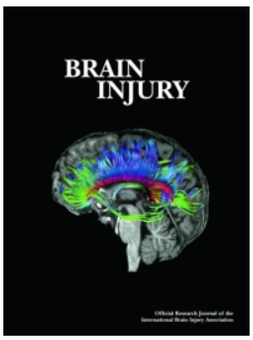

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ORIGINAL ARTICLE

Increased gamma connectivity during working memory retention following traumatic brain injury

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ABSTRACT

Primary objective: Alterations to functional connectivity following a traumatic brain injury (TBI) may lead to impaired cognitive performance and major depressive disorder (MDD). In particular, functional gamma band connectivity is thought to reflect information binding important for working memory. The objective of this study was to determine whether altered functional gamma connectivity may be a factor in MDD following TBI (TBI-MDD).

Research design: This study assessed individuals with TBI-MDD, as well as individuals with TBI alone and MDD alone using electroencephalographic recordings while participants performed a working memory task to assess differences in functional connectivity between these groups.

Methods and procedures: Functional connectivity was compared using the debiased weighted phase lag index (wPLI). wPLI was measured from a group of healthy controls ($n = 31$), participants with MDD ($n = 17$), participants with TBI ($n = 20$) and participants with TBI-MDD ($n = 15$).

Main outcomes and results: Contrary to the predictions, this study found both the groups with TBI and TBI-MDD showed higher gamma connectivity from posterior regions during WM retention.

Conclusions: This may reflect dysfunctional functional connectivity in these groups, as a result of maladaptive neuroplastic reorganization.

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Gamma; EEG connectivity; major depression; traumatic brain injury

Introduction

After a traumatic brain injury (TBI), rates of major depressive disorder (MDD) are significantly higher than in the general population, with most estimates suggesting ~ 20–40% [1–3]. The rate of MDD following TBI (TBI-MDD) is also higher than the rate seen following a spinal injury of equivalent severity, suggesting that the elevated rates are not solely related to psychosocial or psychological factors [4]. However, very little research has examined the changes in neural function in TBI-MDD. In particular, very little research has examined functional connectivity between brain regions, despite the likelihood that alterations to functional connectivity contribute to information processing impairments, which are thought to be an important component in the aetiology of depression [5], and previous research has indicated that an impaired functional network between the limbic system and cortical regions contributes to the development of MDD [6]. Connectivity disruptions in TBI have been suggested to lead to post TBI-MDD [7], and research using diffusion tensor imaging (DTI) has demonstrated weakened white matter pathways in TBI-MDD [8].

However, changes in functional connectivity (defined as the temporal correlation between activity in separate brain regions [9]) are not easily detected with imaging techniques. Research in animal models has indicated that, even when morphological changes are almost undetectable even by direct examination of individual axons, electrophysiological measures reveal altered nerve function [10]. This animal research suggests that, even when no connectivity changes are detected by structural imaging, altered functional connectivity may be present, reducing the synchronization of activity between brain regions necessary for effective cognition. Fortunately, recent advances in analysis techniques for scalp recorded electroencephalography (EEG) allow for the calculation of phase synchronization—a measure of how oscillations at one brain region are coupled to oscillations at another region, in contrast to frequency or time locked EEG analysis, which reflects activation of brain regions rather than coupling between brain regions [11]. This reflects functional connectivity between brain regions [12].

EEG and MEG measures of functional connectivity have shown altered theta and alpha connectivity during resting recordings in MDD and TBI [13–22]. Following a TBI, coherence measures of functional connectivity were found to be amongst the best predictors of outcome [21] and to relate to MRI indicators of white matter microstructure [20]. However, the results of studies examining resting activity are inconsistent and do not necessarily relate to cognitive processes, which are disrupted both in TBI and MDD [23,24]. Working memory (WM) is a cognitive construct referring to the short-term store and manipulation of a limited amount

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/ibij.

of information [25] and is one aspect of cognition that is frequently affected by both TBI and MDD, and is affected to an even greater extent in TBI-MDD [24,26,27]. As such, measuring connectivity during WM is likely to offer information beyond that offered by resting recordings. WM refers to the brief storage of information in order to enable manipulation of that information by other executive functions [25]. WM can be separated into three periods—the encoding period, during which an internal representation of the information is created, the retention period, during which the encoded information is maintained, and the retrieval period, when the internal representations are recalled to guide behaviour. Unlike most WM tasks, the Sternberg [28] task is constructed so that each WM period is temporally segmented, allowing separate analysis of neural processes specific to each period [29]. The function of these WM periods, in particular the retention period, relies on functional connectivity between frontal-central and frontal-posterior brain regions [30,31].

Only one study has focused on changes in functional connectivity during a WM task following a TBI. Reductions in alpha and theta coherence were found when the group with TBI was compared to a healthy control group in visual WM using the Sternberg task [17]. However, EEG coherence measures are vulnerable to false positive results for connectivity comparisons between groups, because the use of a reference electrode common to all active recording electrodes means calculations of EEG signal variations common to both electrodes in a pair can be inflated by the volume conduction of non-brain related activity (refer to Vinck et al. [11] for a more detailed explanation). The current research used the debiased estimator of the weighted phase lagged index (wPLI), which minimizes the contribution of zero lag connectivity (produced by volume conduction or non-brain related EEG artefact) between electrodes to calculations of functional connectivity, and as such is not vulnerable to the same false positives [11]. Additionally, no research has examined functional connectivity during WM in MDD, nor in TBI-MDD.

As such, the aim of this study was to examine whether individuals with TBI, MDD and TBI-MDD show a disruption in functional connectivity during WM, which may offer information as to why some individuals develop MDD following TBI while others do not. It was expected that both the groups with TBI and MDD would show decreases in functional connectivity compared to the control group in the WM task due to injury-related connectivity alterations and depression-related disrupted network function, respectively, and the group with TBI-MDD would show even further reductions due to the overlap of both neural insults.

Methods

Participants

Thirty-four healthy controls, 20 participants with MDD, 20 participants with TBI, and 16 participants with TBI-MDD were recruited to the study. A number of these participants were excluded after testing due to excessive recording artefact (two participants with MDD), equipment fault (two controls), scoring outside the designated group's depression rating score cut-off (one control and one participant with MDD), and possible medication effects (one participants with TBI-MDD medicated with oxycontin). This left a total of 31 control, 17 participants with MDD, 20 participants with TBI, and 15 participants with TBI-MDD. All participants were recruited through a participant database, the Alfred Hospital emergency department, or community advertising. Ethical approval for the study was obtained from the Alfred Hospital and Monash University's ethics committees, and all participants gave written informed consent. The data from these participants have been published in an analysis of WM related alpha event-related synchronization [29], but have not been analysed for connectivity.

Participants had normal or corrected to normal vision and were aged 17–65 years. Some participants in the groups with MDD and TBI-MDD were medicated (see Table 1). Inclusion criteria for the groups with MDD and TBI-MDD involved a diagnosis of MDD (following the TBI in the TBI-MDD group). This was confirmed by the MINI International Neuropsychiatric Interview for DSM-IV [32]. Current depression severity was moderate–severe for all participants with MDD and TBI-MDD, defined as a score above 19 on the Montgomery-Asberg Depression Rating Scale (MADRS) [33]. Co-morbid psychiatric diagnoses detected with the MINI were excluded (with the exception of anxiety disorder for the groups with MDD and TBI-MDD, because of the symptom overlap and significant comorbidity of anxiety and depression [34]) and all psychiatric diagnoses were excluded in the groups with TBI and control group. Participants with TBI-MDD were included only if the MDD was deemed to be causally related to the TBI by the study psychiatrist (PBF). As such, depression prior to the TBI was an exclusion criterion. For the groups with TBI and TBI-MDD injury information was obtained from hospital records where possible and patient report otherwise. Participants with TBI and TBI-MDD were excluded if their injury was open or if focal lesions were detected in post-injury hospital MRI or CT scans. The purpose of this exclusion criterion was to avoid the significant heterogeneity in neural activity that focal lesions would introduce. Individuals with severe TBI were excluded as their neural activity is more likely to be affected by focal lesions. Mild-to-moderate injury severity was determined by patient reports and hospital records of a loss of consciousness (LOC) of less than 24 hours and an initial Glasgow Coma Scale score (GCS) of more than 9 [1]. To ensure injuries were at least mild, a LOC or post-traumatic amnesia (PTA) of at least 10 minutes or an initial GCS of < 15 was required [35,36]. All participants with TBI and TBI-MDD were tested at least 6 weeks post-injury.

Table 1. Current medication for the MDD and TBI-MDD groups.

	MDD	TBI-MDD
No medication	7	7
SNRI	4	3
SSRI	5	3
Tricyclic	1	2

SNRI, Serotonin-Norepinephrine Reuptake Inhibitor; SSRI, Selective Serotonin Reuptake Inhibitor.

Procedure

All participants were assessed over two sessions conducted within 2 weeks of each other. One session involved collection of demographic, TBI history and depression severity data. These measures were all collected by a single trained researcher (NWB). Current depression severity was assessed with the Beck Depression Inventory-II (BDI-II) [37] and the Montgomery-Asberg Depression Rating Scale (MADRS) [33]. Pre-morbid IQ was estimated using the Weschler Test of Adult Reading (WTAR), which is demonstrated to be valid following TBI [38]. The Edinburgh Handedness Inventory (EHI) was used to assess hand preference [39]. The second session involved EEG recording during a Sternberg WM task (described below).

Task and stimuli

The Sternberg task [28] was presented with Neuroscan STIM2 software (Compumedics, Melbourne, Australia). This task simultaneously presented a set of five or seven letters to remember, followed by a probe letter. Participants were instructed to respond with a yes or no button press with their right hand to indicate whether they had seen the letter in the preceding memory set. A set of 15 consonants were used as stimuli (B, C, D, F, H, J, K, L, N, R, S, T, Y, W, and Z). Either five or seven simultaneously presented letters were used in each memory set. Letters were selected pseudo-randomly so that no letter appeared in the same location twice in a row. Trial sequence was also pseudo-randomly determined so that no more than three of each WM load (i.e. five vs seven letters) appeared consecutively. Crosses were placed at the ends of the five letter sets so they subtended the same visual angle as the seven letter memory sets. Participants were instructed to attend to the letters and ignore the crosses. Probe letters were present in the memory set at a 50% probability. The order of this was also pseudo-randomly determined so that no more than three 'probe present' or 'probe absent' trials occurred consecutively. No letter was presented as the probe twice in succession. Trials began with a fixation cross (517 ms) followed by a blank screen (500 ms). The memory set (encoding period) was then presented (3017 ms), followed by another blank screen for the retention period (3017 ms). The probe letter was then presented (2017 ms) followed by a brief visual mask (133 ms) and a blank screen pause before the next trial's fixation cross (1867 ms). Participant responses were only recorded during the presentation of the probe—responses outside of this time were considered incorrect. All participants performed a brief practice version prior to the recording, and all were presented with the same sequence, consisting of six blocks of 20 trials per block. In addition to EEG activity, accuracy and reaction times were recorded for each participant. Task design is illustrated by Figure 1.

Electrophysiological recording and pre-processing

Recordings were performed in a darkened and sound attenuated room. A Neuroscan 64 channel quick cap with Ag/AgCl electrodes recorded EEG activity to Neuroscan Acquire software using a Synamps 2 amplifier (Compumedics, Melbourne, Australia). Electrodes were referenced online to an electrode between Cz and CPz and grounded to AFz. Vertical and horizontal eye movements were recorded from electrodes above and below the left eye and outside the outer rim of each eye. Electrode impedances were kept below 5 kΩ. Digital conversion took place at 500 Hz, with a bandpass filter of 0.1–100 Hz (24 dB/octave roll-off).

Data was analysed offline in MATLAB (The Mathworks, Natick, MA) using EEGLAB for pre-processing (sccn.ucsd.edu/eeglab) [40] and fieldtrip for frequency and connectivity analysis (http://www.ru.nl/donders/fieldtrip) [41]. Second order Butterworth filtering was applied to the data with a bandpass from 1–80 Hz and also band stop filter 45–55 Hz. Data was then epoched from the onset of the blank screen to the offset of the probe for each trial, with only correct responses selected to be analysed. Epochs were visually inspected by an experimenter experienced with EEG analysis and blinded to the group of each participant, and periods containing muscle artefact or excessive noise were excluded. Each participant provided 20 or more accepted epochs for each condition, and no significant differences were detected between groups in number of accepted epochs ($p > 0.10$). Fast independent component analysis (FastICA) [42,43] was used to manually select and remove eye movements and remaining muscle activity artefacts. The 'symmetric approach' and the 'tanh' contrast function were used for the algorithm. Recordings were re-referenced offline to an averaged reference. Activity during the retention period (0–3000 ms time-locked to the onset of the blank screen) from each trial from each participant was then submitted to a single Hanning taper time-frequency transform to determine instantaneous phase values for the complex Fourier-spectra from 4–45 Hz with a 1

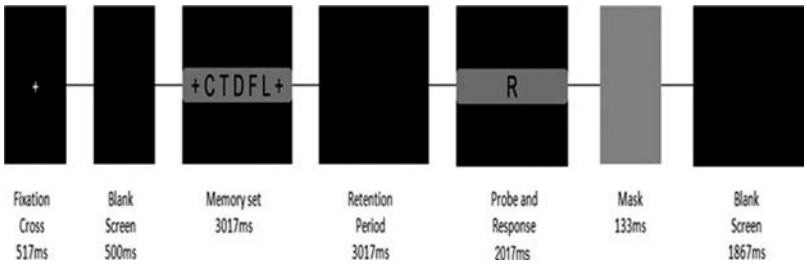

Figure 1. Task design and stimuli timing for the Sternberg task. All letters in the memory set were presented simultaneously. Memory sets contained either five or seven letters.

Hz resolution across sliding time windows corresponding to 3 oscillation cycles in length.

Connectivity computation

The debiased estimator of the weighted phase lagged index (wPLI) was calculated between each electrode. The wPLI is a conservative measure of phase synchronization between electrodes. It has the advantage of being robust against the effects of volume conduction, non-brain related artefact and activity from a common reference, because phase lags between sensors of near zero contribute minimally to the wPLI measure, preventing the detection of false positive connectivity due to these artefacts [11]. The wPLI has good test–re-test reliability [44]. wPLI provides a value for each pair of electrodes between 0–1, with higher values reflecting more connectivity between the two electrodes. In order to calculate wPLI, the following operations are performed [11]:

X is a complex-valued random-variable referred to as the non-diagonal part of the cross-spectrum, defined as

$$X \equiv Z_1 Z_2^{\star}$$

where $Z_2^{\star}$ is the complex conjugate of Z_2 and $Z = AY$, where $Y \equiv (Y_1, \ldots, Y_K)^T$ is a column vector of K complex-valued random variables whose observed values represent the Fourier spectrum of the sources activities, and $Z \equiv (Z_1, Z_2)^T$ is a column vector of two complex-valued random variables, whose observed values represent, for a particular frequency, the Fourier spectra of the two signals observed at the two sensors respectively.

For linearly uncorrelated source activities, $E\{Y_K Y_l^{\star}\} = 0$, where $E\{.\}$ is the expected value operator. However, if $E\{Y_K Y_l^{\star}\} \neq 0$, source activities are linearly correlated. More formally, let $\Im\{X\}$ denote the imaginary part of the cross-spectrum (the PLI). If sources are uncorrelated, then $E\{\Im\{X\}\} = 0$. Note that the PLI is signed (sgn), that both the PLI and wPLI are only based on the imaginary component of the cross-spectrum, which are not inflated by noise sources causing signal amplitude increases, and that the wPLI weights the signed PLI $sgn(\Im\{X\})$ by the absolute PLI $|\Im\{X\}|$.

So, finally, to calculate wPLI:

$$WPLI \equiv \frac{|E\{\Im\{X\}\}|}{|\{E\{\Im\{X\}\}|} = \frac{(|E\{\Im\{X\}\}|sgn(\Im\{X\})|}{E\{|\Im\{X\}|\}}$$

Statistical analysis

Demographic, severity and behavioural analyses

One-way analysis of variance (ANOVA) compared BDI and MADRS depression severity measurements between groups, as well as years of education, WTAR, age and EHI scores. Independent samples *t*-tests compared GCS, LOC, PTA, and time since injury between the groups with TBI and TBI-MDD. Three-way repeated measure ANOVAs compared both percentage correct and reaction times, with WM load (five or seven letters) and probe (present or absent) as within-subject factors and group (control, TBI, MDD and TBI-MDD) as the between-subject factors. For the sake of brevity, only between-group differences are reported. Post-hoc Tukey tests were used to control for multiple comparisons where omnibus ANOVAs indicated significant between-group differences.

Statistical analyses of connectivity

The average wPLI values for each participant were averaged in the frequency domain into four bands—theta (4–8 Hz), alpha (9–13 Hz), beta (14–29 Hz) and gamma (30–45 Hz). These averaged values were then averaged in the time domain for the first, second and third seconds of the retention period separately for seven and five letter WM loads (as functional connectivity during retention varies over time and load size [45,46]). The network-based statistic (NBS [47]) was used to compare wPLI connectivity across the four groups using an ANOVA design separately for each of the seven and five letter WM loads and the 3 seconds of the retention period in the theta, alpha, beta and gamma bands. The NBS is a non-parametric statistical method (robust against unequal sample sizes) that uses the principles of cluster analyses to allow for null hypothesis testing across the network level of values from each pair of potentially connected nodes, while still controlling for the family-wise error rate [47]. First, the NBS tests the null hypothesis at every pair of nodes, providing a test statistic value for each pair. Pairs with a test statistic exceeding a primary threshold provide the pairs for the cluster based null hypothesis test. The primary threshold was set at $p < 0.001$ to ensure only strong between-group differences in connectivity between electrode pairs pass this threshold to be compared at the cluster level. Pair connections that exceeded this threshold were then compared by cluster in topological space using permutation testing, so that only interconnected clusters that differ in a sufficient number of connections (extent of cluster) between groups resulted in the rejection of the null hypothesis. Five thousand permutations were used for each statistical comparison. See Zalesky et al. [47] for further information on this analysis technique. The secondary threshold for familywise corrected null hypothesis testing was set at $p = 0.05$. Time windows and bands that showed significant differences in the omnibus ANOVA were further explored with *t*-test designs using the NBS, comparing each group to the control group. To assess whether differences in connectivity between groups were related to differences in performance, Pearson's correlations were performed between the connectivity networks in conditions showing differences between groups using NBS and working memory performance (accuracy and reaction time). Correlations were performed for each group separately. To extract the relative contribution of each individual to the overall network, eigenvalues of the principal component explaining the most variance between significant edges were calculated (first principal component; PC1).

Results

Demographic and injury severity analyses

Means and standard deviations for the demographic and depression severity scores can be viewed in Table 2 and injury information can be viewed in Table 3. Unfortunately, some participants had missing data from single measures (one control participant lacked years of education, a participant with TBI lacked BDI-II, a participant with MDD

Table 2. Demographics, depression rating scores and head injury measures.

	Controls	TBI	MDD	TBI-MDD
n	31	20	17	15
Gender (F/M)	18/13	5/15	9/8	8/7
Age	38.48 (13.67)	33.15 (13.83)	38.47 (12.18)	43.73 (10.44)
Years of formal education	17.87 (3.26)	16.98 (3.41)	15.71 (3.58)	14.87 (3.67)
WTAR pre-morbid IQ	111.59 (3.43)	107.47 (5.66)	107.31 (7.78)	109.69 (5.94)
MADRS	1.73 (1.70)	2.45 (2.42)	26.47 (4.47)	16.47 (7.75)
BDI	2.45 (2.97)	3.30 (3.53)	24.41 (10.01)	29.36 (9.75)
EHI	80.97 (44.52)	75.54 (48.32)	86.29 (43.66)	66.64 (64.11)
GCS		13.00 (1.41)		13.67 (0.58)
LOC (hours)		1.28 (2.88)		1.49 (3.29)
PTA (hours)		7.68 (12.02)		10.62 (13.59)
Time since injury (months)		22.89 (59.66)		176.77 (197.68)
Co-morbid anxiety (Yes/No)	0/31	0/20	9/8	5/10

WTAR, Weschler Test of Adult Reading; MADRS, Montgomery-Asberg Depression Rating Scale; BDI, Beck Depression Inventory; EHI, Edinburgh Handedness Inventory; GCS, Glasgow Coma Scale; LOC, Loss of Consciousness; PTA, Post Traumatic Amnesia.

Table 3. Participant details for the TBI and TBI-MDD groups.

Group	Age	Gender	Time since injury (months)	Severity	Nature of injury
TBI	54	Male	3	Mild	Cycling MVA
TBI	34	Male	5	Mild	Cycling MVA
TBI	62	Female	250	Moderate	MVA
TBI	30	Male	7	Mild	Sport
TBI	24	Male	8	Moderate	MVA
TBI	27	Female	2	Mild	Cycling MVA
TBI	26	Male	112	Moderate	MVA
TBI	27	Male	3	Mild	Assault
TBI	24	Male	3	Moderate	Cycling MVA
TBI	19	Male	2	Mild	Fall
TBI	58	Male	2	Mild	MVA
TBI	51	Male	4	Mild	Cycling MVA
TBI	27	Male	3	Mild	Cycling MVA
TBI	25	Female	4	Mild	Cycling MVA
TBI	17	Male	4	Moderate	MVA
TBI	28	Male	12	Moderate	MVA
TBI	29	Female	5	Mild	Cycling MVA
TBI	17	Female	11	Mild	MVA
TBI	35	Male	26	Moderate	MVA
TBI	49	Male	84	Moderate	Assault
TBI-MDD	52	Male	360	Moderate	MVA
TBI-MDD	52	Male	6	Mild	Fall
TBI-MDD	43	Female	156	Mild	Cycling MVA
TBI-MDD	50	Male	34	Moderate	Fall
TBI-MDD	40	Female	42	Mild	MVA
TBI-MDD	46	Female	122	Moderate	MVA
TBI-MDD	40	Male	30	Moderate	Cycling MVA
TBI-MDD	39	Female	20	Moderate	Sport
TBI-MDD	21	Female	2	Mild	MVA
TBI-MDD	25	Female	252	Mild	Fall
TBI-MDD	55	Female	480	Moderate	MVA
TBI-MDD	60	Male	560	Mild	Sport
TBI-MDD	48	Male	14	Moderate	Cycling MVA
TBI-MDD	45	Female	48	Mild	MVA
TBI-MDD	40	Male	300	Mild	Cycling MVA

MVA, motor vehicle accident.

lacked MADRS score and two participants with TBI and one participant with TBI-MDD lacked accurate time since injury information). No significant group differences were present in age, handedness or WTAR estimated pre-morbid IQ (all p's > 0.10). Significant differences were found for years of education ($F(3,78) = 2.96$, $p < 0.05$), post-hoc Tukey showed the group with TBI-MDD had fewer years of education than the control group ($p < 0.05$). Groups significantly differed in BDI-II ($F(3,78) = 223.29$, $p < 0.01$) and MADRS scores ($F(3,78) = 86.95$, $p < 0.01$). As expected the groups with TBI-MDD and MDD showed significantly higher MADRS and BDI scores than the control and group with TBI (all p's < 0.01). The control and group with TBI did not differ from each other on either measure, nor did the group with TBI-MDD and MDD (all p's > 0.10). The group with TBI and TBI-MDD did not differ on any measure of injury severity (GCS, LOC or PTA, all p's > 0.10). The group with TBI-MDD showed a significantly longer time since injury than the group with TBI ($t(30) = 2.78$, $p < 0.05$).

Sternberg working memory performance data

Behavioural data is summarized in Table 4. Omnibus group comparisons indicated there was a significant difference in accuracy between groups ($F(3,79) = 3.91$, $p < 0.05$). Post-

Table 4. Percentage accuracy and reaction times for Sternberg task performance.

	Controls	TBI	MDD	TBI-MDD
Percentage correct, Mean (SD)				
Seven Letters – Probe Present	83.9 (13.7)	86.8 (9.6)	78.8 (13.0)[a]	79.0 (14.8)
Seven Letters – Probe Absent	88.5 (10.6)	89.0 (9.7)	80.7 (17.6)[a]	83.6 (8.8)
Five Letters – Probe Present	90.8 (9.8)	92.3 (4.7)	87.1 (9.3)[a]	87.0 (8.4)
Five Letters – Probe Absent	92.5 (7.5)	91.6 (6.9)	84.5 (16.0)[a]	89.7 (6.1)
Reaction time (ms), Mean (SD)				
Seven Letters – Probe Present	976 (162)	973 (167)	1096 (130)[b]	1119 (169)[c]
Seven Letters – Probe Absent	1061 (204)	1069 (220)	1219 (183)[b]	1192 (154)[c]
Five Letters – Probe Present	879 (139)	923 (179)	1029 (164)[b]	997 (123)[c]
Five Letters – Probe Absent	964 (177)	982 (182)	1128 (203)[b]	1066 (139)[c]

[a] Percentage correct: MDD < Controls and TBI, $p < 0.05$.
[b] MDD < Controls, $p < 0.01$, and MDD < TBI, $p = 0.05$.
[c] Reaction time: TBI-MDD < Controls, $p = 0.05$.

hoc tests indicated this was due to the group with MDD displaying lower accuracy than the group with TBI and control group (both $p < 0.05$), and the group with TBI-MDD displaying lower accuracy than the control group ($p < 0.05$), but no other between-group differences were significant (all p's > 0.10). Reaction time also differed between groups ($F(3,79) = 5.18$, $p < 0.05$). Post-hoc tests indicated the group with MDD showed slower reaction times than the control group ($p < 0.01$) and group with TBI ($p = 0.05$), and the group with TBI-MDD showed slower reaction times than the control group ($p < 0.05$).

Functional connectivity outcomes

The NBS ANOVA comparing gamma functional connectivity during the middle second of the seven letter WM load retention period showed a significant difference between groups ($p = 0.018$). Post-hoc t-tests indicated that this was due to the group with TBI and TBI-MDD showing more gamma connectivity than the healthy control group ($p = 0.015$ and $p = 0.016$, respectively). Differences between the group with TBI and control group can be viewed in Figure 2 and differences between the group with TBI-MDD and control group can be viewed in Figure 3. No other band

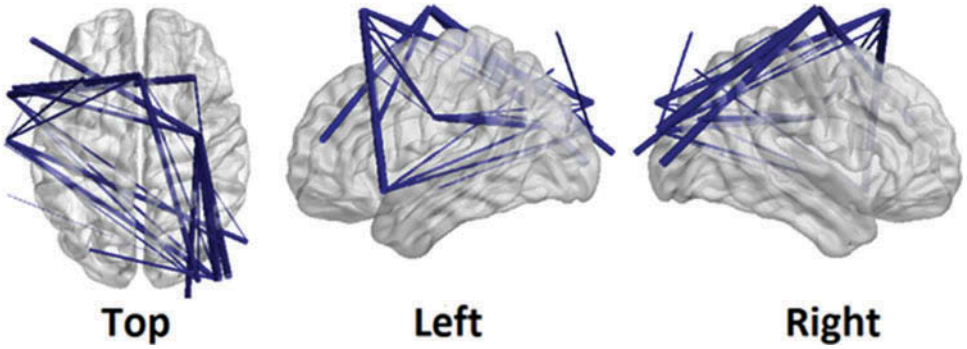

Figure 2. Significantly higher values of gamma wPLI between electrodes comparing the TBI and control groups in the middle second of the retention period (primary connection threshold, $p < 0.001$; family-wise corrected secondary, $p = 0.015$). Lines reflect higher between electrode connectivity in the TBI group than the control group from data averaged across all correct seven letter WM load trials and all individuals in each group. Lines are weighted to indicate the strength of the between-group differences.

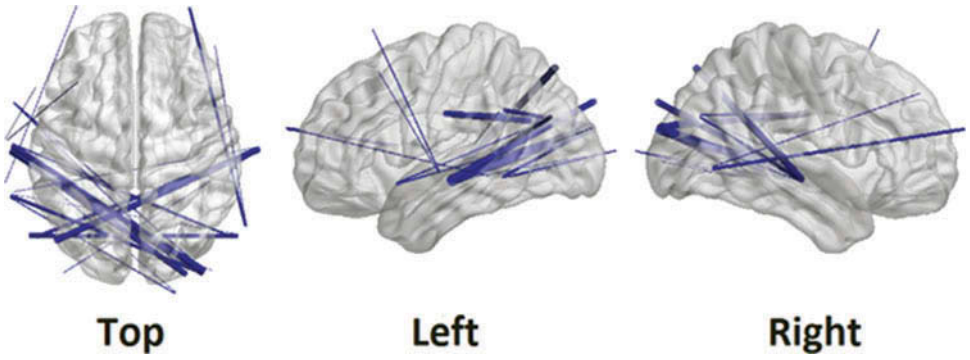

Figure 3. Significantly higher values of gamma wPLI between electrodes comparing the TBI-MDD and control groups in the middle second of the retention period (primary connection threshold, $p < 0.001$; family-wise corrected secondary, $p = 0.016$). Lines reflect higher between electrode connectivity in the TBI group than the control group from data averaged across all correct seven letter WM load trials and all individuals in each group. Lines are weighted to indicate the strength of the between-group differences.

or time window showed significance for the seven or five letter WM loads (all $p > 0.05$).

The first principal component (PC1) of the network of significant edges explained 71.71% of the variance in the overall network. Percentage correct in the seven letter condition correlated with PC1 within both the control ($r = 0.380$, $p = 0.035$) and group with MDD ($r = 0.605$, $p = 0.01$), but not within the groups with TBI or TBI-MDD (both p's > 0.05). There were no significant correlations between reaction time in the seven letter condition and PC1 eigenvalues in any group (all p's > 0.05).

Discussion

This study compared functional connectivity during WM retention in individuals with MDD, TBI and TBI-MDD. It was found that the groups with TBI-MDD and MDD exhibited poorer WM performance than healthy controls, while WM performance was unaffected in the group with TBI. In contrast to the hypothesis that individuals with TBI and TBI-MDD would show reduced functional connectivity, measures of EEG connectivity indicated that both the groups with TBI and TBI-MDD exhibited increased long range interhemispheric gamma connectivity for seven letter WM loads compared with the healthy control group. The group with TBI showed increased left temporal/inferior frontal to right parieto-occipital and fronto-central connectivity and the group with TBI-MDD showed increased bilateral temporal to parieto-occipital connectivity. Increased seven letter WM load gamma connectivity in this network related to better seven letter WM load WM performance in the control and group with MDD, but not for the groups with TBI or TBI-MDD.

The higher inter-hemispheric WM connectivity in the groups with TBI and TBI-MDD has two potential explanations—neural compensation for impairment in another process or dysfunctional connectivity as a result of the injury. The first possible explanation—that connectivity between the hemispheres is increased in TBI and TBI-MDD in order to compensate for impairment in another neural process—implies the presence of an impairment that was not detected by the current study (which may be an impairment in connectivity that the measures used in the current study were not sensitive enough to detect or a non-connectivity related impairment). This unknown processing impairment in the groups with TBI and TBI-MDD might increase the task demands on the processes that require increased gamma connectivity and in response these groups showed increased inter-hemispheric gamma connectivity to compensate and allow WM retention. Increased gamma connectivity has been shown to relate to recollection of information, although between frontal and parietal regions rather than inter-hemispherically between temporal and parieto-occipital regions [45]. Increased gamma connectivity is also thought to relate to increased attention, perhaps as a neural mechanism to improve information binding [48]. Examples of an increase in functional connectivity to compensate for an impairment in another process have not been shown in previous literature, but functional MRI research has indicated that increased activity in one brain area may compensate for inefficiency in order to maintain memory performance in healthy ageing [49]. As such, the increased gamma connectivity in the current study may reflect neural compensation to increase attention or improve information binding in individuals with TBI and TBI-MDD. This may reflect neuroplastic recovery following a TBI. The fact that the group with TBI showed a pattern of increased frontal to parietal connectivity while the group with TBI-MDD showed only interhemispheric parietal-temporal connectivity may suggest that the group with TBI performed this compensation more effectively, as frontal-parietal connectivity has been suggested to be important for executive processes underlying WM performance [50–52]. This may explain the lack of behavioural differences in the group with TBI while the group with TBI-MDD showed impaired performance.

The compensation explanation assumes that increased connectivity functions to improve performance. This interpretation has supporting evidence, with increased alpha, beta and gamma fronto-parietal synchronization found to predict individual WM performance [46]. The research by Palva et al. [46] also indicates that increased synchronization occurs for larger WM loads, with maximal synchrony occurring at an individual's WM limit. This could suggest that the increased gamma synchrony in the groups with TBI and TBI-MDD during seven letter WM load retention, but not five letter WM loads, reflects a typical neural process for performance at their WM capacity. This WM capacity may be lower than the healthy control group's due to a disruption to other brain function/s not measured by the current analyses. However, there are also reasons to suspect that increased connectivity could be associated with impaired performance. Although increased gamma connectivity has not previously been associated with pathology, increased gamma power has been found in ADHD, epilepsy and during positive symptoms in schizophrenia [53]. Additionally, higher connectivity in other frequency bands has been detected in a number of groups with different pathologies [13,15,18,22,54,55]. Increases in connectivity found soon after a TBI also return to normal during cognitive recovery [14] and increased connectivity has been found to relate to lower IQ [56]. Additionally, while increased gamma connectivity related to better performance in the control and groups with MDD, there was no relationship between performance and connectivity in the groups with TBI or TBI-MDD.

A more parsimonious (but not necessarily more accurate) explanation is that the increased gamma connectivity in the groups with TBI and TBI-MDD reflects a dysfunction (it is the impairment, rather than a compensation for the impairment). Although no previous research has shown that increased gamma connectivity is related to dysfunction in a pathological condition, several lines of evidence suggest that increased connectivity can reflect impairment. For example, Castallanos et al. [14] found decreased delta and theta connectivity, but increased alpha and beta connectivity post-TBI, which decreased following rehabilitation. Higher connectivity is also detected in a number of groups with different pathologies that exhibit impaired cognitive performance [13,15,18,22,54,55]. Additionally, higher coherence in all bands has been found to relate to lower IQ [56]. Also, from a theoretical perspective, alpha power in the parieto-occipital regions is thought to increase during the retention period of WM tasks in order to disrupt gamma synchronization, so that gamma information binding (reflecting ongoing neuronal

computation) in areas not relevant for WM retention is prevented from impeding the signal from areas that are important for WM retention [57]. As such, the increased gamma connectivity in the groups with TBI and TBI-MDD may reflect a more 'non-relevant' signal during WM retention, which may disrupt activity in the left temporal and inferior frontal regions, important for phonological WM processing [58]. In support of this explanation, previous examination of alpha power in the current data set indicated the group with TBI-MDD showed reduced alpha power in the parieto-occipital regions during WM retention [29].

From this perspective, the relationship between gamma connectivity and performance in the control and group with MDD may be indicative of typical gamma connectivity functioning, during which increased gamma synchronization relates to better WM performance [46]. The increased gamma synchronization in the groups with TBI and TBI-MDD may reflect a dysfunction of typical gamma synchronization (which is usually short range rather than the long range connectivity found in the groups with TBI and TBI-MDD [57]) and as a result the functional benefits to WM performance may be lost. If this interpretation of the increased connectivity in the groups with TBI and TBI-MDD is accurate, it may reflect a maladaptive neuroplastic reorganization that might take place following a DAI [59]. While the scalp connectivity measures might indicate increased gamma connectivity, cognitive processing signal fidelity within the brain may be reduced. Thatcher et al. [56] suggested the association between higher performance and lower connectivity is indicative of more regional specificity, resulting in more complexity in the higher performing brain.

This may reflect a decreased ratio of local gamma activity to long range gamma connectivity to clustering of gamma activity, leading to a reduction in small world network configuration of activity and less efficient processing, similar to that found in patients with schizophrenia during working memory [60]. In terms of information processing in the brain, the increased long range gamma connectivity detected in the groups with TBI and TBI-MDD may reflect more noise and less signal, resulting from an inability to modulate brain activity as effectively in response to task demands in these groups. The result may be a reduced ability to generate regional specificity for cognitive processing [56], leading to lower performance in the group with TBI-MDD.

One issue with the dysfunction interpretation of the increased gamma connectivity in the groups with TBI and TBI-MDD is that behavioural performance was not reduced in the group with TBI. The lack of behavioural differences and connectivity differences in the five letter WM load may reflect a ceiling effect, where the task was not difficult enough to challenge the impaired processes in the group with TBI. However, it may also support the compensation explanation —the increased gamma connectivity compensated sufficiently in the group with TBI to maintain performance, but not in the group with TBI-MDD. Future research should use more difficult tasks in order to determine whether connectivity alterations following TBI relate to cognitive impairments. Additionally, while impaired behavioural performance was found in the group with MDD, no alterations to functional connectivity were shown. This suggests that WM performance impairment in MDD is not related to functional connectivity alterations, so must be explained by alterations to another process—for example impaired generation of upper alpha activity in the parietal regions is a likely candidate [29].

It should also be noted that the two explanations (compensation and dysfunction) are not mutually exclusive. It may be that increased gamma connectivity represents dysfunctional connectivity, driven by a non-adaptive compensatory process in these groups. Regardless of whether increased WM retention gamma connectivity represents compensation or dysfunction, the increases seem to be a marker specific to TBI, appearing in both TBI and TBI-MDD, but not MDD alone. As such, future research should examine increases in gamma connectivity as a potential predictor of TBI and as a potential target for treatment.

There are a number of limitations to the current study. The first limitation is that the four groups could not be completely matched with regards to all potential confounds. In particular, the groups with TBI and TBI-MDD differed in time since injury, so, although the most salient difference between these groups is the presence of MDD, the group with TBI-MDD had longer for neuroplastic recovery. Also, the group with TBI-MDD had fewer years of education than the control group and some participants were medicated. Additionally, a number of participants in both the group with MDD and group with TBI-MDD suffered co-morbid anxiety. However, despite the presence of MDD in one of the groups with TBI and not the other, the difference in years of education, medication, the difference in age and wide age ranges, and the difference in time since injury, both the group with TBI and the group with TBI-MDD showed the same pattern of reduced interhemispheric gamma connectivity, suggesting this pattern is specific to TBI, regardless of variability in other factors. The presence of anxiety in the group with MDD but lack of gamma synchronization changes, in contrast to the lack of anxiety in the group with TBI-only (which did show increased gamma synchronization) suggests that TBI is the factor that caused increased gamma synchronization in the group with TBI-MDD, rather than anxiety. From a signal-to-noise perspective, the common finding between the two groups with TBI, despite variations in other factors, could be viewed as a strength of the study—the signal of increased gamma connectivity following a TBI was strong enough to stand out from the noise of the other factors that varied between these groups, suggesting increased gamma connectivity following a TBI is a finding that may be generalizable.

In addition to the imperfect matching between groups, the study involved an only moderate sample size with unequal group sizes. However, the non-parametric statistics used are robust against unequal group sizes [47] and the sample size in the smallest group matches typical sample sizes in examinations of connectivity following TBI [14] and is almost exactly the sample size that has been recommended for neuroimaging research to ensure enough, but not too much power [61].

The second limitation is that wPLI is a conservative method of measuring phase synchronization, particularly when the phase of synchronization is close to zero [11]. While this is also an advantage of the current study (reducing the likelihood of false positive results due to the volume

conduction of EEG artefacts), it may be that connectivity alterations are present in other bands, but wPLI is too conservative to reveal these alterations. Indeed, previous research has shown reduced theta, alpha and beta coherence during WM in TBI [17]. However, coherence measures are vulnerable to false positive increases in connectivity resulting from volume conduction, so, to ensure the conclusions drawn in the current study are likely to represent true rejections of the null hypothesis, this analysis has been restricted to wPLI. Additionally, the analysis was restricted to between-group effects, as the NBS method is not suited to testing interactions between condition and more than two groups and the research question was focused on between-group differences rather than interactions with memory load.

The third limitation is that the current study was of cross-sectional design. This design was used because of the focus on the group with TBI-MDD, which would have been incredibly difficult to recruit prospectively. However, because the study design was not prospective, it cannot answer the question of causality. Does TBI lead to increased long range gamma WM-related connectivity or are individuals with higher long range gamma WM-related connectivity more likely to sustain a TBI? The authors believe it is unlikely that increased WM related gamma connectivity would increase the probability of suffering a head injury, but prospective studies are required to answer this question. Future research recruiting and testing athletes at high risk of suffering head injury both at the start of a season (pre-injury) and again after some participants suffer head injuries would be a suitable avenue to answer the question of causality. Similarly, longitudinal research would allow researchers to address the question posed by the current results—does the increased WM-related gamma connectivity reflect compensation or dysfunction? If the increased gamma connectivity is not found in early scans, but develops over time in association with improved behavioural performance, then the increased connectivity is likely to reflect compensation rather than dysfunction.

Lastly, conclusions drawn from this study may only be applicable to mild-to-moderate head injury. Although DAI is more likely to occur and be more widespread in severe brain injury (leading to more significant connectivity alterations), severe and open head injuries were excluded from the current study in order to minimize the increased variation that heterogeneous lesion locations would contribute if severe injuries were included.

Conclusions

Previous literature has indicated that increases in functional connectivity between brain regions can be found in individuals with TBI or MDD. The current study extends these findings, indicating that increased inter-hemispheric gamma connectivity is found during seven letter WM load retention in individuals with TBI and TBI-MDD. These increases might reflect dysfunctional connectivity following DAI, resulting in a loss of the benefits to WM performance from increased gamma synchrony. Alternatively, the increased gamma connectivity may reflect compensation for impairment in another process. This study provides the first evidence that TBI may result in changes to WM gamma connectivity between brain regions. Future research may be able to use this information to develop assessments of outcome following TBI and use a connectivity approach to develop novel treatment techniques for TBI.

Declaration of interest

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