Received: 15 November 2021 | Revised: 19 June 2022 | Accepted: 22 June 2022

DOI: 10.1002/hbm.26003

RESEARCH ARTICLE

WILEY

Memory retrieval brain–behavior disconnection in mild traumatic brain injury: A magnetoencephalography and diffusion tensor imaging study

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Funding information
Brain and Behavior Research Foundation; Defence Research and Development Canada; Canadian Institutes of Health Research; Brain & Behavior Research Foundation; Innovation for Defence Excellence and Security (IDEaS) Program; Canadian Institute of Military and Veteran Health Research (CIMVHR); Defence Research and Development Canada (DRDC)

Abstract

Mild traumatic brain (mTBI) injury is often associated with long-term cognitive and behavioral complications, including an increased risk of memory impairment. Current research challenges include a lack of cross-modal convergence regarding the underlying neural–behavioral mechanisms of mTBI, which hinders therapeutics and outcome management for this frequently under-treated and vulnerable population. We used multi-modality imaging methods including magnetoencephalography (MEG) and diffusion tensor imaging (DTI) to investigate brain–behavior impairment in mTBI related to working memory. A total of 41 participants were recruited, including 23 patients with a first-time mTBI imaged within 3 months of injury (all male, age = 29.9, SD = 6.9), and 18 control participants (all male, age = 27.3, SD = 5.3). Whole-brain statistics revealed spatially concomitant functional–structural disruptions in brain–behavior interactions in working memory in the mTBI group compared with the control group. These disruptions are located in the hippocampal–prefrontal region and, additionally, in the amygdala (measured by MEG neural activation and DTI measures of fractional anisotropy in relation to working memory performance; $p < .05$, two-way ANCOVA, nonparametric permutations, corrected). Impaired brain–behavior connections found in the hippocampal–prefrontal and amygdala circuits indicate brain dysregulation of memory, which may leave mTBI patients vulnerable to increased environmental demands exerting memory resources, leading to related cognitive and emotional psychopathologies. The findings yield clinical implications and highlight a need for early rehabilitation after mTBI, including attention- and sensory-based behavioral exercises.

KEYWORDS
diffusion tensor imaging, hippocampus, magnetoencephalography, mild traumatic brain injury, working memory

1 | INTRODUCTION

Traumatic brain injury is caused by an external force that can take place during sports activities, at work, in traffic, at home, or on the battlefield. Current challenges in clinical research and patient management in the field include inconsistent imaging evidence regarding the underlying neural mechanisms, and therefore, a lack of targeted therapeutics and optimization of outcome (Levin & Diaz-Arrastia, 2015; Sandsmark & Diaz-Arrastia, 2021) Mild traumatic brain injury (mTBI, commonly referred to as a concussion) results in approximately 2.5 million emergency department visits each year in the United States alone (Silverberg et al., 2020; Taylor et al., 2017) While its prognosis is generally favorable with spontaneous recovery typically occurring within 3 months (Bigler, 2013; Feigin et al., 2013; Levin & Diaz-Arrastia, 2015; Roehr, 2012), it has generally, clinically speaking, been neglected because many of the enduring alterations in neurocognitive functions are sometimes subtle but distressing, and are not readily identifiable by conventional clinical examinations. Unlike moderate or severe forms of TBI, the presence of a prototypical lesion or abnormality often does not exist in mTBI, and neurocognitive or behavioral deficits are unreliably identified by existing clinical tools, making injury management, and prognosis challenging. Prior research shows a significantly increased risk of dementia and Parkinson's disease in patients with mild-to-severe TBI (Gardner et al., 2014, 2018). In addition, patients with mTBI can also develop long-term cognitive and behavioral complications (Centers for Disease Control and Prevention, 2009) that impact work performance and social interactions, and reduce quality of life (Nelson et al., 2019; Silverberg et al., 2020) Because the underlying neurobehavioral mechanisms of mTBI are unclear, therapeutic options and preventive strategies are limited (Lancet Editorial, 2011; Nelson et al., 2019; Silverberg et al., 2020). In order to advance current clinical knowledge, we need to find new ways to better understand the neural-behavior mechanism of mTBI.

In this study, we investigate whether mTBI impairs working memory performance with respect to brain–behavior regulation, an area that is insufficiently understood in prior research. This investigation of the two-dimensional interface, brain–behavior regulation related to working memory performance, complements previous mTBI research that primarily focused on single-dimensional brain or behavioral deficits and report inconsistent findings (Dunkley et al., 2015, 2018; Gosselin et al., 2011; Pardini et al., 2010; Smits et al., 2009) First, existing fMRI data on mTBI are divergent, with mixed findings involving the frontal, temporal, and parietal networks involved in working memory processing, including reports of attenuated activity (Chen et al., 2007; Gosselin et al., 2011; Mayer et al., 2009) while others report increased or additional activation in mTBI (Jantzen et al., 2004; Lovell et al., 2007; McAllister et al., 1999, 2001; Slobounov et al., 2010; Smits et al., 2009; Zhang et al., 2010) Other studies include reports of mixed hyper-/hypo-activation(Chen et al., 2004; Chen et al., 2008; McAllister et al., 2006; Pardini et al., 2010; Shah-Basak et al., 2018; Witt et al., 2010) Second, factors at the individual behavioral level have been overlooked and should be considered to understand the vulnerability of specific circuits and individual variability in cognitive functionality after mTBI. Meta-analyses of fMRI studies suggest that the diverse hyper-/hypoactive neural recruitment in mTBI during working memory paradigms may be task-dependent, possibly due to different types of processes among the tasks (i.e., discrete encoding, maintenance, retrieval processes, or a general continuous processing effort; Bryer et al., 2013; Golkar et al., 2012). In the current study, we propose a two-dimensional hypothesis, that mTBI would impair the brain–behavioral interface (or interaction) of working memory performance related to the memory retrieval process, and this would involve the hippocampus and related limbic–frontal circuitry.

We used functional and structure neuroimaging techniques, applying event-related whole-brain magnetoencephalography (MEG) combined with an event-subtraction strategy (Hung et al., 2013) to access the neural processing related to *memory retrieval*. MEG measures the magnetic fields arising directly from neural activation in pyramidal neurons and is a highly sensitive imaging modality able to precisely localize event-related neural dynamics at a millisecond time scale, including deep-brain activity in the limbic system (Quraan et al., 2011) This real-time temporal resolution makes MEG well-suited to capture the rapid and transient neural events in ways that conventional fMRI research cannot. For structural indices, we employed whole-brain diffusion tensor imaging (DTI, using Tract-Based Spatial Statistics [TBSS]; Smith et al., 2006) and evaluated its spatial concordance to MEG findings, and uncover the brain–behavior relationship to working memory after mTBI. DTI provides information about white matter by characterizing the strength and directionality of connectivity (e.g., fractional anisotropy [FA]) related to axonal and myelin sheath microstructure (Beaulieu, 2002; Hutchinson et al., 2018). We also implemented DTI tractography to reveal white matter pathways involved in the areas exhibiting neural abnormalities.

This study revealed reliable neurobehavioral mechanisms underlying memory vulnerability in mTBI. Results of this study yield rehabilitation insights and prevention strategies to motivate and guide further brain injury research that could improve prognostication and aid neurorehabilitative development for populations suffering from a concussion or related brain trauma and cognitive dysfunctions.

2 | MATERIALS AND METHODS

2.1 | Participants

A total of 41 English-speaking adult male participants aged 20–40 years were recruited, including 23 subacute mTBI patients with a first-time mTBI, diagnosed by clinicians in the emergency department at the Sunnybrook Health Sciences Centre, Toronto. Demographic information can be seen in Table 1. The inclusion criteria included: No or <30-min loss of consciousness; no or <24 h post-traumatic amnesia; Glasgow Coma Scale ≥13; nonlesion CT scan and no skull fracture assessed within 24 h of injury; and, time since injury was >2 weeks and <3 months to the study participation. Exclusion criteria included the presence of pre-existing neurological and/or psychiatric disorders;

TABLE 1 Demographics and working memory profiles

	Controls	mTBI	*p* value
Number	18	23	
Age (years)	27.3 (±5.3)	29.9 (±6.9)	.20
Handedness (right/total)	17/18	20/23	
IQ (WASI)	115.7 (±6.3)	106.7 (±14.8)	.01*
1-back working memory task accuracy (%)	96.9 (±3.0)	95.2 (±5.3)	.21
1-back working memory reaction time (ms)	477.6 (±89.9)	467.8 (±70.6)	.68

Note: Standard deviation in parentheses; *t*-test statistical significance at $p < .05$ marked as *. IQ was controlled as the covariate for all analyses and was not significantly correlated with any imaging findings. Abbreviation: WASI, Wechsler Abbreviated Scale of Intelligence.

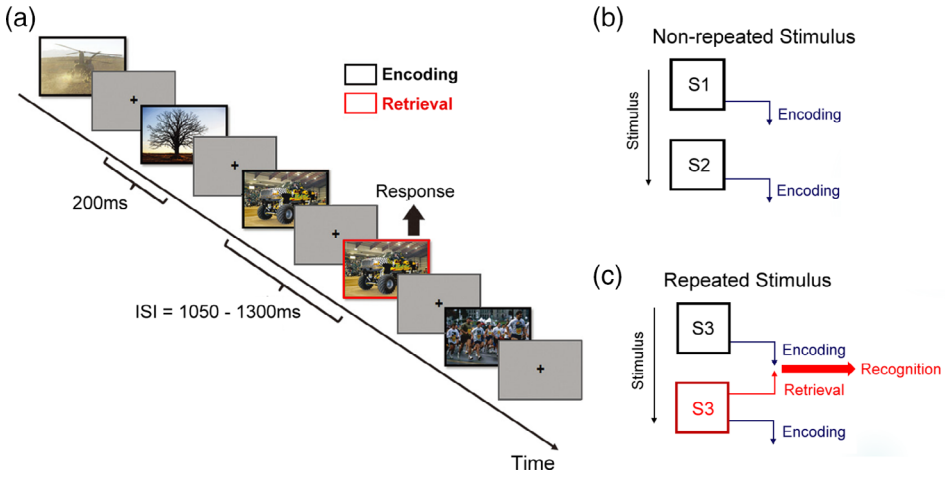

FIGURE 1 Working memory task. (a) a modified 1-back visual working memory task was used for the MEG and integrated with trial-subtraction, revealing neural dynamics attributed to memory retrieval. Participants view a series of daily-life scenes and press the response button as soon as when detecting a repeated scene. (b) Trials of nonrepeat items elicit neural activity subserving the encoding process. (c) Trials of repeat items evoke neural responses related to memory retrieval processes. Subtracting the effect of new trials from the repeats reveals the neural dynamics attributed to memory retrieval. *Source*: https://stocksnap.io/

active substance abuse, or use of anticonvulsants, benzodiazepines, and/or GABA antagonist medications; requiring major orthopedic procedures; contraindications to MRI or MEG acquisition, such as the presence of ferrous metal or implanted medical devices that precluded participation in the study. The control participants were recruited via community outreach flyers. Same exclusionary criteria were applied for recruiting the control participants, who had no history of mTBI. All participants provided written informed consent. The study was approved by the Research Ethics Boards at the Hospital for Sick Children and Sunnybrook Hospital.

2.2 | Working memory task

A modified one-back visual working memory task was used during MEG recording. Participants were presented with a series of daily-life scenes and were instructed to press a button as quickly as they could when a scene was repeated (Figure 1a). We implement a behavioral subtraction strategy to investigate the *memory retrieval*-related processes using the one-back paradigm with the MEG. Neural activity serving memory encoding is elicited by the nonrepeat items (Figure 1b), whereas memory retrieval is elicited by the repeat items (Figure 1c). We subtract the effect of new trials from the repeat to derive the neural dynamics attributed to memory retrieval. Two hundred and five photos of everyday life scenes were used. Twenty percent of the total photos were randomly selected to repeat immediately in consecutive order.

The task was presented and responses were recorded using Presentation software (NeuroBehavioral Systems, Inc.). The screen was at a distance of 78 cm from the participant's eyes, resulting in a visual angle of 21° horizontally and 13° vertically when viewing stimulus images. Reaction time and accuracy scores for the correctly responded repeated stimuli were calculated for each participant.

2.3 | Imaging acquisition

MEG data were obtained using a CTF Omega 151-channel axial gradiometer system (CTF MEG, Coquitlam, Canada) at a 600 Hz sampling rate. Fiducial coils were placed on the nasion, left and right pre-

auricular points of the participant to provide a continuous measure of head location in the MEG scanner. These fiducials were replaced by radio-opaque markers for anatomical MRI imaging. T1-weighted anatomical MRI images were obtained using a 3T MRI scanner (Magnetom Tim Trio, Siemens AG, Erlangen, Germany) using three-dimensional magnetization-prepared rapid gradient echo (3D MPRAGE) sequences [repetition time (TR) = 2300 ms; echo time (TE) = 2.9 ms; flip angle = 9°; field of view (FOV) = 28.8 × 19.2 cm; 256 × 256 matrix; 192 slices; 1 mm slice thickness]. The DTI scan was acquired on a Siemens Trio 3T scanner with a 12-channel head coil using a spin-echo EPI acquisition sequence [60 directions, b = 1000 s/mm^2, TE/TR = 87/8800 ms, FOV = 244 × 244 × 140 mm, resolution: 2 mm isotropic].

2.4 | Anatomical processing

The T1-weighted anatomical MRI images were first processed using the Freesurfer automated image reconstruction software (http://surfer.nmr.mgh.harvard.edu/), and the reconstructed output were utilized by the following DTI and MEG data processing. The Freesurfer reconstruction includes processing of motion correction and averaging of T1-weighted images, removal of nonbrain tissue using a hybrid watershed/surface deformation procedure, segmentation of the subcortical white matter and deep gray matter volumetric structures, intensity normalization, tessellation of the gray matter white matter boundary, automated topology correction. Freesurfer morphometric procedures have been demonstrated to show good test–retest reliability across scanner manufacturers and across field strengths (Han et al., 2006; Reuter et al., 2012).

2.5 | Event-related MEG analysis and quality control

MEG data were processed using the Brainstorm software toolbox (Tadel et al., 2011, 2019; http://neuroimage.usc.edu/brainstorm) integrated with the Freesurfer anatomical reconstruction output, including the following automated standard processing pipeline. Fiducial points were marked in the individual anatomical images. The timing of event markers was automatically corrected accounting for time delays of stimulus triggers to ensure accurate timing of brain responses to the data. Head position was corrected for head movements occurring during the MEG task, by calculating the distance at each time point with respect to the initial reference head position, and then replacing it with an adjusted position that better represents the head position (mid-point position) throughout the recording. Continuous MEG data were bandpass-filtered for 1-50 Hz. The automated artifact detection signals were then examined; artifacts from eye blink, heartbeats, and other noise components were removed using the Signal-Space Projection/Principal Component Analysis (SSP/PCA) procedure (Uusitalo & Ilmoniemi, 1997) combined with Independent Component Analysis (ICA) procedure (Touretzky et al., 1996) in Brainstorm. The artifact detection was followed by bad segment and bad channel detection and removal. The cleaned data were then epoched for −200 to 800 ms with respect to the stimulus onset. A head model was generated based on surface model and overlapping spheres. The data were baseline corrected with a noise covariance matrix generated with the baseline epoch −200 to 0 ms. The time-locked event trials (Repeat, and New) were averaged per condition per subject. Source estimation for each subject for each event type was carried out applying the minimum norm imaging method using the current density map and constrained dipole orientations. To identify the memory retrieval-specific sources, event subtraction was computed at the source level between Repeat vs. New source files within-subject. These subtracted, memory-retrieval source data were normalized by baseline (−200 to 0 ms) to *Z* scores, and then co-registered to standard space using ICBM152 brain template (MNI coordinate system).

The projected surface source maps of memory retrieval were transformed into the volumetric map by Brainstorm for group-level statistical testing by FSL. We were interested in capturing the memory-retrieval source activity occurring during the active time window of 50–300 ms post-stimulus onset, excluding early subliminal processing (before 50 ms) and later processing close to motor responses (after 300 ms). A 75 ms analysis window was used, with a 25 ms sliding interval, producing eight assessment windows: 50–125, 75–150, 100–175, 125–200, 150–225, 175–250, 200–275, and 225–300 ms. As a validation of the working memory task, the group analysis was first carried out across all participants for each time window to identify significant sources in the subtracted source files of Repeat versus New in GLM design to determine whether neural activity in the Repeat condition is greater than the New condition (memory retrieval) or smaller than the New condition across at the group level. The interaction test was then carried out in a voxel-wise, nonparametric two-way ANCOVA by testing how the effects between the Group factor and each of the two task performance indices (accuracy and RT) impact on the memory-retrieval source files, in other words, to identify whether there is a significant difference between the two study groups on the relationship (the slope) between memory retrieval source activity and the behavioral performance. These group-level analyses were conducted using the FSL Randomise program for nonparametric permutation testing (5000 permutations), correcting for multiple comparisons using the threshold-free cluster enhancement method, and controlling for the family-wise error rate (thresholded at $p < .05$). All analyses were carried out using nonparametric statistics.

For quality control, head movement was monitored using the MEG reference channel during the entire recording. A total head movement score (in millimeters) was calculated for each participant for the raw data of the entire MEG run. This score was by default modeled as a covariate for the MEG imaging analysis, as most analysis software, including Brainstorm, assume a single fixed head position for their computations. This "reference position" was measured by Brainstorm just before the MEG recording started and was saved separately from the continuous head localization channels.

Finally, for significant results, the MEG signals (standardized Z scores) from the peak voxel of the significant activated cluster were extracted and plotted against continuous time points to visualize the time series of memory-retrieval source activity.

2.6 | DTI processing and quality control

The diffusion data were preprocessed by TRACULA pipeline (TRActs Constrained by UnderLying Anatomy; Yendiki et al., 2011) with the Freesurfer reconstructed output images. The diffusion-weighted imaging (DWI) series were aligned to the first nondiffusion-weighted image using affine registration and the corresponding diffusion-weighting gradient vectors were reoriented accordingly. This procedure reduces misalignment between images due to head motion and eddy currents. The preprocessed data were then fed into the TBSS processing pipeline (Track-Based Spatial Statistics; Smith et al., 2006) The fractional anisotropy (FA) data were nonlinearly registered to a standard anatomical space; FMRIB58_FA image was used as the target image for this linear registration. Each participant's FA images were generated and thinned to create an alignment-invariant tract representation (e.g., the "mean FA skeleton") representing the centers of all tracts common to the group. All participants' diffusion data were then aligned on the skeleton space as 4D series for group statistical testing (threshold = 0.2).

For quality control, four DTI motion measures were derived by TRACULA processing pipeline (Yendiki et al., 2014) including the average translation score, rotation score, signal drop-out score (percentage of bad slices), and signal drop-out severity. A composite head motion score was computed for each participant based on these four motion measures (Yendiki et al., 2014) which was by default modeled as a covariate for the DTI imaging analysis.

Voxelwise analysis on the skeletonized FA map throughout the whole brain was carried out following TBSS using general linear models (GLM) by comparing the FA between the two groups and by testing interaction effects on the FA in nonparametric two-way ANCOVAs between the Group factor and each of the following task performance indices: the accuracy score and reaction time (RT) of the *n*-back working memory task for the (correctly responded) repeat items. These tests identify brain regions that show significant differences between the two study groups either on the FA values or on the relationship (the slope) between FA and the task performance. A nonparametric permutation test was performed (number of permutations = 5000; Winkler et al., 2014) using the FSL Randomise program (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise/UserGuide), correcting for multiple comparisons using the threshold-free cluster enhancement method (Smith & Nichols, 2009) and controlling for the family-wise error rate ($p < .05$). JHU DTI-based atlases were used (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) to determine the location of significant white-matter results. Significant TBSS result images are filled into the group-averaged FA space for presentation purposes.

To visualize the white-matter pathways connected with the TBSS-significant regions, probabilistic tractography was performed using the TBSS-identified clusters as the tractography seeds. The FMRIB software library (FSL) tractography toolbox (FDT) was used for automated probabilistic reconstruction of major white-matter pathways from individual DWIs in native space. This method repetitively samples from the distributions on voxel-wise principal diffusion directions and computes a streamline through these local samples to generate a probabilistic streamline (sample) from the distribution on the location of the true streamline. The local diffusion directions were calculated using the BEDPOSTX toolbox that allowed modeling multiple fiber orientations per voxel. For details about probabilistic tractography implemented by FDT (Behrens et al., 2003) The output images of individual connectivity paths were corrected by individual total counts of established samples by dividing each voxel value by the way total number, correcting for individual variations. Finally, the individual path images were nonlinearly registered to the standard space for group averaging for visualization.

The demographic variables of IQ and handedness were controlled for in all analyses above as the covariates. This was done because IQ was not matched between groups, and the mTBI patients showed a significantly lower IQ score profile than the control group; handedness was not matched between or within groups (Table 1). For significant findings, age was further added as an additional covariate to the imaging statistical testing, and the results remained consistent and significant (detailed in the Supplementary Material).

3 | RESULTS

3.1 | MEG results

3.1.1 | Memory retrieval activates hippocampal–prefrontal circuit across all participants

This analysis revealed the neural sources serving memory retrieval processing across all participants as a validation of the task (Hung et al., 2013) which successfully activated the hippocampus associated with memory retrieval functions (Maguire et al., 2001; McCormick et al., 2015). Voxelwise event-related MEG analysis across all participants ($N = 41$) showed significant activation for memory retrieval in the Repeat >New contrasts in the temporal pole and parietal cortex (150–250 ms), followed by the hippocampus, insula, and orbital frontal cortex (200–275 ms), lateralized to the right hemisphere (Figure 2a; one-way ANCOVA, $p < .05$, nonparametric permutation tests, corrected). Neural time series were computed from significant peak activations in the right hippocampus and orbitofrontal cortex (Figure 2b), both showing a primary peak in early latencies at 100–200 ms followed by an extended differential activation after 200 ms (Figure 2b). There were no significant between-group differences in neural sources found across any of the analyzed time windows.

3.1.2 | Impaired hippocampal–prefrontal and amygdala regulation of working memory in mTBI

Whole-head interaction tests showed that the association between retrieval-related neural activation and working memory task accuracy significantly differed between the two groups in the 100–200 ms time windows. Specifically, neural activity–accuracy associations (slope)

FIGURE 2 Significant hippocampal–prefrontal activation serving memory retrieval across all participants. (a) Event-related whole-brain MEG reveals hippocampal and prefrontal activation during working memory retrieval across all study participants. Significantly greater spatiotemporal activation for memory retrieval (in repeat > new event) is localized to the temporal pole (TP) and parietal cortex (PC) at 150–250 ms followed by the hippocampus, insula, and the orbital frontal cortex (OFC) at 200–275 ms. (b) Time series from peak locations in both the right hippocampus and the orbitofrontal cortex show a primary peak activation early on at 100–200 ms, followed by an extended differential activation after 200 ms. TP, temporal pole (including the superior, middle, and inferior temporal cortex); PC, parietal operculum cortex. ICBM152 brain template used. Note that the cortical sources reflect the surface map used in MEG source analysis

were significantly lower in the mTBI group compared to controls, localized to the right hippocampus and amygdala, as well as the right orbitofrontal cortex (extending into the subcallosal cortex) (Figure 3a; two-way ANCOVA, $p < .05$, nonparametric permutation tests, corrected). Within-group post-hoc evaluation (Figure 3b) showed that the above between-group brain–behavior interaction was driven by a significant positive correlation between working memory accuracy and the retrieval-related neural activity (across significant active time windows) in the control group ($\rho = 0.54$, $p < .05$, Spearman's correlation test), whereas no significant relationship was evident in the mTBI group ($\rho = -0.15$, $p > .05$). There were no significant group differences for the retrieval-related neural activation.

3.2 | DTI results

3.2.1 | Impaired limbic–cortical white matter connectivity in mTBI

Interaction tests showed that the two groups also differed in the associations between FA and working memory accuracy, with a significantly lower FA-accuracy relationship in mTBI compared to controls. This effect was located in the limbic–cortical tract, along the inferior fronto-occipital fasciculus, extending anteriorly into the prefrontal cortex through the external capsule that connects with the limbic–frontal tract, and extending posteriorly into occipital, parietal, and

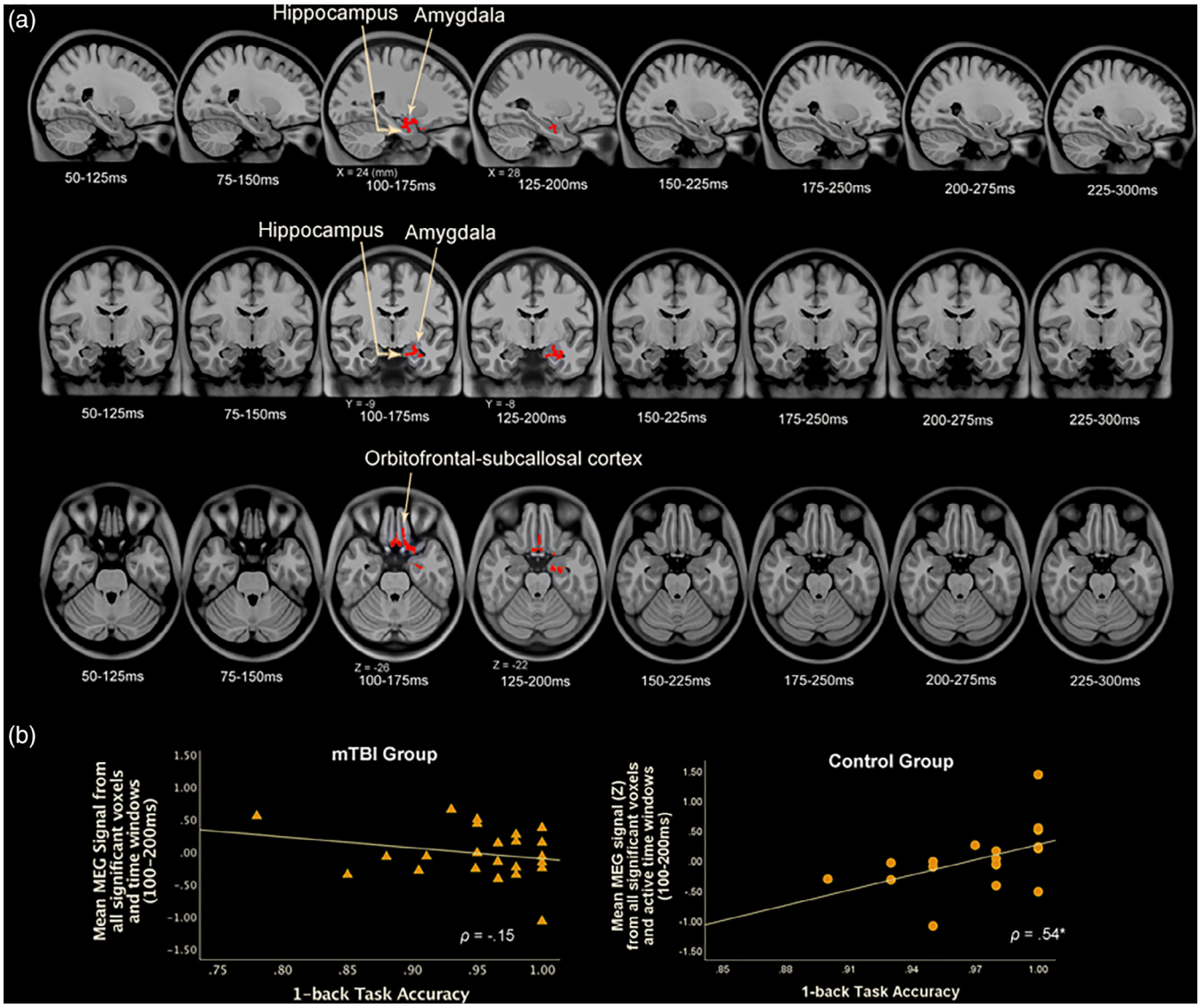

FIGURE 3 Impaired brain–behavior regulation of memory in mTBI between memory retrieval activation and task performance. (a) Compared with the control group, the mTBI group exhibited a significantly lower degree of association between retrieval-related neural activation and working memory accuracy, localized to the right hippocampus and the orbitofrontal–subcallosal regions, and an additional source in the amygdala. (b) Within-group examination revealed that the above brain–behavior interaction between-group was driven by a significant positive correlation between working memory accuracy and the memory-retrieval neural activity observed in the control group in the identified locations (at 100–200 ms), whereas no significant brain–behavior relationship was observed in mTBI. The * sign in the control group indicates a significance level of $p < .05$ for the correlation. ICBM152 brain template used. Note that the cortical sources reflect the surface map used in MEG source analysis

temporal areas (Figure 4a; $p < .05$, nonparametric permutation tests, corrected for multiple comparisons). Probabilistic tractography using the TBSS-significant cluster as the seed to the whole brain revealed the connection pathways of association in white matter tracts of the right hemisphere, including the limbic–frontal tract that extends anteriorly into the ventral frontal region (i.e., orbital frontal area), and connects with the temporal-lobe and posterior association tracts into the occipital and parietal lobes (Figure 4b). Post-hoc assessment of mean FA values extracted from significant voxels showed controls had a significant positive correlation between FA and working memory accuracy (Figure 4c; $p < .05$, Spearman's correlation coefficient $\rho = .60$), while this relationship was absent in the concussion group ($\rho = -.04$, $p > .05$). There were no significant differences in FA observed between groups.

3.2.2 | Structural–functional relationship in limbic–frontal and connected areas

A significant positive structure–function correlation was found in the limbic–frontal and connected areas between MEG functional activation and FA measures (Figure 4d; $\rho = .43$, $p < .05$).

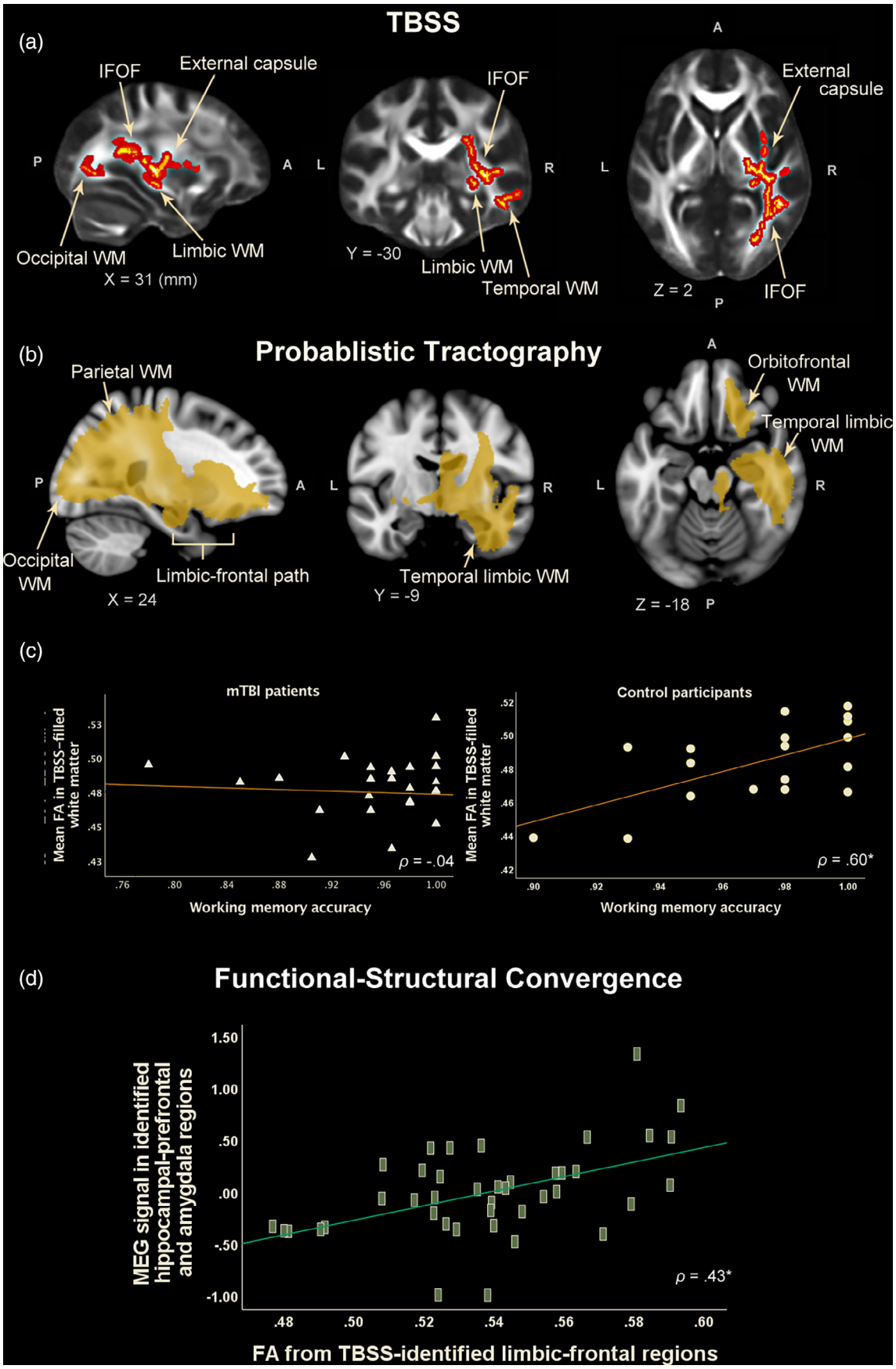

FIGURE 4 Legend on next page.

4 | DISCUSSION

In this study, we found robust cross-modality evidence of impaired brain–behavior associations in the hippocampal–prefrontal and amygdala–prefrontal circuits involved working memory processing. Functionally, brain–behavioral associations between neural activity in the hippocampal–prefrontal circuits and working memory retrieval performance were impaired in the mTBI group, compared with the control participants. Microstructurally, the association between the magnitude of neural connectivity and working memory performance, as reflected by the FA in DTI, was found impaired in mTBI in the limbic pathways. The study used multi-modality imaging and a two-dimensional approach to investigate the brain–behavior interface rather than a one-dimensional model predominantly used in prior research, and identified the locus of brain–behavior disconnection underlying the vulnerability of memory systems in mTBI. The results of this study provide clinical implications and markers for interventional strategies for early rehabilitation of mTBI.

4.1 | Brain–behavior disconnection in mTBI: Impaired neural regulation and a need for early rehabilitation

Brain–behavior dysconnectivity, localized to the limbic–prefrontal circuits associated with memory performance, represents a disruption of neural specialization and reflects a state of brain disorganization and dysregulation of memory function that may leave mTBI patients vulnerable for memory and related psychopathologies (Gardner et al., 2014; Gardner et al., 2018). Behaviorally, while the mTBI patients did not show a lower level of memory performance compared to the healthy controls, they failed to show the normal-level brain–behavior regulation of memory engaging the limbic–frontal circuits. This impaired brain–behavior regulation suggests decreased brain specialization and behavioral control, which may leave these patients vulnerable to increased environmental demands exerting memory, when increased neural resources are not deployable as can be done in an uninjured brain.

The identified neurobehavioral impairments in the limbic–frontal system reflect underlying capacity challenges linked to compromised axonal health. While functional neural hypoactivation in mTBI is suggestive of underlying deficits in neural processing capabilities (Chen et al., 2004, 2008) decreased anisotropy has been indicative of potential axonal injury of the neurons (Hutchinson et al., 2018; Johnson et al., 2013), myelin damage or loss in the oligodendrocytes (Hutchinson et al., 2018; Jiang et al., 2011; Laitinen et al., 2015) or astrocyte reactivity (i.e., neuroinflammation, and glial scar formation; Budde et al., 2011; Hutchinson et al., 2018) after brain injury. Further research (e.g., combining animal studies, or blood-based imaging) is required to confirm the specific underlying mechanisms related to the identified markers and deficits in the current study.

The current findings provide the psychophysiological foundation for much-needed early intervention efforts that use behavioral and cognitive rehabilitative approaches for patients diagnosed with mTBI (Barman et al., 2016; Tsaousides & Gordon, 2009). Behavioral training that engages an array of cognitive components, including attention, perception, and memory/working memory tasks, could be considered when managing patients with mTBI to retrain impaired brain–behavior circuits, to re-establish control of and optimize memory processes, and potentiate neural plasticity after brain injury.

4.2 | Impaired thalamo-hippocampus process in mTBI: Implications for sensory rehabilitative training

In the MEG results, the hippocampal–prefrontal neural dynamics showed a two-stage temporal activation serving memory retrieval, with a rapid early peak (100–200 ms) followed by a slow and extended secondary activation (>200 ms). This pattern of activation indicates that working memory may be supported by an initial stage of rapid, feed-forward processing followed by a second stage of slow, feedback-related processing that relies on top-down input from higher-order cortical regions and requires additional time for information to be integrated for a conscious decision (Bicanski & Burgess, 2020; Halgren et al., 2006). This two-stage processing characteristic of the memory system enables a fast and reflexive learning

FIGURE 4 Whole-brain DTI shows impaired limbic white matter pathways in mTBI related to working memory performance. (a) Compared to the control group, the mTBI group showed a significantly lower degree of brain–behavior association between working memory task accuracy and the FA localized to the limbic white matter regions along with the inferior fronto-occipital fasciculus (IFOF), extending anteriorly into the frontal lobe via the external capsule, connecting with the limbic–frontal tracts, and extending posteriorly into the occipital, parietal, and temporal areas. WM, white matter; MRIB58_1mm brain template used. (b) Probabilistic tractography reveals the limbic–frontal tract that extends anteriorly into the ventral frontal and orbitofrontal regions, and connects with the temporal-lobe and posterior association tracts into occipital and parietal areas using the TBSS-significant region as the seed. Image arbitrarily thresholded at showing 99% of maximum streamlines; ICBM152 brain template used. (c) The control group exhibits a significant positive correlation between FA and working memory accuracy (right panel); whereas this relationship is absent in the mTBI group (left panel). *X*-axis = working memory task accuracy; 1 means 100% accurate (hit rate). *Y*-axis = mean FA values averaged from all the TBSS-significant voxels. (d) Significant positive correlation is observed between the individual MEG neural activation and FA values from the identified hippocampal/limbic–frontal regions across participants. *X*-axis shows mean FA from TBSS-identified limbic–frontal white matter path. *Y*-axis shows mean MEG signal in memory retrieval localized in hippocampal–frontal and amygdala clusters during significant time windows

versus a slow and refined feedback-based learning behavior—a cycle that is susceptible to acquired brain injury.

The impairment of the hippocampal–frontal regulation of working memory in mTBI took place in the first processing stage rather than in the second stage. This suggests that memory impairment in mTBI may arise from a dysregulated bottom-up (feedforward) process driven by a direct sensory-hippocampal input, whereas the slow, cortical–hippocampal feedback process remains relatively intact (where we observed no group differences). This differentiation may inform future research into developing specific, targeted rehabilitative strategies, for example, utilizing sensory-stimulative and perceptual-driven behavioral exercises to re-establish the impaired sensory-hippocampal feedforward pathway in the memory system.

4.3 | Amygdala dysregulation in mTBI: Potential cognitive-exerted emotional vulnerability

We also identified a functional deficit in the amygdala in mTBI. The amygdala is well-established as the emotional processing and regulatory center of the brain (Hung et al., 2010; Morris et al., 1998). The amygdala was not activated during memory retrieval (in Repeat vs. New either within-group or across all participants), but when accounting for working memory performance, results revealed a deficiency in the mTBI group. Therefore, the amygdala dysregulation in relation to cognitive performance here may reflect a compensatory process: when performing the memory-loading tasks, individuals with mTBI may maintain the expected level of typical task performance at the cost of amygdala functioning. Clinically, emotional dysregulation has been frequently found to occur in mTBI in addition to physical and cognitive symptoms, and it worsens with mental exertion (Silverberg et al., 2020) sadness and fatigue were among the most commonly reported post-concussion emotional symptoms in mTBI patients 3 months post-injury (Levin & Diaz-Arrastia, 2015; Ponsford et al., 2011). The current link observed between the amygdala and hippocampal dysregulation in mTBI may provide evidence of emotional circuit vulnerability that explains why individuals with mTBI are susceptible to developing emotion-related comorbid psychopathologies (Zheng et al., 2019) including depression (Bombardier et al., 2010; Madsen et al., 2018; Stein et al., 2019; Thombs, 2010) and anxiety disorders, and post-traumatic stress disorder (Betthauser et al., 2018; Santhanam et al., 2019; Stein et al., 2019; Vanderploeg et al., 2009) which are known comorbid conditions highly developed in mTBI (Levin & Diaz-Arrastia, 2015).

In addition, the orbital frontal cortex (OFC), here activated during memory retrieval, and disrupted in mTBI, receives inputs from sensory and limbic systems, and codes for outcome appreciation in decision making (Dede et al., 2017) as well as emotion processing and relation of emotions (Dede et al., 2017; Golkar et al., 2012). In addition, the insula is associated with an integrative role between the homeostatic, affective, and cognitive systems (Kurth et al., 2010; Menon & Uddin, 2010). The anterior insula area, in particular, plays an essential role in cognitive control and inhibition (Hung et al., 2018) and is hypothesized to act as an "internal gate" of the brain in adjusting task-relevant brain activity and coordinating with other areas of the brain to ensure stable task performance as part of a salience network (Craig, 2010; Menon & Uddin, 2010).

4.4 | Impaired connectivity in limbic–cortical pathways in mTBI: Structural–functional convergence

DTI provides useful information about white matter microstructure in mTBI, by measuring the diffusivity in water molecule movements along white matter tracts. Fractional anisotropy (FA) reflects the strength of directionality and the magnitude of structural neural connectivity in white matter tracts and is related to axonal and myelin sheath integrity (Beaulieu, 2002; Hutchinson et al., 2018). Decreased FA has been linked to impaired neuronal structure and axonal injury (Churchill et al., 2019; Hutchinson et al., 2018; Lipton et al., 2012) and demyelination in the chronic phase after brain injury (Armstrong et al., 2016; Hutchinson et al., 2018). Increased FA has been attributed to adaptive remyelination, neural proliferation, neuroplasticity (i.e., sprouting, arborization; Hutchinson et al., 2018; Meaney & Smith, 2015; Werner & Stevens, 2015), or neural reorganization (Hutchinson et al., 2018).

We found disrupted structural connectivity in mTBI that aligns with the functional findings, suggesting an impaired limbic–frontal and limbic–cortical regulatory circuit serving memory. This impaired brain–behavior regulation is located in the limbic white matter and the inferior fronto-occipital fasciculus, which are key brain pathways connecting the ventral brain, linking the limbic system anteriorly to the prefrontal area (via uncinate fasciculus) and posteriorly with the visual area of the brain, as shown in the tractography results. These ventral white matter pathways, particularly the limbic–frontal tracts that have been consistently identified to be associated with increased risks of emotional dysfunctions (Huang et al., 2011, 2017), provide supportive structural evidence for the functional observations of the current study.

We further identified a significant structural–functional relationship in regions of impaired brain–behavior regulation in mTBI. The structural connectivity along the limbic–frontal and limbic–cortical white matter pathways is positively correlated and predictive of the functional activity in the hippocampal–frontal and amygdala regions regarding memory retrieval capacity. The stronger the connectivity, the greater the neural activity in these overlapping limbic–frontal cortical networks. This finding is consistent with previous multimodal neuroimaging reports which showed that connectome measures using DTI can effectively predict functional brain responses using fMRI, both cross-sectionally (Saygin et al., 2012) and longitudinally (Saygin et al., 2016), and therefore together offer reliable multimodal evidence characterizing conditions of the brain.

4.5 | Future directions

Further research is required to address how the multi-modality relationship involving the hippocampal–frontal and amygdala limbic networks may predict symptom progression and the interaction between cognitive performance and emotional susceptibility after brain injury. For example, further studies might investigate limbic–frontal network functionality, particularly involving the amygdala, and how this interaction predicts cognitive symptom severity and longitudinal symptom progression. The level of emotional stress has been found to serve as a critical predictor for mTBI symptom recovery at 6 months following the injury (van der Naalt et al., 2017). Further, future studies might investigate how early cognitive training programs might reduce the risk of developing cognitive–emotional complications and prevent related comorbidities after brain injury. Research has indicated that neurophysiological measurement using electroencephalography can distinguish fast versus slow recovery rates in patients with acute TBI, and can differentiate patients with better longitudinal outcomes at 12-month follow-up (Claassen et al., 2019). Finally, future studies might investigate neural biomarkers in animal models to confirm the underlying neural mechanisms. They might also use other imaging modalities, such as combining blood-based markers of neural inflammation and neurological injury (e.g., neurofilament light chain) to confirm the neuromarkers revealed in the current study.

4.6 | Strengths and limitations

Using multi-modality neuroimaging techniques integrated with a two-dimensional, brain–behavior interactive framework, we identified neuromarkers that may underlie vulnerability and increased risk for negative memory and emotional dysfunctions in mTBI (Gardner et al., 2014; Gardner et al., 2018). The study provides new insights that promote the development of targeted early neurorehabilitative programs that improve recovery rates and may prevent potential negative prospects or later impacts after brain injury. The study recruited male participants only in order to reduce the variance from the physical impacts of mTBI on gender differences. Future studies may consider including both genders to address gender differences in the brain's structure–function architectures in mTBI and their associations with memory performance.

5 | CONCLUSIONS

This study presents a new mechanistic understanding of dysfunction in the limbic–prefrontal circuitry as an early indicator of mTBI memory impairment. Brain–behavior disconnections identified in the limbic–prefrontal circuits related to memory performance suggest brain dysregulation of memory processes, which may leave mTBI patients vulnerable and at increased risk for memory dysfunction and related psychopathologies. The results of this study indicate a need for early interventions after mTBI. These findings yield clinical implications and rehabilitative insights that should motivate clinical communities and future brain injury researchers to develop early intervention and rehabilitative strategies for vulnerable populations suffering from concussions and related brain trauma.

AUTHOR CONTRIBUTIONS

All authors contributed intellectually to the study. Specifically, data analysis and drafting the paper: Iris Yuwen Hung; revising the paper: Iris Yuwen Hung; technical support: Marlee Vandewouw, Zahra Emami, Nicole Rudberg, Sonya Bells, Benjamin T. Dunkley; data collection: Leodante da Costa, Benjamin T. Dunkley; conception of the study, obtaining funding, and supervision for the study: Benjamin T. Dunkley.

ACKNOWLEDGMENTS

This research was funded by Defence Research and Development Canada (DRDC), the Canadian Institute of Military and Veteran Health Research (CIMVHR), and the Innovation for Defence Excellence and Security (IDEaS) Program to Benjamin T. Dunkley. This work was also supported by the Brain & Behavior Research Foundation in the United States, and the Canadian Institutes of Health Research, which awards to Iris Yuwen Hung. We would also like to thank Drs Margot Taylor and Elizabeth Pang at the Hospital for Sick Children for their help in this study.

CONFLICT OF INTEREST

All authors declare no competing interests.

DATA AVAILABILITY STATEMENT

All data are available upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Hung, Y., Vandewouw, M., Emami, Z., Bells, S., Rudberg, N., da Costa, L., & Dunkley, B. T. (2022). Memory retrieval brain–behavior disconnection in mild traumatic brain injury: A magnetoencephalography and diffusion tensor imaging study. *Human Brain Mapping*, *43*(17), 5296–5309. https://doi.org/10.1002/hbm.26003