate Analysis of Variance (MANOVA) with *group* (2 levels: mTBI, controls) and *sex* (2 levels: women, men) as between subject factor, *task* (2 levels: total immediate recall, delayed recall) as within subject factor, and *age* as covariate (all MANOVAs and ANOVAs are Greenhouse-Geisser corrected). For post hoc analyses of the effects on the two memory tasks, we carried out separate univariate ANOVAs with *group* (2 levels: mTBI, controls) and *sex* (2 levels: women, men) as between subject factor and *age* as covariate. We next calculated a MANOVA with *group* (2 levels: mTBI, controls) and *sex* (2 levels: women, men) as between subject factor and *subtask* (3 levels: trial 1, trial 2, trial 3 of immediate recall) as within subject factor and *age* as covariate.

We further computed a univariate ANOVA for the recognition score, with *group* (2 levels: mTBI, controls) and *sex* (2 levels: women, men) as between subject factor and *age* as covariate. We repeated these analyses for the scores obtained at follow-up. We set the alpha value at 0.05 and used Bonferroni-Holm correction for multiple comparisons.

Next, to verify relation between memory scores and years of education we performed Spearman's ranks correlations (recognition scores were not normally distributed), between baseline and follow-up HVLT subtests (immediate recall, delayed recall and recognition). Again, we set the alpha value at 0.05 and used Bonferroni-Holm correction for multiple comparisons.

Results

Baseline

For baseline data, the MANOVA revealed a significant interaction between *group* and *task* ($F(1, 101) = 4.196$; $p = 0.043$; $R^2 = 0.040$) and significant main effects of *group* ($F(1,101) = 4.462$; $p = 0.037$; $R^2 = 0.042$) and *task* ($F(1, 101) = 286.832$; $p < 0.001$; $R^2 = 0.740$), indicating lower memory ability in patients. We did not observe any other significant main effect of sex or age or any other interaction. Post hoc ANOVAs revealed a significant *group* effect for total immediate recall ($F(1, 101) = 4.890$; $p = 0.029$; $R^2 = 0.046$; n.s. after correction) but failed to reach significance for delayed recall ($F(1, 101) = 2.371$; $p = 0.127$; $R^2 = 0.23$) (See Table 1 and Figure 1). When looking at Trial 1, 2 and 3 scores separately from total immediate recall between each group, only difference at Trial 3 remains significant after correction ($F(1, 101) = 7.175$; $p = 0.009$; $R^2 = 0.066$; see Table 1). For the recognition score, no significant difference was found ($F(1, 101) = 2.463$; $p = 0.120$; $R^2 = 0.24$). We observed a significant linear correlation between years of education and Immediate recall ($r = 0.247$; $p = 0.011$), but not with the other HVLT scores (all $p>0.09$).

Follow up

We observed no significant difference regarding *sex* and *age* between the participants who returned for follow-up and participants who did not, with the exception of *years of*

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educations that were significantly different between participants who returned (15.0 (2.7) years) and participants who did not (16.3 (2.9) years; *t*=2.19, p=0.03).

The MANOVA revealed a significant interaction between *sex*, *task* and *group* ($F(1, 65) = 5.36$; $p = 0.024$; $R^2 = 0.076$), a significant main effect of *sex* ($F(1,65) = 7.134$; $p = 0.010$ $R^2 = 0.099$) and *task* ($F(1, 65) = 188.187$; $p < 0.001$; $R^2 = 0.743$). Importantly, the main effect of *group* failed to reach significance ($F(1,65) = 3.232$; $p = 0.077$; $R^2 = 0.047$), as did the interaction between *group* and *task* ($F(1, 65) = 2.067$; $p = 0.155$; $R^2 = 0.031$). We did not observe any other significant main effect or interaction.

When looking at the individual trials for immediate recall scores in men only, scores were significantly lower in mTBI patients than controls (recall 1: $F(1, 14) = 11.04$; $p = 0.005$ $R^2 = 0.441$; recall 2: $F(1, 14) = 14.47$; $p = 0.002$; $R^2 = 0.508$; recall 3: $F(1, 14) = 12.36$; $p = 0.003$; $R^2 = 0.469$) (See Figure 2).

We did not observe any difference between groups for delayed recall scores ($F(1,28) = 1.373$; $p = 0.251$; $R^2 = 0.047$). Similarly, for recognition, we did not observe any main effect of groups ($F(1, 65) = 0.495$; $p = 0.484$; $R^2 = 0.008$) or any other interactions. Further, we did not observe any significant linear correlations between HVLT scores and years of education (all p>0.065).

EXPERIMENT 2

Material and methods

Participants

A subgroup of 20 mTBI patients and 20 controls from Experiment 1 underwent MRI. They were the first 20 participants of each group who accepted to take part to the MRI segment of the study. 3/15 patients who had a CT scan in the sub-sample (20 mTBI) had the presence of complicated mTBI. The subgroup did not differ from the large sample in term of age, sex and education. We did not observe any trauma related abnormalities in any of the MRI scans.

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Methods

Magnetic resonance imaging: MRI data acquisition: We acquired MRI scans from 40 participants at the *Unité de Neuroimagerie Fonctionnelle* of the *Institut universitaire de gériatrie de Montréal* (unf-montreal.ca). Specifically, we obtained high-resolution T1-weighted images using magnetization-prepared rapid acquisition with gradient-echo (MP-RAGE) on a 3-tesla Siemens TrioTIM scanner (Siemens, Erlangen, Germany), with a 12-channel head matrix coil. The parameters of acquisition were the following: repetition time 2.3s, echo time 2.91ms, inversion 900ms, 9-degree flip angle, 176 slices, 256 x 256 mm field of view, 256 x 256 matrix resolution (voxel size: 1 x 1 x 1 mm^3), and 240 Hz/Px bandwidth. We used the Tissue Volumes Utility tool in SPM12 to calculate total intracranial volume (TIV) for each participant.

Hippocampal data: Global volumes (in mm^3) for hippocampi were calculated using the FIRST tool available in FSL 5.0.9 (Oxford Centre for Functional MRI of the Brain, Oxford, UK) by counting the number of voxels inside the boundaries for each structure obtained using optimal parameters (Patenaude & al., 2011). All volumes were finally adjusted for head size by multiplying all values by a scaling factor generated from SIENAX (Smith et al., 2002), another tool included in FSL.

Procedure

Within one week after inclusion into the study, participants were invited to the imaging center. Here, we carried out scanning, which lasted approximately 30 minutes.

Analysis

Memory assessment: to confirm the similarity of this sample to the overall group, we repeated the same statistical analyses as in Experiment 1.

Hippocampal volume at baseline: In order to compare hippocampal volume between groups at baseline, we performed a MANOVA with *group* (2 levels: mTBI patients, controls) and *sex* (2 levels: women, men) as between subject factor and *side* (2 levels: left, right) as within subject factor as well as *age* and *TIV* as covariates (all MANOVAs and ANOVAs were Greenhouse-Geisser corrected). For post hoc analyses of the effects of both hippocampi,

we carried out separate univariate ANOVAs with *group* (2 levels: mTBI, controls) and *sex* (2 levels: women, men) as between subject factor as well as *age* and *TIV* as covariate.

Next, to verify relation between memory scores and hippocampal volume, we performed Spearman's ranks correlations (recognition scores were not normally distributed), between baseline and follow-up HVLT subtests (immediate recall, delayed recall and recognition) and left and right hippocampi for each group separately. Again, we set the alpha value at 0.05 and used Bonferroni-Holm correction for multiple comparisons.

Results

Memory assessment

The MANOVA revealed a significant interaction between *group* and *task* ($F(1, 35) = 5.288$; $p = 0.028$; $R^2 = 0.131$) and significant main effects of *group* ($F(1,35) = 6.406$; $p = 0.016$; $R^2 = 0.155$) and *task* ($F(1, 35) = 145.822$; $p < 0.001$; $R^2 = 0.806$) in the baseline scores. We did not observe any other significant main effect of sex or age or any other interaction.

Post hoc ANOVA revealed a significant difference in the total immediate recall scores ($F(1, 35) = 6.859$; $p = 0.013$; $R^2 = 0.164$) and in the delayed recall ($F(1, 35) = 4.421$; $p=0.043$; $R^2 = 0.112$ (n.s. after correction). When looking at the individual Trial 1, 2 and 3 of the immediate recall tasks, only difference at trial 3 remained significant after correction ($F(1, 35) = 8.782$; $p = 0.005$; $R^2 = 0.201$). For the recognition score, the MANOVA revealed no significant interaction or main effect of *group* or *sex* (see Table 2).

Hippocampal volume

The MANOVA revealed a main effect of *group* ($F(1, 34) = 4.705$; $p = 0.037$; $R^2 = 0.122$) and *sex* ($F(1, 34) = 5.260$; $p = 0.28$; $R^2 = 0.134$), where women had a bigger hippocampus volume, but no interaction between *side* and *group* ($F(1, 34) = 2.254$; $p = 0.143$; $R^2 = 0.62$) and no main effect of *side* ($F(1, 34) = 0.276$; $p = 0.603$; $R^2 = 0.008$). We decided to carry out post hoc ANOVAs in an exploratory approach to compare each hippocampus between groups. They revealed a significant group difference for the right hippocampus volumes

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($F(1, 34) = 6.977$; $p = 0.012$; $R^2 = 0.170$) but not for the left hippocampus volumes ($F(1, 34) = 1.127$; $p = 0.296$; $R^2 = 0.000$; see Figure 3).

Correlation between memory scores and hippocampal volume

We did not observe any significant linear correlations between hippocampal volumes and HVLT scores in any groups (Immediate recall and left ($r = 0.242$; $p = 0.133$), right hippocampus volume ($r = 0.175$; $p = 0.279$; See figure 4); Delayed recall and left ($r = 0.185$; $p = 0.252$), right hippocampus volume ($r = 0.184$; $p = 0.256$); Recognition and left ($r = 0.136$; $p = 0.402$), right hippocampus volume ($r = 0.062$; $p = 0.704$).

Discussion

This study aimed at evaluating verbal episodic memory within acute and long-term phase after a single mTBI. To our knowledge, this study was also the first to investigate the hippocampus volume in the acute phase of a single mTBI and to explore its link with episodic memory. This supports the notion that verbal episodic memory is altered within the first month after the trauma but may return to subnormal-to-normal levels at follow up. On a neuroanatomical level, hippocampal volume was smaller in mTBI patients compared to controls in the acute mTBI phase although it was not correlated with memory scores.

We evaluated verbal episodic memory in both experiments and observed that immediate recall and delayed recall – in Experiment 2 only – were impaired in the acute phase in patients suffering from mTBI. This is in line with the notion that delayed recall impairment is common after a mTBI and that this specific deficit is not only observable in concussed athletes [24, 25]. Thus, our results suggest that episodic memory is altered in the acute phase of a mTBI. Indeed, in both of our experiment episodic memory was altered and this is in line with other reports not limited to mTBI [26]. In contrast, recognition seems to be relatively conserved after a single mTBI, which suggests a significant role of TBI severity on this particular memory feature [27, 28].

We further observed a smaller hippocampal volume in mTBI patients. This is somewhat in line with earlier reports, which reported mTBI patients to show smaller hippocampal

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volumes in the chronic phase years after a mTBI [20, 29]. We show that reduced hippocampal volume can already be observed in the acute phase. It is important to note that Zagorchev and al. (2016) did not find any differences in hippocampal volumes in the subacute phase (i.e. 2 months after the mTBI). It is unclear what drives these volume differences; potential candidates being gray matter volume, white matter volume or both [30]. Different hypotheses can be put forward why hippocampal reduction was observable within the acute phase of the present study, but only in the chronic phase of the earlier reports. First, patients' characteristics may be different between studies. In other words, although they were all diagnosed with a first mTBI, patients in the present study may be more heavily affected than those from the earlier report. Unfortunately, Zagorchev et al. did not assess memory performance which would have allowed to test this hypothesis. Second, different hitherto unknown overlapping pathomechanisms may lead to volume reduction in the acute phase, volume normalization in the subacute phase and subsequent volume reduction in the chronic phase following a mTBI. Recent studies suggest non-hemoglobin-bound (non-heme) iron as a potential candidate causing chronic volume reduction [31-33]. Excessive iron levels in the brain lead to oxidative stress causing cellular dysfunction and death resulting in structural atrophy, as well as encouragement of tau phosphorylation and the formation of neurofibrillary tangles [31, 34]. Hence, non-heme iron is augmented in neurodegenerative diseases and also observed in the hippocampus [35-37]. Interestingly, chronic mTBI is associated with increased levels of non-heme iron in subcortical brain tissue, although the hippocampus was not investigated [38]. It is however unclear if these mechanisms can explain hippocampal volume reduction within weeks after a mTBI. Future studies are needed to understand the underlying mechanisms leading to volume changes.

Our study supports the notion that verbal episodic memory scores and hippocampal volume are not linearly associated. Previous studies conducted on athletes in the chronic phase of a mTBI and using similar MRI techniques (T1 MPRAGE) showed inconsistent results: some studies reported a significant correlation between episodic memory scores and hippocampal volume in mTBI [11, 39] while others did not [40, 41]. Nevertheless, one must be careful when comparing athletes with non-athletes, as the former consist of a particular population because of (1) the risk of multiple mTBI, (2) whole body impact and (3) the urge

to reinstate the competition and thus potential downplay of symptoms [42, 43]. Future studies are needed to understand the link between hippocampal volume and memory scores.

It is possible that the observed memory decline is related by other underlying cognitive functions and thus brain regions. One potential region is the frontal lobe, which plays a major role in attention, and which is particularly vulnerable after a head injury [44, 45]. Another possible explanation could be the higher depression scores obtained for the mTBI group (Beck Depression Inventory (BDI-II)) as described in the same cohort [22]. Depression is known for its negative effects on episodic memory performance after an mTBI [46]. However, no correlations and interaction were found in our sample between these two variables and the hippocampal volume.

Our study has some limitations; the most important ones being that we did not carry out MRI in the whole sample and that MRI was not repeated at follow up. Further, special MRI acquisition paradigms such as Susceptibility Weighted Imaging (SWI) which is sensitive to microhemorrhages and may reveal subtle effects not visible to standard MRI[47] may be useful in future studies. Also, only 66 % of participants at baseline have returned for the follow-up which might contribute to the divergence in memory scores between baseline and follow-up. In addition, we opted to not include years of education as additional covariate in order to not lose statistical power due to the relatively small sample size. Still, the correlation between immediate recall and years of education at baseline might have influenced the observed effect and future studies should control for this variable. Finally, the second experiment was carried out on a relatively small sample with 40 participants. Therefore, the results of the current study should be interpreted cautiously.

In conclusion, after a single mTBI, verbal episodic memory is altered in patients compared to healthy controls within the first month post-trauma. On a neuroanatomical level, this memory alteration is accompanied by an atrophy of the bilateral hippocampus, a memory-related structure. Futures studies should invest the possible role of MRI measurement in post-trauma acute phase as a marker of chronic symptoms after even a mTBI.

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Conflict of interest

The authors declare no conflict of interest.

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Figures

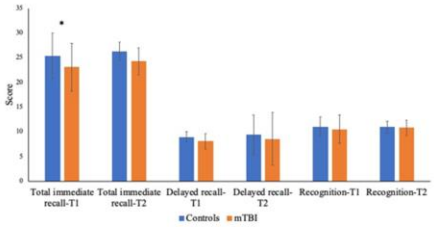

Figure 1. HVLT scores comparison between controls and mTBI patients at both baseline and follow-up. (** p < .05; ** p < .01, uncorrected.)*

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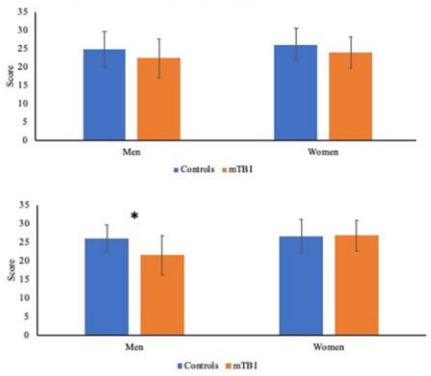

Figure 2. HVLT immediate total score comparison between men and women at both baseline and follow-up. (** p < .05; ** p < .01, uncorrected.)*

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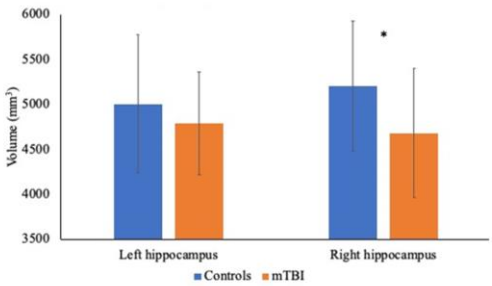

Figure 3. Hippocampal volumes comparison between controls and mTBI patients scanned 2-4 weeks post-trauma. (** p < .05; ** p < .01, uncorrected.)*

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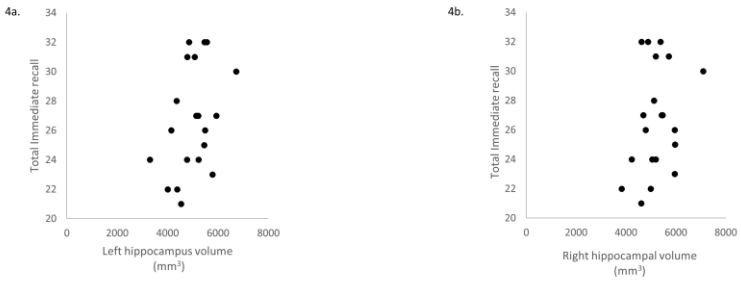

Figure 4. Correlation between HVLT immediate total score and hippocampal volumes.

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Tables

Table 1: Experiment 1: *Statistics of patients with mild TBI and controls at baseline and follow-up (SD: standard deviation; HVLT: Hopkins Verbal Learning Test; a Chi-square test; b Controlled for age and sex; * p < .05; ** p < .01, uncorrected)*

Baseline	Controls	Mild TBI	*p*
n	54	52	
Age in years (SD)	31.30 (9.19)	33.12 (12.22)	.387
Women, n (%)	27 (50%)	23 (44.2%)	.552[a]
Years of Education (SD)	15.58 (2.49)	15.25 (3.15)	.547
HVTL trial 1 (SD)	6.18 (1.86)	5.75 (1.84)	.326[b]
HVTL trial 2 (SD)	9.00 (1.90)	8.08 (1.95)	**.029**[b*]
HVTL trial 3 (SD)	10.20 (1.57)	9.27 (1.72)	**.009**[b**]
Total immediate recall (SD)	25.39 (4.68)	23.10 (4.88)	**.029**[b*]
Delayed recall (SD)	8.96 (1.91)	8.13 (2.72)	.127[b]
Recognition (SD)	11.09 (1.05)	10.54 (1.58)	.120[b]
Follow-up	Controls	Mild TBI	*P*
n	39	31	
Age in years (SD)	31.64 (9.72)	34.77 (13.66)	.267
Women, n (%)	17 (44%)	16 (51%)	.504[a]
Years of Education (SD)	15.08 (2.44)	14.90 (3.03)	.791
HVTL trial 1 (SD)	6.72 (1.49)	5.87 (2.00)	**.043**[b*]
HVTL trial 2 (SD)	9.15 (1.79)	8.71 (1.94)	.316[b]
HVTL trial 3 (SD)	10.43 (1.21)	9.71 (2.02)	.081[b]

Total immediate recall (SD)	26.30 (4.03)	24.29 (5.32)	.072[b]
Delayed recall (SD)	9.44 (1.94)	8.61 (2.89)	.203[b]
Recognition (SD)	10.97 (1.16)	10.86 (1.55)	.484

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Table 2: Experiment 2: *Statistics of patients with mild TBI and controls at baseline (MRI subgroups) (SD = standard deviation; HVLT: Hopkins Verbal Learning Test; a Chi-square test; b Controlled for age and sex; * p < .05; ** p < .01, uncorrected).*

Baseline	Controls	Mild TBI	*P*
N	20	20	
Age in years (SD)	30.50 (10.36)	31.20 (10.70)	.835
Women, n (%)	8 (40)	10 (50)	.525[a]
Years of Education (SD)	16.15 (2.62)	15.45 (2.09)	.356[b]
HVTL trial 1 (SD)	6.75 (1.55)	5.75 (1.68)	.079[b]
HVTL trial 2 (SD)	9.45 (1.50)	8.10 (2.00)	**.032**[b*]
HVTL trial 3 (SD)	10.50 (1.19)	9.00 (1.86)	**.005**[b**]
Total immediate recall (SD)	26.70 (3.63)	22.85 (5.04)	**.013**[b*]
Delayed recall (SD)	9.30 (1.66)	7.55 (3.20)	**.043**[b*]
Recognition (SD)	11.20 (0.89)	10.30 (1.95)	.794[b]