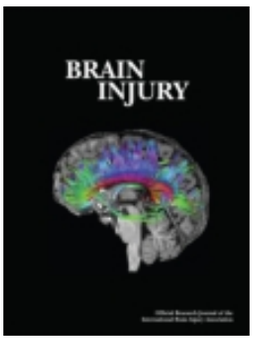

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REVIEW

Does acute TBI-related sleep disturbance predict subsequent neuropsychiatric disturbances?

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Abstract

Primary objective: To determine whether sleep disturbance in the acute post-traumatic brain injury (TBI) period predicts symptoms of depression, anxiety or apathy measured 6 and 12 months after TBI.
Research design: Longitudinal, observational study.
Methods and procedures: First time closed-head injury patients ($n = 101$) were recruited and evaluated within 3 months of injury and followed longitudinally, with psychiatric evaluations at 6 and 12 months post-injury. Pre- and post-injury sleep disturbances were measured via the Medical Outcome Scale (MOS) for Sleep. Subjects were also assessed for anxiety, depression, apathy, medical comorbidity and severity of TBI.
Main outcomes and results: Sleep disturbance in the acute TBI period was associated with increased symptoms of depression, anxiety and apathy 12 months post-injury.
Conclusions: Sleep disturbances experienced soon after trauma (i.e. $<$3 months after injury) predicted neuropsychiatric symptoms 1 year after injury, raising two important clinical questions: (1) Is sleep disturbance soon after trauma a prognostic marker of subsequent neuropsychiatric symptoms? and (2) Can early treatment of sleep disturbance during the post-TBI period reduce subsequent development of neuropsychiatric symptoms? Future studies with larger sample sizes and appropriate control groups could help to answer these questions, using evidence-based methods for evaluating and treating sleep disturbances.

Keywords

Traumatic brain injury, sleep disturbance, depression, anxiety.

History

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Introduction

Traumatic brain injury (TBI) is an ongoing major health problem with an annual incidence of 1.7 million individuals in the US [1]. Sleep disturbance is one of the most disabling consequences of TBI and interferes with both rehabilitation and quality-of-life [2–7]. Early identification of sleep disturbance following TBI could be important because treatment may reduce TBI morbidity.

Preliminary work by this group [8] found that the rate of sleep problems, as assessed by the Medical Outcome Scale (MOS) in the acute post-TBI period (i.e. within 3 months of injury), was increased, compared to pre-injury rates in most domains (other than snoring). It was also found that sleep disturbance was associated with new onset anxiety and depressive disorders during the first 3 months after TBI and that TBI severity, as assessed by the Glasgow Coma Scale (GCS), was not a significant predictor of new onset psychiatric symptomatology. Other researchers [3,9,10] have also noted high rates of psychiatric comorbidity in persons with TBI and sleep disturbances. Cantor et al. [3] followed 343 persons with moderate–severe TBI for 1–2 years after injury and noted that those with insomnia and fatigue, compared to those without, had higher rates of depression and anxiety disorders. Similarly, Chaput et al. [9] conducted a retrospective chart analysis in 443 patients with mild TBI and noted that patients with sleep disturbances 10 days after injury were 6.3- and 4.8-times more likely to have depressive symptoms and irritability, respectively, at 6 weeks post-TBI. Another recent study [10] of 29 640 male US Navy and Marine Corps members analysed the Post-Deployment Health Assessment (PDHA) and associated Post-Deployment Health Reassessment (PDHRA) forms. Sleep problems were shown to mediate 26% of TBI's effects on the development of PTSD and 41% of TBI's effects on the development of depression, suggesting that sleep problems may be an early indicator of risk for PTSD or depression in patients with TBI.

Based on these previous findings, a second investigatory analysis was conducted in a larger sample size (additional subjects were enrolled since the original preliminary analysis). The purpose of this continued investigation and secondary analysis was to: (1) determine the extent to which TBI-related sleep disturbances persist 3, 6 and 12 months after TBI; and (2) evaluate the longer-term relationship between sleep disturbance in the acute TBI period and symptoms of depression, anxiety and apathy at 6 and 12 months after TBI. Based on previous findings [8], it was hypothesized that, compared to their pre-TBI condition,

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participants would have higher overall sleep disturbance scores as assessed by the Medical Outcome Scale for Sleep (MOS) 3, 6 and 12 months post-TBI.

It was also hypothesized that there would be a positive association between sleep disturbances in the acute TBI period (<3 months post-TBI) and depressive and anxiety symptoms observed 6 and 12 months after TBI.

Methods

Participants and procedures

Subjects with first-time TBIs were recruited within 3 months of trauma from the acute trauma unit of the Johns Hopkins Hospital and the brain injury (rehabilitation) unit of Kernan Hospital at the University of Maryland. For the purpose of the study, TBI was defined as having *at least one of the following*: (a) clear history of loss of consciousness; (b) Glasgow Coma Score less than 15; and/or (c) evidence of trauma (contusion or haemorrhage) on computerized tomography (CT) scans done as part of clinical work-up. Other inclusion criteria included: (a) ability to provide consent personally, (b) $\geq$18 years of ag, and (c) admission to the hospital for evaluation of head trauma. Exclusion criteria included: (a) prior TBI, (b) an open-head injury (e.g. a displaced skull fracture or a gunshot wound) and (c) a history of any other type of brain illness (e.g. stroke, seizure, encephalitis).

An arbitrary cut-off of 3 months or less was used to define the acute TBI period and >3 months as the chronic TBI period, as other TBI studies have used a similar cut-off [11,12]. In addition, most of the participants in this study who had sustained severe injury underwent their initial evaluation between the 2nd and 3rd months after trauma, because sufficient time was needed to stabilize medically and provide informed consent.

Determination of the ability of participants to provide informed consent was based on their treating physicians' opinions and the ability of potential participants to accurately summarize the study and their roles in it. All participants were evaluated three or four times during the year post-TBI. Participants who were medically stable underwent their initial evaluation within 2 weeks after trauma. The initial assessment evaluated subjects' lifetime history of psychiatric problems, pre-TBI sleep problems and psychosocial functioning (Visit at baseline; V0). Subsequent evaluations were conducted within the first 1–3 months post-TBI (visit between 1–3 months; V3), 6 months post-TBI (visit at 6 months; V6) and 12 months post-TBI (visit at 12 months; V12) and included assessment of neuropsychiatric problems and psychosocial functioning. However, for those subjects who were unable to give consent within the first 2 weeks of trauma, both the pre-TBI and post-TBI status were assessed at the time they were able to provide informed consent, i.e. within the first 3 months of TBI. This included assessment of pre-TBI status (lifetime history of psychiatric problems, pre-TBI sleep problems and psychosocial functioning) and assessment of neuropsychiatric problems and psychosocial functioning within 3 months post-TBI. Follow-up continued at 6 and 12 months post-TBI. Information from a collateral informant was collected whenever possible, on both the pre-TBI and post-TBI status, for all psychosocial measures.

Measures

All participants were interviewed by a neuropsychiatrist (VR) at baseline and at each of the follow-up visits. The following instruments were used:

- *Medical Outcome Scale for Sleep (MOS)*: Sleep problems before and after TBI were determined using the 12-item MOS. The scale has good psychometric properties and has been found to be useful to assess sleep problems in adults [13]. This instrument assesses several sleep domains: sleep disturbance (trouble falling asleep, time required to fall asleep, restless sleep, awakening during sleep with trouble falling back asleep), snoring, awakening with shortness of breath or headache (SOBHA), sleep adequacy (the feeling of restfulness upon waking in the morning and feeling as though one has received the needed amount of sleep) and daytime somnolence (drowsiness during day, trouble staying awake during the day and daytime napping). In addition, two summary index measures were used to assess overall sleep problems as part of the MOS: the Sleep Problem Index 1 and Sleep Problem Index 2. The Sleep Problem Index 1 is a short summation index of sleep disturbances that includes awakening with shortness of breath or with headache (SOB/HA), trouble staying awake during the day, trouble falling asleep, awakening during sleep with trouble falling back asleep and feeling not well rested on awakening. Sleep Problem Index 2 is a more thorough summation index that includes all of the items in Sleep Problem Index 1, as well as other sleep indices, such as time required to fall asleep, restless sleep and sleepiness or drowsiness during the day. All domain scales and index measures were scored on a transformed 0–100 metric, with higher scores indicating more severe sleep problems.
- *Glasgow Coma Scale (GCS)*: The severity of TBI was determined by the Glasgow Coma Scale (GCS) [14], the most widely used instrument for quantifying TBI severity. The GCS was administered by the trauma staff or emergency room personnel during the initial trauma evaluation. The GCS has a range of 3–15. GCS scores of 3–8 are considered severe TBI, 9–12 moderate TBI and 13–15 mild TBI.
- *Hamilton Depression Rating Scale (HAM-D)*: The Hamilton Depression Rating scale (HAM-D) is a 17-item scale that evaluates depressed mood in addition to vegetative and cognitive symptoms of depression. It is a widely used instrument that has previously been used in patients with TBI [15,16].
- *Clinical Anxiety Scale (CAS)*: The CAS [17] is a derivative of the Hamilton Anxiety scale and was used to measure anxiety symptoms. This scale is not somatically focused and does not have items for depression. It is a valid instrument for the assessment of anxiety in persons with medical illness.
- *Apathy Evaluation Scale (AES)*: The AES [18,19] is a 17-item scale with each item rated on a 4-point scale, from 1 (not at all characteristic) to 4 (very characteristic), that has been validated for the evaluation of apathy in neurological diseases. The total possible score is 72, with higher scores indicating more severe apathy. The clinician version of the AES was used in this analysis.

- *General Medical Health Rating (GMHR)*: Medical comorbidity was assessed using the General Medical Health Rating (GMHR) scale [20]. The GMHR scale ranges from 1 (poor health) to 4 (excellent health) and provides a global assessment of a person's medical problems and medications. Data on the number, but not type, of prescription medications used by each patient was collected.
- *Psychosocial functioning*: Participants' pre- and post-TBI psychosocial functioning was assessed using the Social Ties Checklist (STC) and the Social Functioning Exam (SFE) [21]. Both of these scales have been used in prior TBI studies [12,15]. Scores on the SFE and STC range from 0.00 (greatest satisfaction) to 1.00 (least satisfaction).
- *Activities of daily lving*: The personal and instrumental activities of daily living were assessed by the Lawton and Brody [22] scale, which has previously been used mainly in dementia studies to assess everyday self-maintenance skills.
- *Cognitive tests*: A comprehensive battery of neuropsychological tests was administered to all study participants at 3 and 12 months post-TBI. The battery consisted of the Mini Mental State Examination (MMSE) [23]; the National Adult Reading Test (NART) [24], the Verbal Fluency Subtest (letter 's' and 'p') and Category Sub-test (animals & supermarket) [25]; the Hopkins Verbal Learning Test-Revised (HVLT-R) [26], the Brief Visuospatial Memory Test-Revised (BVMT-R) [27], the Trail Making Test [28], the Stroop Color and Word Test [29], the Brief Test of Attention (BTA) [30] and the Wisconsin Card Sorting Test (WCST) [31].

Statistical methods

ANOVAs with post-hoc pairwise comparisons by Bonferroni adjustments were used for comparing sleep problems pre-TBI and at 3, 6 and 12 months post-injury. Univariate regression analyses were used to determine the relationship between sleep problems at less than 3 months after TBI and psychiatric and cognitive symptoms at 6 and 12 months post-injury. Multivariate regression analyses were then conducted, controlling for dependent variables that had been found to be significant in univariate regression analyses including age, sex, severity of TBI, medical problems and psychiatric symptom scores obtained in the immediate post-injury period.

$p < 0.05$ was used as the threshold for statistical significance. All analyses were conducted using STATA Version 11.0 (StataCorp, College Station, TX).

Results

Demographics

A total of ~1000 people admitted to the trauma unit at Johns Hopkins School of Medicine and the Brain Injury unit at Kernan Hospital, University of Maryland were screened over a 2.5 year period. Of these, a total of 142 were enrolled. The majority of potential subjects who were excluded did not qualify for inclusion because of prior head injury. Other reasons for exclusion included age below 18, absence of clear history of loss of consciousness and refusal to participate. Most patients who refused to participate did not offer reasons for declining participation, other than stating that they could not commit themselves to a research study.

Of the subjects enrolled, 41 were subsequently excluded because they failed to return for any follow-up visits or did not have baseline evaluations. The final study sample was 101. There were no clinical or demographic differences between subjects who failed to return for follow-up and those who completed the study.

The mean age of the sample was 42.9 years (SD = 17.9), the mean education level was 12.9 years (SD = 2.9) and the mean Glasgow Coma Scale score was 12.4 (SD = 3.5). GCS was unknown in 16 subjects. With regards to severity of TBI as assessed by loss of consciousness (LOC), 60 subjects (59.4%) had mild TBI (LOC less than 30 minutes) and 38 (37.6%) had moderate/severe TBI; the duration of LOC in three subjects was unknown. Males accounted for 62.4% and Caucasians for 52.5% of the sample. The majority (83.8%) was either married or had a partner, was employed (75.2%) and had an annual income of at least US $20 000 or greater (57.4%). Over half (57.6%) sustained TBI in a motor vehicle accident; otherwise, assault (21.2%), falls (20.2%) and unknown or 'found down' (1%) accounted for the injury. A total of 10 (9.9%) underwent brain surgery after the trauma and 64 (63.4%) had also sustained body trauma.

Comparison of sleep scores before and after TBI

As seen in Table I compared to pre-TBI sleep scores, MOS scores (sleep problem index 1 and 2) were significantly increased after TBI, reflecting increased sleep disturbances at each of the follow-up visits. When analysed by individual sleep symptoms, scores on 'daytime sleepiness' were increased at each of the follow-up visits. Scores on 'shortness of breath/headache (SOBHA)' were increased at 3 and 12 months and ratings on the domains 'sleep disturbance' and 'sleep adequacy' were significantly increased at 3 and 6, but not 12 months post-injury. There was no increased score in the MOS domain of snoring at any of the visits compared to pre-TBI.

Relationships between sleep scores in the acute post-TBI period and psychiatric symptoms 6 and 12 months after TBI

To determine the relationship between sleep scores in the acute period (< 3 months post-TBI) and psychiatric symptoms at 6 and 12 months, univariate regression analyses were first conducted using the overall sleep score (Sleep Index 2) at <3 months as the independent variable and scores on the HAM-D, CAS, AES and SFE as dependent variables (Table II). At both 6 and 12 months after TBI, there was a positive relationship between sleep scores during the acute post-TBI period and scores on HAM-D, CAS and AES. Higher sleep scores 1 year post-injury were also associated with poorer social functioning during the same time period, as assessed by SFE. However, there was no statistically significant relationship between sleep scores in the acute period and scores on social networking (as assessed by Social Ties Checklist), global cognitive functioning (as assessed by MMSE) or activities of daily living (as assessed by Lawton Activities of Daily living scale).

Table I. Comparison of sleep problems at baseline and at < 3, 6 and 12 months post-injury.

Variable	Time	*n*	*M*	SD	*F* (*p* value)*Each visit compared to baseline	Domain*F* (*p* value)*
Sleep disturbance	V0	101	18.4	19.26		4.51 (0.00)
	V3	101	29.4	25.49	11.07 (0.01)	
	V6	72	31.0	30.23	12.66 (0.01)	
	V12	70	24.8	28.85	6.45 (0.65)	
Snoring	V0	101	28.5	35.25		0.73 (0.54)
	V3	101	24.0	35.22	−4.55 (1.00)	
	V6	72	21.7	34.19	−6.85 (1.00)	
	V12	70	28.0	34.29	−0.51 (1.00)	
SOB/HA	V0	101	1.4	6.49		6.83 (0.00)
	V3	101	14.5	28.16	13.07 (0.00)	
	V6	72	8.9	18.66	7.50 (0.15)	
	V12	70	12.3	27.30	10.90 (0.01)	
Sleep adequacy	V0	101	25.8	26.88		4.58 (0.00)
	V3	101	37.6	30.92	11.78 (0.03)	
	V6	72	41.1	31.78	15.27 (0.01)	
	V12	70	32.4	27.89	6.59 (0.90)	
Daytime sleepiness	V0	101	18.1	17.62		8.37 (0.00)
	V3	101	32.9	25.77	14.76 (0.00)	
	V6	72	31.2	23.63	13.10 (0.00)	
	V12	70	30.8	25.95	12.71 (0.00)	
Sleep Problem Index 1	V0	101	14.9	14.38		9.33 (0.00)
	V3	101	28.5	23.07	13.55 (0.00)	
	V6	72	28.8	21.67	13.82 (0.00)	
	V12	70	24.4	23.41	9.44 (0.02)	
Sleep Problem Index 2	V0	101	17.4	13.82		8.77 (0.00)
	V3	101	29.9	21.65	12.43 (0.00)	
	V6	72	30.9	21.96	13.49 (0.00)	
	V12	70	26.3	23.26	8.87 (0.03)	

* *F* (*p*): ANOVA and Bonferroni.
V0 = Baseline recall of sleep status before TBI, V1 = Assessment of sleep status within 3 months after TBI; V6 and V12 = Assessment of sleep status at 6 and 12 months after TBI.
SOB/HA, Shortness of breath/headache.

Table II. Relationship between sleep problems in the acute TBI period and psychiatric illness at visit 6 and 12 months post-injury.

Dependent variables	Time	B	SE	*Z*	*p*	95% CI
AES	V6	0.151	0.069	2.190	0.032	0.013–0.288
AES	V12	0.196	0.050	3.940	0.000	0.097–0.295
CAS	V6	0.155	0.030	5.100	0.000	0.094–0.216
CAS	V12	0.155	0.030	5.100	0.000	0.094–0.216
HAMD	V6	0.202	0.049	4.130	0.000	0.105–0.300
HAMD	V12	0.202	0.049	4.130	0.000	0.105–0.300
SFE	V6	0.001	0.001	1.480	0.144	0.000–0.300
SFE	V12	0.002	0.001	3.260	0.002	0.001–0.004
STC	V6	−0.004	0.011	−0.330	0.740	−0.025–0.018
STC	V12	−0.005	0.007	−0.620	0.535	−0.019–0.010
ADLs & IADLs	V6	0.033	0.023	1.460	0.149	−0.012–0.079
ADL & IADLs	V12	0.003	0.021	−0.127	0.899	−0.046–0.040
MMSE	V6	0.005	0.011	0.439	0.663	−0.018–0.028
MMSE	V12	0.019	0.015	1.25	0.216	−0.011–0.048

Independent variable: Sleep Problem Index 2 at < 3 months TBI.
V6 and V12 = Assessment of sleep status at 6 and 12 months after TBI.
AES, Apathy evaluation scale; CAS, Clinical Anxiety scale; HAMD, Hamilton Depression scale; SFE, Social Functioning Exam; STC, Social Ties Checklist; ADL & IADLs, Personal & instrumental activities of daily living.

Relationships between sleep scores in the acute post-TBI period (3 months) and cognitive function 6 and 12 months after TBI

No relationship was found between acute sleep disturbance and cognitive function 6 or 12 months post-TBI, as assessed by the Mini Mental State Exam and a comprehensive battery of neuropsychological tests.

Multivariate models: Sleep disruption during acute TBI period as a predictor of neuropsychiatric symptoms 6 and 12 month after injury

Multivariate regression analyses were then conducted using only dependent variables that were significant in the univariate regression analyses, controlling for age, sex, severity of TBI, medical problems and scores of the dependent variable at the initial visit (i.e. during the acute TBI period; Table III). There were statistically significant associations between sleep scores in the acute TBI period (<3 months post-TBI) and (a) HAM-D scores at 12 months (model accounting for 53% of the variance) and (b) CAS scores at 12 months (model accounting for 35% of the variance).

An additional analysis was conducted in the sub-group of patients with mild TBI only ($n = 60$), using the same dependent, independent and control variables (Table IV). Among this group, there were also associations between sleep scores in the acute TBI period (< 3 months post-TBI) and the following dependent variables at 12 months: (a) depressive symptoms, (b) apathy symptoms and (c) anxiety symptoms. Interestingly, sleep disturbance was associated with higher scores on the MMSE in this sub-group.

Table III. Relationship between sleep problems in acute TBI period* and psychiatric symptoms at 1 year post-injury after controlling for confounds** in persons with all severities of TBI.

Dependent variables	β (SE)	p Value	Adjusted R^2
Hamilton Depression Scale	0.192 (0.044)	0.000	0.528
Apathy Evaluation scale	0.089 (0.061)	0.152	0.386
Activities of Daily Living	0.001 (0.007)	0.904	0.155
Clinical Anxiety Scale	0.121 (0.031)	0.000	0.349
Social Functioning Examination	0.001 (0.001)	0.210	0.333
Mini Mental State Exam	0.02 (0.015)	0.173	0.392

* Sleep Index 2 score at < 3 months TBI.
** Age, gender, general medical health, Glasgow Coma Scale, Psychiatric symptoms in the acute TBI period, i.e. < 3 months.

Table IV. Relationship between sleep problems in the acute TBI period* and psychiatric symptoms at 1 year post-injury after controlling for confounds** in persons with mild TBI.

Dependent variables	β (SE)	p Value	Adjusted R^2
Hamilton Depression Scale	0.255 (0.074)	0.002	0.417
Apathy Evaluation scale	0.153 (0.076)	0.054	0.336
Activities of Daily Living	0.001 (0.01)	0.929	0.126
Clinical Anxiety Scale	0.111 (0.033)	0.002	0.411
Social Functioning Examination	0.001 (0.001)	0.287	0.309
Mini Mental State Exam	0.041 (0.018)	0.035	0.573

* Sleep Index 2 score at <3 months TBI.
** Age, gender, general medical health, psychiatric symptoms in the acute TBI period, i.e. <3 months.

Discussion

Results from this study indicate that sleep disturbances are common and persistent throughout the 12-month period following TBI, regardless of the severity of initial head injury. In addition, sleep disturbance during the acute TBI period was found to predict the development of anxiety and depressive symptoms during the chronic period in persons with all severities of TBI. In subjects with mild TBI, acute sleep problems also predicted the subsequent development of apathy.

The finding that sleep disturbances are common following TBI is consistent with previous studies in different clinical samples [32–39]. Previous cross-sectional studies in patients with TBI have also noted a relationship between sleep problems, anxiety and depression [36,38]. Although no previous studies have examined sleep disturbance in the early TBI period as a potential predictor of apathy in the chronic period, studies in Alzheimer's disease have noted an association between sleep disturbances and apathy [40].

Analyses of the different domains of sleep on the MOS scale revealed that scores in most domains were significantly higher 6 months after TBI than during the pre-TBI period. Scores in the 'daytime sleepiness' and 'shortness of breath/headache' domains continued to be significantly higher than baseline levels 1 year after TBI, while scores on the other scales no longer differed from baseline. Cohen et al. [11] also noted differences in the profile of sleep disturbance in the acute vs chronic TBI period. In particular, higher rates of insomnia were noted in the acute period, whereas excessive daytime sleepiness was seen in the chronic post-TBI period. This study did not use specific scales to capture insomnia or excessive daytime sleepiness and, hence, the authors are unable to comment specifically on changes in these particular symptoms over time.

The domain SOBHA was captured by a single question: 'How often during the past 4 weeks did you awaken short of breath or with a headache?' High scores on this domain at the 12-month time-point reflect the presence of either one or both of these problems in the chronic period. Although the questionnaires did not distinguish between these two symptoms, existing literature suggests that headaches are common and persistent after TBI [41–43]. That having been said, anxiety, sleep panic attacks, sleep apnea and nightmares can all be associated with abrupt awakenings and a sense of shortness of breath. As such, future research will be necessary to further evaluate the basis for high scores on the SOBHA scale following TBI.

It is surprising that scores on snoring (captured by a single question, 'How often during the past 4 weeks did you snore during your sleep?') were no different from baseline at any of the visits. A recent metaanalysis of 21 studies [2] found snoring to be the most prevalent sleep problem in patients with TBI, with a prevalence of 60%. It is likely that failure to detect an increase in snoring post-TBI was because patients are not always aware that they snore and no formal polysomnographic measures were obtained.

Sleep problems following TBI can be secondary to a myriad of factors, including injury to brain structures responsible for sleep regulation [44,45], pain, co-morbid medical problems, side-effects of medications or secondary to psychiatric disorders [46]. Psychiatric disorders are common after TBI. The entire spectrum of TBI severity is associated with high rates of psychiatric disorders [47,48]. Roughly 40% of persons with TBI suffer at least one or more Axis I psychiatric disorder [49,50]. Depression is the most common psychiatric disorder in this population, with prevalence rates ranging from 27% [51] to 61% [51]. Jorge et al. [15] noted major depressive disorder in 33% of 91 patients with all severities of TBI during the first year of TBI; co-morbid anxiety and aggression in 77% and 57%, respectively, in those patients with depression.

The association of sleep disturbance in the early TBI period (in the mild TBI sub-group) and higher MMSE scores in the late injury period is an interesting and unexpected finding. A simplistic explanation for the presence of prolonged psychiatric symptoms and preserved cognitive functions in this group may be that this is a 'worried well' group. However, this explanation would be highly speculative. The real answer lies in future studies investigating sleep disturbances in mild TBI subjects, using formal polysomnographic measures, and cognitive testing at various time points, to assess the relationship between the various types of sleep disturbances and cognitive functioning.

Sleep disturbance and psychiatric disturbances have a bidirectional relationship; they share common neurotransmitter systems and common neuroanatomical correlates. As noted by Chaudhuri and Behan [52], sleep disturbances after TBI can occur because of injury to the ascending reticular activating system, limbic system and the basal ganglia with resultant dysfunction of the striatal-thalamic-frontal

cortical tract. The same brain regions have been implicated in mood dysregulation after TBI [12,15]. However, sleep and neuropsychiatric disturbances after TBI are related not only to the pathophysiological aspects of brain trauma; psychosocial factors also play an important role. Studies of TBI-related depression by Jorge et al. [12] reveal that early onset major depression (onset within 3 months of TBI) is associated with lesions in the left dorsolateral frontal region, basal ganglia and subcortical regions. In contrast, the same group found that late onset depression (onset after 3 months TBI) is not associated with brain lesions, but with significant psychosocial impairment. It was hypothesized that the aetiology of early onset depression may be biological and related to brain lesions, whereas late-onset depression may be a psychological reaction to trauma and its consequences. A similar explanation may hold true for sleep disturbances after TBI (particularly since sleep disturbance is common in depression and various anxiety disorders and, indeed, is a core symptom of PTSD).

Although the aetiology of sleep and psychiatric disturbances in the acute vs chronic post-TBI periods may be different and multifactorial, the analyses suggest that sleep disturbance in the acute post-TBI period has the potential to serve as an early clinical marker for development of neuropsychiatric symptoms in the chronic TBI period. Results from the present study, when considered with previous studies that have evaluated sleep and neuropsychiatric symptoms following TBI, support the need for future research. Among the key questions to be addressed is whether detection and treatment of sleep disorders soon after brain injury could reduce the incidence of neuropsychiatric disturbances in the chronic TBI period.

The major limitation of the current study is that only subjective measures were used to assess sleep disturbance and, thus, results may have been influenced by recall bias. In addition, those with pre-TBI sleep disturbances or sleep disorders were not excluded, as the primary focus of the study was determining risk factors for TBI-related depression. However, a sub-analysis was conducted to look at the relationship between pre-TBI sleep disturbances and scores on AES, HAM-D and CAS at 6 and 12 months. The only statistically significant finding was a positive relationship between pre-TBI sleep disturbance and apathy symptoms at 6 months, but not at 12 months. It would be clinically useful for future studies to focus on the relationship between pre-TBI sleep disturbances and neuropsychiatric outcomes using comprehensive sleep instruments. Also, as discussed in a previous paper [8], information was not collected on specific medical issues (e.g. pain, number and type of medications, presence/absence of ongoing treatment), which limits the ability to determine the potential role of these medical factors on the outcome measures. Finally, although this study, like others, defined the acute TBI period as within 3 months of injury, this period may not be the best window for predicting downstream neuropsychiatric syndromes.

Despite these limitations, this is the first study to demonstrate that sleep disturbances in the acute post-TBI period are associated with neuropsychiatric symptoms in the chronic period, in persons with all severities of TBI, including mild TBI. This finding raises two important clinical questions: (1) Can acute sleep disturbance following TBI serve as a prognostic marker of subsequent neuropsychiatric morbidity? (2) Can treatment of sleep disturbance in the acute post-TBI period reduce or prevent subsequent neuropsychiatric disturbances?

Conclusion

In summary, sleep disturbances are common in persons with TBI during the year after injury. The present results suggest that sleep disturbances during the acute post-TBI injury period may have the potential to serve as prognostic markers of TBI-related neuropsychiatric morbidity. These findings need to be replicated in future longitudinal studies using appropriate control groups and objective sleep measures. Future research should be conducted to address the possibility that treatment of sleep disturbances in the acute post-TBI period, using evidence-based methods, prevents development of subsequent, chronic neuropsychiatric comorbidity.

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Declaration of Interest

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