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Research article

Altered Sleep Mechanisms following Traumatic Brain Injury and Relation to Waking Function

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Abstract: Sleep difficulties are commonly reported following traumatic brain injury (TBI), but few studies have systematically examined the neurophysiological characteristics of sleep. Sleep EEG was quantified over multiple nights to examine mechanisms underlying sleep disruption in individuals who had sustained a TBI and to explore the relationship between sleep disruption and waking function. Sleep was recorded from 20 individuals with a TBI (18–64 years) and 20 age-matched controls over two uninterrupted nights, as well as during a night where auditory stimuli were delivered. All participants underwent neuropsychological testing and waking performance assessment. Compared to controls, the TBI group had subjective complaints of falling asleep, delayed sleep onset on polysomnography (PSG), less Slow Wave (< 1 Hz) and delta (1–4 Hz) EEG power in non-REM sleep, fewer spontaneous and evoked k-complexes, reduced periodicity of spontaneous k-complexes, and lower amplitude of evoked k-complexes. While for controls, the density, duration and periodicity of sleep spindles diminished with deepening of non-REM as typically observed, this pattern was disrupted in the TBI group with peak spindle presentation occurring in Stage 3 sleep. Night-to-night-stability of Stage 2 spindles was high for controls but absent for the TBI group. Greater injury severity was related to fewer evoked k-complexes and lower spindle density. Greater spindle production predicted better waking function in the TBI group. Taken together, these data demonstrate impairment in sleep regulatory and inhibitory mechanisms as factors

underlying sleep complaints following a TBI. Spindle generation may be adaptive or a marker of resiliency following TBI.

Keywords: traumatic brain injury (TBI); sleep; sleep regulation; electroencephalography (EEG); k-complexes; sleep spindles

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1.   Introduction

Individuals who have sustained a traumatic brain injury (TBI) often report disrupted sleep and experience waking neurocognitive deficits. Sleep complaints following TBI are highly prevalent, and include trouble falling asleep, staying asleep, waking up too early, and sleeping too much [1–3]. Evidence for sleep disturbance following head injury has come mainly from surveys, and very little systematic research has been done to characterize the nature of sleep complaints and underlying mechanisms. Studies assessing polysomnography (PSG) or quantitative electroencephalography (qEEG) in TBI samples have yielded mixed results [1]. The purpose of the present study was therefore to assess sleep quantitatively in individuals who had sustained a TBI, over multiple nights in the sleep laboratory, specifically examining sleep inhibition and regulation processes through analysis of sleep architecture, power spectral analysis of the EEG, and characteristics of sleep phasic events (spindles and k-complexes). As well, the role of sleep disruption in individual differences in waking neurocognitive function was explored.

Some studies have used PSG to describe sleep architecture of individuals with a TBI. The earliest reports indicated that patients with severe brain injuries had reduced amplitude evoked k-complexes over the injured hemisphere [4], and less total sleep time, deep sleep, vertex sharp waves, k-complexes, and sleep spindles [5]. A more recent study investigated sleep overnight and during repeated daytime naps in individuals with "minor" TBI [6]. Nighttime sleep in participants with a TBI was shorter than controls, with more Stage 2 and less REM sleep. During naps, participants with a TBI fell asleep more frequently and more quickly. Thus, even those with a minor TBI showed some evidence of sleep/wake dysregulation, including lighter nighttime sleep and greater daytime sleepiness. There has been other evidence reported of lighter and more disrupted sleep following TBI including more Stage 1 [7], and longer sleep onset and more fragmentation [8]. Recently, one study reported that subjective complaints of poor sleep quality in a sample of 44 individuals with TBI was predicted by poor sleep efficiency and less Stage 2 sleep on PSG measures [9]. They suggested that disruption to Stage 2 in particular may underlie the sleep difficulties in this group, and that spindles may play a role. However, other researchers have reported that individuals with a TBI have more deep SWS than controls [10–13]. Still others have observed disruptions to REM sleep [6,10]. These disparate findings may be explained by sample and design differences, including injury severity, time since injury, co-morbidities, and medications. Notably, sleep can be

highly variable over nights and thus recording from a single night may not capture the dynamics of sleep. As well, the amount of Slow Wave or delta EEG activity in a sleep period will depend on the quality of that given night, and whether or not an individual is following a relatively good or poor night of sleep on the prior night. Observations of greater delta EEG may also be specific to the recovery phase; one report noted an increase in delta EEG and more consolidation of sleep in a sample studied 6 months post-injury [14].

Less commonly, sleep has been examined with quantitative measures of EEG. In an early report of sleep following TBI, qEEG methods showed changes in EEG 72 hours after the injury, and then again 6 and 12 weeks after the injury in eight adolescents with minor head injury [15]. They found that broad-band EEG power was elevated immediately following injury. A more recent study reported PSG and qEEG in individuals with a mild TBI and insomnia symptoms compared to healthy controls [16]; the TBI group had higher variability in delta, theta, and sigma power at sleep onset. One study reported no differences in qEEG of sleep in a sample of 10 athletes with a history of concussion compared to non-concussed athletes [17]; the lack of difference could have been due to the mild severity of injury, small sample size, or the fact that qEEG analyses were carried out on all non-REM sleep stages collapsed across the night rather than within sleep stages. A subsequent study by this group [18], recorded sleep from 11 EEG sites in acute mild TBI participants (less than 4 months post injury), 8 TBI individuals with pain and 16 without pain, compared to 18 healthy controls. Both groups of acute mild TBI participants with and without pain had lower delta EEG in Stage 2 at the C4 site only, and lower delta EEG in SWS and REM at the O2 site only. The mild TBI with pain group exhibited more broad-band EEG power including more high frequency beta/gamma EEG compared to both other groups. In a follow-up, the same group examined EEG frequencies and spindles from F3, C3, and O1 left-hemisphere sites in mild TBIs and controls using a combined sample from the two previously described studies including those that reported pain [19]. Those with a TBI had more beta EEG at O1 for non-REM sleep collapsed across the first three sleep cycles, which is consistent with qEEG findings in primary insomnia samples reflecting hyperarousal. No differences between groups were observed in delta slow wave EEG activity or spindles in that study.

In summary, surveys indicate that sleep complaints are prevalent following TBI; however, few studies have objectively investigated sleep physiology in this group. The current study aimed to better understand changes in sleep physiology following TBI using quantitative measures over multiple nights in a sample that varied in TBI severity. Based on prior research suggesting changes in sleep continuity following TBI [1–16,18–19], and based on the widespread damage to cortical, subcortical, and brainstem regions typical of TBI [20–22], it was hypothesized that individuals with a TBI would show impairment in sleep regulatory and inhibitory mechanisms which would explain the ubiquitous subjective complaint of poor sleep. Specifically, it was expected that there would be reduced sleep efficiency, and changes to the number and character of phasic events that reflect inhibition in sleep (such as spontaneous k-complexes and spindles). Auditory stimuli were delivered on an additional night and TBI participants were predicted to have alterations to the evoked

k-complex reflecting deficits in inhibition of information processing during sleep. Further, the TBI group was expected to have more EEG power in alpha (reflecting non-restorative sleep) and beta/gamma EEG bands (due to hyper-arousal consistent with insomnia) compared to controls. It was also expected that the TBI group would have less power in Slow Wave (SW), delta and theta bands (reflecting impaired sleep homeostatic mechanisms), and less power in the sigma band (consistent with impaired memory consolidation). As well, the degree of sleep disruption was expected to be related to injury severity. Relationships between sleep disruption and waking function were also explored.

2. Methods

2.1. Participants

Participants were recruited through advertisements at the university and in newspapers, and contact with community organizations and Psychologist offices. All participants were required to be between 18 and 65 years of age, with regular sleep/wake schedules, no history of or current shift work, taking no medications, and minimal caffeine users. Control participants were required to be healthy, good sleepers, with no report of head injury. TBI participants must have sustained a closed head injury from a traumatic event (such as a motor vehicle collision, sports accident, fall, or assault), more than 6 months prior to intake; this type of injury notably results in damage to the frontal brain regions and diffuse axonal sheering as a result of the rapid acceleration-deceleration movement of the brain within the skull [20–22]. A range of TBI severity was recruited; participants were characterized as having a mild, moderate, or severe TBI based on length of loss of consciousness and/or post-traumatic amnesia, where the longer of these two criteria formed the basis for severity grouping [23]. Participants were also assigned a numerical score from 0 to 20 representing injury severity, which was comprised from responses in a semi-formal interview provided by a referring neuropsychologist. The interview asked about a variety of neurodiagnostic indicators of injury, including length of loss of consciousness, memory loss before and after injury, and symptoms following the injury (e.g., vomiting, headache, etc). Participants were not recruited on the basis of a specific type of sleep complaint, but were excluded if primary sleep disorders such as apnea and periodic limb movement were present during a screening PSG.

The final sample included 40 participants; of these, 20 had sustained a traumatic brain injury (11 women, $M_{age} = 29.75$, $SD = 14.17$), and 20 good sleepers were age-matched controls (10 women $M_{age} = 29.40$, $SD = 14.68$). There was one left-handed person in the control group, and two left-handed persons in the TBI group. While control participants were all non-smokers and free from pain, psychiatric conditions, and medications as is commonly controlled in sleep studies, some exceptions were needed for the TBI patient sample that typically have co-morbidities. Three TBI participants were occasional smokers who reported no difficulty refraining from smoking for overnight sessions. Two TBI participants took hypnotic medications on an as needed basis; a two-week washout period

was required before enrollment. Given the nature of the cause of brain injury, a number of participants self-reported ongoing pain issues ($n = 6$); none were taking narcotics or pain medication on a regular basis and no medication was taken during the study. While TBI participants were required to be free of pre-morbid psychiatric disorders, three TBI participants reported experiencing depressive symptoms that occurred following the TBI; they scored in the moderate severity range on the Beck Depression Inventory (BDI), but were not formally diagnosed or receiving treatment.

2.2. Procedures

Advertisements were used to recruit participants for a study on sleep physiology and waking performance in individuals who had sustained a TBI and non-injured good sleepers. To screen for eligibility, participants underwent a telephone interview, and visited the laboratory for an orientation session and an overnight sleep study (which also served as a habituation night). Questionnaires completed during orientation included a sleep/wake habits and history inventory, Perceived Stress Questionnaire [24], Morningness-eveningness tendency [25], fatigue questionnaire [26], BDI [27], and Beck Anxiety Inventory (BAI) [28]. In a separate visit, participants completed a neuropsychological test battery including tasks from the Wechsler Adult Intelligence Scale-III (WAIS-III: Digit Span, Digit-Symbol Coding) [29], Auditory Consonant Trigrams (ACT) [30], California Verbal Learning Test-II (CVLT-II) [31], Delis-Kaplan Executive Functioning System (D-KEFS: Trail Making Test, Colour-Word Interference, Tower Test, Design Fluency) [32], and the Comprehensive Test of Nonverbal Intelligence (CTONI) [33]. Participants also completed the Spot-the-Word portion of the Speed and Capacity of Language Processing Test (SCOLP) [34], a measure of verbal intelligence thought to be an estimate of pre-morbid IQ. Following this, a daily home diary was completed to provide information on habitual sleep times and caffeine use. Following the off-protocol screening/habituation night, the main study protocol was run over three consecutive nights in the sleep laboratory. The first two nights were "recording nights" and the third was a "stimulus delivery night". All study procedures were cleared by the local Research Ethics Board. Participants were provided a $125 honorarium for participation.

On each of the two recording nights, participants had a 20-channel EEG montage applied. Participants completed a pre-sleep questionnaire to assess subjective alertness and the PANAS mood scale [35]. Sleep was recorded between 23:00 and 07:00 h. Upon awakening, participants completed a post-sleep questionnaire which contained subjective rating scales and information about quality of the previous night's sleep. Following each night, participants were free to leave the laboratory for the daytime, with instructions to follow their usual habits with respect to caffeine consumption and daily activities, and to refrain from napping.

The purpose of stimulus delivery on the third night was to measure sensory and cognitive processing of auditory stimuli during sleep; stimuli employed in these paradigms were not chosen with the aim to disturb or challenge sleep. A 20-channel EEG montage was applied and then

participants were administered two auditory ERP tasks while awake, a paired-click paradigm and a basic odd-ball task. Pre- and post-sleep questionnaires and the PANAS were again completed, and sleep was recorded between 23:00 and 07:00 h. Participants were fitted with a pair of insert earphones to be worn throughout the night; these were secured to both ears with medical tape to ensure continuity of stimulus input. Once participants achieved five minutes of consolidated Stage 2 sleep, stimulus delivery was initiated. The same ERP paradigms that were delivered in the waking state were administered in sleep in 10-minute blocks in random order. Participants were told that they could ask for stimulus delivery to be paused if they found stimuli disruptive, but no participants requested stimuli be paused. Evoked k-complex data from the stimulus delivery night are reported in the present paper; ERPs in sleep and wake are not reported here.

2.3.   *Electrophysiological recording and analyses*

Standard PSG recording procedures were employed on a screening night, including electroencephalography (EEG) from C3 and C4 scalp sites, electrooculography (EOG) from the outer canthus of each eye, and electromyography (EMG) from beneath the chin. For assessment of clinical sleep disorders, breathing was monitored with respiratory effort bands placed around the chest and abdomen and EMG was recorded from the calf of each leg. PSG was recorded at 250 Hz using Mizar Digital amplifiers with Sandman Elite software (Tyco, Inc.). On the recording and stimulus delivery nights, a 20-channel EEG montage (FP1, FP2, F7, F3, Fz, F4, F8, FCz, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2) [36] was recorded. FPz was the recording reference and AFz was the ground; EOG and submental EMG were recorded as above. Data were sampled at 1000Hz on the recording and stimulus delivery nights using 64-channel SynAmps2 amplifiers with Neuroscan software (Compumedics Inc.). No hardware or software filters were applied during recording. Nights were stage scored using a modified version of traditional scoring criteria [37]; stage changes were marked at the precise moment of their occurrence as opposed to the end of each 30-sec epoch. This scoring technique ensures 2-sec EEG epochs are binned according to the precise sleep stage for frequency and evoked potential analysis.

Spontaneous k-complexes were visually identified at Fz in Stage 2 sleep on both recording nights as 75 μV waveforms with the characteristic morphology being at least 0.5-sec in duration. K-complexes were not counted in SWS because large amplitude delta waves make them difficult to reliably visually identify. Density (number of k-complexes per minute of Stage 2 sleep) was calculated; as well, the mean inter-k-complex time interval was calculated as a measure of periodicity. To identify sleep spindles, Cz and Pz channels were spatially filtered to display frequencies between 12 and 16 Hz [38]. Spindles were counted and duration measured at Cz in Stage 2, 3, and 4 on all three nights. Sleep spindles were required to be 0.5-sec in duration and have a fusiform shape. Density (number of spindles per minute of sleep) and mean duration (seconds) were calculated; as well, the mean inter-spindle time interval was calculated as a measure of periodicity.

Evoked k-complexes were measured in Stage 2 sleep on the stimulus delivery night to oddball target stimuli (salient stimuli are more likely to evoke k-complexes [39–41]). Participants were presented with a series of auditory tones (70 dB, 50 ms, inter-stimulus interval 1000–2000 ms) delivered binaurally via insert earphones. Standard stimuli (1000 Hz) were presented on 80% of trials, while target tones (2000 Hz) were presented at random on 20% of trials. EEG data were divided offline into trials beginning 100 ms prior to stimulus onset and continuing for 2000 ms. Data were manually inspected to reject trials with movement or electrical artifact. The N550 component of the evoked k-complex was identified in the grand average waveforms at Fz where it was maximal. N550 amplitude and latency were measured at all 20 sites for individual participants relative to pre-stimulus baseline in order to explore any topographic changes to its usual fronto-central distribution.

Prior to spectral analysis of the EEG, data were visually inspected for movement and artifact. EEG data were re-referenced offline to an average of A1 and A2. Power spectral analysis (PSA) was performed on EEG data recorded from 20 sites during sleep using Fast-Fourier Transform analysis techniques in Neuroscan (Compumedics Neuroscan Inc.). EEG data were quantified as the absolute power (μV^2/Hz) of each of the following pre-defined frequency bands: Slow Wave (SW) < 1 Hz; delta 1–4 Hz; theta 4–8 Hz; low alpha 8–10 Hz; high alpha 10–12 Hz; low sigma 12–14 Hz; high sigma 14–16 Hz; beta 16–35 Hz; low gamma 35–45 Hz; high gamma 65–75 Hz. Sleep-scored data from each night were submitted to PSA according to stage, in 2-second periods using hanning windowing with 75% overlap. EEG data were log transformed prior to statistical analysis to eliminate the skewness inherent in the data.

2.4. Statistical analyses

Analyses are reported for the sample of 20 age-matched pairs except where outliers ($\pm$ 3 SD) or missing data are specified. Paired analyses were used to compare matched groups [42]. Analysis of variance (ANOVA) was run to test for the hypothesized Group effects and interactions with Night and/or sleep Stage depending on the variable. Greenhouse-Geisser corrections were used for violations to sphericity where appropriate. For qEEG data, Group by Night ANOVAs were carried out at the site where EEG power for each band was largest. For evoked k-complex data, Group by Anterior/Posterior (frontal, central/temporal, parietal) by Medial/Lateral (left ventral, left dorsal, midline, right dorsal, right ventral) ANOVAs were used to explore topographic variation in the data [43]. Significant ANOVA tests were followed up with Bonferroni pairwise comparisons. Correlations were run between nights 1 and 2 in each group to investigate night-to-night stability of sleep phasic events. Correlations were also run to describe the relationship between sleep-related variables and injury severity in the TBI sample. Preliminary correlation analyses between sleep-related variables (delta EEG, k-complexes, spindles) and waking function data in the TBI group revealed consistent and robust relationships with sleep spindle activity; thus, regression analyses were run to further describe the extent to which spindle activity predicted waking function in the TBI group. Statistical

trends are reported when in the direction of hypothesized effects and/or consistent with significant effects on related variables.

3. Results

3.1. Sample characteristics

Participants varied in TBI severity based on the length of loss of consciousness and/or post-traumatic amnesia [23]; specifically six individuals were categorized as having a mild TBI, eight moderate, and six severe. Continuous scores of injury severity comprised from responses in a semi-formal interview ranged from 4 to 15 ($M = 10.90$, $SD = 3.64$). The average time since last injury was 6.7 years (range: 1 to 20); five TBI participants had sustained a prior TBI or concussion. As typically reported in surveys [reviewed in 1–3], TBI participants in this sample were heterogeneous with respect to type of subjective sleep complaint. Of the 20 TBI participants, 16 reported difficulty with sleep upon presentation: 10 (50% of sample) reported predominantly trouble getting to and/or maintaining sleep, 6 (30% of sample) reported predominantly daytime fatigue; and, 4 (20% of sample) reported no difficulties with sleep or fatigue. Of the four with no subjective sleep complaints, two of these participants had delayed sleep onset latencies on all three nights in the laboratory; their mean sleep latency for the three nights was 40 and 52 minutes respectively. Only two TBI participants had no subjective complaint or objective evidence of poor sleep in the laboratory; these participants were not outliers on any measures and therefore were included in final analyses. No relationship was found between injury severity (mild, moderate, severe) and subjective sleep complaint categories, $X^2_{(4)} = 1.99$, $p = 0.70$.

To further characterize the sample, comparisons were made between groups on a number of subjective mood and alertness variables. Level of stress across the previous month on the Perceived Stress Questionnaire [24] and morningness-eveningness tendency [25] did not differ between groups. Groups differed significantly on fatigue ratings over the past week [26] (TBI $M = 11.50$, $SD = 6.57$; Control $M = 6.60$, $SD = 5.38$; $t_{(19)} = -2.35$, $p = 0.03$), and anxiety on the BAI [28], (TBI $M = 7.23$, $SD = 6.66$; Control $M = 3.50$, $SD = 3.68$; $t_{(19)} = -2.15$, $p = 0.045$), but not depression on the BDI [27], (TBI $M = 8.53$, $SD = 7.89$; Control $M = 5.10$, $SD = 4.95$). During the study, no group differences were apparent on subjective sleepiness, fatigue, or sleep quality ratings taken pre- and post-sleep each night. On post-sleep questionnaires, the TBI group reported taking longer to fall asleep than controls on night 1 (TBI $M = 43.40$, $SD = 39.94$; Control $M = 25.25$, $SD = 14.09$; $t_{(19)} = -2.15$, $p = 0.04$) and night 3 (TBI $M = 31.67$, $SD = 23.58$; Control $M = 18.94$, $SD = 10.69$; $t_{(19)} = -2.13$, $p = 0.048$), with a trend for the same effect on night 2 (TBI $M = 34.33$, $SD = 24.49$; Control $M = 21.39$, $SD = 13.48$; $t_{(19)} = -1.96$, $p = 0.067$). The TBI group also reported significantly less total sleep time than controls on night 2 (TBI $M = 6.52$ hrs, $SD = 1.38$; Control $M = 7.43$ hrs, $SD = 0.59$; $t_{(19)} = 2.47$, $p = 0.02$). During performance assessment batteries administered in the evening and morning of nights 1 and 2,

the TBI group reported significantly more positive affect than controls on the PANAS [35] on both night 1 (TBI $M = 27.75$, $SD = 9.65$; Control $M = 20.40$, $SD = 6.01$; $t_{(19)} = -2.90$, $p = 0.01$), and night 2 (TBI $M = 26.45$, $SD = 9.47$; Control $M = 19.30$, $SD = 7.12$; $t_{(19)} = -2.61$, $p = 0.02$).

3.2.   Sleep architecture

Group by Night (2) ANOVAs were run to compare groups on sleep architecture during the two consecutive recording nights. Group main effects indicated that compared to controls, the TBI group took significantly longer to fall asleep ($n = 19$ pairs; TBI $M = 24.52$, $SE = 3.76$; Control $M = 15.89$, $SE = 1.92$; $F_{(1,18)} = 6.76$, $p = 0.02$, $\eta^2 = 0.27$), and spent significantly more time awake ($n = 17$ pairs; TBI $M = 2.96$, $SE = 0.37$; Control $M = 1.82$, $SE = 0.40$; $F_{(1,16)} = 7.58$, $p = 0.01$, $\eta^2 = 0.32$). There were no group differences or interactions for sleep efficiency, total sleep time, or percent time in any of the sleep stages. Paired t-tests were run to compare groups on the stimulus delivery night. The TBI group had significantly more movement time than controls on night 3 (TBI $M = 6.20$, $SD = 2.82$; Control $M = 4.32$, $SD = 1.70$; $t_{(19)} = -2.71$, $p = 0.01$). See Table 1 for means and standard deviations for sleep architecture variables each night by group.

Table 1. Sleep architecture on each protocol night for the TBI group and controls.

		Night1		Night2		Night3	
		TBI	Controls	TBI	Controls	TBI	Controls
Total Sleep	M	440.11	444.74	442.98	450.99	442.46	449.89
Time (min)	SD	28.82	23.00	19.96	15.94	22.52	16.29
Sleep	M	91.12	92.32	91.87	93.47	91.85	93.39
Efficiency (%)	SD	5.69	4.82	3.52	3.25	3.76	3.28
Sleep Onset	M	22.95	14.81	26.09	16.99	23.49	15.76
Latency (min)	SD	17.80	8.24	22.05	10.83	18.36	8.66
Wakefulness	M	2.84	2.00	3.09	1.63	2.05	1.88
(%)	SD	1.98	2.16	2.18	1.68	1.83	2.35
Stage 1 (%)	M	7.88	7.86	8.02	6.69	12.77	12.12
	SD	4.95	6.01	3.86	5.37	7.93	6.58
Stage 2 (%)	M	45.03	45.82	40.51	45.10	44.40	44.01
	SD	8.97	7.53	7.64	6.05	7.75	5.56
Stage 3 (%)	M	4.23	4.41	4.14	4.24	4.11	4.29
	SD	1.52	1.36	1.98	1.43	1.60	1.59
Stage 4 (%)	M	17.21	16.18	17.07	16.02	13.01	13.79
	SD	5.55	6.26	5.10	5.23	4.74	5.51
REM sleep (%)	M	17.40	18.76	22.31	22.02	18.19	19.82
	SD	5.77	5.68	5.44	5.17	3.77	4.39
Movement	M	5.23	5.17	5.34	4.44	6.20	4.32
Time (%)	SD	1.78	3.37	2.10	1.83	2.82	1.70

3.3. Quantitative electroencephalography (qEEG) during non-REM sleep

Analyses to test the hypothesized group effects were carried out at the site where EEG power was maximum for each band (i.e., SW and delta at Fz, alpha 1 and 2 and theta at FCz, sigma1 at FCz, sigma2 at Pz, beta at Cz, and gamma1 and gamma2 at FCz). Group by Night (2) ANOVAs examined EEG on the two recording nights in each stage of non-REM sleep. Compared to controls, the TBI group had significantly less SW power in Stage 2 ($F_{(1,19)} = 7.91$, $p = 0.01$, $\eta^2 = 0.29$), with a trend for the same difference in Stage 3 ($F_{(1,19)} = 4.16$, $p = 0.056$). Similarly, the TBI group had less delta power than controls in Stage 2 ($F_{(1,19)} = 8.33$, $p = 0.01$, $\eta^2 = 0.31$), Stage 3 ($F_{(1,19)} = 5.05$, $p = 0.04$, $\eta^2 = 0.21$), and Stage 4 ($F_{(1,19)} = 5.67$, $p = 0.03$, $\eta^2 = 0.23$). There was a significant Group by Night interaction for high sigma power (14–16 Hz) in Stage 2, ($F_{(1,19)} = 4.90$, $p = 0.04$, $\eta^2 = 0.21$); for the TBI group, there was more sigma power on night 2 compared to night 1 ($t_{(19)} = 2.08$, $p = 0.05$), but for good sleepers, there was no differences in sigma power between nights. See Figure 1 for illustration of SW, delta and sigma EEG power in non-REM sleep. No other EEG bands differed between groups on nights 1 and 2. Paired t-tests compared groups on the stimulus delivery night; there were no robust effects.
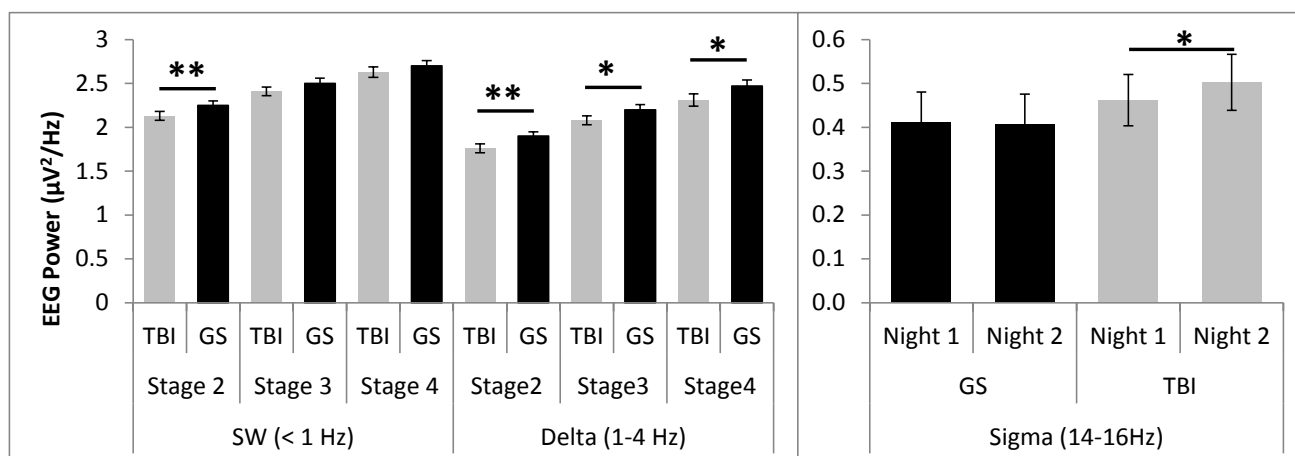

Figure 1. EEG Power in SW (< 1 Hz), Delta (1–4 Hz) and Sigma (14–16 Hz) bands. Left-panel depicts SW and delta power increasing with depth of sleep stage; the TBI group had less SW and delta power than Good Sleeper (GS) controls overall. Right-panel depicts that the TBI group had more sigma power on night 2 compared to night 1. Error bars are standard error. Significance is indicated by ** for $p < 0.01$, * for $p < 0.05$.

3.4. Sleep phasic events

3.4.1. Spontaneous k-complexes

Group by Night (2) ANOVAs were run to investigate the generation of spontaneous k-complexes. Group main effects were found for k-complex density and the inter-k-complex time interval; no interactions were found. The TBI group had a significantly lower k-complex density ($M = 2.75$, $SE = 0.20$) than controls ($M = 4.24$, $SE = 0.29$), $F_{(1,19)} = 12.23$, $p = 0.002$, $\eta^2 = 0.39$. As well, the TBI group had a significantly larger time interval between k-complexes ($M = 17.77$ s, $SE = 1.44$) than controls ($M = 13.36$ s, $SE = 0.87$), $F_{(1,19)} = 5.30$, $p = 0.03$, $\eta^2 = 0.22$, indicating that k-complexes occurred further apart in time.

3.4.2. Evoked k-complexes

Evoked k-complexes were measured to oddball target stimuli in Stage 2 sleep on Night 3; two participants and their matched pairs were lost due to technical difficulties with stimulus delivery. The TBI group had significantly fewer evoked k-complexes than controls (TBI $M = 64.11$, $SD = 49.23$; Control $M = 105.06$, $SD = 70.88$; $t_{(17)} = 2.71$, $p = 0.02$), consistent with results for spontaneous k-complexes. Because groups differed systematically on the number of k-complexes evoked, and waveforms will attenuate with an increasing number of trials in an average, to examine k-complex amplitude the number of trials was controlled by including the first 50 evoked k-complexes for each participant in the average. Four pairs were thus removed from this analysis due to a small number of evoked k-complexes (sample includes 14 pairs; 3 mild, 6 moderate, 5 severe). Group by Anterior/Posterior by Medial/Lateral ANOVAs for N550 latency and amplitude were carried out. For amplitude, there was a significant Group main effect, ($F_{(1,104)} = 4.94$, $p = 0.045$, $\eta^2 = 0.28$), and a Group by Medial-Lateral interaction, ($F_{(4,104)} = 3.51$, $p = 0.032$, $\eta^2 = 0.21$). Follow-up one-tailed t-tests at all 20 sites indicated that the TBI group had a smaller amplitude N550 than controls at Fz ($p = 0.05$), F4 ($p = 0.03$), FCz ($p = 0.03$), Cz ($p = 0.02$), C4 ($p = 0.02$), P3 ($p = 0.03$), Pz ($p = 0.03$), P4 ($p = 0.005$), and P8 ($p = 0.01$). The largest group difference in amplitude was visible at Fz (Control = −87.72 µV; TBI = −72.99 µV), and while the difference was large along the midline and right-hemisphere, it was not as robust in the left-hemisphere (See Figure 2). There were no Group effects or interactions for N550 latency.
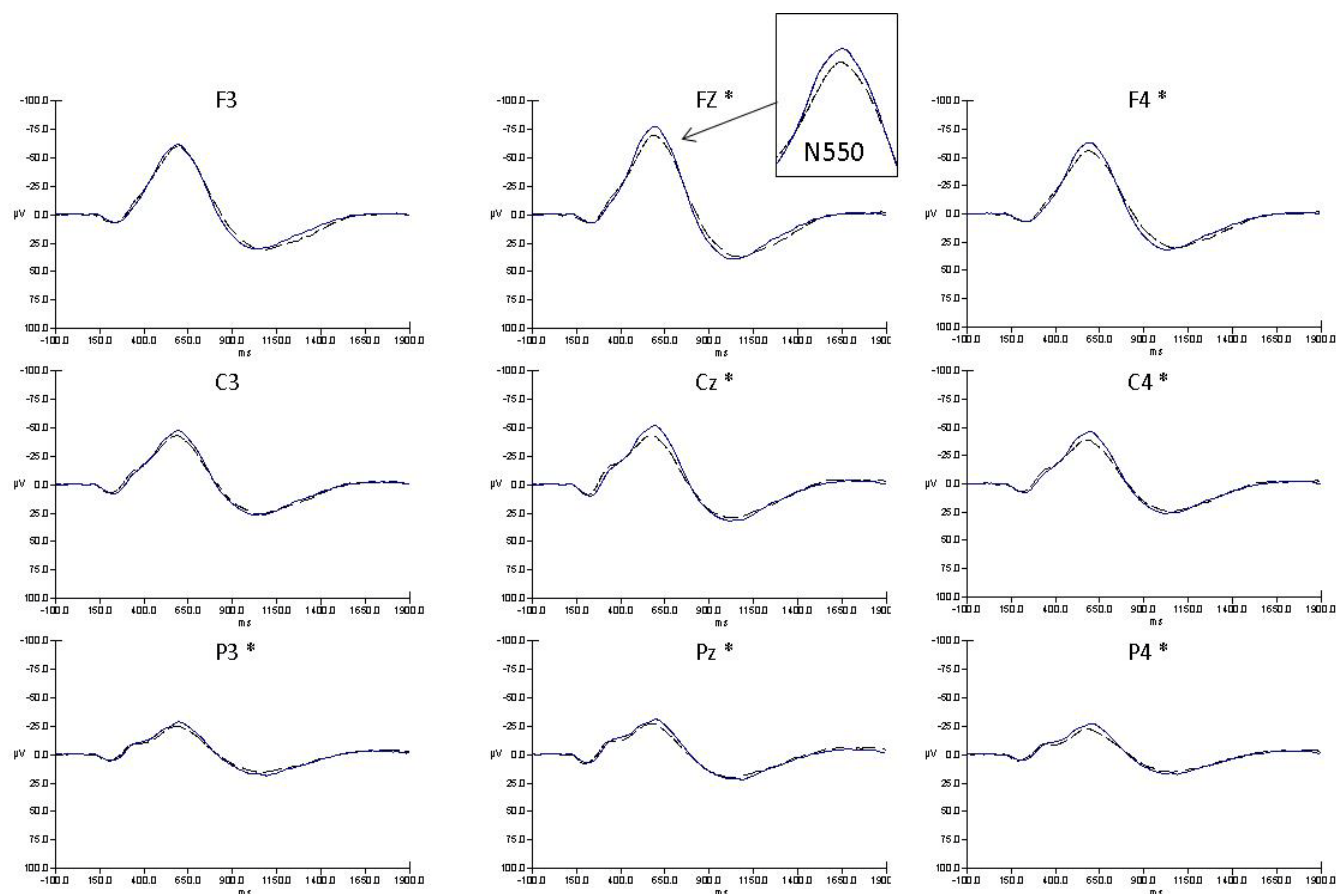
Figure 2. Evoked k-complex. Grand average waveform of the evoked k-complex to oddball target stimuli in Stage 2 on Night 3. Solid lines represent good sleeper controls, dashed lines represent the TBI group. Stimulus onset occurred at 0 ms; downward deflections are positive in polarity; data are filtered at 30 Hz. Note the zoom window of the Fz site where the N550 component is largest. Significance is indicated by * for $p < 0.05$ at each site label.

3.4.3. Sleep spindles

Group by Night (3) by Stage (2, 3, 4) ANOVAs were run to investigate spindle density, spindle duration, and the inter-spindle time interval. One pair of participants was excluded from analysis because of no SWS on night 3. Means and standard deviations are detailed in Table 2. For spindle density, a Group by Stage interaction was found, $F_{(2,36)} = 3.58$, $p = 0.04$, $\eta^2 = 0.17$. To follow up, Stage by Night ANOVAs were run in each group separately. In good sleeper controls, there was a significant main effect of Stage, $(F_{(2,72)} = 6.27$, $p = 0.01$, $\eta^2 = 0.26$; Bonferroni comparisons indicated that significantly fewer spindles were generated in Stage 4 ($M = 8.57$; $SE = 0.64$) compared to Stage 3 ($M = 10.18$; $SE = 0.69$). In the TBI group there was also a main effect of Stage, $(F_{(2,72)} = 6.03$, $p = 0.01$, $\eta^2 = 0.25$; however, Bonferroni comparisons indicated that significantly more spindles were generated in Stage 3 ($M = 10.62$; $SE = 0.47$) compared to Stage 2 sleep ($M = 9.30$; $SE = 0.31$).

Table 2. Sleep Spindles in Non-REM Sleep on Each Protocol Night for the TBI Group and Controls.

		Night 1		Night 2		Night 3	
		TBI	Controls	TBI	Controls	TBI	Controls
Stage 2							
Density (#/min)	*M*	9.55	10.29	9.45	10.06	8.90	9.77
	SD	1.04	2.72	1.79	2.67	3.39	2.87
Spindle Duration (s)	*M*	1.37	1.38	1.38	1.37	1.30	1.37
	SD	0.18	0.12	0.18	0.12	0.19	0.20
Inter-Spindle Interval (s)	*M*	4.08	4.22	4.26	4.32	4.39	4.41
	SD	0.77	1.31	1.16	1.34	1.43	1.65
Stage 3							
Density (#/min)	*M*	10.12	9.99	10.93	9.95	10.80	10.58
	SD	2.29	2.83	2.37	3.42	3.38	3.71
Spindle Duration (s)	*M*	1.27	1.19	1.25	1.19	1.23	1.23
	SD	0.12	0.13	0.15	0.13	0.20	0.13
Inter-Spindle Interval (s)	*M*	3.62	4.73	3.53	4.99	3.65	4.00
	SD	0.99	2.51	0.92	2.78	1.36	1.64
Stage 4							
Density (#/min)	M	8.87	8.63	9.86	8.48	9.67	8.59
	SD	2.93	3.09	2.33	2.93	2.47	3.06
Spindle Duration (s)	*M*	1.21	1.10	1.17	1.10	1.07	1.06
	SD	0.12	0.12	0.13	0.11	0.14	0.09
Inter-Spindle Interval (s)	*M*	5.04	6.27	4.83	6.62	5.13	6.38
	SD	2.11	3.17	1.72	3.62	2.07	3.09

For spindle duration, there was a significant Group by Stage interaction, $F_{(2,36)} = 5.02$, $p = 0.01$, $\eta^2 = 0.22$ and a significant Group by Night interaction, $F_{(2,36)} = 7.69$, $p = 0.002$, $\eta^2 = 0.30$. To follow up, Stage by Night ANOVAs were run in each group separately. In good sleeper controls, there was a main effect of Stage, $F_{(2,36)} = 98.78$, $p < 0.001$, $\eta^2 = 0.85$. Bonferroni comparisons indicated that spindles were significantly shorter in duration with each successive stage of sleep (Stage 2 $M = 1.37$ s, $SE = 0.03$; Stage 3 $M = 1.21$ s, $SE = 0.03$; Stage 4 $M = 1.09$ s, $SE = 0.02$). In the TBI group, there was a Stage by Night interaction, $F_{(4,72)} = 2.93$, $p = 0.03$, $\eta^2 = 0.14$. Follow-up paired t-tests were run to examine spindle duration across nights for each sleep stage: in Stage 2 sleep, spindle duration was significantly shorter on night 3 compared to nights 1 ($p = 0.003$) and 2 ($p = 0.011$), but there was no difference between nights 1 and 2. Similarly, in Stage 4, spindle duration was significantly shorter on night 3 compared to nights 1 ($p < 0.001$) and 2 ($p = 0.002$), but there was no difference between nights 1 and 2; spindle duration did not differ across nights within Stage 3 sleep.

For the inter-spindle interval, there was a Stage main effect, ($F_{(2,34)} = 22.79$, $p < 0.001$, $\eta^2 = 0.57$), and a trend for a Group by Stage interaction, ($F_{(2,34)} = 3.00$, $p = 0.095$). Given the Group by Stage interaction for both spindle density and duration, follow-up tests were investigated to explore the nature of the trend. Stage by Night ANOVAs in controls led to a significant main effect of Stage, ($F_{(2,34)} = 12.08$, $p < 0.001$, $\eta^2 = 0.42$); Bonferroni comparisons indicated that there was a significantly longer interval in Stage 4 ($M = 6.19$ s, $SE = 0.72$) compared to both Stage 2 ($M = 4.12$ s, $SE = 0.25$) and Stage 3 ($M = 4.16$ s, $SE = 0.33$), consistent with generating fewer phasic events in deep sleep which is typical of normal sleep. In TBIs, there was also a main effect of Stage, ($F_{(2,34)} = 14.32$, $p < 0.001$, $\eta^2 = 0.46$); Bonferroni comparisons indicated that the inter-spindle interval was shorter in Stage 3 ($M = 3.54$ s, $SE = 0.23$) than either Stage 2 ($M = 4.21$ s, $SE = 0.22$) or Stage 4 ($M = 4.92$ s, $SE = 0.44$), consistent with the higher spindle density seen in Stage 3 in the TBI group.

3.5. Night-to-night stability in sleep phasic activity

Night-to-night stability was examined for density of spontaneous k-complexes ($n = 20$ pairs) and spindles ($n = 19$ pairs) for each group separately. In good sleepers, there was high concordance for spindles in Stage 2 between nights 1 and 2 ($r = 0.94$, $p < 0.001$), nights 1 and 3 ($r = 0.67$, $p = 0.002$), and nights 2 and 3 ($r = 0.75$, $p < 0.001$), but no stability across nights for the TBI group (night 1–2: $r = -0.13$; night 1–3: $r = 0.07$; night 2–3: $r = 0.03$). See Figure 3 for scatterplots. In Stages 3 and 4 sleep, there was relative night-to-night stability in spindle density for both groups, although the TBI group had lower correlations overall compared to controls (e.g., night 1–2 in Stages 3 and 4 respectively: Controls, $r = 0.93$ and $r = 0.83$; TBIs, $r = 0.59$ and $r = 0.69$). Spontaneous k-complexes in Stage 2 were also highly stable across recording nights 1 and 2 for both the good sleeper ($r = 0.74$, $p < 0.001$) and TBI ($r = 0.78$, $p < 0.001$) group.
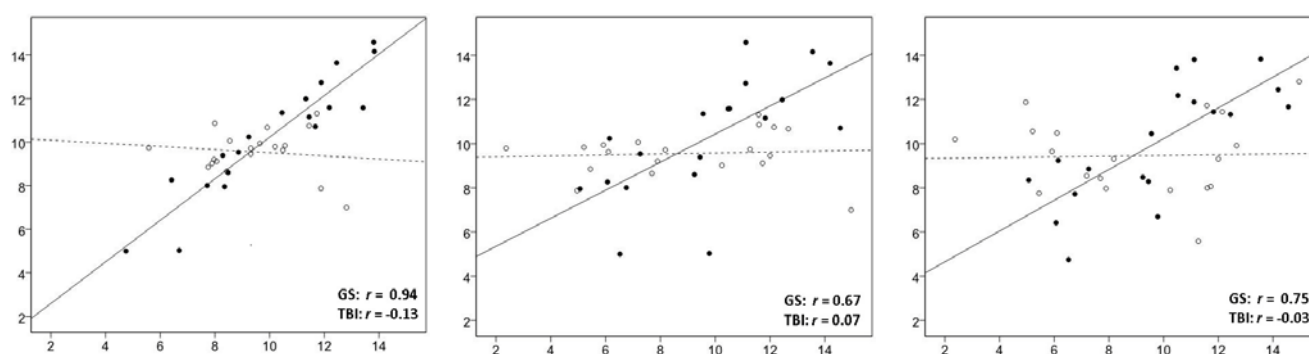

Figure 3. Night-to-Night stability of spindle density in Stage 2 sleep. Left-panel is Night 1 to 2; middle-panel is Night 1 to 3; right-panel is Night 2 to 3. Spindle density was highly correlated between nights for Good Sleeper controls (solid line with solid circles), but not for the TBI group (dashed line, open circles). Magnitude for bivariate correlations is indicated in each panel.

3.6.   Relationship between injury severity and sleep disturbance

3.6.1. Sleep architecture and qEEG

There were no associations between injury severity and any of the sleep architecture variables, or between injury severity and SW and delta power at Fz in all non-REM stages for each night.

3.6.2. K-complexes

Correlations between injury severity and the number, amplitude and latency of evoked k-complexes were run in the sub-sample of 14 who had a sufficient number of trials for signal averaging. Injury severity was significantly negatively correlated with the number of evoked k-complexes ($r = -0.60$, $p = 0.02$); those with a more severe injury generated fewer evoked k-complexes (see Figure 4). There was no association between injury severity and the density or average time interval of spontaneous k-complexes.
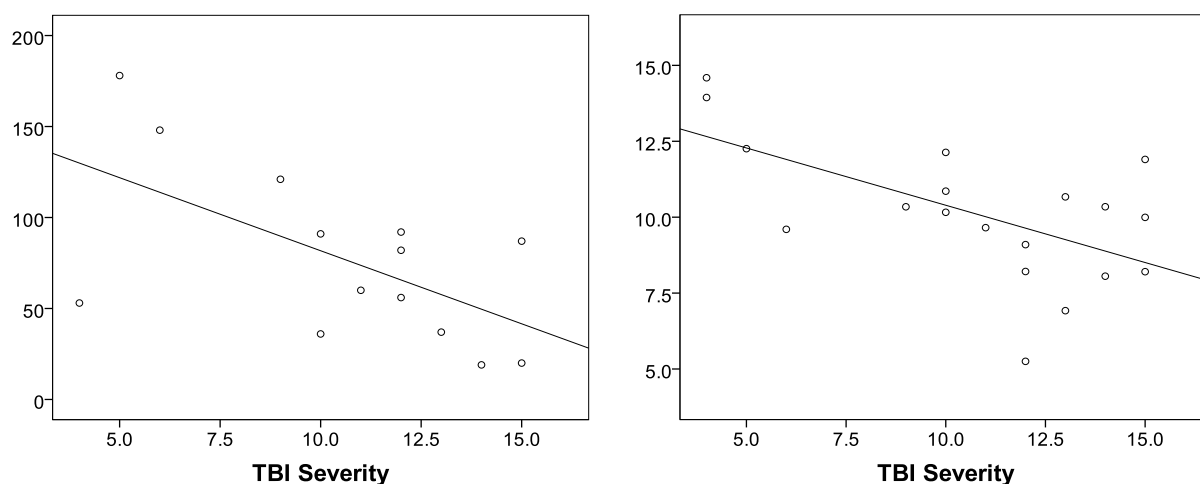

Figure 4. Scatterplots depicting relationships between injury severity and phasic EEG events in sleep. Correlations between injury severity in TBI and the number of evoked k-complexes (left-panel) and the density of spindles in stage 3 sleep on night 1 (right panel). Note: greater injury severity was associated with generation of fewer sleep phasic events.

3.6.3. Spindles

Correlations were run between injury severity and spindle density, duration, and inter-spindle interval on all three nights ($n = 19$). Injury severity was significantly negatively related to spindle density in Stage 3 on night 1 ($r = -0.60$, $p = 0.006$) (see Figure 4), with a trend for the

same relation in Stage 2 on night 1 ($r = -0.39$, $p = 0.099$); those with a more severe injury generated fewer spindles.

3.7. Relationship between sleep spindles and waking function

Regression analyses were run to explore the relationship between spindle activity (controlling for injury severity, pre-morbid IQ and age), and measures of waking function on neuropsychological tests [29–33]. Predictors were composite scores across nights 1 and 2 for spindle density, duration and inter-spindle interval. Regression models consisted of severity, pre-morbid IQ [34] and age entered on Step1 and spindle activity in Stages 2, 3, 4 entered (stepwise) on Step2; analyses were repeated for spindle density, duration and inter-spindle interval respectively.

Overall, lower spindle generation was associated with worse neuropsychological functioning. Data reported are the standardized Beta coefficients for significant sleep spindle predictors (which represent their unique predictive power when also considering severity, IQ, and age), the associated p-value for the t-test, and sr^2 (the proportion of variance accounted for by the single sleep spindle predictor). From the WAIS-III [29], greater spindle density in Stage 3 predicted number of correct trials (forward and back combined) on the Digit Span task (Beta = 0.45, $p = 0.012$; $sr^2 = 0.21$), and number of correct number-symbol parings on the Digit-symbol Coding task (Beta = 0.55, $p = 0.033$; $sr^2 = 0.21$). A shorter inter-stimulus interval (i.e., more spindles) in Stage 4 also predicted the number of correct number-symbol parings (Beta = -0.46, $p = 0.044$; $sr^2 = 0.19$). From the D-KEFS [32] tests of executive functioning, both spindle density and inter-spindle interval in Stage 4 predicted better performance on subscales of the Trails test (i.e., less time to complete). Specifically, greater spindle density in Stage 4 uniquely predicted less time on visual scanning (Beta = -0.70, $p = 0.013$; $sr^2 = 0.47$), number sequencing (Beta = -0.59, $p = 0.014$; $sr^2 = 0.34$), and motor speed (Beta = -0.62, $p = 0.005$; $sr^2 = 0.36$). Shorter inter-spindle interval in Stage 4 predicted less time on visual scanning (Beta = 0.68, $p < 0.001$; $sr^2 = 0.43$), number sequencing (Beta = 0.56, $p = 0.025$; $sr^2 = 0.29$), number-letter switching (Beta = 0.45, $p = 0.046$; $sr^2 = 0.18$) and motor speed (Beta = 1.01, $p = 0.002$; $sr^2 = 0.43$. In the Colour-Word Interference test, shorter inter-spindle interval in Stage 4 predicted less time to complete the switching subscale (Beta = 0.42, $p = 0.043$; $sr^2 = 0.16$). On the Auditory Consonant Trigrams (ACT) [30] task, a measure of complex attention, the total number of letter strings correctly recalled was associated with greater spindle density in Stage 2 (Beta = 0.33, $p = 0.008$; $sr^2 = 0.10$) and longer spindle duration in Stage 3 (Beta = 0.45, $p = 0.003$; $sr^2 = 0.12$). On the California Verbal Learning Test-II (CVLT-II) [31], greater spindle density in Stage 2 was associated with the number of words recalled on fifth (last) trial (Beta = 0.41, $p = 0.014$; $sr^2 = 0.16$), and total number of words recalled correctly across five trials (Beta = 0.39, $p = 0.018$; $sr^2 = 0.14$). Longer spindle duration in Stage 2 was associated with better performance for the number of words recalled on fifth (last) trial (Beta = 0.57, $p = 0.003$; $sr^2 = 0.22$), the total number of words recalled correctly across five trials (Beta = 0.48, $p = 0.013$; $sr^2 = 0.15$), number of words recalled in an interference trial (Beta = 0.54,

$p = 0.024$; $sr^2 = 0.20$), and number of words recalled after a long delay (Beta = 0.44, $p = 0.038$; $sr^2 = 0.13$). Longer spindle duration in Stage 3 was associated with fewer non-target word intrusions on recall trials (Beta = −0.64, $p = 0.043$; $sr^2 = 0.25$). For the Comprehensive Test of Nonverbal Intelligence (CTONI) [33], spindle density in Stage 2 predicted better performance on pictorial categories (Beta = 0.48, $p = 0.044$; $sr^2 = 0.22$), while shorter inter-spindle interval in Stage 4 predicted geometric analogies (Beta = −0.53, $p = 0.035$; $sr^2 = 0.26$) and longer spindle duration in Stage 4 predicted geometric categories (Beta = 0.53, $p = 0.008$; $sr^2 = 0.27$).

4. Discussion

This study aimed to examine multiple nights of sleep quantitatively to determine mechanisms underlying disrupted sleep in individuals who had sustained a TBI. Compared to controls, the TBI group had delayed sleep onset latency as well as lower SW and delta EEG power in non-REM sleep. Most notably, non-REM sleep phasic events were disrupted in the TBI group compared to controls. Specifically, there were fewer spontaneous and evoked k-complexes generated in Stage 2 sleep. The time interval between generation of spontaneous k-complexes was also reduced reflecting impairment in periodicity of the EEG events. In addition, the amplitude of the evoked k-complex was lower for the TBI group compared to controls at widespread midline and right-hemisphere scalp sites. Spindle activity showed an atypical presentation over non-REM sleep stages for the TBI group. Specifically, in the control participants, spindle density and duration decreased, and the interval between spindles increased, as non-REM sleep deepened for controls as is typically observed [44]; however, this pattern was disrupted in the TBI group: more spindles were generated and the inter-spindle time interval was shorter in Stage 3 compared to Stage 2. Night-to-night-stability of Stage 2 spindles was high for controls but absent for the TBI group. Greater injury severity was related to fewer evoked k-complexes and lower density of spindles. Greater spindle production was associated with better waking function in the TBI group, over and above contributions from injury severity, IQ, and age. Together, these data provide evidence for deficits in sleep regulatory and inhibitory mechanisms following a TBI and provide some novel insights into the relationship between sleep disruption and waking function following a TBI.

4.1. Subjective and objectives measures of sleep

The subjective complaint of difficulty falling asleep and less total sleep time, as well as delayed sleep onset latency and greater time awake on PSG for the TBI group was consistent with previous research [1–3,7–8]. There were no group differences in sleep efficiency or time spent in the various sleep stages. Specifically, the current study did not find evidence of greater time in SWS reported in a few previous studies [10–13], which may be explained by sample characteristics such as severity, time since injury, and nature of sleep complaint. Quantitative analysis of sleep EEG revealed

significant disruptions to sleep despite minimal evidence for changes in sleep architecture with traditional PSG measures. Specifically, as hypothesized, delta EEG power was reduced in Stage 2, 3, and 4 on non-REM sleep and SW power was reduced in Stage 2 for the TBI group. This is consistent with one previous report [18] that observed lower delta EEG in a sample of acute mild TBI compared to healthy controls that was apparent at C4 in Stage 2 and O2 in SWS. These data reflect that non-REM sleep was not as deep and restorative following a TBI and provide evidence of disruption to a specific brain mechanism, that is, the homeostatic control of non-REM sleep. The brain regions and thalamocortical circuitry underlying the generation of non-REM sleep waveforms are widespread [45] and thus appear vulnerable to the diffuse brain damage typical of TBI. Future research is needed to investigate disruption to sleep regulatory mechanisms following TBI, including manipulations to sleep pressure through sleep deprivation, napping, or pharmaceuticals. Further, drugs that increase SWS in particular could be investigated for treatment of sleep maintenance difficulties following TBI. There was no evidence in the current study for the hypothesized greater alpha (non-restorative sleep), more beta or gamma (hyper-arousal previously reported in insomnia patients, [46]), or reduced theta (also marking sleep homeostasis) in the TBI group. It is plausible that theta EEG may be lower in Stage 1 (during the transition to sleep), or higher in the waking state (reflecting greater sleep pressure), but only stages 2, 3, and 4 non-REM sleep were investigated here.

4.2.   Sleep phasic activity

K-complexes and spindles are characteristic brainwaves unique to non-REM sleep which have a phasic pattern. Those with a TBI had fewer k-complexes in Stage 2 sleep than control participants, including spontaneous k-complexes on the recording nights and evoked k-complexes on the stimulus delivery night. There was also evidence of disruption to the periodicity of spontaneous k-complex generation in the TBI group. These findings support hypotheses and replicate and extend some of the earliest reports of sleep changes following TBI in those with a severe brain injury [4,5]. The k-complex is generally viewed as playing a protective or inhibitory role [47]. Thus, sleep inhibitory mechanisms were disrupted in Stage 2 sleep over multiple nights for those with a TBI. Given that k-complexes are a slow wave with a low frequency oscillation, it is possible that the reductions in SW and delta EEG power observed in the current study may have been due to the changes with k-complexes. However, since k-complexes are maximal in Stage 2, and both SW and delta power increased with depth of non-REM sleep (as in Figure 1), at least some part of the EEG power differences between groups must have been independent from the k-complex activity.

The evoked k-complex is time-locked to auditory stimulus and is thus thought to index information processing and represent a sleep inhibitory or gating process in particular [47]. The amplitude of the N550 peak was reduced in the TBI group compared to controls at widespread scalp sites, but the effect was most robust at central and right-hemisphere sites. TBI thus disrupts sleep mechanisms specific to inhibition and gating of stimuli that are necessary for maintenance of sleep.

The effects may have been more prominent in the right-hemisphere because of the role that the right-hemisphere plays in arousal [48]. The k-complex has been described as a so-called forerunner of delta EEG, its pattern of generation related to the subsequent occurrence of delta EEG in SWS [49]. The reduced generation, periodicity and amplitude of k-complex activity observed in the TBI group may therefore signify a breakdown in the mechanisms that transition the sleeper from Stage 2 to restorative SWS. In the current study, the physical characteristics of the auditory stimuli were selected to best probe general information processing in sleep with a basic oddball task since sleep ERPs had not been investigated in this group previously. However, to optimally elicit k-complexes, stimuli should be infrequent, salient, and abrupt [40,41]; thus, subsequent research should investigate evoked k-complex activity in TBI samples using such paradigms. Specifically, loud or relevant stimuli (e.g., one's own name) would allow gating mechanisms to be challenged in sleep.

Spindles are phasic events in non-REM sleep which have been shown to have an inhibitory function [50], play a role in sleep-dependent memory consolidation [51,52], and be correlated with IQ [53]. Individuals with a TBI were expected to have fewer and shorter spindles reflecting impairments in inhibitory mechanisms. In healthy good sleepers, spindles are generated most in light Stage 2 non-REM sleep, and reduce systematically with increasing depth of sleep in Stages 3 and 4 [44]. This was the pattern observed in the healthy, good sleeper control group for spindle density, duration and interval. However, for the TBI group, they generated more spindles in Stage 3 than Stage 2, and had a shorter time interval between spindles in Stage 3 compared to either Stages 2 or 4. The duration of spindles was affected by the stimulus delivery on night 3 for the TBI group in Stages 2 and 4, but not Stage 3. In other words, the atypical peak presentation of spindles in Stage 3 seen in the TBI group may have been protective of the disturbance from auditory stimuli. Greater spindle production in SWS for the TBI group could be considered maladaptive in that their presence may prevent delta EEG from being generated. Alternatively, spindle activity may be compensating for lower delta in SWS by engaging other sleep inhibitory mechanisms.

4.3.   Stability of sleep

In good sleepers, sleep is remarkably stable from night to night. Indeed, for controls, correlations for spindle density between nights 1 and 2 were highly stable in all of non-REM sleep. However, for the TBI group, Stage 2 spindle density showed no stability between nights. Consistent with this was the finding that sigma EEG power in Stage 2 sleep varied between nights in the TBI group only. K-complexes and spindles in SWS were highly stable from night to night in both groups, although less so in the TBI group. The instability in generation of spindles further supports impairments in sleep regulatory and inhibitory mechanisms that may explain vulnerability to disrupted sleep in this group. More research is needed to determine factors that may underlie the within subject instability of Stage 2 spindle generation in particular. Further investigation of sleep spindle generation could be done using experiments designed to elicit increased spindle activity via

sleep-dependent learning protocols. A recent study of this nature was carried out in a TBI sample and reported null results [13]; however, further studies are needed in this area, employing different memory tasks in different samples, in order to better understand how disruption to non-REM sleep phasic events following TBI may impact waking neurocognitive function. Important questions include whether changes to sleep-dependent learning processes occur following a TBI, and if individual differences in spindle activity can predict severity of waking memory impairments or prognosis in TBI patients.

4.4. Relationship between sleep and waking function

Given the group differences in sleep, we explored the relationship between altered sleep and waking function. Regression analyses indicated that greater spindle activity was related to better waking function in the TBI group. Specifically, spindles predicted performance on a broad range of neuropsychological tests, over and above the predictive power of injury severity, IQ and age. The intelligence and executive function tasks were predicted by increased spindle activity in SWS in particular. These relationships were strong, with spindle variables predicting between 18% and 47% of the variance in performance. Verbal learning was better predicted by Stage 2 spindle activity. These data suggest that sleep spindle generation may represent an adaptation or resiliency following TBI.

4.5. Limitations, implications, and future directions

A sample of TBI patients without co-morbidities is both difficult to find and non-representative. The current sample included six participants who reported some on-going pain issues and three participants who reported depressive symptoms. While groups did not differ statistically on the inventory of depression (BDI), the TBI group scored higher on the inventory of anxiety (BAI). Thus, it is important to compare the sleep findings in this sample to those from the literature on insomnia, depression, anxiety, and chronic pain. The TBI participants in the present study had a unique constellation of sleep changes including delayed sleep onset, less SW (< 1 Hz) and delta (1–4 Hz) EEG power, fewer k-complexes, lower amplitude evoked k-complexes, and an atypical presentation and night-to-night instability in spindles. Together, these data reveal disruptions to sleep homeostatic mechanisms and profound changes to sleep phasic activity despite minimal evidence for changes in sleep architecture with traditional PSG measures. Individuals with insomnia have been reported to have higher beta/gamma EEG reflective of hyper-arousal [46], but no changes to k-complex or spindle generation [54,55]. Fibromyalgia patients have a characteristic alpha EEG intrusion in SWS [56] that was not observed in the current sample. As well, a recent study reported that mTBI patients with pain had elevated EEG power in a number of bands including theta, alpha, sigma, beta and gamma, but not delta EEG [18]. Sleep and qEEG has been well-studied in depression [57]; typically there is delayed sleep onset, more light sleep, less deep sleep, early morning awakenings, and abbreviated

REM latency; depressed people also show higher alpha and beta EEG in sleep, and lower delta EEG. Sleep in generalized anxiety disorder is consistent with insomnia, but sleep architecture is unremarkable [58]. Thus, the sleep disruption following TBI reported here appears to be quite distinct from the phenomena of insomnia, depression or anxiety, or that seen in chronic pain conditions.

The sample in the current study was recruited to be heterogeneous with respect to sleep complaint and injury severity. Although disturbed sleep has been reported in both mild and severe samples [1–16,18–19], few studies have directly investigated the relationship between TBI severity and sleep disturbance. Two studies have examined this relationship but reported no association between post-traumatic sleep-wake disturbances on PSG measures and injury severity in TBI patients 6 months after injury [59] or 3 year after injury [60]. As our sample varied in time since injury, it is possible that the association between sleep/wake disturbances and injury severity may only be apparent after a longer duration following injury. One study reported that patients with mild TBI self-reported more sleep disturbance than patients with severe TBI [61]. The associations with injury severity in the current study were found with the number of sleep phasic events generated (i.e., spindles and k-complexes); there were no associations with gross sleep architecture or subjective complaints of sleep. This underscores the need to look at sleep physiology quantitatively to assess the extent of sleep disturbance following TBI. That the degree of impairment in sleep phasic events was related to severity of injury in TBI in the current study suggests an important link between the extent of damage/impairment and disruption to sleep inhibitory processes. Future research should investigate sleep in larger samples that include a range of severity. It will be important to use consistent methods of rating severity and/or to systemically investigate the impact of different methods of indexing severity. This is particularly needed for investigation of mild TBI which is highly prevalent and for which clinical ratings scales such as the Glasgow Coma Scale are not always available. The type of sleep complaint also varies in the TBI population and is often dichotomized into those with secondary insomnia or those with excessive daytime fatigue (sometimes labeled post-traumatic Narcolepsy). In reality, after a TBI, individuals will report both difficulties with sleep onset/maintenance and associated daytime fatigue. In the current study, we included these different types of sleep complaints together in the TBI sample, as well as individuals with no subjective sleep complaint. It will be important for future research to investigate sleep physiology in large groups to systematically investigate the impact of type of sleep complaint and severity. Of particular interest is the subgroup of individuals with no subjective sleep complaint; 2 of 4 in our sample had objective evidence of poor sleep despite no complaints. Even individuals without the perception of poor sleep or without current evidence of poor sleep on PSG measures may show altered sleep/wake mechanisms which make them vulnerable to state instability and development of poor sleep.

5. Conclusions

Previous research on sleep following TBI has been limited to survey data and a small number of polysomnographic and qEEG studies. The current study was a controlled and systematic investigation of sleep EEG over multiple nights that led to novel findings which appear to be distinct to the TBI population. Specifically, the TBI group had less Slow Wave (< 1 Hz) and delta (1–4 Hz) EEG power in non-REM sleep, providing evidence of disruption to homeostatic sleep mechanisms. In addition, fewer spontaneous and evoked k-complexes, and reduced periodicity and reduced amplitude of k-complexes revealed disrupted sleep inhibitory and information processing mechanisms that are necessary for maintenance of sleep. Sleep spindles, also known to play an important inhibitory role in sleep, showed an atypical pattern for those with a TBI, with spindles not decreasing systematically with sleep depth. Instability over multiple nights in the generation of spindles further supported evidence of impairments in sleep regulatory and inhibitory mechanisms. These data improve our conceptual understanding of the fragile sleep that follows TBI and provide direction for future investigations to manipulate sleep inhibitory and regulatory mechanisms in this group. Given that greater injury severity was related to fewer evoked k-complexes and lower spindle density, future studies must consider the role of severity when investigating sleep following TBI. The current study also explored the relationship between sleep and waking function; greater spindle generation predicted resiliency in waking function. A better understanding of changes to sleep following TBI and the impact on waking function may help to direct strategies to improve sleep for those with a TBI which may lead to cognitive improvements that allow patients to achieve greater benefit from rehabilitation.

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Conflicts of Interest

All authors declare no conflicts of interest in this paper.

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