BRAIN COMMUNICATIONS

On the time-course of functional connectivity: theory of a dynamic progression of concussion effects

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The current literature presents a discordant view of mild traumatic brain injury and its effects on the human brain. This dissonance has often been attributed to heterogeneities in study populations, aetiology, acuteness, experimental paradigms and/or testing modalities. To investigate the progression of mild traumatic brain injury in the human brain, the present study employed data from 93 subjects (48 healthy controls) representing both acute and chronic stages of mild traumatic brain injury. The effects of concussion across different stages of injury were measured using two metrics of functional connectivity in segments of electroencephalography time-locked to an active oddball task. Coherence and weighted phase-lag index were calculated separately for individual frequency bands (delta, theta, alpha and beta) to measure the functional connectivity between six electrode clusters distributed from frontal to parietal regions across both hemispheres. Results show an increase in functional connectivity in the acute stage after mild traumatic brain injury, contrasted with significantly reduced functional connectivity in chronic stages of injury. This finding indicates a non-linear time-dependent effect of injury. To understand this pattern of changing functional connectivity in relation to prior evidence, we propose a new model of the time-course of the effects of mild traumatic brain injury on the brain that brings together research from multiple neuroimaging modalities and unifies the various lines of evidence that at first appear to be in conflict.

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Abbreviations: EEG = electroencephalography; ERP = event-related potential; FC = functional connectivity; mTBI = mild traumatic brain injury; WPLI = weighted phase-lag index

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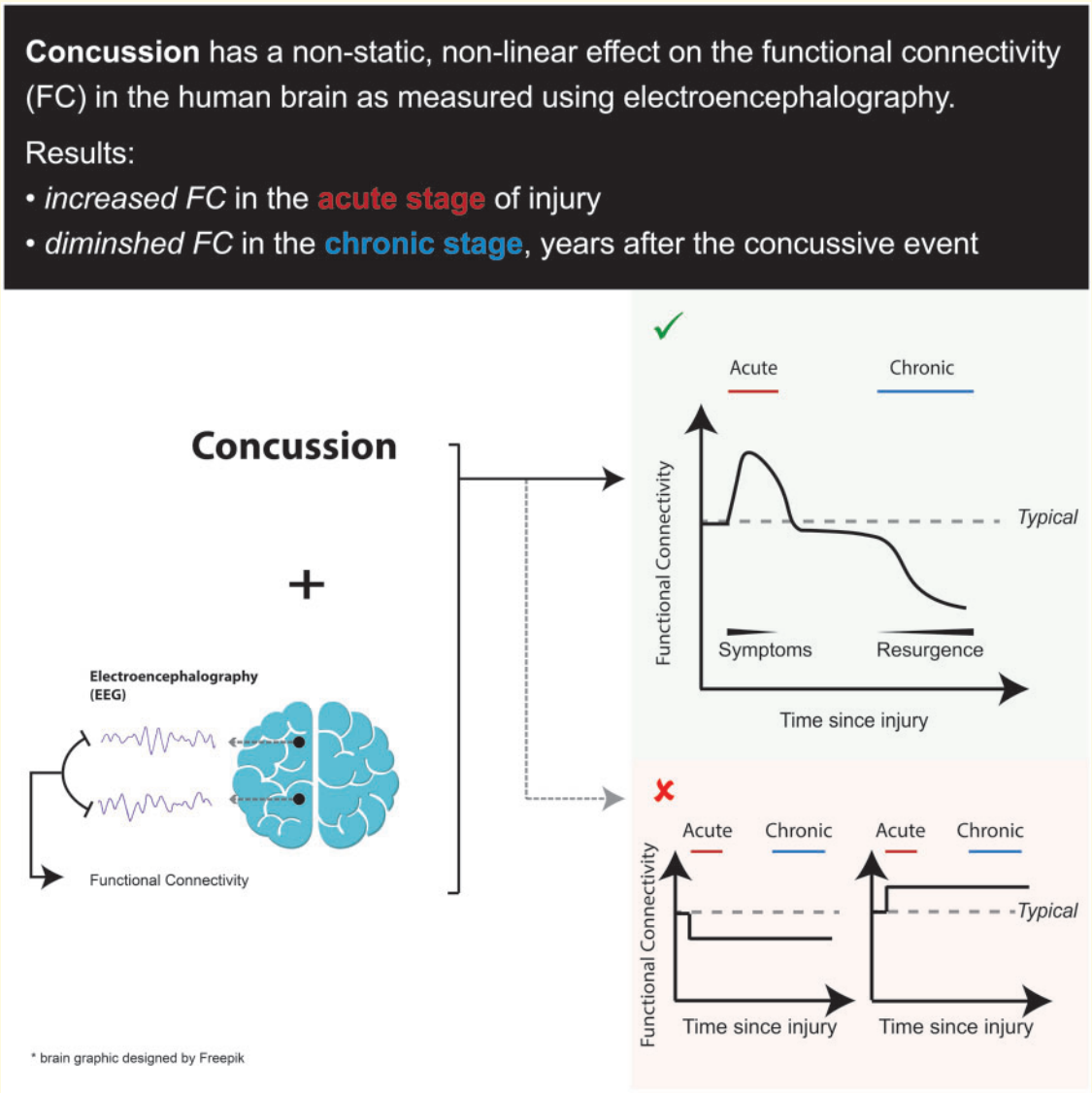
Graphical Abstract



Introduction

Concussions, also termed mild traumatic brain injury (mTBI; Kay *et al.*, 1993), can prove difficult to detect using common brain imaging methods (e.g. computed tomography and magnetic resonance imaging) due to their predominantly functional effects on the brain. Work spanning a multitude of testing modalities supports a connection between concussions and multiple forms of cognitive dysfunction (McCrory *et al.*, 2017). With increasing awareness of the condition, concussion diagnosis is at an unprecedented high (Langer *et al.*, 2020); however, clinical practices for identification, treatment and management remain inadequate (Broglio *et al.*, 2007, 2017). Refinements in assessment tools have predominantly targeted the disentanglement of concussion's constellation of symptoms. Several methodologies have shown promise, such as eye movements (Heitger *et al.*, 2009; Johnson *et al.*, 2012), balance assessments (Broglio *et al.*, 2017), functional brain imaging (McAllister *et al.*, 2001) and electrophysiology (Broglio *et al.*, 2009; De Beaumont *et al.*, 2009; Ruiter *et al.*, 2019). In the last category, event-related potentials (ERPs) as recorded with electroencephalography (EEG) were shown to be altered following concussion (Gaetz *et al.*, 2000; Gosselin *et al.*, 2006; De Beaumont *et al.*, 2007; Broglio *et al.*, 2011). ERPs are widely studied in the literature, and the parameters (i.e. latency, amplitude and topography) of a particular ERP component in response to specific stimulation designs are seen to index a cognitive function neurophysiologically. The extent of ERP alterations after concussion was demonstrated to correlate with number of hits

to the head, severity of injury and time elapsed since injury (De Beaumont *et al.*, 2007; Broglio *et al.*, 2011). Most prominent in concussion research, the N2b—indexing executive control and response inhibition—and the P300—associated with attention, orientation, and memory—have been shown to be particularly affected after insult, either in response latency, amplitude, or both (Gosselin *et al.*, 2006; De Beaumont *et al.*, 2007, 2013; Broglio *et al.*, 2009; Ruiter *et al.*, 2019). The association between these ERPs and specific cognitive processes has provided a valuable tool to pinpoint the functional and cognitive effects of concussion that have been reported to linger after symptom resolution (Gosselin *et al.*, 2006; De Beaumont *et al.*, 2007; Baillargeon *et al.*, 2012). However, it remains unclear how the effects of concussion progress over the years following injury.

Most findings on the neurophysiological effects of concussion to date describe an attenuation or delaying of brain responses (Gosselin *et al.*, 2006; De Beaumont *et al.*, 2007, 2013; Broglio *et al.*, 2009; Ruiter *et al.*, 2019). Contrary to these findings, several studies have reported hyperactivation post-injury during mentally taxing tasks (McAllister *et al.*, 2001). These opposing findings have been attributed to heterogeneities in study populations, aetiology, acuteness, experimental paradigms and others, none of which have been conclusive. There exists a need for an investigation specifically into these disagreements to assess whether the present understanding of concussion may be expanded to account for and explain these opposing reports.

Increase in activation post-injury has been posited to result from the allocation of extra resources to compensate for the damage (McAllister *et al.*, 2001; Iraji *et al.*, 2016). This compensatory mechanism is argued to reflect the discrepancy often found between behavioural assessments and neurological measurements from electrophysiology (De Beaumont *et al.*, 2009, 2012; Ruiter *et al.*, 2019) and functional hemodynamics (McAllister *et al.*, 2001; Hocke *et al.*, 2018). Subsequently, the notion of a cognitive reserve (Kesler *et al.*, 2003; Stern, 2009; Broglio *et al.*, 2012) has been hypothesized to explain the overall neurocognitive decline in previously concussed individuals through aging (De Beaumont *et al.*, 2009, 2012; Broglio *et al.*, 2012; Broglio, 2017). According to the cognitive reserve theory, a previously injured brain loses the ability to sustain its compensatory mechanisms with age, resulting in an abnormal aging process with a resurgence of symptoms and other cognitive deficits (De Beaumont *et al.*, 2009, 2012; Broglio *et al.*, 2012; Broglio, 2017). For the purposes of the present study, we define three broad stages of concussion progression: (i) 'acute', denoting the time directly after injury and extending to 4 weeks after wherein the primary symptoms of mTBI are most apparent, (ii) 'post-acute', pertaining to the time after the acute stage to late-stage symptom resurgence, during which the behaviourally observable symptoms of mTBI appear to be most resolved but underlying pathology is reportedly still observed in ERP work and (iii) 'chronic', referring to the state of injury decades after insult where the behaviourally observable effects of concussion have been reported to resurface, typically seen in the late adulthood. Notably, these stages are built primarily around notions of clinically observable deficits and self-reports and secondarily on neurophysiological reports of concussion. Moreover, it is not understood, which aspects of cognition are irreparably affected and whether clinical intervention may prevent or delay the onset of what is defined above as the chronic stage.

While there is consensus that brain function is altered following concussion in the acute stage, there has been little work clarifying the progression of post-concussive effects throughout aging and the relationship between those effects to observable symptomatology. Consolidation of results from different imaging methods is also minimal in the literature. The notion that neurophysiological sequelae of concussion progress in a non-linear fashion is not new. Increased functional connectivity (FC; defined below) has been reported directly after a concussive episode followed by a return to normal levels 30 days after injury (Zhu *et al.*, 2015). Similar findings were reported in the literature where tests in the acute phase revealed a hyperconnected brain (Nakamura *et al.*, 2009; Shumskaya *et al.*, 2012; Messé *et al.*, 2013; Bharath *et al.*, 2015; Sours *et al.*, 2015; Iraji *et al.*, 2016; Bernier *et al.*, 2017), whereas tests conducted after the acute stage of injury had elapsed showed reduced FC (Robinson *et al.*, 2015; Hocke *et al.*, 2018), and one study reported no effect of mTBI on FC (Churchill *et al.*, 2017). These studies utilized a wide array of brain imaging methodologies and experimental protocols, including recording brain activity in resting-state designs or under active cognitive load induced by different tasks.

FC, as opposed to structural connectivity, broadly describes statistically correlated activity and synchronization between brain regions (Bastos and Schoffelen, 2016). This correlated activity can be due to information transmission between communicating brain regions, or simply due to different brain regions contributing to a common task. In EEG analysis, FC can be measured using a variety of methods, each contributing different information about how brain activity is synchronized across regions (Vinck *et al.*, 2011; Bastos and Schoffelen, 2016; Blain-Moraes *et al.*, 2016). These can be computed across EEG sensors or estimated brain sources and can describe temporally correlated changes in the power spectrum or phase coupling. Two complementary methods are used in this study: magnitude-squared coherence and the weighted phase-lag index (WPLI). Both of these methods have been widely used in the literature to describe non-directed connections between two signals (i.e., they do not specifically indicate which signal influences the other; see the 'Materials and methods' section).

FC as measured using EEG has been investigated for application in mTBI with several reports of deficits

observed in resting-state EEG after concussion (Cao and Slobounov, 2010); however, the effects of post-acute mTBI on resting-state EEG have been questioned (Nuwer *et al.*, 2005). Related work on more severe TBI showed a reduced FC effect that was unique to a working memory task, as opposed to resting state (Kumar *et al.*, 2009). This work raised the issue that FC effects in mTBI might require an active cognitive load for the separation to be observed, a hypothesis that is compatible with fMRI research on mTBI (McAllister *et al.*, 2001; Johnson *et al.*, 2012, 2015). To date, no prior studies have been conducted to investigate the progression of neurphysiological FC effects of mTBI using EEG during active cognitive tasks. Moreover, there is limited work attempting to connect the effects observed in EEG/ERP measures to the neuroimaging literature, which places a greater emphasis on FC. Here, we show that functional brain connectivity observed in EEG at different time periods following concussion provides valuable information on how concussion impacts brain activity over time.

In the present article, we investigate the effects of concussion on brain connectivity, as well as the development of these effects from youth into late adulthood. The study employed experiments designed to elicit canonical ERPs studied in concussion research (the N2b and P300) to examine a cognitively taxed brain using event-related FC. The study examined two hypotheses. First, in accordance with prior literature (Kumar *et al.*, 2009), we expected a comparison between concussed subjects and age-matched controls to reveal a difference in FC. Second, we postulated that, while some changes in connectivity would normalize after the acute stage, there would remain differences in FC between concussed subjects in the chronic stage and their age-matched controls. Separate ANOVAs were run for each type of coherence and WPLI measures calculated between six clusters of electrodes to convey different categories of FC (Fig. 1; see the 'Materials and methods' section). FC was assessed across the main canonical EEG frequency bands and investigated the effects of group (control vs. concussed) and cohort (young vs. old). Evidence of effects during the post-acute stage of concussion was used from separate studies and compared in the discussion. In addition to presenting our experimental findings, we propose a new theory of the effects of concussion on the brain that integrates cognitive reserve theory to explain how our data can be synthesized with the evidence found within the existing neuroscientific literature on mTBI to understand how concussion affects the brain over the lifespan.

Materials and methods

Participants

To investigate the progression of FC changes from acute concussion to late after injury, data were collected from a total of 93 participants (48 controls) split across two age-groups in a cross-sectional manner (see Table 1). Data were collected as part of independent studies conducted using the same set of EEG/ERP paradigms as defined below.

Acute (AC) dataset

The first cohort comprised 26 participants (19 females) with an average age of 15.4 years that had sustained a head injury. All concussed participants were clinically diagnosed with a concussion and were subsequently tested an average of 20.15 days after injury. Data from 28 healthy participants (average 19.2 years; 22 females) acted as a control group for the AC cohort.

Chronic (CH) dataset

A total of nineteen male retired football athletes were recruited with an average age of 57.6 years. The retired athletes played an average of 7.84 years in the Canadian Football League (CFL), self-reported an average of 4.05 previous concussions and indicated an average of 28.11 years between day of testing and the last reported head injury. A group of 20 healthy individuals (all males; mean age = 53.7) acted as controls for this cohort.

All control participants reported no history of neurological disorders or head injury. All subjects reported normal hearing and provided written consent prior to participating in the study. The study was approved by the Hamilton Integrated Research Ethics Board (HiREB; Ontario, Canada) and was in accordance with the ethical standards of the Declaration of Helsinki.

EEG stimuli

Each subject completed two separate EEG/ERP protocols designed to examine brain responses in both active and passive task conditions separated by a distractor task (Ruiter *et al.*, 2019). Only data from the active protocol, presented first, were used in the present study. The protocol was a multi-deviant auditory-oddball task adapted from (Todd *et al.*, 2008). The standard tone (Std) was a 1000-Hz pure-tone presented at 80-dB sound pressure level (SPL) for 50 ms. Three different tones, each similar to the Std in all but one sound characteristic, were presented as deviants within the standard tone sequence: frequency deviant (FDev; 1200 Hz), duration deviant (DDev; 100 ms) and intensity deviant (90 dB SPL). Standard tones were presented 492 times (82%) while each of the deviants was presented 36 (6%) times for a total of 600 stimulus presentations. Participants were tasked to actively attend to the tones and respond by pressing one button to standards and another button for all deviants. All segments with incorrect responses were discarded from further analysis. Technical issues rendered intensity deviants unusable in the AC recordings; thus, to facilitate

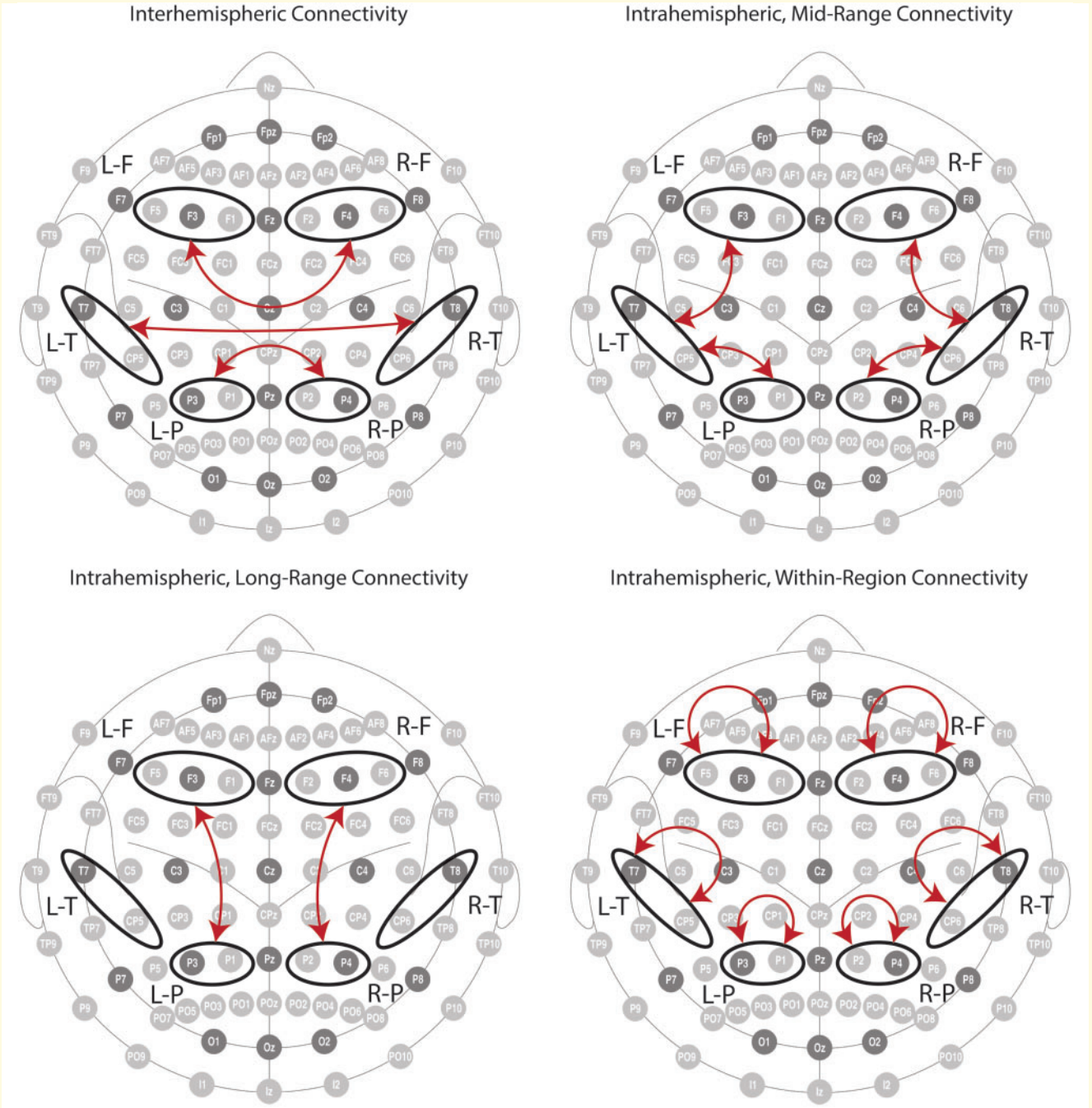


Figure 1 Connectivities and electrode clusters: different connectivity types and their respective electrode clusters as defined and adapted from Kumar *et al.* (2009).

comparisons between the two age groups, responses to intensity deviants were discarded for all further analysis.

EEG procedure

Participants were seated in a dimly lit and sound-attenuated room. Noise-cancelling earphones (Etymotic ER-2) were used to deliver all binaural auditory stimuli. Participants were instructed to fixate on a cross placed in the centre of a computer monitor as they responded using two buttons to auditory stimulation as described above. Buttons were counterbalanced between participants. Presentation of all stimuli and respective EEG markers was done using Presentation software (NeuroBehavioral Systems; NBS). The protocol used for this study lasted a total of 10 min in addition to a break halfway through presentation. Participants were instructed to switch buttons for the second half of the protocol.

Table 1 Patient information for both cohorts including sex, number of previous concussions at the time of testing and self-reported symptomatology as measured by the Post-Concussion Symtpom Scale

Cohort	Participant	Sex	# previous concussions	Symptomatology at time of testing
AC	1	F	6	109
	2	F	0	55
	3	F	1	54
	4	M	2	20
	5	M	2	64
	6	M	2	33
	7	F	2	35
	8	F	6	94
	9	F	1	92
	10	F	1	67
	11	F	1	50
	12	M	5	101
	13	F	1	41
	14	F	4	24
	15	F	3	58
	16	F	0	17
	17	F	1	12
	18	M	2	46
	19	F	1	53
	20	M	1	55
	21	F	0	59
	22	F	2	60
	23	F	2	80
	24	F	1	55
	25	M	1	32
	26	F	1	66
CH	27	M	7	9
	28	M	1	4
	29	M	2	17
	30	M	2	4
	31	M	4	52
	32	M	2	7
	33	M	11	12
	34	M	3	5
	35	M	2	14
	36	M	8	27
	37	M	6	11
	38	M	2	17
	39	M	3	13
	40	M	3	25
	41	M	4	27
	42	M	2	0
	43	M	3	1
	44	M	1	9
	45	M	11	13

EEG recording

Continuous EEG was recorded from 64 Ag/AgCl active electrodes using the Biosemi ActiveTwo system. Electrodes were placed according to the extended 10–20 system using an elastic cap and referenced online to the driven right leg circuit. Data from five external electrodes were recorded: two electrodes were placed separately to record eye movements placed above and over the outer canthus of the left eye, two electrodes on the mastoid processes and one on the tip of the nose. Data from all electrodes were digitized at 512 Hz and passed through a 0.01–100-Hz bandpass filter.

EEG data preprocessing

Offline, data were passed through a 0.1–30-Hz (24 dB/oct) filter in addition to a 60 Hz notch filter. Using visual inspection, all segments containing non-ocular artefacts were marked for deletion. Independent component analysis was conducted on the remaining continuous data, and components correlated with either external electrode placed around the left eye were removed. Following data cleaning, the EEG signals were re-referenced to the averaged mastoids and segmented for all experimental conditions from 200 ms before stimulus onset to 1000 ms after. All segments were baseline-corrected (−200 to 0 ms) before separating segments by condition and exporting to binary files for connectivity analysis. All the prior steps were conducted using Brain Vision Analyzer (v2.1; Brain Products GmbH).

Connectivity analysis

We perform our analyses using two complementary measures of FC: one that expresses amplitude-related synchronization and one that expresses synchronization in phase space.

Magnitude-squared coherence, or simply coherence, is a measure of FC that describes the degree of linear similarity between two signals (in our case, two channels) in terms of their power spectrum (Nolte *et al.*, 2004; Murias *et al.*, 2007; Kumar *et al.*, 2009). Specifically, it is the normalized magnitude-squared cross-spectral density of two signals in a given frequency band f and thus primarily describes amplitude-related synchronization. Coherence is calculated as

$$C_{xy}(f) = \frac{P_{xy}(f)^2}{P_{xx}(f)P_{xy}(f)}, \quad (1)$$

where P_{xy} is the cross-spectral density of two signals x and y and P_{xc} and P_{yy} are their respective power spectral densities. However, unlike WPLI, coherence is susceptible to influence from volume conduction and noise (Vinck *et al.*, 2011; Bastos and Schoffelen, 2016).

WPLI is a measure of FC that provides information primarily about phase-synchronization and is designed to be robust to influence from volume conduction and noise Vinck2011—all features that are crucial to channel-space analysis of EEG. WPLI is calculated using the imaginary component of the cross-spectrum, which we denote as $\mathrm{Im}C_{xy}(f)$, and which gives the phase-synchronization between two signals. It is then weighted by its sign, $\mathrm{sign}(\mathrm{Im}C_{xy}(f))$, which indicates which of the two signals leads or lags in phase-space. Putting these together, WPLI is calculated as follows:

$$\mathrm{WPLI} = \frac{E\{\mathrm{Im}C_{xy}(f)\}}{E\{|\mathrm{Im}C_{xy}(f)|\}} = \frac{E\{\mathrm{Im}C_{xy}(f)\mathrm{sign}(\mathrm{Im}C_{xy}(f))\}}{E\{|\mathrm{Im}C_{xy}(f)|\}}. \quad (2)$$

We assessed brain connectivity as measured in sensor space by computing pairwise FC for regions of interest that were defined similarly to Kumar *et al.* (2009). Fourteen electrodes were clustered based on their topographical location: laterally on the right (R) and left (L) hemispheres; and caudally at the frontal (F), temporal (T) and parietal (P) regions (see Fig. 1). The six clusters of 2–3 electrodes each were L-F (F3, F5 and F1); R-F (F4, F2 and F6); L-T (T7 and CP5); R-T (T8 and CP6); L-P (P3 and P1); and R-P (P4 and P2). Using the six clusters, four categories of connectivity were defined:

- Interhemispheric: described connections between the left and right hemispheres and was split to frontal (between R-F and L-F), temporal (between R-T and L-T) and parietal (between R-P and L-P).
- Intrahemispheric, long range: defined connections that spanned from the frontal region to the parietal region within the same hemisphere. In the right hemisphere, they were defined as all combinations between R-F and R-P, whereas in the left hemisphere they were connections between L-F and L-P.
- Intrahemispheric, mid range: described fronto-temporal and temporo-parietal connections in both hemispheres. In the frontal region: left fronto-temporal (between L-T and L-F) and right fronto-temporal (between R-T and R-F). In the parietal region: left temporo-parietal (between L-T and L-P) and right temporo-parietal (between R-T and R-P).
- Intrahemispheric, within region: contained all pairwise comparisons within each electrode cluster described above.

For each category of connectivity, WPLI and coherence were calculated between each electrode pair for each experimental condition using Python MNE (Gramfort *et al.*, 2013). Connectivity was assessed across five canonical, non-overlapping EEG bands: delta (1–4 Hz), theta (4.5–8 Hz), alpha (8.5–14 Hz) and beta (14.5–23 Hz). The spectral densities were estimated using the Morlet wavelet with central frequencies $f_i \in 1, 2, \ldots, 23$ and corresponding cycles $c_i = \min(0.75 \times f_i, 7)$. FC values were averaged for the duration spanning between stimulus onset and 800 ms after.

Statistical analysis

Statistical analyses were adapted from (Kumar *et al.*, 2009) and modified to reduce the number of multiple comparisons. Mixed-effects analysis of variance (ANOVA; $\alpha = 0.01$) was used to examine whether concussion affected brain connectivity as measured by the WPLI and coherence independently. Separate univariate ANOVAs were run for each type of connectivity and spectral band such that the dependent variable was the connectivity metric (WPLI or coherence) to investigate the effect of group (2 levels: control and concussed), condition (three levels: Std, FDev and DDev), site (as described above for each connectivity category) and cohort (two levels: young and old). In cases of Sphericity violations (assessed using Mauchly's test), Greenhouse–Geisser estimates of epsilon were used to correct for the degrees of freedom. In instances of significant interactions, Bonferroni-corrected *post hoc* analyses were conducted to investigate the effect.

Data availability

All connectivity data from both groups and cohorts in addition to the R code used to conduct all statistical analyses in the present study are publicly available at https://github.com/boshra/Connectivity_Analysis.

Results

Coherence

Coherence was heavily influenced by cohort differences. This manifested as a significant main effect of cohort as well as a reliable effect of cohort × condition interaction in all connectivity types across all frequency bands when observing coherence (see Table 2). These effects are omitted for brevity from the detailed results below.

Interhemispheric

The cohort × site interaction was observed for coherence in all frequency bands ($P < 0.01$; Table 2). For WPLI, a significant group × cohort interaction was observed only in the theta band ($P < 0.01$; Fig. 2).

Intrahemispheric, long range

A significant cohort × site interaction was observed for coherence in all bands ($P < 0.01$; Table 2). In addition, a significant 3-way interaction of group × cohort × site manifested in delta ($P < 0.01$) and theta ($P < 0.01$). WPLI analysis indicated a significant group × cohort interaction in the theta band ($P < 0.01$; Fig. 2). In addition, in theta, a group × site interaction was significant ($P < 0.01$). *Post hoc* analysis in both bands showed that in the CH cohort, FC was lower in the left hemisphere than in the right hemisphere.

Intrahemispheric, mid range

Results indicated a significant group × cohort interaction in coherence for the delta and theta bands ($P < 0.01$; see Table 2). In WPLI, a main effect of cohort was found in delta ($P < 0.01$) and theta ($P < 0.01$). A significant group

Table 2 ANOVA tables for the connectivity types and bands for the WPLI and coherence values

Predictor	df Num	df Den	Delta band				Theta band				Alpha band				Beta band			
			Coherence		WPLI		Coherence		WPLI		Coherence		WPLI		Coherence		WPLI	
			F	*P*	*F*	*P*	*F*	*P*	*F*	*P*	*F*	*P*	*F*	*P*	*F*	*P*	*F*	*P*
Interhemisphere connectivity																		
Group	1	89	2.84	0.095	0.42	0.518	2.2	0.142	0.37	0.547	0.28	0.598	1.98	0.163	0.06	0.813	1.06	0.306
Cohort	1	89	2012	0	0.81	0.372	2507.94	0	2.32	0.131	1525.23	0	0.44	0.511	2084.18	0	1.24	0.269
Group × cohort	1	89	4.92	0.029	2.26	0.137	6.7	0.011	7.36	0.008	2.99	0.087	1.85	0.178	0.58	0.448	0.51	0.476
Group × condition	2	178	1.21	0.299	0.07	0.927	0.01	0.993	0.7	0.491	0.39	0.67	1.52	0.223	1.86	0.16	1.42	0.245
Cohort × condition	2	178	79.27	0	1.61	0.204	104.6	0	0.43	0.643	84.59	0	0.77	0.459	187.81	0	1.52	0.222
Group × site	2	178	0.76	0.467	0.66	0.516	1.01	0.362	0.21	0.772	0.86	0.418	0.49	0.585	1.81	0.173	0.74	0.461
Cohort × site	2	178	55.43	0	1.3	0.274	208.11	0	1.31	0.27	335.65	0	2.26	0.116	471.64	0	0.33	0.69
Group × cohort × condition	2	178	0.48	0.621	2.03	0.136	0.36	0.693	0.05	0.943	0.9	0.404	1.44	0.24	1.6	0.206	0.54	0.581
Group × cohort × site	2	178	0.1	0.899	0.32	0.723	0.72	0.481	1.17	0.305	1.29	0.276	0.86	0.41	1.07	0.337	0.31	0.7
Intrahemisphere—long connectivity																		
Group	1	89	0.67	0.417	0.98	0.324	1.71	0.194	1.59	0.21	0.11	0.746	2.3	0.133	0.04	0.848	2.43	0.123
Cohort	1	89	594.03	0	0	0.944	1439.51	0	0.54	0.463	420.39	0	1.38	0.243	962.4	0	0.34	0.564
Group × cohort	1	89	2.63	0.108	4.18	0.044	5.21	0.025	8.09	0.006	4.79	0.031	0.81	0.37	1.13	0.255	1.84	0.178
Group × site	1	89	0.22	0.637	1.43	0.234	0.06	0.809	7.06	0.009	0.72	0.399	0.39	0.533	2.21	0.14	0.05	0.828
Cohort × site	1	89	10.45	0.002	1.54	0.218	13.06	0	3.92	0.051	20.51	0	0.02	0.898	26.29	0	0.55	0.459
Group × cohort × site	1	89	8.14	0.005	5.21	0.025	7.03	0.009	1.11	0.295	1.73	0.192	0.01	0.932	0.33	0.565	3.27	0.074
Group × condition	2	178	0.87	0.414	0.11	0.887	1.92	0.153	1.94	0.149	0.11	0.879	1.09	0.333	0.31	0.725	0.19	0.81
Cohort × condition	2	178	110.46	0	0.1	0.896	77.89	0	3.21	0.046	6.37	0.003	0.79	0.441	84.93	0	0.69	0.492
Group × cohort × condition	2	178	0.47	0.616	2.03	0.136	0.35	0.686	4.08	0.02	0.44	0.621	0.6	0.531	0.34	0.705	0.16	0.842
Intrahemisphere—mid connectivity																		
Group	1	89	1.69	0.197	0.8	0.372	0.52	0.473	0.06	0.809	0.41	0.523	1.56	0.215	0.09	0.767	0.5	0.482
Cohort	1	89	1100.06	0	8.1	0.006	1806.52	0	26.98	0	918.3	0	5.6	0.02	1831.18	0	0.57	0.454
Group × cohort	1	89	8.64	0.004	10.16	0.002	10.33	0.002	16.26	0	4.84	0.03	2.83	0.096	2.45	0.121	3.47	0.066
Group × condition	2	178	1.3	0.273	0.22	0.797	0.64	0.526	0.3	0.738	1.26	0.284	2.72	0.076	1.38	0.255	0.1	0.895
Cohort × condition	2	178	106.73	0	0.35	0.698	94.76	0	3.57	0.03	42.9	0	0.25	0.753	284.13	0	1.57	0.212
Group × site	3	267	2.67	0.062	2.78	0.062	0.52	0.608	0.7	0.514	1.17	0.318	0.37	0.736	2.33	0.095	1.69	0.177
Cohort × site	3	267	0.24	0.823	9.83	0	0.19	0.839	10.9	0	8.92	0	2.1	0.112	46.14	0	3.74	0.016
Group × cohort × condition	2	178	1.04	0.354	4.8	0.01	0.4	0.668	0.4	0.671	0.43	0.638	0.35	0.674	1.44	0.24	3.13	0.05
Group × cohort × site	3	267	3.65	0.021	4.87	0.008	0.68	0.519	0.66	0.536	0.26	0.818	0.7	0.525	1.74	0.175	0.64	0.569
Intrahemisphere—within connectivity																		
Group	1	89	0.83	0.363	1.15	0.287	0.21	0.645	0.14	0.713	0.8	0.374	2.36	0.128	0.18	0.674	0.79	0.376
Cohort	1	89	2795.02	0	37.52	0	4992.42	0	48.11	0	5638.83	0	11.11	0.001	5539.13	0	3.07	0.083
Group × cohort	1	89	23.35	0	14.47	0	16.68	0	14.86	0	10.29	0.002	4.61	0.035	7.04	0.009	7.13	0.009
Group × condition	2	178	3.8	0.025	0.45	0.635	0.48	0.62	0.07	0.936	1.15	0.317	2.63	0.077	1.01	0.363	0.1	0.899
Cohort × condition	2	178	115.97	0	0.13	0.874	191.83	0	2.37	0.097	129.43	0	0.09	0.903	411.19	0	0.61	0.542
Group × site	5	445	0.71	0.584	0.65	0.624	1.28	0.28	2.15	0.073	1.35	0.258	1.61	0.174	0.73	0.538	2.31	0.064
Cohort × site	5	445	22.66	0	2.53	0.041	57.63	0	8.34	0	52.7	0	1.82	0.127	76.4	0	2.22	0.073
Group × cohort × condition	2	178	1.09	0.337	4.66	0.011	0.11	0.892	0.27	0.766	0.14	0.861	0.5	0.602	1.39	0.251	2.44	0.092
Group × cohort × site	5	445	0.77	0.542	1.3	0.27	1.59	0.18	2.1	0.079	0.85	0.472	1.21	0.305	0.23	0.886	2.78	0.031

× cohort interaction was found in delta and theta ($P < 0.01$; Fig. 2B). An additional cohort × site interaction was observed in delta and theta ($P < 0.01$). *Post hoc* analysis in both bands showed that FC in the AC cohort measured between FT-L and FT-R was higher than between TP-L and TP-R. That effect was reversed in the older CH cohort. The two 3-way interactions (group × cohort × condition and group × cohort × site) were found significant in the delta band ($P < 0.01$). Investigation of the first interaction showed that the group × cohort interaction was not observable to standard tones (see the 'Materials and methods' section). *Post hoc* analysis of the second interaction showed that FC observed from FT-L showed a significant effect of group as well as a reliable group × cohort interaction in TP-L and TP-R.

Within region

Analysis of coherence yielded significant group × cohort and cohort × site interactions in all bands ($P < 0.01$). An additional group × condition was observed in delta ($P < 0.05$). For WPLI, a main effect of cohort was found in all but the beta band ($P < 0.01$), whereas a group × cohort interaction was observed in all bands but alpha ($P < 0.01$; Fig. 2). The cohort × site interaction was significant in the theta band ($P < 0.01$). *Post hoc* analysis showed FC to be larger in the AC cohort compared to the CH cohort in all but the frontal sites (L-F and R-F).

Discussion

Our results introduce new evidence illustrating the evolution of the effects of mTBI on the human brain over

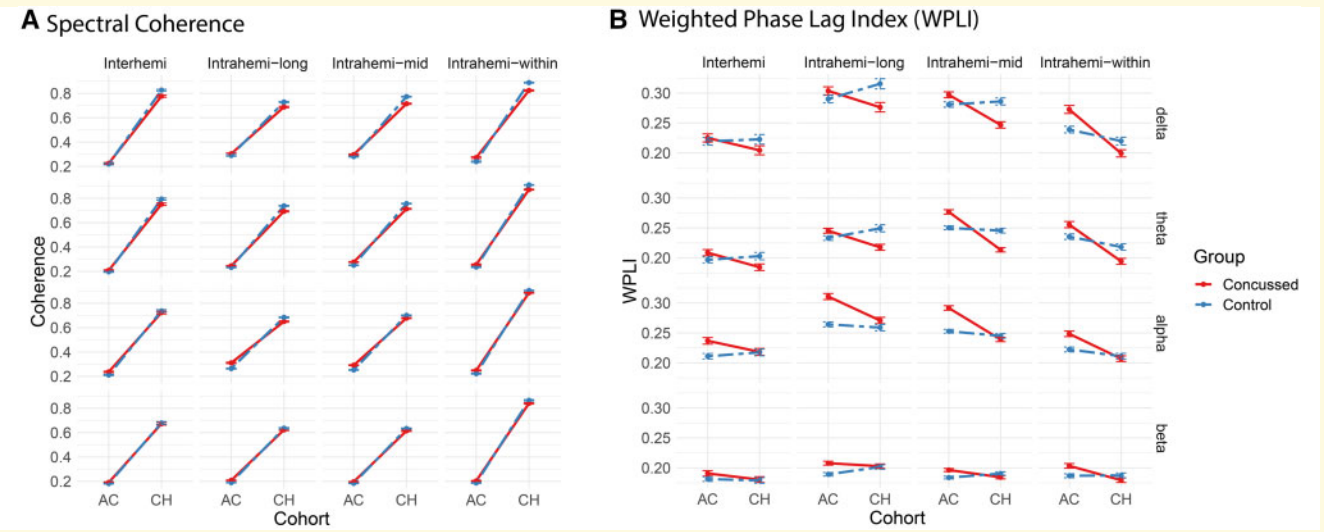


Figure 2 Group × cohort interaction: the figure shows the group × cohort interaction over different connectivity types as seen across the four bands in spectral coherence (**A**) and weighted phase-lag index (**B**). Error bars represent the 95% confidence intervals.

time. We show that while an increase in connectivity from baseline may follow from concussion soon after injury, a reversal towards reduced connectivity may in part characterize the long-term effects (see Fig. 2). In light of these findings, we argue for a critical component of our hypotheses: the effects of mTBI on the brain are dynamic and must be contextualized by how long the brain has been adapting to them. Concordantly, the interaction between history of concussion and cohort (age) had a significant effect on FC, while the fact that concussion had taken place in the past did not, in and of itself, prove to be significant.

Our results showed the group × cohort interaction to be strongest in the theta band as well as in delta and alpha to a lesser extent (see Table 2 and Fig. 2). Different EEG bands are typically coupled with a number of cognitive activities; however, such links are non-specific and tend to vary across subjects (e.g., alpha peaking at different frequencies for different individuals; Klimesch 1999; Trammell *et al.*, 2017). Furthermore, the literature reports EEG frequency changes throughout the normal aging process, which is likely to interact dynamically with a history of mTBI (Trammell *et al.*, 2017). Overall, band-specific results, particularly in mTBI, are reportedly inconsistent in the literature, rendering interpretations rather tenuous with the current data (Nuwer *et al.*, 2005).

Whether FC was measured with coherence to capture power synchronization or with WPLI, to capture phase synchronization, the chronically concussed group showed a widespread reduction in FC. While this result appears to conflict with a previous study (Kumar *et al.*, 2009), the findings may in fact be complimentary. Notably, Kumar *et al.* found reduced FC in concussed individuals an average of 2–3 months since last concussion. When comparing more recently concussed individuals (an average of just 21 days post-injury) with controls, we instead found increased levels of FC. One possible explanation is that there may be a sharp increase in FC shortly after injury, followed by a decrease in FC below pre-injury levels, a finding supported by longitudinal imaging studies (Zhu *et al.*, 2015; Iraji *et al.*, 2016). However, another explanation is that Kumar *et al.*'s study included individuals who suffered from more severe brain injuries than concussion that resulted in observable anatomical abnormalities (12 out of 30 subjects), which have been linked to severe decreases in FC (Davey *et al.*, 2000).

A new model of mTBI

We propose a nuanced view of the progressive effects of mTBI on the human brain. Specifically, we posit a model of the dynamic effects of mTBI on event-related FC that accounts for stage of injury (acute, post-acute and chronic), age and task-related cognitive load. A diagram of the theorized model, its three stages and corresponding effects are illustrated in Fig. 3. We describe our model in terms of its three stages below.

In the acute stage of the model, the brain enters a state of hyperactivity and hyperconnectivity immediately after injury (we acknowledge that the mechanism for this is not entirely understood) that is reflected in a number of studies in the acute stage of concussion (Shumskaya *et al.*, 2012; Zhou *et al.*, 2014; Johnson *et al.*, 2015; Zhu *et al.*, 2015; Iraji *et al.*, 2016). The proposed model theorizes that an increased recruitment of neuronal resources is particularly observable after injury, requires minimal task complexity and can even be observed at rest (see Fig. 3, red). Moreover, this stage is hypothesized to overlap with the period prior to clinical symptom recovery, as well as cognitive deficits observed in

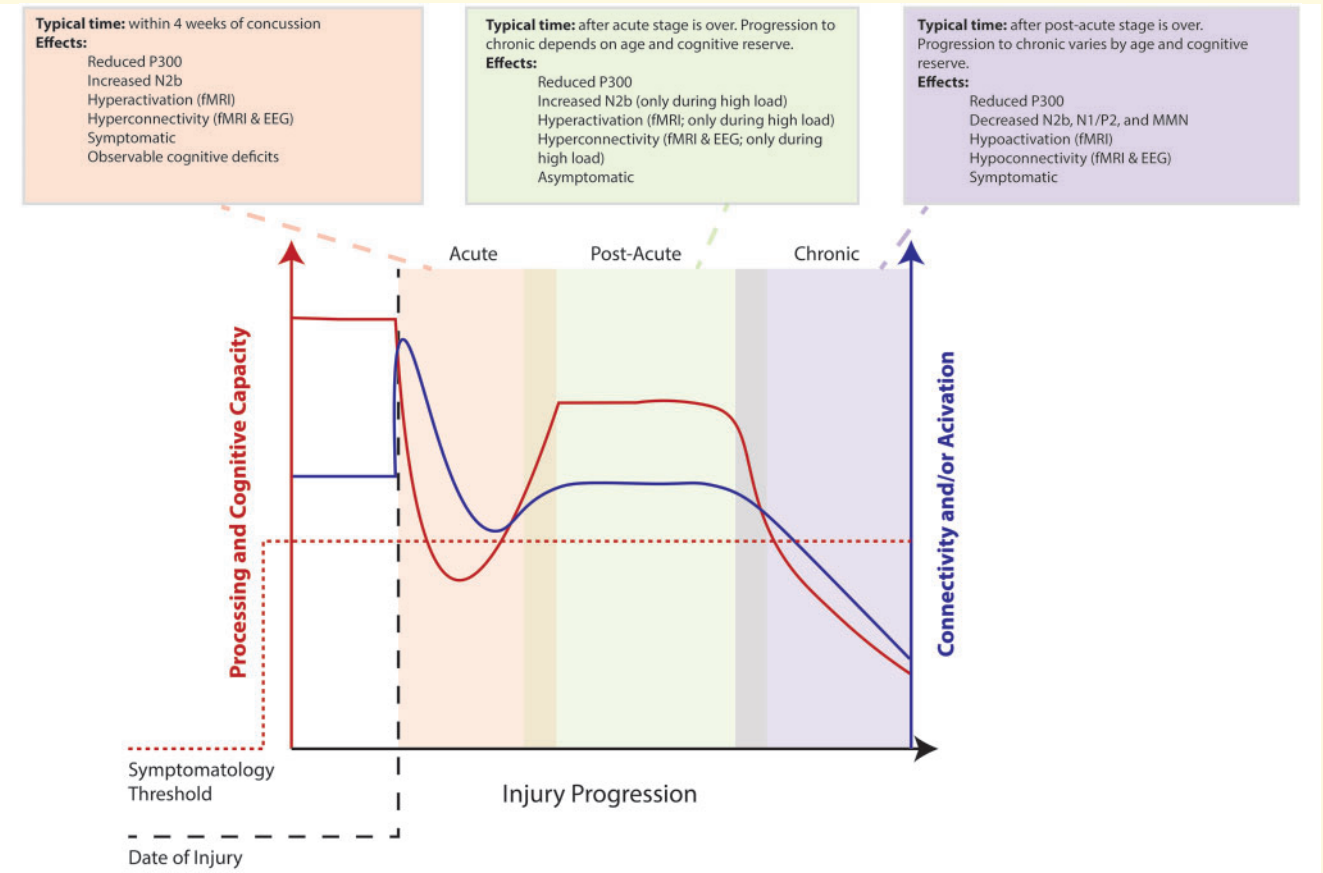


Figure 3 Theorized model of mild traumatic brain injury: the theorized model with its three stages of injury progression: acute, post-acute and chronic. Note the overlap between the stages in time, signifying an unclear transition point between them.

neuropsychological and other behavioural batteries (McCrory *et al.*, 2017). Since the increase in activity and FC observed in the acute stage can be observed in fMRI while the subject is at rest, it might be unrelated to cognitive load and may reflect the increased internal rumination and arousal often seen in recently concussed individuals (Sours *et al.*, 2015; Zhu *et al.*, 2015). Moreover, hyperactivity and hyperconnectivity have been shown in animal studies of concussion, where the effect is described as part of a post-concussion metabolic cascade (Giza and Hovda, 2001). Our model further suggests that this brain response plays a functional role in the brain adaptation to compensate for lost and impaired functionality. We posit that hyperactivity and hyperconnectivity facilitate a search for suitable ways of rerouting information processing to enable optimal, albeit flawed, compensation for the reduced cognitive functioning that resulted from injury, akin to the hyperconnected state observed in infants prior to neural pruning (Huttenlocher and de Courten, 1987; Rakic *et al.*, 1994).

In typical cases of concussion, the brain is able to adapt and progress past the acute stage, signified by a relief of symptomatology and other observable cognitive deficits (McCrory *et al.*, 2017). Our model proposes that this post-acute stage, and thus behavioural symptom resolution, co-occurs with the re-normalization of resting-state functional brain activation and connectivity. This is supported by a lack of significant differences in resting-state FC between controls and subjects with past concussion in the post-acute stage found in a number of fMRI and EEG studies alike (McAllister *et al.*, 2001; Nuwer *et al.*, 2005; Bharath *et al.*, 2015; Churchill *et al.*, 2017). However, the brain's solution to counteract mTBI-related cognitive loss is not perfect. A high processing load enforced by a complex task requires the injured brain to compensate and thus activate more than the uninjured brain, to maintain task performance (see Fig. 3, green) (McAllister *et al.*, 2001). Notably, we identify the mechanism of compensation as a likely explanation for the apparent normalization of behaviourally measured cognitive functions after symptom resolution (Martini *et al.*, 2017). Our model is compatible with an earlier hypothesis suggesting that even though behaviourally observed symptoms of concussion appear to resolve, the brain does not truly recover fully from the injury (De Beaumont *et al.*, 2009).

Lastly, as part of a typical aging process, the brain progressively loses its ability to sustain the compensatory

strategy developed in the acute stage and maintained throughout the post-acute stage (see Fig. 3, blue). This reduction and resurgence of symptoms has been linked strongly to the notion of a cognitive reserve (Kesler *et al.*, 2003; Stern, 2009; Broglio, 2017). This chronic stage marks a downward trend in brain activity and FC. As no fMRI FC has targeted the chronic stage of injury (Henry *et al.*, 2017), we base this stage of the model on three sets of observations: previous ERP studies conducted by our group and others (described below); the observed resurgence of behavioural and cognitive symptoms caused by cognitive decline in old age (Broglio *et al.*, 2012); and the results presented in this paper. In addition, we suggest that this stage may coincide with reported findings of tauopathy in retired athletes and potential link to chronic traumatic encephalopathy (CTE; Stern *et al.*, 2019).

ERP-specific implications

There has been a considerable amount of research on the effect of mTBI on ERPs. One challenge in understanding mTBI is to explain why some ERPs appear to be affected in consistent ways across the different stages of injury, while the effects on other ERPs appear to change over time. Our model provides a means to interpret these findings.

There is broad consensus regarding the effect of concussion on the P300, which is manifest as an attenuated and often delayed peak (Brush *et al.*, 2018). This effect is demonstrably consistent across acute, post-acute and chronic stages of injury (Broglio *et al.*, 2009; Baillargeon *et al.*, 2012; Boshra *et al.*, 2019*b*; Ruiter *et al.*, 2019). In contrast, the effects are not consistent on earlier ERP components, such as the mismatch negativity (Ruiter *et al.*, 2019) and the N1/P2 complex (Boshra *et al.*, 2019*a*). These responses were unaffected in acute and post-acute concussed subjects but were attenuated in individuals who had sustained their concussions decades earlier and were thus considered to be in the chronic stage of concussion at the time of testing. Our model predicts that this ERP component would be enlarged in the acute stage while at rest and in the post-acute stage while under cognitive load. Of note, it has been argued that the emergence of deficits in these earlier ERP components may be associated with an irreversible return of concussion-related cognitive decline.

The N2b response is also reported to be affected in a way that changes through the stages of concussion. This component was found to be unaffected in some cases in the post-acute stage (Moore *et al.*, 2014), amplified in other cases in the post-acute stage (Moore *et al.*, 2014, 2015; Ledwidge and Molfese, 2016) and attenuated in the chronic stage (De Beaumont *et al.*, 2009; Brush *et al.*, 2018; Ruiter *et al.*, 2019). The apparent modulation of the N2b proves similar to results from FC in fMRI. Our model predicts an enlarged N2b in the acute stage, as well as in the post-acute stage, albeit only when task-related cognitive load is sufficient to elicit neural over-compensation (Moore *et al.*, 2014, 2015; Ledwidge and Molfese, 2016). The model predicts an absence of N2b effects when the task is sufficiently simple (see oddball task Moore *et al.*, 2014). Lastly, the model predicts an attenuated N2b in the chronic stage (De Beaumont *et al.*, 2009; Ruiter *et al.*, 2019).

In summary, there is an indication that ERPs may be affected by mTBI in one of the three ways. For the P300, the effect appears to remain consistent throughout all stages of concussion. For the MMN and the N1/P2 complex, the effects seem to appear only in the chronic stage, possibly indicating more severe consequences of the injury (Boshra *et al.*, 2019*a*, *b*). Finally, for the N2b, the effect is more complex: the component appears to be affected in different ways depending on the stage of concussion and the degree of cognitive load under which the EEG is recorded. This makes the N2b a potential target for monitoring the progression of concussion. Furthermore, the time-course of the effects of concussion on the N2b most closely matches what has been observed in the fMRI literature and the FC findings in the present study showing hyperconnectivity immediately after injury followed by a tendency to normalize unless the participant is subjected to mentally taxing task.

General model implications

To conserve a parsimonious level of explanation, the model does not account for many of the factors argued in the literature to influence the state of concussion, including the number of previous concussions, the severity and location of impact, and age at the time of injury. While the model is not intended to provide precise predictive power at this finer resolution, it provides an overarching view of the brain's response to concussion and may even extend to brain injury more broadly depending on the severity and type of injury.

We argue that the model provides, for the first time, a falsifiable explanation of the time-course of the effects of concussion on the brain that directly relates three primary modalities used in concussion research: behavioural assessments, fMRI, and EEG/ERP. Our model also synthesizes some of the inconsistencies found in the broader literature, particularly the seemingly contradictory findings between studies exploring resting-state brain activity versus task-based studies that impose a high processing load on the participants. In particular, our model suggests that this contradiction is not simply due to extraneous factors as previously suggested, such as differences in experimental paradigms, but is instead part of a more complex dynamic nature of the effects of concussion over the lifespan.

Our model also has implications for post-concussion syndrome (long-term persistence of symptoms of concussion) as well as for more severe TBI. Both of these phenomena

can be described as types of injuries in which the post-acute phase is skipped: post-concussion syndrome because the brain fails, for one reason or another, to compensate for the injury and TBI because the injury is too severe for the brain to compensate in principle. Instead, the brain progresses directly from the acute stage to the chronic stage, as evidenced by studies that show reduced FC levels and clinical symptoms that are consistent with the chronic stage of concussion as described in our model (Kumar *et al.*, 2009; Messé *et al.*, 2013; Robinson *et al.*, 2015; Hocke *et al.*, 2018). Interestingly, the proposed model is in accordance with the accelerated decline model that describes the abnormal ageing trajectories in previously concussed individuals (Broglio *et al.*, 2012).

While the present study sheds some light on both the early and late stages of mTBI, there are important questions that require data from individuals across the full spectrum of age groups representing a continuity of stages of injury (from acute to chronic and in between). Further data will enable an investigation of when hyperconnectivity subsides and clarify the interaction between normalizing resting-state connectivity, symptom resolution, and processing loads. In addition, it is pertinent to identify what initiates the transition to a hypoconnected state later in life (time elapsed since injury, biological disposition, age, etc.), and whether that deterioration can be counteracted. This investigation is critical, as the decline into hypoconnectivity late in adulthood has been linked to severe consequences in other pathologies and was associated with more advanced forms of neurodegeneration (Hillary and Grafman, 2017). Moreover, as argued in Boshra *et al.* (2019*a*, *b*), experimental designs that facilitate single-subject analyses are necessary to understand the inter-subject variability of mTBI and its effects, as well as to build towards a clinical tool leveraging these findings.

Limitations

One potential confound in our study was the vast difference in age between the CH and the AC cohorts, leaving open the possibility that differences in FC could be naturally occurring due to age as opposed to injury stage. Indeed, when looking only at spectral coherence, our less robust measure of FC, we found a significant effect of cohort. This effect was observable for both the control group and the patient group and thus appears to be dominantly age-related and not mTBI specific. In contrast, measuring WPLI revealed a clear pattern of changes in FC that was unique to the concussed group as can be seen in Fig. 2B. In almost all cases, there was no change in WPLI-derived FC across cohorts for the controls, while a pronounced decrease was notable in almost all comparisons for the concussed group. The two instances of a main effect of cohort in FC in the control group showed increases in FC (mid-range intrahemispheric and within-region FC), where the same measures showed an age-related decrease in FC. Altogether, this indicates that phase synchronization, as measured by WPLI, may be significantly reduced through aging, specifically for those with a history of concussion.

The present study was made possible by aggregating data collected by our group for two studies using the same methodology and the same equipment. We note that combining two datasets as done in this study comes with the risk that statistical differences found in the study are due to heterogeneities between the datasets themselves. Specifically, the study samples differ by age, sex composition and profession. Sex differences reported in the literature convey subjective appraisal and/or reporting of symptoms (Merritt *et al.*, 2019). Moreover, reported effects tend to not cross from one study to another; thus, our results, as the literature exists presently, are likely to be unaffected by the uneven numbers of women across the cohorts. In our statistical analyses, we mitigated overall risk by adapting analysis procedures from earlier work to include a reduced number of comparisons and by adopting a more conservative significance threshold (Kumar *et al.*, 2009). Moreover, inclusion of data from both age groups in the same models was done in an effort to control for the potential confound of age, as discussed in the 'Materials and methods' section.

Our theoretical model of mTBI was constructed by integrating the results of the quantitative analyses presented here with a synthesis of prior evidence related to the short-, medium- and long-term effects of concussion. The data presented in this study formed much of the basis for our understanding of the acute and chronic stages of mTBI, while evidence supporting our interpretation of the post-acute stage was provided by other studies; it is important to note that these studies were based on different experimental methods. We therefore present our model as a framework that helps us to identify the most important testable hypotheses that will allow us to confirm or amend our current understanding of how concussion impacts the brain over the lifespan.

Another limitation is the use of coherence as a measure of FC in channel space, which is sensitive to volume conductance. We validated the results found with coherence by using a complimentary measure of FC, WPLI, which is invariant to volume conduction. WPLI was particularly useful in highlighting the changing effect of concussion on FC across the age groups.

In summary, we were not able to control for potential confounds as mentioned above; however, given the strength of the reported results (Fig. 2B), it is reasonable to expect that the effect of these confounds would not substantially impact the interpretation of our data.

Conclusion

The present study introduces a novel model of the time-course of mTBI that synthesizes the neuroimaging and EEG literature, while generating targeted

hypotheses that direct future research towards a more coherent understanding of mTBI. We argue that several points of contention, and apparently conflicting data, with respect to altered brain activity following concussion can be explained by a complex, dynamic, and non-linear response by the human brain that involves pathophysiological reactions, healing mechanisms and compensatory actions. The study reported event-related FC as measured by the EEG during an active oddball task from 93 subjects. Our results support previous work indicating that concussion alters brain FC as measured by the WPLI and spectral coherence. Strikingly, our results demonstrated a clear shift in connectivity as acute effects of concussion gave way to chronic neurophysiological alterations, causing a salient switch from an increased to decreased FC in concussed individuals relative to age-matched controls, respectively. The study presents the first report linking established trends in fMRI and neuroimaging literature to cognitive function manifesting in ERPs. We conclude that further work to elucidate the dynamics of that trajectory towards failure to compensate is critical to understanding the mechanisms behind late-adulthood symptom re-emergence, which are thought to be reflective of severe neuropathological consequences of concussion.

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Competing interests

The authors declare no competing financial interests.

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