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Sleepiness and fatigue following traumatic brain injury

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Abstract

Objectives: To compare individuals with traumatic brain injury (TBI) to healthy controls (CTLs) on measures of sleepiness, fatigue, and sleep, and explore correlates of sleepiness and fatigue separately for each group.

Methods: Participants were 22 adults with moderate/severe TBI (time since injury ≥ 1 year; mean = 53.0 ± 37.1 months) and 22 matched healthy CTLs. They underwent one night of polysomnographic (PSG) recording of their sleep followed the next day by the Maintenance of Wakefulness Test (MWT). They also completed a 14-day sleep diary, the Epworth Sleepiness Scale (ESS), the Functional Outcomes of Sleep Questionnaire (FOSQ), and the Multidimensional Fatigue Inventory (MFI).

Results: There were no significant group differences on measures of objective (MWT) or subjective (ESS) sleepiness, both groups being quite alert. However, TBI participants reported greater consequences of sleepiness on their general productivity (FOSQ), spent more time in bed at night, and napped more frequently and for a longer time during the day. Subjective fatigue was significantly higher in TBI participants on the general, physical, and mental fatigue MFI subscales. There were no between-group differences on any sleep parameters derived either from PSG or sleep diary.

Conclusions: Fatigue appeared to be a more prominent symptom than sleepiness when assessed between 1 and 11 years after TBI. Participants with TBI used compensatory strategies such as increasing time spent in bed and daytime napping in this sample. Future research should document the time course of sleepiness and fatigue after TBI and investigate treatment options.

Keywords: Brain injury, sleepiness, fatigue, sleep, neurological disorders, case-control study

Regarded as a “silent epidemic,” traumatic brain injury (TBI) is a major public health issue with an incidence of 1,565,000 in the US in 2003 [1]. Although the vast majority of injuries are classified as mild, more severe TBI is associated with poorer outcome, as illustrated by a 43.3% long-term disability rate among injuries necessitating hospitalization [2]. In addition to more noticeable consequences in the physical, psychiatric, and cognitive domains, sleepiness, fatigue, and sleep disturbances are increasingly recognized as prevalent and persistent outcomes following TBI.

According to recent reviews, 30–70% of TBI survivors report sleep–wake disturbances [3]. Excessive sleepiness is one of the most common ones, both as a self-reported complaint assessed by questionnaires and as an objective physiological symptom measured by daytime polysomnography [4-6]. Sleepiness may present as a stand-alone symptom or as part of a sleep disorder such as sleep apnea, narcolepsy, or posttraumatic hypersomnia [3,7]. In many cases, sleep–wake disturbances are directly related to the brain trauma, persist for months or years after the injury, and may impede the recovery process and return to premorbid functioning [3,8,9]. Fatigue is also a very common symptom following TBI, with prevalence estimates ranging from 43% to 73% by self-report [10]. Fatigue is chronic in many cases, remaining as prevalent several years after the TBI [11,12], and has been linked to impairments in quality of life, instrumental activities of daily living, and social functioning [11,13].

Despite overlapping features leading patients, clinicians and researchers alike to confuse them, sleepiness and fatigue are distinct concepts [14,15]. For instance, sleepiness can be defined as the “inability to maintain a desired level of alertness or wakefulness during the day” [16] while “central” (as opposed to peripheral or muscular) fatigue is a multifaceted phenomenon which has been described as the “failure to initiate or sustain attentional tasks (“mental fatigue”) and physical activities (“physical fatigue”) requiring self motivation” [17]. Further complicating their differentiation is the fact that both sleepiness and fatigue can be present in specific populations and both can be exacerbated by underlying sleep disorders. Thus, it is crucial to investigate these phenomena concurrently in order to better understand their common and unique manifestations and ultimately orient treatment plans. Only a few studies have done so in individuals with TBI. An investigation of 76 consecutive TBI patients conducted six months after the injury suggested that sleepiness, fatigue and hypersomnia were the most prevalent sleep–wake disturbances [18]. The same sample was re-assessed three years post-injury, showing an increase in the prevalence of fatigue and a decrease in the prevalence of sleepiness [8]. Chaumet et al. observed that, while subjective fatigue correlated with sleepiness in TBI

individuals at least six months after their injury, the levels of both objective and subjective sleepiness were within the normal range and did not significantly differ from those of healthy controls [19].

Despite emerging scientific literature in recent years, little is known, still, regarding the nature, course, and correlates of sleepiness and fatigue following TBI, especially after more severe injuries. Indeed, most published studies have been conducted on samples including mild TBIs only or combined with moderate/severe TBIs despite the well documented discrepancies in expected short- and long-term outcomes between these severity levels. This study aimed to (1) compare individuals with moderate/severe TBI assessed at least one year post-injury to matched healthy controls on measures of sleepiness, fatigue, and sleep, and (2) explore correlates of sleepiness and fatigue separately for each group.

Methods

The study protocol was approved by the Institutional Research Ethics Boards of the *Institut de réadaptation en déficience physique de Québec* and the *Centre de recherche Université Laval Robert-Giffard*, both affiliated with Université Laval, Québec, QC, Canada.

Participants

TBI participants (*N* = 22) had to have sustained a moderate or severe TBI at least one year prior to their participation in the study. They were recruited through a review of medical records (*n* = 8) and referrals from healthcare professionals (*n* = 6) working at a local rehabilitation center, and from solicitation of members of a regional association of TBI survivors (*n* = 8). TBI severity was validated by consulting medical records and was based on an algorithm [20] taking into account standard criteria such as the duration of loss of consciousness, duration of posttraumatic amnesia (PTA), initial score on the Glasgow Coma Scale (GCS) [21], results of brain imaging, and neurological exam. Healthy controls (CTL; *N* = 22) were matched with TBI participants on gender, age (±3 years), and education (±3 years or same highest academic degree). They were recruited via personal referrals (*n* = 8), referrals from ongoing studies at the sleep center (*n* = 3), and advertisements in educational and healthcare institutions (*n* = 11). All participants had to have a valid current or past driver's license. Exclusion criteria for all participants were: (a) active or progressive medical condition susceptible to cause sleepiness or fatigue or interfere with cognitive functioning; (b) sensory (e.g., visual or auditory) or motor impairment susceptible to interfere with test administration or performance; (c) history of bipolar

or psychotic disorder; (d) current major depressive episode; (e) evidence of sleep-related breathing disorder; (f) regular use of hypnotic medication or antidepressant (unless dosage had been stable for at least three months); (g) night- or rotating-shift work within the past year; and (h) atypical sleep/wake schedule (i.e., habitual bedtime later than 2 am or habitual rising time later than 10 am).

Procedure

The study involved two visits to the sleep center. The first one included obtaining informed consent, verifying selection criteria using sections of structured clinical interviews for psychiatric [22] and sleep [23] disorders, and completing self-reported measures. Participants were also given a sleep diary to be completed prospectively for two weeks, as well as a collateral informant version of the Epworth Sleepiness Scale. The second visit involved one night of polysomnographic recording and completion of several tests on the following day: Maintenance of Wakefulness Test, visual analogue scales, neuropsychological tests, and a driving simulator task. Neuropsychological and driving simulator data will be discussed in a separate paper currently in preparation. During the experimental day, participants were asked to take their medication as usual and limit their caffeine intake to one cup at breakfast. A financial compensation of C$ 75 and a summary of test results were provided.

Measures

Polysomnography (PSG). Participants underwent one night of PSG recording. Time spent in bed was kept between 8 and 9 h to provide a uniform recording time across participants. The preferred sleep schedule of each participant was taken into account along with logistical considerations (e.g., preparation time in the evening, staff availability) were taken into account to determine bedtime, which ranged from 9:53 to 11:30 pm, and rising time, which ranged from 5:52 to 7:36 am. A standard PSG montage was used and sleep stages were scored according to standard criteria [24] by experienced technologists blind to each participant's condition. To assess the presence of apneas/hypopneas and limb movements, respiration, oxygen saturation, and anterior tibialis electromyogram were monitored. Dependent variables included measures of sleep continuity (sleep onset latency [SOL], wake time after sleep onset [WASO], total sleep time [TST], time spent in bed [TIB]), sleep architecture (percentage of sleep time spent in stage 1, stage 2, stages 3–4, and REM sleep; REM sleep latency), and indexes (number of events/hour) of micro-arousals, apnea–hypopnea events (AHI), and periodic limb movements associated with arousal (PLMAI).

Maintenance of Wakefulness Test (MWT). The MWT was preferred over the Multiple Sleep Latency Test (MSLT) as the former was deemed more appropriate to assess the capacity of individuals to remain awake during the day [25]. The protocol consisted of four daytime PSG recordings performed at 2-h intervals with the first trial beginning 1.5 h after arising time. Trials took place in a dark and quiet bedroom following standard recommendations [26]. Participants were asked to sit still in bed and remain awake as long as possible without using extraordinary measures. Trials ended if sleep was recorded (i.e., after three consecutive epochs of stage 1 or one epoch of any other stage) or after 40 min if no sleep occurred. Dependent variables were mean SOL (with shorter values suggesting higher sleepiness/lower alertness) and number of sleep onset REM sleep periods (SOREMPs).

Epworth Sleepiness Scale (ESS). The ESS [27] is a measure of subjective sleep propensity in recent times in eight daytime situations using a four-point scale. Total score ranges from 0 to 24, with scores higher than 10 suggesting clinically significant subjective sleepiness [28]. An adapted version was also completed by a collateral informant between the participant's first and second visit to the sleep center.

Functional Outcomes of Sleep Questionnaire (FOSQ). The FOSQ [29] is a questionnaire assessing the functional impact of sleepiness on 30 activities of daily living using a four-point scale. When the activity is impeded by a factor other than sleepiness, the item is discarded for scoring purposes. The FOSQ includes a total score (range: 5–20) and five subscales (range: 1–4) measuring the impact of sleepiness on general productivity, social outcome, activity level, vigilance, and intimacy and sexual relationships. Lower scores indicate greater impairment.

Multidimensional Fatigue Inventory (MFI). The MFI [30] is composed of 20 statements using a five-point scale and assessing five dimensions of fatigue (general fatigue, physical fatigue, mental fatigue, reduced motivation, reduced activities) in recent times. Subscale scores range from 4 to 20. A total MFI score was derived by adding up scores from the five subscales.

Visual analogue scales (VAS). VAS for sleepiness (VAS-s) and fatigue (VAS-f) were completed hourly on the experimental day and consisted of 100-mm horizontal lines, with the left extremity corresponding to the absence of either sleepiness or fatigue and the right extremity to its maximum level. Participants had to draw a vertical line crossing the horizontal line at a position corresponding to their current level of sleepiness or fatigue. They were instructed how to differentiate sleepiness and fatigue. The distance between the left extremity of the horizontal

line and the intersection yielded a score from 0 to 100. Although they use arbitrary units, VAS have been shown to be sensitive to variations in psychophysiological states [31].

Sleep diary. A sleep diary was completed for 14 consecutive days, with questions about napping, use of medication, bedtime and rising time, time taken to fall asleep, number and duration of nighttime awakenings, duration of last awakening, and sleep quality (SQ; average of two questions using a five-point scale to assess subjective sensation upon awakening and sleep depth). Two items were added to assess sleepiness and fatigue experienced in the previous day (1 = not at all; 5 = almost all day). Dependent variables from the sleep diary associated to sleepiness, fatigue, or hypersomnia included TIB, sleepiness rating, fatigue rating, and weekly frequency and duration of napping, while variables related to nighttime sleep were SOL, WASO, duration of early morning awakening (EMA), TST, sleep efficiency (SE), and SQ.

Insomnia Severity Index (ISI). The ISI [32] is a seven-item instrument assessing the nature, severity, and impact of sleep disturbances in the past month. Total score ranges from 0 to 28 (0–7: absence of insomnia; 8–14: subthreshold insomnia symptoms; 15–21: moderate insomnia; 22–28: severe insomnia).

Beck Depression Inventory II (BDI-II). The BDI-II [33] contains 21 items assessing depressive symptoms in the past two weeks. Total score ranges from 0 to 63 (0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; 29–63: severe depression).

State-Trait Anxiety Inventory – Trait part (STAI-Trait). The Trait part of the STAI [34] includes 20 statements asking participants to what extent they apply to their situation in general. The total score ranges from 20 to 80, with higher scores indicating higher anxiety levels.

Statistical analyses

Data were entered by two independent research assistants. Missing data were investigated using standard procedures [35]. All analyses were performed using SPSS for Windows [36]. Between-group comparisons were performed using parametric independent *t*-tests for continuous variables and Chi-square tests for categorical variables. Independent Mann–Whitney non-parametric tests were also conducted for continuous variables to investigate the impact of the small sample size and potentially non-normal distributions. However, as the results were almost identical to the parametric *t*-tests, only the *t*-tests will be presented. In the TBI group, participants using medication were compared to unmedicated participants on mean

SOL on MWT, ESS, and MFI total score using independent t-tests. VAS-s and VAS-f data were analyzed with mixed models' repeated measures analyses of variance (ANOVAs) using a factorial group (TBI vs. CTL) × time (nine hourly ratings) design and first-order autoregressive covariance structure to account for inter-correlations between time levels. For all analyses, alpha level was set at bilateral .05. Effect sizes (*d*) for t-tests were computed using the following formula:

$$d = \frac{M_{TBI} - M_{CTL}}{\sqrt{(((n_{TBI} * SD_{TBI}^2) + (n_{CTL} * SD_{CTL}^2)) / N_{TBI+CTL})}}$$

and were interpreted using Cohen's criteria [37]: small ($d \geq 0.20$), moderate ($d \geq 0.50$), and large ($d \geq 0.80$). Pearson correlations were computed between selected measures separately for each group.

Results

Sample description

Table 1 presents between-group comparisons on participants' characteristics and table 2 presents sociodemographic and clinical characteristics for each TBI participant. Groups were comparable on age, education, and gender, validating the matching procedure. TBI and CTL groups were not significantly different on body mass index (BMI) and marital status. Participants with TBI were significantly less likely than CTLs to be currently working or studying and more likely to be on long-term medical disability. There were no significant between-group differences on measures associated with sleep related breathing disorders, AHI (TBI, 0.48 ± 0.77 vs. CTL, 0.78 ± 1.31), $t(42) = -0.91$, $p = .37$; $d = 0.28$, or movement disorders, PLMAI (TBI, 0.25 ± 0.90 vs. CTL, 0.24 ± 0.56), $t(42) = 0.07$, $p = .94$; $d = 0.01$. No TBI participant and only one CTL participant (AHI = 5.90) had either an AHI or a PLMAI equal to or greater than 5. Regarding TBI characteristics, the majority of injuries were in the severe range (77.3%) and caused by a motor vehicle – traffic accident (81.8%). Time elapsed since injury varied between 13 and 141 months (mean, 53.00 ± 37.08 months). Mean GCS score was 7.23 ± 3.60, mean duration of coma was 9.76 ± 9.47 days, and mean duration of PTA was 25.20 ± 15.71 days.

Insert tables 1 and 2 here

Psychotropic medication use was significantly more common in TBI than in CTL participants (50% vs. 18.2%), χ^2 (1, N = 44) = 4.96, p = .03. Eleven TBI participants used a total of 13 medications (see table 2), 11 on a daily basis. CTLs used a total of four prescribed medications (methylmorphine, n = 1; venlafaxine, n = 1; zopiclone, n = 2), one on a daily basis. TBI and CTL groups were also compared on their weekly use of caffeine, alcohol, energy drinks, tobacco, and street drugs. Groups were similar on all accounts except for a nearly significant difference for energy drinks (TBI, 0.75 ± 1.37 vs. CTL, 0.22 ± 0.50 drinks/week), t(42) = 1.72, p = .09; d = 0.51.

Sleepiness and fatigue measures

Table 3 presents between-group comparisons for sleepiness and fatigue measures. There were no significant between-group differences on mean SOL across the four MWT trials (see figure 2.1). Figure 2.2 presents the distribution of mean SOL on the MWT in TBI and CTL groups. Comparable proportions of participants in both groups had a mean SOL shorter than 32.75 min (8/22 TBI participants, 7/22 CTL participants), χ^2(1, N = 44) = 0.10, p = .75, corresponding to the 75th percentile of published normative values [25]. Five TBI participants compared to one CTL had a mean SOL shorter than 20 min, χ^2(1, N = 44) = 3.09, p = .08. SOREMPs were detected in two unmedicated TBI participants for a total of three SOREMPs. Regarding subjective sleepiness, there were no significant between-group differences on the self- and informant-reported versions of the ESS. Four TBI (18.2%) and six CTL (27.3%) participants had an ESS score greater than 10, χ^2(1, N = 44) = 0.52, p = .47, suggestive of clinically significant sleepiness [28]. Compared to CTLs, TBI participants reported a significantly greater impact of sleepiness on the general productivity subscale of the FOSQ. Non-significant trends in the same direction were found on the FOSQ total score, and social outcome, activity level, and intimacy and sexual relationships subscales, but not on the vigilance subscale.

Insert table 3, figures 1 and 2 here

Participants with TBI reported significantly higher levels of fatigue on the MFI total score, as well as on the general fatigue, mental fatigue, and physical fatigue subscales, with moderate-to-large effect sizes. A nearly significant difference was also found on the motivation subscale, with greater impact of fatigue on motivation in the TBI group, while the activities subscale did not differ between groups. TBI participants were significantly more likely (72.7%) than CTLs (27.3%)

to exceed age- and gender-adjusted cut-offs on the general fatigue subscale, $\chi^2(1, N = 44) = 9.09$, $p = .003$, which were used to define the prevalence of fatigue in a previous study [38].

With regard to sleep diary variables associated to sleepiness, fatigue, or hypersomnia, individuals with TBI spent significantly more time in bed at night and napped significantly more frequently and for a longer time compared to CTLs, with large effect sizes for the latter two differences. Participants with TBI also displayed significantly higher average daily levels of both sleepiness and fatigue compared to their CTL counterparts.

Results for the hourly ratings of sleepiness and fatigue (VAS-s, VAS-f) on the experimental day are shown in figure 2.3. Mean VAS-s across the nine hourly ratings was 22.46 ± 20.42 (range: 1.88–84.11) for TBI and 14.23 ± 9.31 (3.11–43.44) for CTL participants, while mean VAS-f was 27.40 ± 21.08 (2.62–84.44) for TBI and 18.07 ± 14.77 (0.33–55.56) for CTL participants. Results of the ANOVAs showed a significant Time effect, both for VAS-s, $F(8, 281) = 4.38$, $p < .001$, and VAS-f, $F(8, 298) = 3.63$, $p < .001$. Group effect was not significant for VAS-f, $F(1, 45) = 2.75$, $p = .10$, but was nearly significant for VAS-s, $F(1, 51) = 3.65$, $p = .06$, with TBI reporting greater sleepiness overall. Group × Time interaction was not significant for VAS-s, $F(8, 281) = 1.38$, $p = .20$, but was significant for VAS-f, $F(8, 298) = 2.62$, $p < .01$, with simple effects tests revealing that after the initial rating fatigue decreased in the CTL group and increased in the TBI group.

Insert figure 3 here

In the TBI group there were no significant differences between psychotropic medication users ($n = 11$) and non-users ($n = 11$) on mean SOL across the four MWT trials (medication users, 30.98 ± 10.05 vs. non-users, 32.30 ± 10.26 min), $t(20) = –.30$, $p = .91$; $d = 0.13$; ESS (medication users, 7.18 ± 3.54 vs. non-users, 8.36 ± 3.85), $t(20) = –.75$, $p = .46$; $d = 0.32$; or MFI total score (medication users, 52.00 ± 10.50 vs. non-users, 46.73 ± 11.75), $t(20) = 1.11$, $p = .28$; $d = 0.47$.

Sleep and psychological measures

Results of between-group comparisons for sleep and psychological measures are shown in table 4. There were no significant differences between TBI and CTL groups on PSG measures of sleep continuity or sleep architecture. Groups were also comparable on micro-arousal index (TBI, 4.44 ± 2.33 vs. CTL, 4.96 ± 2.92), $t(42) = –0.65$, $p = .52$; $d = 0.20$. With

regard to the 14-day sleep diary, there were no significant between-group differences on the nighttime sleep quantity or quality variables. TBI participants displayed significantly greater insomnia symptoms on the ISI and depression symptoms on the BDI-II, although most participants in both groups were classified in the "absence of insomnia" (TBI, *n* = 14; CTL, *n* = 20) and "minimal depression" (TBI, *n* = 18; CTL, *n* = 21) categories. Between-group comparison on the STAI-Trait was nearly significant, with greater anxiety in the TBI group.

Insert table 4 here

Correlations

Objective (MWT mean SOL) and subjective (ESS-participant) sleepiness measures were not significantly associated, TBI: $r(22) = .31$, $p = .16$; CTL: $r(22) = –.21$, $p = .34$. Fatigue (MFI total score) did not correlate with objective, TBI: $r(22) = –.04$, $p = .86$; CTL: $r(22) = –.15$, $p = .51$, or subjective, TBI: $r(22) = –.24$, $p = .28$; CTL: $r(22) = .26$, $p = .24$, sleepiness in either group. Fatigue correlated with depression, BDI-II; TBI: $r(21) = .44$, $p = .046$; CTL: $r(22) = .79$, $p < .001$, and anxiety symptoms, STAI-Trait; TBI: $r(22) = .68$, $p < .01$; CTL: $r(22) = .63$, $p < .01$, in both groups, and with insomnia symptoms in the CTL group only, ISI; TBI: $r(21) = .29$, $p = .18$; CTL: $r(22) = .68$, $p < .001$. Objective and sleepiness measures did not correlate with insomnia, depression, or anxiety in either group (rs < |.30|; ps > .20).

Discussion

This study explored the presence and severity of sleepiness and fatigue 1–11 years following moderate to severe TBI. Results revealed that subjective fatigue was higher in the TBI group compared to the CTL group. TBI participants were very alert and did not differ from CTLs on objective and on most subjective measures of sleepiness, but reported a greater impact of sleepiness on daily functioning, spent more time in bed, and napped more frequently and for a longer time during the day compared to CTL participants. With regard to nighttime sleep, there were no between-group differences on objective or subjective measures. Insomnia and depression symptoms were greater in the TBI group but were seldom clinically significant. Fatigue, but not sleepiness, correlated with depression and anxiety symptoms in both groups.

The most consistent finding from this study concerns greater fatigue complaints in TBI individuals several years after their injury. This corroborates previous research using a very similar methodology, albeit a different subjective fatigue measure (i.e., Fatigue Severity Scale)

[19]. While the MFI does not have standard clinical cut-offs, it can be argued that the level of fatigue reported by TBI individuals in the present study was clinically significant. Indeed, 16 of the 22 participants exceeded previously used [38] threshold scores for significant fatigue based on age- and gender-adjusted 75th percentiles derived from a large community sample [39]. Moreover, when comparing obtained results with recently published data on the MFI from a US population sample, the TBI group was similar to the chronically "unwell" group from the validation study while the CTL group was similar to the "well" group [40]. Another interesting result from this investigation concerns self-reported fatigue on the experimental day. While fatigue decreased in the early hours after awakening in the CTL group, TBI participants displayed the opposite pattern. This early morning increase in fatigue complaints could have potential repercussions on the motivation to face the upcoming day, the carrying out of planned activities, or the use of compensatory strategies (e.g., canceling appointments, napping) for individuals with TBI. However, it should be noted that the limitation of caffeine intake on the experimental day could have had an impact on fatigue ratings. While caffeine use habits were similar between groups, medication use was far more common in the TBI group, and because of pharmacological interactions caffeine might have been clearing the system at the time when different fatigue rating patterns were observed between TBI and CTL participants. Results from our study also revealed that fatigue correlated with depression and anxiety symptoms. As these issues are prevalent following TBI, it is crucial that rehabilitation workers address their interaction with fatigue manifestations.

TBI participants spent more time in bed at night than healthy CTLs and napped more frequently and for longer times during the day. Frequent napping after TBI has been observed in previous research [41,42]. Whether this type of behavior is the result of fatigue, sleepiness, lack of meaningful activities, or a combination of these or other factors still needs to be investigated. Nevertheless, increasing sleep opportunities at night and during the day, which can be an effective strategy to alleviate sleepiness, especially early on after TBI, might be detrimental to nighttime sleep quality [43] and participation in daily activities in the long run when done excessively or inappropriately. Therefore, education about the risks and benefits of such practices and a thorough assessment of associated factors should be included in rehabilitation programs to optimize sleep and rest practices once TBI individuals return in the community.

As a group, individuals with TBI were not pathologically sleepy, and were, rather, quite alert, when assessed between 1 and 11 years post-TBI. Several studies found the opposite, with much lower mean SOL on daytime PSG recordings and higher proportions of TBI individuals

meeting criteria for excessive daytime sleepiness (mean SOL <5 or <10 min) [4,6,18]. However, sleep apnea, which is common after TBI [44] and typically presents with significant sleepiness as its core daytime feature, was an exclusion criterion in our study. Additionally, the vast majority of studies to date used the MSLT to assess physiological sleepiness. Although the MSLT is more useful for diagnostic purposes, the MWT is presumably more ecologically valid, as situations in which people have to make efforts to remain awake (MWT) are more common in everyday life than situations in which people have to fall asleep quickly (MSLT). Besides, the present findings are in line with those from another investigation using the MWT, with normal levels of physiological sleepiness being observed in TBI and CTL groups [19]. Thus, depending on how objective sleepiness is defined and measured, the prevalence of "pathological" or "excessive" sleepiness is likely to differ. Despite the absence of clinically significant physiological sleepiness as a group, a few TBI participants displayed some sleepiness (mean SOL < 20 min.; n = 5) or SOREMPs (n = 2). Narcolepsy features such as increased daytime sleep propensity, SOREMPs, and cataplexy without meeting full criteria for the disorder have been documented in other TBI samples [18,45]. It has been hypothesized that these symptoms could arise from disrupted wake-promoting neurotransmitting systems (e.g., hypocretin), well documented in idiopathic narcolepsy [46] and increasingly recognized after TBI [47]. Hypocretin levels tend to normalize after acute post-injury recovery [47], which could explain why objective sleepiness was not a common feature in our study (time since injury ≥ 1 year).

Similar subjective sleepiness on the ESS between TBIs and CTLs corroborates previous findings [19,41]. The rate of participants exceeding the commonly-used cut-off for clinically significant subjective sleepiness (ESS > 10) was even lower in the TBI (18.2%) than in the CTL (27.3%) group and was similar to what was observed in a Norwegian population-based investigation (17.7%) [48]. While other studies have found higher rates of clinically significant subjective sleepiness in TBI survivors [18], some authors have questioned the use of the ESS as an appropriate assessment tool because of a lack of exposure to certain situations included in the questionnaire (e.g., driving) and the potential interference of cognitive problems on retrospective responding [41]. Prospective assessment methods like daily ratings averaged across several days may be more suitable to assess sleepiness complaints in TBI individuals. In the present study TBI participants presented a higher mean subjective sleepiness level compared to CTLs on daily ratings included in the sleep diary. It may be that the latter assessment method captured a different aspect of the sleepiness experience than what was

measured by the ESS, or that participants confounded sleepiness and fatigue on the daily ratings despite our efforts in instructing participants on how to differentiate them.

Even if they presented levels of objective and subjective sleepiness comparable to those of healthy controls, TBI participants reported a greater impact of sleepiness on their general productivity on the FOSQ, and there were trends in the same direction for other functional aspects. While this combination of findings appears counter-intuitive at first sight, it could be that, following TBI, coping with normal daily variations in alertness becomes more challenging or requires greater resources [49]. As a result, even mild levels of sleepiness could disrupt functional capacities. Results on the FOSQ could also be related to a lack of self-awareness, as suggested by Castriotta et al. to account for their results showing better sleep-related quality of life in sleepy and sleep-disordered TBI participants than in non-sleepy and non-sleep-disordered ones [4].

TBI individuals did not differ from CTLs on any PSG or diary nighttime sleep parameters, and while insomnia symptoms were greater in TBIs, they were seldom clinically significant. These results are somewhat surprising given the frequently observed impairments in sleep macrostructure and the high prevalence of insomnia in this population [3,43]. However, insomnia has been found to be more prevalent in mild TBI individuals [3,43], who were excluded in our study. Also, participants were 1–11 years post-injury and it could be that PSG-measured sleep alterations gradually normalize with the passage of time, although this has yet to be confirmed.

Taken together, findings from this investigation suggest that fatigue could be a more common feature than sleepiness, a year or more after a moderate or severe TBI. Despite some strengths (e.g., inclusion of a well-matched control group, concomitant assessment of sleepiness and fatigue using several measures), the current study is limited by some methodological caveats precluding us from drawing firm conclusions. First, findings might not generalize to the whole moderate/severe TBI population since participants were presumably at the higher end of the functional ability spectrum (as suggested by the degree of involvement required by the protocol). Second, despite the matching procedure for gender, age, and education, groups might still have differed on other confounding factors that either masked or inflated between-group differences on dependent variables. However, features such as unemployment and use of psychotropic medication, on which groups did indeed differ, are inherent to life after TBI and cannot be overlooked. Third, with a sample size of 22 participants per group, statistical power was clearly insufficient to detect statistically significant differences for small and moderate effect

sizes. Regardless of these limitations, current findings contribute to the recent surge of scientific interest on sleepiness and fatigue following TBI. Among the many challenges awaiting future investigators, areas to focus on include gathering longitudinal prospective data to increase our understanding of the distinct time course of sleepiness and fatigue problems, refining the assessment of fatigue by using more objective measures such as time-on-task effects and neuroimaging, and exploring the benefit of pharmacological and behavioral treatment options in reducing the severity and impact of fatigue, sleepiness, and sleep disturbances.

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Table 1 - Characteristics of participants by group

	TBI (*N* = 22) M ± SD (range)	CTL (*N* = 22) M ± SD (range)	Comparison
Age in years	37.46 ± 13.26 (18-59)	36.96 ± 14.08 (18-58)	$t(42) = 0.12$, $p = .90$
Education in years	12.41 ± 2.46 (9-18)	13.09 ± 2.41 (9-18)	$t(42) = -0.93$, $p = .36$
BMI	27.05 ± 6.10 (18.56-42.21)	24.75 ± 3.34 (19.77-33.78)	$t(42) = 1.55$, $p = .13$
	TBI (*n* = 22) *n* (%)	CTL (*n* = 22) *n* (%)	Comparison
Gender (women)	5 (22.73%)	5 (22.73%)	χ^2 (1, $N = 44$) = 0.00, $p = 1.00$
Married/common-law	9 (40.91%)	9 (40.91%)	χ^2 (1, $N = 44$) = 0.00, $p = 1.00$
Occupation			
Working/studying	7 (31.82%)	20 (90.91%)	χ^2 (1, $N = 44$) = 16.20, $p < .001$
Long-term medical disability	13 (59.09%)	0 (0%)	χ^2 (1, $N = 44$) = 18.45, $p < .001$
Current driver's license	18 (81.82%)	22 (100%)	χ^2 (1, $N = 44$) = 4.40, $p = .04$

Abbreviations: BMI = body mass index; CTL = control; M = mean; SD = standard deviation; TBI = traumatic brain injury.

Table 2 - Sociodemographic and clinical characteristics of TBI participants

Age in years (gender)	Months since TBI	TBI severity	TBI cause	GCS score	Injury type	Duration of coma, PTA (days)	Medication
18 (M)	25	Severe	MVT	3	FC, SAH	16, 25	None
58 (F)	27	Moderate	Fall	10	ICH, SGH	0, 7	None
31 (F)	27	Severe	MVT	7	FC, SDH, EICP, DAI	27, 47	None
57 (M)	99	Moderate-severe	MVT	15	ICH, SDH	0, 25	Venlafaxine
44 (F)	141	Severe	MVT	4	FC, SDH, EICP	30, 77	None
28 (M)	68	Severe	MVT	6	FC	10, 21	None
47 (M)	52	Severe	MVT	14	FC	NA, 10	Zopiclone
59 (M)	51	Severe	MVT	7	FC, SAH	17, 34	None
35 (M)	28	Severe	MVT	9	FC, EDH, SAH, EICP	13, 16	Phenytoin
30 (M)	54	Moderate-severe	MVT	11	FC, EDH, SAH	0, 14	None
30 (M)	31	Severe	Assault	7	FC, EDH, SAH, SDH	NA, NA	Quetiapine
56 (M)	70	Severe	Struck against	8	FC	NA, 21	Amitriptyline, Lorazepam
48 (M)	136	Severe	MVT	7	FC	8, 22	Venlafaxine
27 (M)	88	Severe	MVT	3	FC	12, 30	Citalopram
23 (F)	56	Severe	MVT	3	FC, SAH, SDH, DAI	12, 12	None
28 (M)	14	Severe	MVT	4	FC, ICH, SDH	15, 38	Quetiapine
23 (M)	13	Severe	MVT	3	SDH	NA, NA	Duloxetine
24 (M)	20	Severe	MVT	8	FC, DAI	NA, 21	None
33 (F)	72	Severe	MVT	6	FC	6, 14	None
29 (M)	16	Moderate	MVT	12	FC, SAH, SDH, EICP	0, 17	None
55 (M)	19	Severe	Fall	3	FC, ICH	0, 21	Zopiclone
41 (M)	59	Moderate	MVT	9	FC, SDH	0, 32	Citalopram, Clonazepam

Abbreviations: DAI = diffuse axonal injury; EDH = epidural hematoma; EICP = elevated intracranial pressure; F = woman; FC = focal contusion(s); GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; M = man; MVT = motor vehicle – traffic accident (including occupant, pedal cyclist or pedestrian involved in a motor vehicle – traffic accident); NA = not available; PTA = posttraumatic amnesia; SAH = subarachnoid hemorrhage; SDH = subdural hematoma; SGH = subgaleal hematoma; TBI = traumatic brain injury.

Table 3 - Between-group comparisons on sleepiness and fatigue measures

	TBI (*n* = 22) M ± SD (range)	CTL (*n* = 22) M ± SD (range)	Comparison	ES *d*
MWT mean SOL (min)	31.64 ± 9.94 (10.63-40)	35.11 ± 6.76 (17.13-40)	*t*(42) = -1.36, *p* = .18	0.41
ESS				
Participant	7.77 ± 3.66 (1-16)	7.64 ± 3.81 (0-14)	*t*(42) = 0.12, *p* = .90	0.04
Significant other [a]	8.88 ± 4.22 (2-15)	7.38 ± 4.06 (10.63-40)	*t*(42) = 1.02, *p* = .31	0.36
FOSQ				
Total score	17.64 ± 2.13 (11.36-20)	18.71 ± 1.93 (12.25-15)	*t*(42) = -1.74, *p* = .09	0.53
General productivity	3.48 ± 0.53 (2-4)	3.79 ± 0.43 (2.14-4)	*t*(42) = -2.15, *p* = .04	0.64
Social outcome	3.60 ± 0.58 (2.5-4)	3.86 ± 0.35 (2.5-4)	*t*(41) = -1.84, *p* = .07	0.55
Activity level	3.41 ± 0.44 (2.44-4)	3.66 ± 0.43 (2.44-4)	*t*(42) = -1.94, *p* = .06	0.58
Vigilance	3.53 ± 0.52 (2.14-4)	3.56 ± 0.60 (1.71-4)	*t*(42) = -0.18, *p* = .86	0.05
Intimacy	3.77 ± 0.35 (3-4)	3.93 ± 0.14 (3.5-4)	*t*(37) = -1.67, *p* = .10	0.60
MFI				
Total score [b]	49.36 ± 11.20 (23-70)	37.95 ± 12.61 (23-76)	*t*(42) = 3.17, *p* < .01	0.96
General fatigue	11.86 ± 3.41 (4-19)	8.73 ± 3.38 (5-18)	*t*(42) = 3.06, *p* < .01	0.92
Physical fatigue	9.09 ± 3.47 (4-16)	6.86 ± 3.14 (4-16)	*t*(42) = 2.27, *p* = .03	0.69
Mental fatigue	11.59 ± 2.99 (6-17)	7.91 ± 3.46 (4-15)	*t*(42) = 3.78, *p* < .001	1.14
Reduced motivation	8.18 ± 2.65 (4-12)	6.59 ± 2.61 (4-14)	*t*(42) = 2.01, *p* = .05	0.61
Reduced activities	8.64 ± 2.95 (4-13)	7.86 ± 2.36 (5-13)	*t*(42) = 0.96, *p* = .34	0.29
Sleep diary				
TIB (min)	514.46 ± 41.12 (456.92-599.64)	484.20 ± 45.05 (388.50-551.07)	*t*(42) = 2.33, *p* = .03	0.70
Naps/week (*n*)	3.26 ± 2.89 (0-8.17)	1.31 ± 1.23 (0-3.5)	*t*(42) = 2.90, *p* < .01	0.88
Nap duration/week (min)	213.13 ± 225.56 (0-597.69)	71.96 ± 88.31 (0-300)	*t*(42) = 2.73, *p* < .01	0.82
Sleepiness daily rating	1.94 ± 0.60 (1-3.08)	1.57 ± 0.55 (1-2.79)	*t*(42) = 2.16, *p* = .04	0.64
Fatigue daily rating	2.50 ± 0.65 (1.31-3.33)	1.85 ± 0.65 (1-3.07)	*t*(42) = 3.32, *p* < .01	1.00

[a] ESS-significant other was available for 32 participants (TBI, *n* = 16; CTL, *n* = 16). [b] MFI total score was computed by adding up scores from the five subscales.

Abbreviations: CTL = control; ES = effect size (Cohen`s *d*); ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; M = mean; MFI = Multidimensional Fatigue Inventory; MWT = Maintenance of Wakefulness Test; SD = standard deviation; SOL = sleep onset latency; TIB = time spent in bed; TBI = traumatic brain injury.

Table 4 - Between-group comparisons on sleep and psychological measures

	TBI (*n* = 22) M ± SD (range)	CTL (*n* = 22) M ± SD (range)	Comparison	ES *d*
PSG				
SOL (min)	16.25 ± 14.02 (3.5-60)	16.80 ± 14.70 (1.5-59.5)	*t*(42) = -0.58, *p* = .90	0.04
WASO (min)	72.43 ± 70.05 (3.5-280.5)	46.86 ± 41.95 (4.5-126.5)	*t*(42) = -1.47, *p* = .15	0.44
TST (min)	386.57 ± 78.43 (137-481)	416.25 ± 54.87 (294.5-484)	*t*(42) = -1.45, *p* = .15	0.44
TIB (min)	489.48 ± 18.98 (442.5-528)	489.93 ± 15.52 (462.5-526)	*t*(42) = -0.87, *p* = .93	0.03
% Stage 1	4.84 ± 4.80 (0-22.89)	4.98 ± 3.61 (1.34-16.92)	*t*(42) = -0.11, *p* = .92	0.03
% Stage 2	55.78 ± 11.00 (38.69-78.48)	58.36 ± 5.55 (49.07-72.06)	*t*(42) = -0.98, *p* = .33	0.30
% Stages 3-4	14.59 ± 12.26 (0-47.92)	11.70 ± 7.17 (0.38-22.68)	*t*(42) = 0.96, *p* = .35	0.29
% REM	24.78 ± 7.29 (8.37-39.42)	24.96 ± 4.61 (14.43-32.63)	*t*(42) = -0.09, *p* = .93	0.03
REM sleep latency (min)	96.16 ± 52.57 (8.5-210.5)	112.41 ± 63.28 (45.5-303.5)	*t*(42) = -0.93, *p* = .36	0.28
Sleep diary				
SOL (min)	19.32 ± 14.58 (3-52.08)	16.03 ± 15.19 (1.57-73.93)	*t*(42) = 0.73, *p* = .47	0.22
WASO (min)	19.53 ± 22.39 (0-86.58)	14.46 ± 29.12 (.14-140.71)	*t*(42) = 0.65, *p* = .52	0.20
EMA (min)	34.30 ± 59.40 (4.14-294.64)	25.15 ± 25.00 (0-122.5)	*t*(42) = 0.67, *p* = .51	0.20
TST (min)	441.75 ± 67.39 (179.64-517.50)	428.52 ± 63.61 (239.43-495.43)	*t*(42) = 0.67, *p* = .51	0.20
SE (%)	86.11 ± 12.60 (35.28-97.87)	88.81 ± 11.09 (44.36-99.19)	*t*(42) = -0.75, *p* = .46	0.23
SQ (1-5)	3.61 ± 0.83 (1.54-4.85)	3.92 ± 0.56 (2.57-4.93)	*t*(42) = -1.47, *p* = .15	0.44
ISI	8.27 ± 6.97 (0-22)	4.05 ± 4.91 (0-20)	*t*(42) = 2.33, *p* = .03	0.70
BDI-II	8.52 ± 5.17 (1-18)	3.32 ± 3.48 (0-14)	*t*(42) = 2.89, *p* < .001	1.19
STAI-Trait	35.27 ± 7.52 (24-48)	31.32 ± 6.42 (22-41)	*t*(42) = 1.88, *p* = .07	0.57

Abbreviations: BDI-II = Beck Depression Inventory II; CTL = control; EMA = early morning awakening; ES = effect size (Cohen`s *d*); ISI = Insomnia Severity Index; M = mean; PSG = polysomnography; REM = rapid eye movement; SD = standard deviation; SE = sleep efficiency; SOL = sleep onset latency; SQ = sleep quality; STAI = State-Trait Anxiety Inventory; TBI = traumatic brain injury; TST = total sleep time; WASO = wake time after sleep onset.

Figure legends

Figure 1 - Mean sleep onset latency for the four MWT trials for TBI and CTL groups.
Error bars represent standard errors. Points are offset horizontally so that error bars are visible.
CTL = control; MWT = Maintenance of Wakefulness Test; TBI = traumatic brain injury.

Figure 2 - Distribution of mean sleep onset latency across the four MWT trials for TBI and CTL groups.
CTL = control; MWT = Maintenance of Wakefulness Test; SOL = sleep onset latency; TBI = traumatic brain injury.

Figure 3 - Results of VAS-sleepiness and VAS-fatigue over time for TBI and CTL groups.
Error bars represent standard errors. Points are offset horizontally so that error bars are visible.
CTL = control; TBI = traumatic brain injury; VAS = visual analogue scale.

Figure 1.

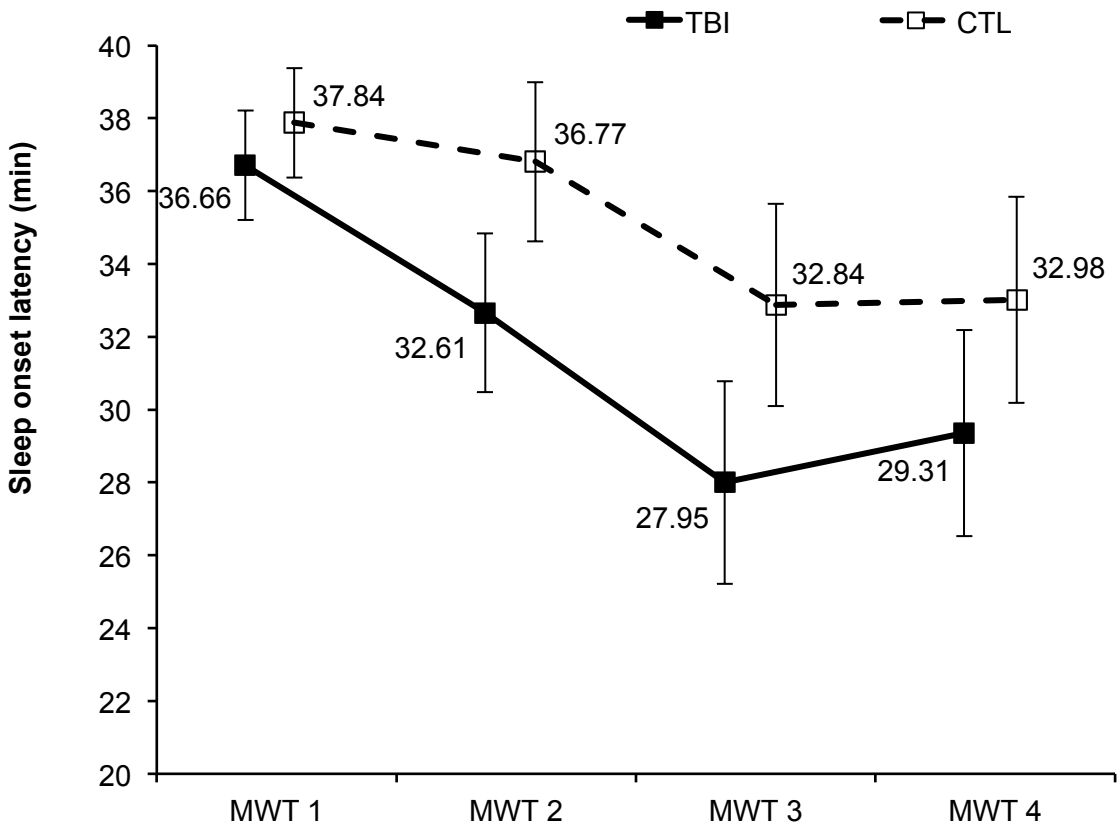

TBI
CTL
Sleep onset latency (min)
40
38
36
34
32
30
28
26
24
22
20
37.84
36.77
36.66
32.84
32.98
32.61
29.31
27.95
MWT 1
MWT 2
MWT 3
MWT 4

Figure 2.

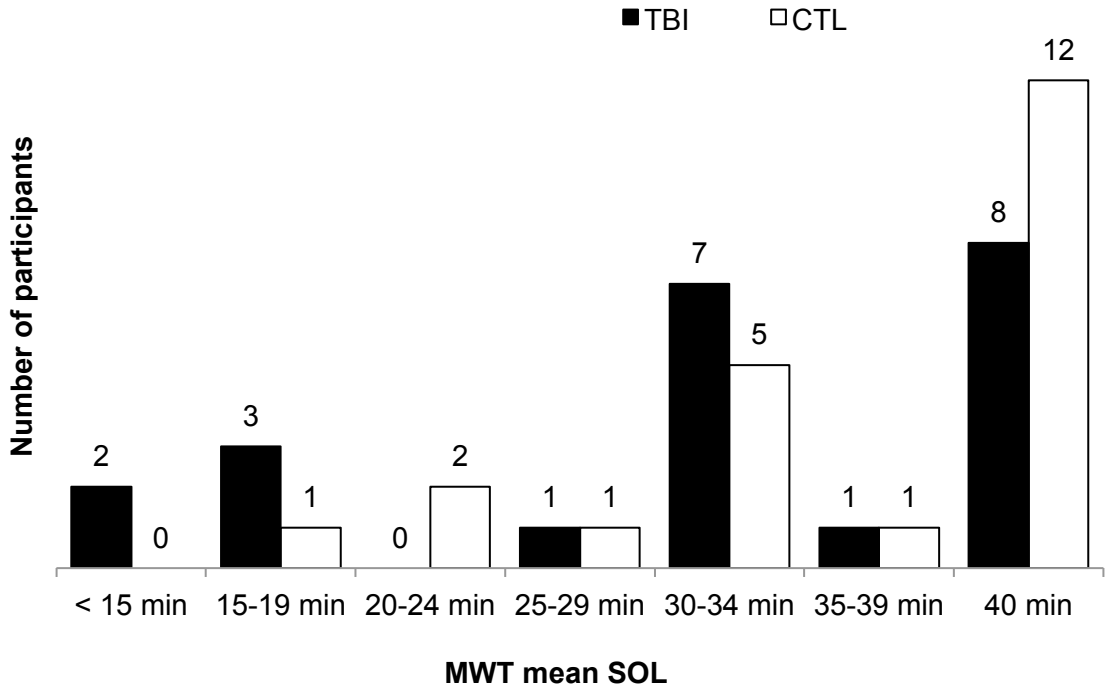
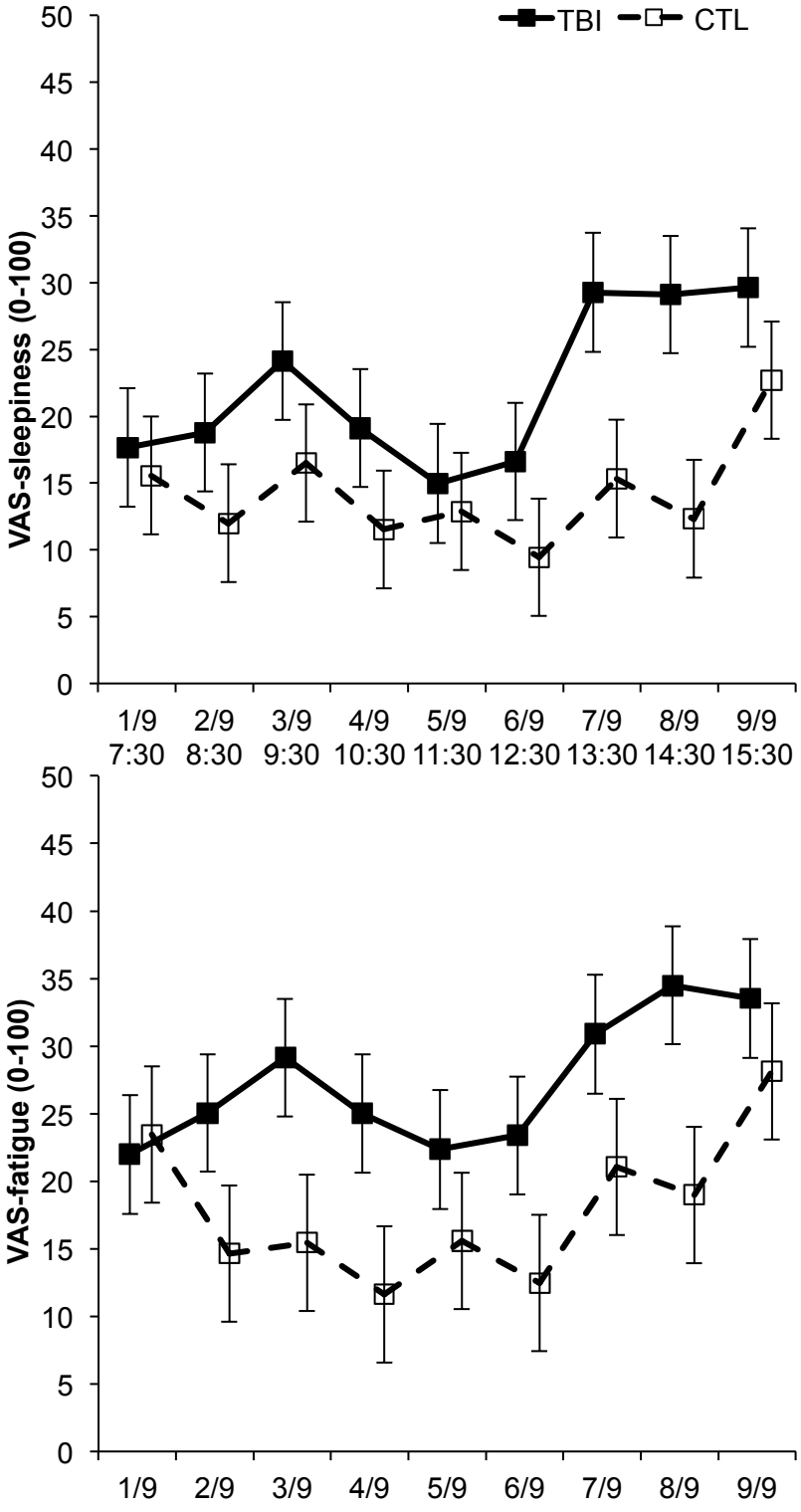

TBI
CTL
Number of participants
2
0
3
1
0
2
1
1
7
5
1
1
8
12
< 15 min
15-19 min
20-24 min
25-29 min
30-34 min
35-39 min
40 min
MWT mean SOL

Figure 3.


TBI
CTL
VAS-sleepiness (0-100)
VAS-fatigue (0-100)
0
5
10
15
20
25
30
35
40
45
50
1/9 7:30
2/9 8:30
3/9 9:30
4/9 10:30
5/9 11:30
6/9 12:30
7/9 13:30
8/9 14:30
9/9 15:30
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