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Research Report

Recovery of clinical, cognitive and cortical activity measures following mild traumatic brain injury (mTBI): A longitudinal investigation

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ABSTRACT

The mechanisms that underpin recovery following mild traumatic brain injury (mTBI) remain poorly understood. Identifying neurophysiological markers and their functional significance is necessary to develop diagnostic and prognostic indicators of recovery. The current study assessed 30 participants in the subacute phase of mTBI (10–31 days post-injury) and 28 demographically matched controls. Participants also completed 3 month (mTBI: $N = 21$, control: $N = 25$) and 6 month (mTBI: $N = 15$, control: $N = 25$) follow up sessions to track recovery. At each time point, a battery of clinical, cognitive, and neurophysiological assessments was completed. Neurophysiological measures included resting-state electroencephalography (EEG) and transcranial magnetic stimulation combined with EEG (TMS-EEG). Outcome measures were analysed using mixed linear models (MLM). Group differences in mood, post-concussion symptoms and resting-state EEG resolved by 3 months, and recovery was maintained at 6 months. On TMS-EEG derived neurophysiological measures of cortical reactivity, group differences ameliorated at 3 months but re-emerged at 6 months, while on measures of fatigue, group differences persisted across all time points. Persistent neurophysiological changes and greater fatigue in the absence of measurable cognitive impairment may suggest the impact of mTBI on neuronal communication may leads to increased neural effort to maintain efficient function. Neurophysiological measures to track recovery may help identify both temporally optimal windows and therapeutic targets for the development of new treatments in mTBI.

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1. Introduction

Mild traumatic brain injuries (mTBI's) have been reported to be associated with a wide range of cognitive, behavioural and affective symptoms (Maas et al., 2017). mTBI pathophysiology has been shown to be associated with symptoms via diffuse and dynamic processes (Giza & Hovda, 2014). White matter tracts (bundles of axons that connect neurons in distal brain regions into functional circuits) are particularly vulnerable to a complex spectrum of axonal changes, known as diffuse axonal injury (DAI) (Armstrong et al., 2016). Another important cellular mechanism affected is the excitation-inhibition (E:I) balance, the ratio of excitatory to inhibitory inputs in a neural circuit which has been shown to maintain neural firing and contribute to the induction of plasticity (Eichler and Meier, 2008). Levels of glutamate (the primary excitatory) and GABA (the primary inhibitory) neurotransmitter have been shown to be linked to homeostatic control of the E:I balance. Crucially, this balance is considered to underpin induction of plasticity (Froemke, 2015) and its dysregulation has been linked to cognitive, behavioural and affective symptoms across neurological and neuropsychiatric disorders (Kegeles et al., 2012; Rubenstein and Merzenich, 2003; Yizhar et al., 2011).

Historically, symptoms were thought to be transient after mTBI, with return to pre-injury functioning occurring within 90 days (Rohling et al., 2011). More recent research has reported the presence of persistent symptoms in a subgroup of individuals months to years' post-injury (McInnes et al., 2017). Variability is likely influenced by the dynamic interaction of the initial injury with an individual's neurobiology at the time of injury and across their recovery trajectory, making the evolution of each mTBI potentially unique (Coyle et al., 2018). Developments in neuroimaging have sought to characterise these trajectories, and structural and functional connectivity changes have been demonstrated in acute and chronic mTBI (Eierud et al., 2014; Medaglia, 2017). Associations between symptoms and network connectivity changes have also been demonstrated; however heterogeneity remains a significant hurdle to the development of diagnostic and prognostic indicators of recovery (Coyle et al., 2018). E:I balance dysregulation has also been proposed to contribute to persistent symptoms in mTBI (Guerriero, et al., 2015). Linking these neurophysiological changes with functional consequences over time will help to clarify heterogeneous recovery trajectories, which will potentially assist with identifying individuals at risk of persistent symptoms.

Electroencephalography (EEG) measures of cortical activity have high temporal resolution and are well placed to probe pathophysiology following mTBI. Recording EEG at rest and during cognitive tasks provides information on cortical activity during passive and active information processing and can detect subclinical abnormalities in brain activity related to cognition (Rapp et al., 2015). Impaired coherence (a measure of functional connectivity) has also been demonstrated following mTBI during verbal and visuo-spatial Sternberg tasks during working memory (WM), but not at rest (Kumar et al., 2009). However, cross-sectional designs and significant variability in mean time since injury (ranging between 45 days and 10 years' post-injury) have limited the temporal specificity and generalisability of findings.

TMS combined with EEG is another powerful way to examine brain function. TMS is a form of non-invasive brain stimulation that can be used to measure cortical activity. In the case of TMS-EEG, the application of TMS to the scalp generates a brief perturbation in neural activity which is detected in the EEG activity—this is referred to as a TMS Evoked Potential (TEP). The spread of TEP activation across the scalp provides information about cortical reactivity. Characteristics of TEP's such as amplitude, latency and polarity suggest time locked properties of underlying mechanisms. For example, the P60 and N100 components have been associated with activation of GABAergic mechanisms (Premoli et al., 2014; Rogasch et al., 2013, Rogasch et al., 2015, Belardinelli et al., 2012, Kaarre et al., 2018, Noda et al., 2017), as well as somatosensory and auditory processing of the TMS pulse (Biabani et al. 2019, 2021; Conde et al., 2019; Nikouline et al., 1999). To date, only TMS measures from the motor cortex, referred to as motor evoked potentials (MEPs), have been assessed using a longitudinal design in mTBI. Greater intracortical inhibition, considered to be indicative of a GABAergic response, was reported at 72-h and 2 months' post mTBI (Edwards & Christie, 2017; Miller et al., 2014). Although MEPs provide valuable information on corticospinal excitability and motor function, the diffuse and dynamic nature of mTBI (with predominately a clinical and cognitive symptom profile) highlights the importance of exploring cortical activity outside of the motor cortex in clinically and cognitively relevant brain regions. To summarise, the major limitations of previous EEG and TMS-EEG research in mTBI have included; primarily cross-sectional designs, significant variations in time since injury, and application of TMS solely to the motor cortex.

A comprehensive characterisation of post-injury symptoms, function, neurophysiology, and repeated measurements across time are necessary to improve our understanding of mechanisms of recovery and interactions between pathophysiology and symptoms following mTBI. To address this, we designed a prospective, longitudinal, controlled cohort study that assessed clinical, cognitive and neural measures in individuals <1 month post mTBI (referred to as the sub-acute time point) and at 3 month and 6 month follow up time points. A demographically matched group of control participants with no history of head injury completed the same protocol. Between-group comparisons at the sub-acute timepoint (<4 weeks) have been reported previously (Coyle et al., 2022).

Our previous research examining the same sample as the current study during the sub-acute period (within 4 weeks following the mTBI) showed that the mTBI group reported greater symptom severity in clinical measures from an anxiety and depression scale, fatigue, and post concussive symptoms (Coyle et al., 2022). The study also showed group differences in an auditory recall test. Additionally, during the sub-acute period, the mTBI participants showed increases in resting EEG alpha power that were most pronounced in the right fronto-central region. Finally, during the sub-acute period, the mTBI group showed smaller (more negative) P60 and greater N100 TMS evoked potentials (TEP) amplitudes

from concurrent TMS and EEG recordings (Coyle et al., 2022). These neurophysiological measures may underpin important cognitive functions with relevance for function following a mTBI. In particular, alpha oscillations have been linked to the inhibition of non-relevant brain regions during the completion of cognitive tasks (Jensen & Mazaheri, 2010), and TEPs are broadly considered a measure of cortical reactivity, with the N100 reflecting neural inhibition and the P60 reflecting excitation (Premoli et al., 2014; Voineskos et al., 2019). As such, these measures were used to assess potential clinical symptom, cognitive and neuroplastic recovery over 6 months in the current study. While it is possible that measures that did not show differences during the sub-acute period may have developed differences at later timepoints due to recovery, compensation, or delayed pathology from the mTBI, we focused on the measures that showed differences in our analysis of the sub-acute timepoint as these measures allowed us to track potential recovery trajectories, and in order to minimize the number of multiple comparisons in our study.

In the present study, we report results from 3 to 6 month follow up time points for the measures that were significantly different between mTBI and controls at 4 weeks' post mTBI. The aim was to comprehensively explore recovery by tracking clinical, cognitive and neurophysiological changes at 3- and 6-months' post-injury (referred to in this study as T1 and T2 respectively). Based on past research demonstrating a relationship between symptoms and pathophysiology, we hypothesised that persistent symptoms will be accompanied by persistent pathophysiological changes. To our knowledge this is the first investigation of TMS-EEG in a longitudinal design in mTBI.

2. Material and methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. A total of 58 participants were recruited (30 mTBI, 28 controls). Sample size was determined on an "as many as possible" basis, as the study was a student project and mTBI participants reflect a difficult to recruit population. The 30 participants with mTBI were recruited from the Emergency Department and trauma wards of the Alfred Hospital, Melbourne (mean days since injury = 19.70, SD = 16.96, range 10–31, mean age at injury = 35.43 years, *SD* = 10.31). As such, our sample should be considered to represent a sample of individuals seeking medical care for a mTBI. 28 demographically matched controls with no history of TBI (mean age = 31.65 years, *SD* = 9.06) were also recruited. No participants had a history of seizures, psychiatric or neurological illnesses, unstable medical conditions, were pregnant or taking prescribed medication known to directly or significantly influence EEG findings (exclusion criteria that were established prior to the commencement of participant recruitment). mTBI was classified as exhibiting an initial Glasgow Coma Scale (GCS) score of 13–15, loss of consciousness <30 min and post-traumatic amnesia (PTA) < 24 h (Carroll et al., 2004). Of the 30 mTBI participants, 13 reported a previous mTBI in addition to the mTBI that led to their recruitment into the study. A total of 13 participants also had positive findings in their CT scans, involving haematomas, haemorrhages, or fractures. mTBI injury characteristics are presented in Supplementary Table 1, and demographic and clinical characteristics are shown in Supplementary Table 2. All participants provided written informed consent prior to commencement of study procedures. The study received approval from both Alfred Health and Monash University Ethics Committees.

2.1. Procedure

To investigate the time course of recovery following mTBI, clinical, cognitive and neural assessments were completed in the sub-acute phase, (i.e. within 4 weeks post-injury, after discharge from the hospital), referred to as the sub-acute time point, and at 3 month follow up and a 6 month follow up time points. Control participants completed the same sequence of assessments to enable comparison between the two groups across all time points. See Supplementary Table 1 and Supplementary Fig. 1 for more information on participants who completed each timepoint. In order to focus the analyses conducted from this substantial data set, our apriori data analysis plan was to only include measures that were identified to be dysregulated (i.e. significantly differentiated the groups at the initial sub-acute assessment). Measures are described in detail below.

2.2. Measures

2.2.1. Clinical and cognitive measures

Clinical measures assessed mood (Hospital Anxiety and Depression scale: HADS) (Zigmond & Snaith, 1983), fatigue (Multidimensional Fatigue Inventory: MFI) (Smets et al., 1995) and post concussive symptoms (Rivermead Post Concussive Symptom Questionnaire: RPQ, Rivermead Head Injury Follow-Up Questionnaire: RHFUQ) (Crawford et al., 1996; King et al., 1995). The sub-acute study results showed that mTBI participants reported greater symptom severity on all clinical measures and so all were examined here (Coyle et al., 2022). In the current analyses data from domains of the MFI (General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity) and HADS (Anxiety symptoms and Depressive symptoms) were individually summed to create total fatigue and total mood scores at each time point. This was completed to reduce the number of outcome variables and multiple comparisons. As the RPQ (16-item) and RHFUQ (10- item) are on different scales, a total percentage severity score was calculated to standardise these measures. Cognitive measures included; Wechsler Test of Adult Reading (WTAR) as a measure of pre-morbid IQ, Trail Making Test A and B (TMT-A, TMT-B), subtests from the Wechsler Adult Intelligence Scale-IV (WAIS-IV) Working Memory Index (WMI) and Processing Speed Index (PSI), Brief Visual Memory Test (BVMT), Rey Auditory Verbal Learning Test (RAVLT) and Controlled Word Association Test (COWAT). For memory measures, the RAVLT and BVMT, alternative forms were used at each time point. At the sub-acute time point, after controlling for pre-morbid IQ, group differences were only demonstrated on

total words recalled on trial 1 (T1) of the RAVLT (Coyle et al., 2022), so this was the only cognitive measure included in the current analyses.

2.2.2. *Neural measures*

Neural measures included resting EEG and TMS-EEG. Task related EEG was also collected during a working memory task, however there were no differences found at the sub-acute time point and so this data was not included in the current analyses (Coyle et al., 2022). Resting EEG and TMS-EEG data were processed and analysed offline using EEGLAB (Delorme & Makeig, 2004), TESA (Rogasch et al., 2017) FieldTrip (Oostenveld et al., 2011) and custom scripts on the MATLAB platform (version R2017a). Please see Supplementary Materials for more detailed information on recording and preprocessing of the EEG and TMS-EEG data.

Resting EEG consisted of recording during eyes open (3 min) and eyes closed (3 min) conditions. For oscillatory power computation, EEG data were submitted to a frequency transformation based on fast Fourier transform using the 'mtmfft' method and Hanning taper (from .1 Hz to 100 Hz in steps of .2 Hz) to calculate the average power within four frequency bands: theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz) and gamma (30–45 Hz). Average total power was calculated across all epochs within each frequency band for each time point (sub-acute, T1, and T2) and condition (eyes open and eyes closed), resulting in a single value for each participant, within each frequency band and each time point and each condition at each electrode. In the sub-acute study (Coyle et al., 2022), cluster-based permutation analyses identified group differences for alpha power that were most pronounced in the right fronto-central region, generating a region of interest (ROI) for the current analyses. As only mean alpha power during eyes closed was found to be significantly different between groups at the sub-acute time point, this was the only resting EEG measure included in the current analyses. For statistical analysis of oscillatory power in the current study, non-parametric cluster based permutation statistics assessed differences between groups in eyes closed alpha at each time point separately. Electrodes in the alpha power ROI included; F2, FC2, FC4, FC6, CZ, C2, C4, C6, T8, CP2, CP4, CP6, P2, P8.

TMS-EEG involved administering 100 single TMS pulses with an inter-pulse interval of 4 s (with a 10% jitter). Intensity was 110% of resting motor threshold (RMT) and TMS was applied over the left dorsolateral prefrontal cortex (DLPFC) at the F3 electrode using the 10/20 system of placement. During TMS-EEG, participants listened to white noise through intra-auricular earphones (Etymotic Research, ER3-14A, USA) to limit the influence of auditory processing of the TMS click (Rogasch et al., 2014). The white noise sound level was adjusted for each participant until they reported that background noise was barely audible. TEP analysis focussed on four separate peaks known to occur following stimulation of the prefrontal cortex, the N45, P60, N100 and P200 (Rogasch et al., 2014, 2015). At the sub-acute time point mTBI participants demonstrated smaller (more negative) P60 and greater N100 TEP amplitudes (Coyle et al., 2022). Differences were most pronounced in the left parieto-occipital region for P60 and the right fronto-central region for N100, forming ROI's for the current analyses. Following previous research, the N100 was defined as the amplitude averaged across the window between .09 and .135 sec following the TMS pulse; while the P60 was identified as the mean amplitude occurring between .05 and .07 sec. For statistical analysis, non-parametric cluster-based permutation statistics assessed differences in mean amplitude between groups for each TEP component for each ROI. Electrodes in the P60 ROI cluster included; CP5, P7, P5, P3, P1, PO7, PO3, POZ, O1 and the N100 ROI cluster included; P7, P5, P3, P6, P8, PO7, PO3, POZ, PO4, PO8, O1, OZ, O2.

2.3. *Statistical analyses*

Statistical analyses were performed using R Studio (version 1.1.463) (Team, 2018). To investigate longitudinal change, whilst accounting for the effects of group and time, mixed linear models (MLM's) were applied for each of our clinical, cognitive and neural outcome measures of interest. MLM's are the recommended method of analysing longitudinal data in clinical samples (Garcia & Marder, 2017). They offer a flexible approach that allows for explicit modelling of the non-independence of repeated measures while accounting for missing data. The modelling was conducted including all participants who were tested in the sub-acute phase of the study using the lme4 package (Bates et al., 2015) with the restricted maximum likelihood (REML) approach.

In total 7 MLM's were conducted. Dependent variables were: mean total fatigue (MFI), mood (HADS), post-concussion symptom severity (RPQ), mean total words recalled for RAVLT list learning trial 1, mean alpha power at right fronto-central ROI, P60 at parieto-occipital ROI and N100 amplitude at right fronto-central ROI. Group, time point and their interaction (group*time) were included as fixed effects, and participant was included as a random effect. Additionally, because pre-injury intelligence might influence verbal the effects of verbal learning, we included WTAR scores as an additional fixed effect for the MLM assessing RAVLT scores. Further details of the determination of the effect structure are provided in the supplementary materials, and Table 1 provides a simple depiction of the details of each model.

Due to violations of normality in specific outcome measures, natural log transformations were conducted for all clinical outcome measures and for alpha power. Log transformation can only be applied to positive data. For mean total

Table 1 – Variables included in the linear mixed model analyses.

Variable	Dependent Variable	Predictor Variable
Time		**Yes**
Group		**Yes**
Group * Time		**Yes**
Mean total fatigue	**Yes**	
Mood (HADS)	**Yes**	
Post-concussion Symptom Severity (RPQ)	**Yes**	
Recall (RAVLT)	**Yes**	**WTAR**
Alpha power	**Yes**	
P60	**Yes**	
N100	**Yes**	

mood and PCS the data included 0, so a constant (log (y + 1)) was added to all values. To assist interpretation of the outcome variables that were on log scale, coefficients and confidence intervals were back transformed for presentation in tables and figures. This involved application of the opposite mathematical function used in the log data transformation, in this case [exp(y)]. Untransformed data was used for cognitive and TMS-EEG outcome measures. Finally, we controlled for multiple comparisons across all main effects of group and interactions between group and time (the analyses of primary interest in our study) using the Benjamini-Hochberg false discovery rate (FDR) procedure (Benjamini & Hochberg, 1995), and report these as FDR-p, as well as the initial *p*-values for comparison with other research.

3. Results

58 participants (30 mTBI) were enrolled between Feb. 2017–March 2019. Of these, 48 (21 mTBI) completed 3-month follow-up and 40 (15 mTBI) completed 6-month follow-up assessments. See Supplementary Table 2 and Supplementary Fig. 1 for more information on participants who completed each timepoint. Missing data per outcome measure and time point did not exceed 25% of the total. At baseline and 3-month follow-up, the groups did not differ significantly on measures of sex, age and pre-morbid intelligence (all $p > .05$), however controls had a higher level of education ($p = .035$). At 6-month follow-up, the control group were younger ($p = .04$) and had a higher level of education ($p = .025$).

3.1. Clinical and cognitive measures

For total mood symptoms, fixed effects of group and the interaction between group*3-month follow up significantly predicted total mood symptoms ($p < .05$). When evaluating model significance, a main effect of group [$F_{(1, 52)} = 8.31$, $p = .006$, *FDR-p* = .011] and a trend group*time interaction effect [$F_{(2, 67)} = 2.96$, $p = .058$, *FDR-p* = .062] were demonstrated. Post-hoc comparisons revealed that mTBI had significantly greater mood scores compared to controls ($p < .001$) at the sub-acute time point, but not at 3-month or 6- month follow up (see Fig. 1A and Supplementary Table 3). The model explained 75.2% of the overall variance.

In the total fatigue analysis, the fixed effects of group, the interaction between group*3-month and group*6-month were shown to significantly predict total fatigue ($p < .05$). When evaluating model significance, a main effect of group [$F_{(1, 43)} = 28.17$, $p < .001$, *FDR-p* = .005], time point [$F_{(2, 60)} = 5.56$, $p = .006$] and interaction effect for group*time point [$F_{(2, 60)} = 6.19$, $p = .004$, *FDR-p* = .008] were demonstrated. Post-hoc comparisons revealed that mTBI had significantly greater total fatigue scores at all time points compared to controls ($p < .05$) (see Fig. 1B and Supplementary Table 3). The model explained 71.4% of the overall variance.

For post-concussion symptoms (PCS), the fixed effects of group and interaction between group*3-month and group*6-month follow up were shown to significantly predict total PCS ($p < .05$). When evaluating model significance, a trend towards a main effect of group [$F_{(1, 53)} = 6.65$, $p = .042$, *FDR-p* = .059], significant main effect of time [$F_{(2, 87)} = 6.65$, $p = .002$], and group*time interaction effect [$F_{(2, 89)} = 14.65$, $p < .001$, *FDR-p* = .002] were demonstrated. Post-hoc comparisons revealed that mTBI had significantly greater PCS scores compared to controls at the sub-acute time point, but not at 3-month or 6-month follow up (see Fig. 1C and Supplementary Table 3). The model explained 47.5% of the overall variance.

When investigating verbal learning performance (i.e. RAVLT T1), only the fixed effect of group was shown to significantly predict RAVLT T1 score ($p < .05$). When evaluating model significance, no main effect of group, time or interaction of group*time were demonstrated. For confirmation of sub-acute findings, exploratory contrasts were conducted, which confirmed that mTBI participants recalled fewer words than controls [t (97) = 2.11, $p = .04$] at the sub-acute time point (see Fig. 1D and Supplementary Table 3). The model explained 45.6% of the overall variance.

MLM coefficients and 95% confidence intervals for fixed effects for clinical and cognitive outcome measures are included in Table 2. Model means (geometric means for log transformed outcome measures and estimated marginal means for untransformed outcome measures) are graphically displayed in Fig. 1. Means, standard error (SE) and post-hoc comparisons are included in Supplementary Table 3.

3.2. Neural measures

3.2.1. Resting EEG

For alpha power, the fixed effect of group and 3-month follow up were significant predictors of alpha power ($p < .05$, FDR-$p < .05$) and the interaction between mTBI group*3-month follow up was at trend level [$t(81) = -1.948$, $p = .055$]. When evaluating model significance, a main effect of time was demonstrated [$F_{(2, 80)} = 14.11$, $p < .001$]. Exploratory within group contrasts demonstrated reduced alpha power at 3 and 6 month follow up compared to the sub-acute time point for mTBI participants and reduced alpha power at 3 month follow up compared to the sub-acute time point for control participants (Supplementary Table 5). For confirmation of the sub-acute findings, exploratory between group contrasts demonstrated alpha power at the sub-acute time point was significantly greater for mTBI participants (see Fig. 2A and Supplementary Table 4) The model explained 88% of the overall variance.

3.2.2. TMS-EEG

Single-pulse TMS over left dorsolateral prefrontal cortex (DLPFC) resulted in the expected characteristic series of negative and positive peaks. For the current analyses only P60 and N100 TEP components were investigated (determined by the differences detected at the sub-acute time point).

For P60 amplitude, the fixed effect of group was a significant predictor of P60 amplitude. Evaluation of model significance demonstrated a main effect of group [$F_{(1, 52)} = 14.04$, $p < .001$, *FDR-p* = .002]. Exploratory post hoc comparisons demonstrated that mTBI participants had smaller (more negative) P60 amplitude at the sub-acute time point and T2

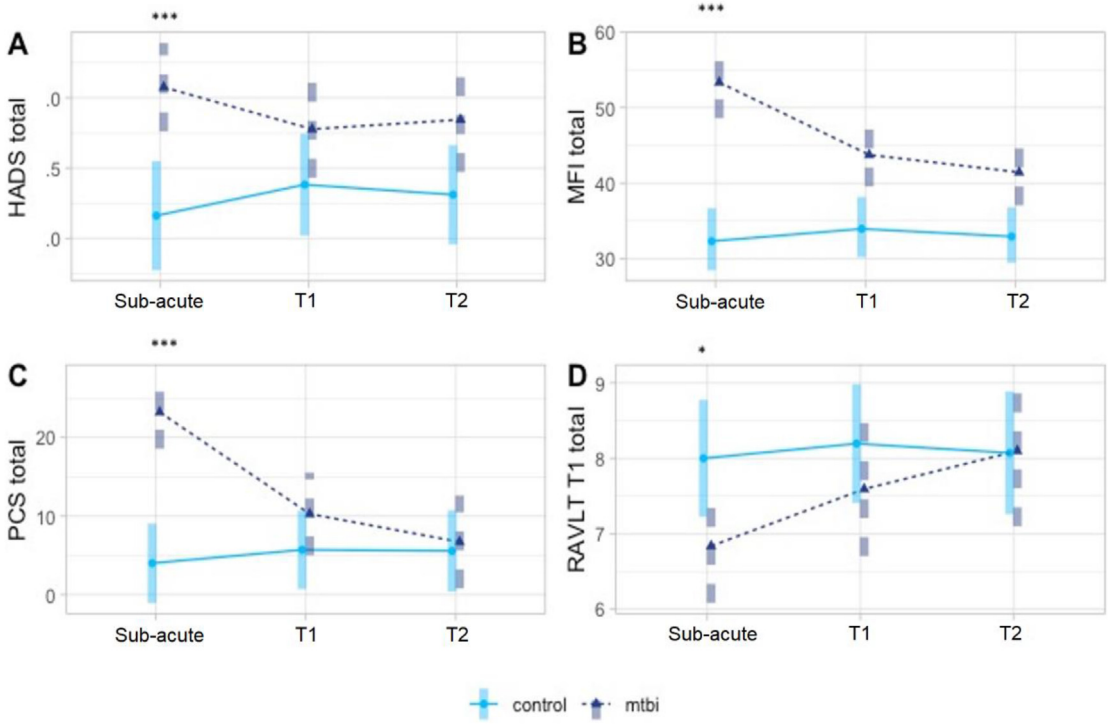


Fig. 1 – Model means by group (control = light blue, mTBI = dark blue) and time point for clinical measures and cognitive measures. A—Hospital Anxiety and Depression Scale (HADS). B—Multidimensional fatigue inventory (MFI). C—Post-concussive symptom (PCS) severity. D—RAVLT trial 1 (RAVLT T1). ***$p < .001$; **$p < .01$; *$p < .05$. Bars indicate 95% confidence intervals.

Table 2 – Regression coefficients and confidence intervals (CI) for each fixed effect from LMM's for clinical and cognitive measures.

Predictors	MFI total (log)		HADStotal [log (y +1)]		PCS total [log (y +1)]		RAVLT Trial 1	
	Estimates	*CI*	*Estimates*	*CI*	*Estimates*	*CI*	*Estimates*	*CI*
Intercept	32.33***	28.56–36.61	3.19***	2.18–4.68	2.99***	1.87–4.77	6.97***	4.13–9.81
3-month f/u	1.05	.93–1.19	1.25	–.91-1.71	1.39	.81–2.39	.20	–.64 - 1.03
6-month f/u	1.02	.90–1.16	1.16	.84–1.60	1.23	.70–2.17	.07	–.78 - .93
mTBI group	1.65***	1.41–1.92	2.50***	1.53–4.08	5.01***	2.66–9.45	–1.16*	–2.24––.08
WTAR							.03	–.04- .09
3-month* mTBI	–.25**	.66–.92	.59*	.39–.91	.17	.08–.38	.56	–.68-1.80
6-month *mTBI	–.27**	–.64 - .90	.68	.43–1.08	.13	–.05- .29	1.19	–.15-2.52
N	46		54		56		54	
Observations	103		120		140		135	
Conditional R^2	.714		.752		.475		.456	

***$p < .001$; **$p < .01$; *$p < .05$.

compared to controls (see Fig. 2C, Supplementary Table 4, and Supplementary Fig. 2). The model explained 40% of the overall variance.

When investigating N100 amplitude, the fixed effect of group was a significant predictor of N100 amplitude. Evaluation of model significance demonstrated a main effect of time [$F_{(2, 82)} = 3.29$, $p = .04$]) and group [$F_{(1, 53)} = 13.24$, $p < .001$, *FDR-p* = .002] but no interaction of group*time ($p > .05$). Exploratory post hoc comparisons demonstrated that mTBI participants had greater (more negative) N100 amplitude at all time points (see Fig. 2D and Supplementary Table 4). No within group differences were demonstrated ($p > .05$). The model explained 70.4% of the overall variance.

MLM coefficients and 95% confidence intervals for fixed effects for neural outcome measures are included in Table 3. Model means (geometric means for log transformed outcome measures and estimated marginal means for untransformed outcome measures) are graphically displayed in Fig. 2. Means, SE and post-hoc comparisons are included in Table Supplementary Table 4.

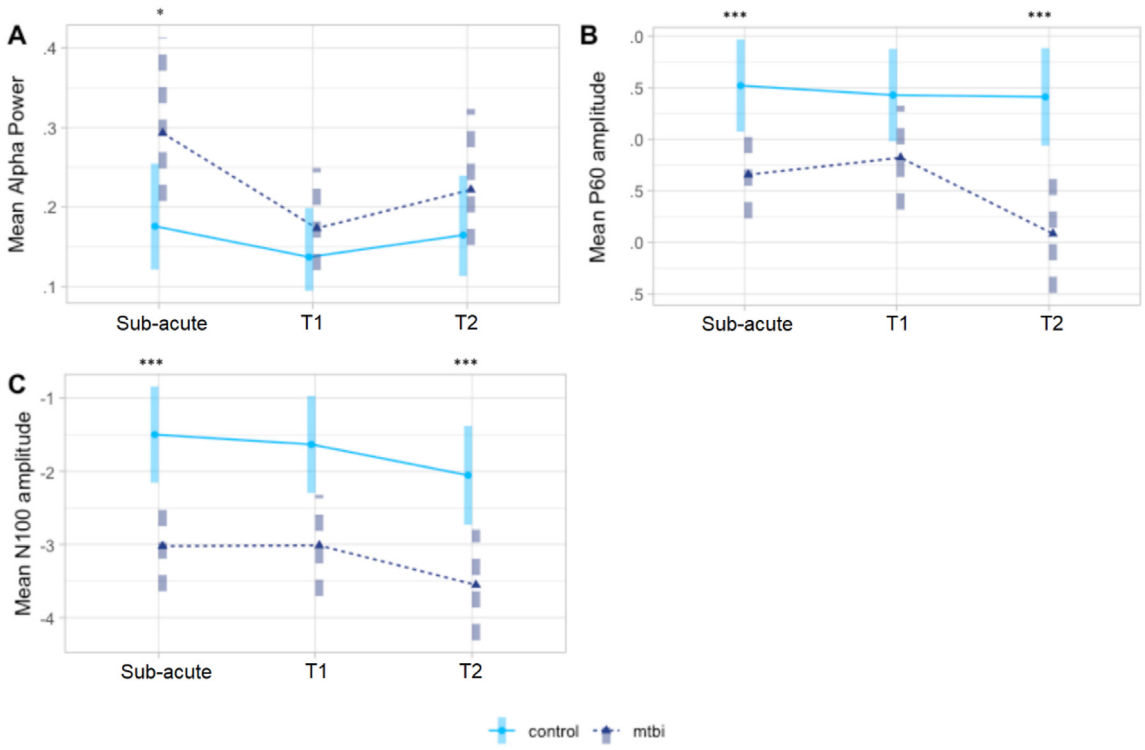


Fig. 2 – Model means by group (control = light blue, mTBI = dark blue) and time point for EEG and TMS-EEG measures. A—Average total alpha power in right fronto-central ROI B—Average P60 amplitude in left parieto-occipital ROI C—Average N100 amplitude in right fronto-central ROI. ***$p < .001$; **$p < .01$; *$p < .05$. Bars indicate 95% confidence intervals.

Table 3 – Regression coefficients and confidence intervals (CI) for each fixed effect from linear mixed effects regression models for neural measures.

	Resting EEG (log)		N100 amplitude		P60 amplitude	
Predictors	*Estimates*	*CI*	*Estimates*	*CI*	*Estimates*	*CI*
Intercept	.18***	.12–.25	−1.50**	−2.14–−.85	.52	.08–.96
3-month f/u	.78*	.65–.94	−.13	−.68 – .42	−.09	−.62-.43
6-month f/u	.94	.77–1.13	−.56	−1.12- .01	−.11	−.65-.44
mTBI group	1.67*	1.01–2.74	−1.52**	−2.41–−.64	−.86**	−1.47–−.26
3-month *mTBI	.76	.58–1.00	.14	−.67 – .96	.26	−.51- 1.03
6-month *mTBI	.81	.60–1.09	.03	−.86 – .91	−.46	−1.29- .37
N	56		56		56	
Observations	139		138		139	
Conditional R^2	.88		.70		.40	

***$p < .001$; **$p < .01$; *$p < .05$.

4. Discussion

The association between clinical and cognitive symptoms and neurophysiological changes following mTBI is poorly understood. The current study used multimodal assessments in a longitudinal design to characterise recovery trajectories. The results showed that on measures of mood, post-concussion symptoms and verbal learning, impairments resolved within 3 months' post-injury. However, greater symptoms of fatigue were reported by the mTBI group across all three time points. For the neural measures, the higher values of resting alpha power seen in the mTBI group at 4 weeks' post-injury were resolved at 3 months with no further changes at 6 months. The P60 TMS-EEG measure at parieto-occipital electrodes demonstrated a similar pattern. Group differences, with mTBI participants demonstrating smaller (more negative) amplitude, were present at 4 weeks' post injury, ameliorated at 3 months, and re-emerged at 6 months. The N100, demonstrated group differences across all three time points, with mTBI participants demonstrating greater (more negative) amplitude.

4.1. *Clinical and cognitive symptom recovery*

Mood and PCS group differences were shown to resolve by 3 months' post-injury, likely reflecting an amelioration of some

acute neurophysiological changes (McKee et al., 2015; Wagner et al., 2021). This is consistent with mTBI literature that has reported that most individuals experience partial or complete symptom resolution within a few weeks to 3 months' post-injury (Rohling et al., 2011). However, our mTBI participants were not completely symptom free at 3 months, with greater fatigue reported and persisting to 6 months' post-injury. Fatigue is a common complaint following neurological insult and has increasingly been recognised following mTBI (Chaudhuri and Behan, 2004). A large longitudinal study reported 68% prevalence of fatigue at 1 week post mTBI, 38% at 3 months and 34% at 6 months (Norrie et al., 2010) and a cross-sectional study reported 33% of their sample experienced severe fatigue at 6 months' post-injury (Stulemeijer et al., 2006, 2010). A possible explanation for persistent fatigue in our mTBI participants is presented by the pattern of results across the cognitive and neural measures. This is discussed below. On a measure of cognitive function that involves information processing, the mTBI group showed impairments at 4 weeks. However, group differences were no longer present at 3 or 6 months' post-injury, suggesting initial verbal learning acquisition deficits had recovered. This is consistent with a systematic review of meta-analyses that have demonstrated the majority of studies report a return to cognitive baseline by 90 days post-injury (Rohling et al., 2011).

4.2. *Neural measures recovery*

Following mTBI, neural measures obtained both while participants were at rest and during response to perturbation with TMS were different between the mTBI and control groups. However, recovery trajectories were somewhat variable across these different measures. mTBI participants' alpha power differences at 4 weeks' post-injury resolved at 3 and 6 month follow up time points. Within group comparisons revealed both groups demonstrated significant alpha power reductions from the first (sub-acute time point) to second session (3 month follow up). However, only mTBI participants demonstrated reductions between the first and third session (6 month follow up), supporting the between group findings that suggest greater alpha power normalises across recovery in mTBI. Alpha power is state and task dependent suggesting it may be vulnerable to environmental stimuli (Bazanova, 2012). Consequently, participants may have become accustomed to the novelty of the laboratory testing environment by the second testing session, resulting in reduced alpha power compared to the first session. Further research establishing the test–retest reliability of alpha power measures in mTBI and healthy controls would be of benefit.

TMS-EEG findings indicated mTBI participants demonstrated smaller (more negative) parieto-occipital P60 TEP amplitude at 4 weeks' post-injury and at 6-month follow up. N100 amplitude was persistently larger (more negative) at all time points. To our knowledge this is the first study to assess TMS-EEG measures in the DLPFC in a longitudinal design in mTBI. P60 is considered a putative marker of excitation and although its functional significance is still being established, research has demonstrated that in response to a paradigm designed to induce inhibition, P60 and N100 modulations are positively correlated (Noda et al., 2017). The authors interpreted these findings as suggestive of an antagonistic or compensatory E: I relationship between the components that represents stable neurophysiological characteristics (Noda et al., 2017). However, other research has suggested that TEPs are significantly influenced by somatosensory and auditory aspects of TMS pulses, and as such the functional relevance of the P60 and N100 is still debated (Biabani et al. 2019, 2021; Conde et al., 2019; Nikouline et al., 1999). Inspection of topoplots demonstrates the pattern of activation is comparable to that in previous research reporting P60 component topography following administration of TMS to the DLPFC (Chung et al., 2018a, 2018b). However, cluster based analyses in our sub-acute study demonstrated P60 group differences were largest in the right parieto-occipital region, which has not previously been reported (Coyle et al., 2022). Furthermore, mTBI participants demonstrated a negative potential during the P60 latency window (see Supplementary Fig. 2). This may reflect dysregulated excitation; however, the paucity of previous research suggests our P60 findings should be interpreted with caution. Alternatively, our N100 findings are consistent with longitudinal studies by Miller et al. (2014) and Edwards and Christie (2017) which reported changes related to inhibitory function in MEPs. As the N100 has been suggested to at least partly reflect measure of $GABA_B$ mediated inhibition and dysregulation is suggestive of changes to GABA-ergic synaptic transmission (Premoli et al., 2014; Rogasch et al., 2013, Rogasch et al., 2015, Belardinelli et al., 2012, Kaarre et al., 2018, Noda 2020).

Magnetic resonance spectroscopy (MRS) has also suggested the N100 reflects a balance between GABA-inhibitory and glutamate-excitatory levels (Du et al., 2018), however using multi-modal tools to investigate the neurobiological mechanisms associated with TEP components warrants further investigation. Cross-sectional research examining TMS-EEG over the DLPFC on average 5 years post-injury also supports our finding of persistent alterations, with greater N100 amplitude being demonstrated in mTBI participants (Tallus et al., 2013). It has previously been proposed that changes to inhibition may be long-term compensatory mechanisms against glutamate excitotoxicity following mTBI (De Beaumont et al., 2012). However, smaller P60 and greater N100 in mTBI suggests the balance is dysregulated in favour of greater inhibition, with potential implications for efficient information processing. Alternatively, it is also possible that differences in the P60 and N100 reflect somatosensory or auditory processing differences (Biabani et al. 2019, 2021; Conde et al., 2019; Nikouline et al., 1999). In summary, the current TEP findings demonstrate altered neural reactivity to TMS pulses following mTBI that persists at 6 months' post-injury. This suggests neurophysiological recovery may be more prolonged than is able to be captured by standard neuropsychological measures.

The TMS-EEG findings suggest persistent altered neural responses, significant differences from healthy controls still being demonstrated 6 months' post mTBI. These changes may reflect alterations to the finely balanced excitation and inhibition of the brain, which is essential for cortical circuit function, and imbalance is thought to lead to inefficient or impaired cognitive function (He & Cline, 2019; Legon et al., 2015). These findings coincide with the persistently elevated

fatigue reported by the participants in our mTBI group, in the presence of normalised cognitive function, and future research should seek to explore these associations further.

The resolution of changes in resting brain activity by 3 months is also of interest. Previous research has hypothesised that compensatory mechanisms during recovery are indicative of the adaptive capacity of neural systems (Dean et al., 2015; Maruishi et al., 2007; Tallus et al., 2013). The brain's capacity to recover and adapt highlights the importance of investigating post-injury plasticity to develop novel approaches to therapeutic intervention. Neuroplasticity mechanisms also offer a possible explanation for variability in our findings across time points, mTBI pathophysiology and compensatory activity uniquely interacting across recovery.

4.3. *Limitations*

Several study limitations should be noted. Firstly, there were challenges related to sample size and characteristics. Attrition bias through the systematic loss of participants across time is a significant complicating factor in most longitudinal clinical research. Our choice of statistical analysis, mixed linear models, mediated information loss by including all available participant data and as such this analysis was more robust to missing data. The possibility that individuals who dropped out may have differed systematically from those who completed all sessions was explored. Analyses demonstrated individuals who did not return for 3 month follow up did not differ on injury severity (as measured by GCS), total mood, fatigue or PCS at the sub-acute time point from those who completed all sessions. Attrition also contributed to a reduced sample size at the 6-month follow up ($N = 15$ in the mTBI group), preventing us from conducting subgroup analyses, such as investigating asymptomatic *vs* symptomatic mTBI participants or positive *vs* negative CT findings. This reduction in sample size also precluded our ability to assess correlations between the neurophysiological measures and the clinical outcome measures, due to the reduced sample size, as our analysis of potential correlations in the sub-acute phase (containing the largest sample size) did not detect any significant correlations (reported in Coyle et al., 2022). While a true lack of any correlation between the neurophysiological differences detected in the mTBI group and clinical/cognitive symptoms is unlikely, the issue of insufficient power to detect potential correlations is even more severe during the recovery timepoints. Similarly, while including covariates in our MLMs might have revealed factors implicated in sub-optimal recoveries, our sample size was too small for us to have confidence in the potential for covariate analysis to reveal these potential relationships. Regarding sample characteristics, it should be noted that our sample included 13 participants who had previously suffered an mTBI, 13 participants who had positive CT findings, and was comprised of individuals seeking medical care after a head injury. As such, our sample may reflect individuals from the more severe end of the mTBI spectrum, as positive CT findings are less common from mTBI, and often people do not seek treatment for an mTBI. Additionally, the control group had a higher level of education than the mTBI group. Although we included pre-morbid IQ as a fixed effect for MLM verbal learning (RAVLT) performance analyses, this difference may have mediated cognitive performance. Furthermore, although alternative forms were used at each time point for cognitive tasks assessing memory, there is the possibility that practice effects may have influenced results for other cognitive measures. Secondly, the study design does not allow us to establish causal mechanisms. Although repeated measures provide information on change over time post-injury, it is possible that group differences may have preceded injury. Alternatively, sleep complaints are common among mTBI patients, and sleep perturbation is known to affect EEG and TMS-EEG measures. As such, sleeping disruptions may offer a potential explanation for our results, and future research should include self-report measures of sleep quality to control for this point. Alternatively, sleep complaints are common among mTBI patients (Raikes et al., 2019), and sleep perturbation is known to affect EEG and TMS-EEG measures (Song et al., 2019, Manganotti et al., 2013). As such, sleeping disruptions may offer a potential explanation for our results, and future research should include self-report measures of sleep quality to control for this point. Thirdly, the application of TMS could be optimised. We used the F3 scalp location as an approximate landmark for the DLPFC, over which single pulse TMS was administered. Although this method has been shown to provide a relatively accurate estimate of the DLPFC (Rusjan et al., 2010) future research utilising MRI-based neuro-navigational software could help to further increase accuracy when targeting this region. Accurate source localisation analyses using individual MRI templates could also improve our understanding of the neuroanatomical bases of our findings.

4.4. *Future directions*

The current findings provide a foundation for future research utilising multimodal investigations to explore recovery in mTBI. Although we have demonstrated the utility of TMS-EEG measures as potential biomarkers for injury and recovery, further research concurrently acquiring information from additional modalities is needed. For example, haemodynamic, microstructural and biochemical changes are relevant following mTBI, highlighting the potential application of concurrent functional magnetic resonance imaging (fMRI), diffusion-weighted or diffusion-tensor imaging (DWI, DTI) and magnetic resonance spectroscopy (MRS) across recovery. A multimodal approach will assist with establishing the functional significance of TEP components, clarifying their diagnostic and prognostic utility and linking changes in excitation and inhibition to functional and structural connectivity. It is also necessary to conduct investigations with larger sample sizes to comprehensively explore variability in recovery trajectories. Lastly, future research should aim to extend the current study by identifying specific treatment targets and therapeutic windows. Neuromodulation for clinical and therapeutic applications to promote recovery in mTBI has previously been proposed and the present findings offer a significant step forward in this regard (Hoy et al., 2019; Li et al., 2015). Longitudinal multimodal approaches with sufficient power will improve our understanding of optimal neural targets and therapeutic windows and potentially help to identify individuals at risk of persistent symptoms.

5. Conclusions

These findings suggest mTBI dysregulates the dynamic equilibrium that underpins efficient neuronal communication and greater effort is required to maintain function. Substantially contributing to our understanding of neurophysiological changes across recovery post mTBI, our study highlights that on sensitive neurophysiological and fatigue measures, persistent alterations are present during the sub-acute phase through to at 6 months' post-injury. In particular, our TMS-EEG measures of putative excitatory and inhibitory functions indicated persistent changes up to 6 months' post-injury, and these changes were concurrent with higher levels of fatigue in the mTBI group. Variability across recovery may also be reflective of the interaction between mTBI pathophysiology and compensatory activity. Comprehensively characterising the multifaceted nature of recovery across time has significant potential to optimise the development of interventions. Future research should aim to improve our understanding of temporally optimum windows and therapeutic targets and link functionally relevant neuroplastic changes to persistent symptoms.

Author contribution

Hannah L Coyle: Conceptualization, Data curation, Formal Analysis, Investigation, Resources, Methodology, Formal Analysis, Interpretation, Visualization, Writing – Original Draft. Neil W Bailey: Supervision, Investigation, Methodology, Formal Analysis, Interpretation, Writing – Review and Editing. Jennie Ponsford: Supervision, Writing – Review and Editing. Kate E Hoy: Conceptualization, Supervision, Investigation, Methodology, Formal Analysis, Interpretation, Writing – Review and Editing, Resources, Project administration, Funding acquisition.

Author disclosure statement

All authors declare that no competing financial interests exist.

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Data and code availability statement

We do not have ethical approval to make this data publicly available, as our approval predated our inclusion of such approvals (which we now do routinely). In order to obtain access to the data ethics committee approval and a data sharing agreement would be required. Readers seeking access to the analytic code can contact the owner: Dr Hannah Coyle, coylehannah@gmail.com.

Materials availability statement

Legal copyright restrictions prevent public archiving of the clinical and cognitive tests used in this research. These tests can be obtained from the copyright holders in the cited references.

Preregistration

No part of the study procedures or analysis plans was preregistered prior to the research being conducted.

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Supplementary data

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REFERENCES

Armstrong, R. C., Mierzwa, A. J., Marion, C. M., & Sullivan, G. M. (2016). White matter involvement after TBI: Clues to axon and myelin repair capacity. *Experimental Neurology, 275*(3), 328–333.

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software, 67*(1), 48.

Bazanova, O. (2012). Comments for current interpretation EEG alpha activity: A review and analysis. *Journal of Behavioral and Brain Science, 2*(2), 239–248.

Belardinelli, P., König, F., Liang, C., Premoli, I., Desideri, D., Müller-Dahlhaus, F., & Ziemann, U. (2012). TMS-EEG signatures of glutamatergic neurotransmission in human cortex. *Scientific Reports, 11*(1), 1–14.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, 289–300.

Biabani, M., Fornito, A., Mutanen, T. P., Morrow, J., & Rogasch, N. C. (2019). Characterizing and minimizing the contribution of sensory inputs to TMS-evoked potentials. *Brain Stimulation, 12*(6), 1537–1552.

Biabani, M., Mutanen, T., Fornito, A., & Rogasch, N. (2021). Characterizing direct cortical responses to TMS. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 14*(6), 1750–1751.

Carroll, L. J., Cassidy, D., Peloso, P., Borg, J., Von Holst, H., Holm, L., Paniak, C., & Pépin, M. (2004). Prognosis for mild traumatic brain injury: Results of the WHO collaborating Centre task force on mild traumatic brain injury. *Journal of Rehabilitation Medicine: Official Journal of the UEMS European Board of Physical and Rehabilitation Medicine*, (43 Suppl), 84–105.

Chaudhuri, A., & Behan, P. O. (2004). Fatigue in neurological disorders. *The Lancet, 363*(9413), 978–988.

Chung, S. W., Rogasch, N. C., Hoy, K. E., Sullivan, C. M., Cash, R. F. H., & Fitzgerald, P. B. (2018a). Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance. *Human Brain Mapping, 39*(2), 783–802.

Chung, S. W., Sullivan, C. M., Rogasch, N. C., Hoy, K. E., Bailey, N. W., Cash, R. F. H., & Fitzgerald, P. B. (2018b). The effects of individualised intermittent theta burst stimulation in the prefrontal cortex: A TMS-EEG study. *Human Brain Mapping*.

Conde, V., Tomasevic, L., Akopian, I., Stanek, K., Saturnino, G., Thielscher, A., Bergmann, T. O., & Siebner, H. R. (2019). The non-transcranial TMS-evoked potential is an inherent source of ambiguity in TMS-EEG studies. *Neuroimage, 185*, 300–312.

Coyle, H. L., Bailey, N. W., Ponsford, J., & Hoy, K. E. (2022). *Clinical symptoms, cognitive performance and cortical activity following mild traumatic brain injury (mTBI)*. MedRxiv.

Coyle, H. L., Ponsford, J., & Hoy, K. E. (2018). Understanding individual variability in symptoms and recovery following mTBI: A role for TMS-EEG? *Neuroscience and Biobehavioral Reviews, 92*.

Crawford, S., Wenden, F. J., & Wade, D. T. (1996). The Rivermead head injury follow up questionnaire: A study of a new rating scale and other measures to evaluate outcome after head injury. *Journal of Neurology, Neurosurgery, and Psychiatry, 60*(5), 510–514.

De Beaumont, L., Henry, L. C., & Gosselin, N. (2012). Long-term functional alterations in sports concussion. *Neurosurgical Focus Other Titles: NSF, 33*(6), 1–7.

Dean, P. J. A., Sato, J. R., Vieira, G., McNamara, A., & Sterr, A. (2015). Multimodal imaging of mild traumatic brain injury and persistent postconcussion syndrome. *Brain and Behavior, 5*(1), 45–61.

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods, 134*(1), 9–21.

Du, X., Rowland, L. M., Summerfelt, A., Wijtenburg, A., Chiappelli, J., Wisner, K., Kochunov, P., Choa, F.-S., & Elliot Hong, L. (2018). TMS evoked N100 reflects local GABA and glutamate balance. *Brain Stimulation, 11*(5), 1071–1079.

Edwards, E. K., & Christie, A. D. (2017). Assessment of motor cortex excitability and inhibition during a cognitive task in individuals with concussion. *Brain Injury, 31*(10), 1348–1355.

Eichler, S. A., & Meier, J. C. (2008). E-I Balance and human diseases – from molecules to networking. *Frontiers in Molecular Neuroscience, 1*, 2.

Eierud, C., Cameron Craddock, R., Fletcher, S., Aulakh, M., King-Casas, B., Kuehl, D., & LaConte, S. M. (2014). Neuroimaging after mild traumatic brain injury: Review and meta-analysis. *Neuroimage Clinical, 4*, 283–294.

Froemke, R. C. (2015). Plasticity of cortical excitatory-inhibitory balance. *Annual Review of Neuroscience, 38*, 195–219.

Garcia, T. P., & Marder, K. (2017). Statistical approaches to longitudinal data analysis in neurodegenerative diseases: Huntington's disease as a model. *Current Neurology and Neuroscience Reports, 17*(2), 14.

Giza, C. C., & Hovda, D. A. (2014). The new neurometabolic cascade of concussion. *Neurosurgery, 75*, 24–33.

Guerriero, R. M., Giza, C. C., & Rotenberg, A. (2015). Glutamate and GABA imbalance following traumatic brain injury. *Current Neurology and Neuroscience Reports, 15*(5), 27.

He, H. Y., & Cline, H. T. (2019). What is excitation/inhibition and how is it regulated? A case of the elephant and the wisemen. *Journal of Experimental Neuroscience, 13*, Article 1179069519859371.

Hoy, K. E., McQueen, S., Elliot, D., Herring, S. E., Maller, J. J., & Fitzgerald, P. B. (2019). A pilot investigation of repetitive transcranial magnetic stimulation for post-traumatic brain injury depression: Safety, tolerability, and efficacy. *Journal of Neurotrauma, 36*(13), 2092–2098.

Jensen, O., & Mazaheri, A. (2010). Shaping functional architecture by oscillatory alpha activity: Gating by inhibition. *Frontiers in Human Neuroscience, 4*, 186.

Kaarre, O., Äikiä, M., Kallioniemi, E., Könönen, M., Kekkonen, V., Heikkinen, N., & Laukkanen, E. (2018). Association of the N100 TMS-evoked potential with attentional processes: A motor cortex TMS–EEG study. *Brain and Cognition, 122*, 9–16.

Kegeles, L. S., Mao, X., Stanford, A. D., Girgis, R., Ojeil, N., Xu, X., Gil, R., Slifstein, M., Abi-Dargham, A., Lisanby, S. H., & Shungu, D. C. (2012). Elevated prefrontal cortex γ-aminobutyric acid and glutamate-glutamine levels in schizophrenia measured in vivo with proton magnetic resonance spectroscopy. *Archives of General Psychiatry, 69*(5), 449–459.

King, N. S., Crawford, S., Wenden, F. J., Moss, N. E. G., & Wade, D. T. (1995). The Rivermead post concussion symptoms questionnaire: A measure of symptoms commonly experienced after head injury and its reliability. *Journal of Neurology, 242*(9), 587–592.

Kumar, S., Rao, S. L., Chandramouli, B. A., & Pillai, S. V. (2009). Reduction of functional brain connectivity in mild traumatic brain injury during working memory. *Journal of Neurotrauma, 26*(5), 665–675.

Legon, W., Punzell, S., Dowlati, E., Adams, S. E., Stiles, A. B., & Moran, R. J. (2015). Altered prefrontal excitation/inhibition balance and prefrontal output: Markers of aging in human memory networks. *Cerebal Cortex*.

Li, S., Zaninotto, A. L., Neville, I. S., Paiva, W. S., Nunn, D., & Fregni, F. (2015). Clinical utility of brain stimulation modalities following traumatic brain injury: Current evidence. *Nephrology, Dialysis, Transplantation, 11*, 1573–1586.

Maas, A. I., Menon, D. K., Adelson, P. D., Andelic, N., Bell, M. J., Belli, A., Bragge, P., Brazinova, A., Büki, A., Chesnut, R. M., & Citerio, G. (2017). Traumatic brain injury: Integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology, 16*(12), 987–1048.

Manganotti, P., Formaggio, E., Del Felice, A., Storti, S. F., Zamboni, A., Bertoldo, A., … Toffolo, G. M. (2013). Time-frequency analysis of short-lasting modulation of EEG induced by TMS during wake, sleep deprivation and sleep. *Frontiers in Human Neuroscience, 7*, 767.

Maruishi, M., Miyatani, M., Nakao, T., & Muranaka, H. (2007). Compensatory cortical activation during performance of an attention task by patients with diffuse axonal injury: A functional magnetic resonance imaging study. *Journal of Neurology, Neurosurgery, and Psychiatry, 78*(2), 168–173.

McInnes, K., Friesen, C. L., MacKenzie, D. E., Westwood, D. A., & Boe, S. G. (2017). Mild traumatic brain injury (mTBI) and chronic cognitive impairment: A scoping review. *PLos One, 12*(4), 1–19.

Medaglia, J. D. (2017). Functional neuroimaging in traumatic brain injury: From nodes to networks. *Frontiers in Neurology, 8*, 407.

Miller, N. R., Yasen, A. L., Maynard, L. F., Chou, L. S., Howell, D. R., & Christie, A. D. (2014). Acute and longitudinal changes in motor cortex function following mild traumatic brain injury. *Brain Injury, 28*(10), 1270–1276.

Nikouline, V., Ruohonen, J., & Ilmoniemi, R. (1999). The role of the coil click in TMS assessed with simultaneous EEG. *Clinical Neurophysiology, 110*(8), 1325–1328.
Noda, Y., Zomorrodi, R., Cash, R. F. H., Barr, M. S., Farzan, F., Rajji, T. K., Chen, R., Daskalakis, Z. J., & Blumberger, D. M. (2017). Characterization of the influence of age on GABA(A) and glutamatergic mediated functions in the dorsolateral prefrontal cortex using paired-pulse TMS-EEG. *Aging, 9*(2), 556–572.
Norrie, J., Heitger, M., Leathem, J., Anderson, T., Jones, R., & Flett, R. (2010). Mild traumatic brain injury and fatigue: A prospective longitudinal study. *Brain Injury, 24*(13–14), 1528–1538.
Oostenveld, R., Fries, R., Maris, E., & Schoffelen, J. M. (2011). FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational Intelligence and Neuroscience, 2011*, 9.
Premoli, I., Castellanos, N., Rivolta, D., Belardinelli, P., Bajo, R., Zipser, C., Espenhahn, S., Heidegger, T., Müller-Dahlhaus, F., & Ziemann, U. (2014). TMS-EEG signatures of GABAergic neurotransmission in the human cortex. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience, 34*(16), 5603–5612.
Raikes, A. C., Satterfield, B. C., & Killgore, W. D. (2019). Evidence of actigraphic and subjective sleep disruption following mild traumatic brain injury. *Sleep Medicine, 54*, 62–69.
Rapp, P. E., Keyser, D. O., Albano, A., Hernandez, R., Gibson, D. B., Zambon, R. A., Hairston, W. D., Hughes, J. D., Krystal, A., & Nichols, A. S. (2015). Traumatic brain injury detection using electrophysiological methods. *Frontiers in Human Neuroscience, 9*(11).
Rogasch, N. C., Daskalakis, Z. J., & Fitzgerald, P. B. (2015). Cortical inhibition of distinct mechanisms in the dorsolateral prefrontal cortex is related to working memory performance: A TMS–EEG study. *Cortex; A Journal Devoted To the Study of the Nervous System and Behavior, 64*, 68–77.
Rogasch, N. C., Thomson, R. H., Farzan, F., Fitzgibbon, B. M., Bailey, N. W., Hernandez-Pavon, J. C., Daskalakis, Z. J., & Fitzgerald, P. B. (2014). Removing artefacts from TMS-EEG recordings using independent component analysis: Importance for assessing prefrontal and motor cortex network properties. *Neuroimage, 101*, 425–439.
Rogasch, N. C., Sullivan, C., Thomson, R. H., Rose, N. S., Bailey, N. W., Fitzgerald, P. B., Farzan, F., & Hernandez-Pavon, J. C. (2017). Analysing concurrent transcranial magnetic stimulation and electroencephalographic data: A review and introduction to the open-source TESA software. *Neuroimage, 147*, 934–951.
Rogasch, N. C., Thomson, R. H., Daskalakis, Z. J., & Fitzgerald, P. B. (2013). Short-latency artifacts associated with concurrent TMS–EEG. *Brain Stimulation, 6*(6), 868–876.
Rohling, M. L., Binder, L. M., Demakis, G. J., Larrabee, G. J., Ploetz, D. M., & Langhinrichsen-Rohling, J. (2011). A meta-analysis of neuropsychological outcome after mild traumatic brain injury: Re-analyses and reconsiderations of Binder et al. (1997), Frencham et al. (2005), and Pertab et al. (2009). *The Clinical Neuropsychologist, 25*(4), 608–623.
Rubenstein, J. L., & Merzenich, M. M. (2003). Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior, 2*(5), 255–267.
Rusjan, P. M., Barr, M. S., Farzan, F., Arenovich, T., Maller, J. J., Fitzgerald, P. B., & Daskalakis, Z. J. (2010). Optimal transcranial magnetic stimulation coil placement for targeting the dorsolateral prefrontal cortex using novel magnetic resonance image-guided neuronavigation. *Human Brain Mapping, 31*(11), 1643–1652.
Smets, E. M. A., Garssen, B., de Bonke, B., & De Haes, J. C. J. M. (1995). The multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *Journal of Psychosomatic Research, 39*(3), 315–325.
Song, P., Lin, H., Li, S., Wang, L., Liu, J., Li, N., & Wang, Y. (2019). Repetitive transcranial magnetic stimulation (rTMS) modulates time-varying electroencephalography (EEG) network in primary insomnia patients: A TMS-EEG study. *Sleep Medicine, 56*, 157–163.
Stulemeijer, M., van der Werf, S., Bleijenberg, G., Biert, J., Brauer, J., & Vos, P. E. (2006). Recovery from mild traumatic brain injury: A focus on fatigue. *Journal of Neurology, 253*(8), 1041–1047.
Stulemeijer, M., Vos, P. E., van der Werf, S., Van Dijk, G., Rijpkema, M., & Fernández, G. (2010). How mild traumatic brain injury may affect declarative memory performance in the post-acute stage. *Journal of Neurotrauma, 27*(9), 1585–1595.
Tallus, J., Lioumis, P., Hämäläinen, H., Kähkönen, S., & Tenovuo, O. (2013). Transcranial magnetic stimulation-electroencephalography responses in recovered and symptomatic mild traumatic brain injury. *Journal of Neurotrauma, 30*(14), 1270–1277.
Team, R. C. (2018). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing.
Voineskos, D., Blumberger, D. M., Zomorrodi, R., Rogasch, N. C., Farzan, F., Foussias, G., Rajji, T. K., & Daskalakis, Z. J. (2019). Altered transcranial magnetic stimulation–electroencephalographic markers of inhibition and excitation in the dorsolateral prefrontal cortex in major depressive disorder. *Biological Psychiatry, 85*, 477–486.
Wagner, A. K., Franzese, K., Weppner, J. L., Kwasnica, C., Galang, G. N., Edinger, J., & Linsenmeyer, M. (2021). 43 - traumatic brain injury. In D. X. Cifu (Ed.), *Braddom's physical medicine and rehabilitation* (6th ed., pp. 916–953.e19). Elsevier.
Yizhar, O., Fenno, L. E., Prigge, M., Schneider, F., Davidson, T. J., O'shea, D. J., Sohal, V. S., et al. (2011). Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature, 477*(7363), 171–178.
Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67*(6), 361–370.