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Parallel recovery of consciousness and sleep in acute traumatic brain injury

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Author Contributions

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Caroline Arbour : analysis and interpretation of data, drafting and revising the manuscript
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Abstract

Objective: To investigate whether the progressive recuperation of consciousness was associated with the reconsolidation of sleep and wake states in hospitalized patients with acute traumatic brain injury (TBI). **Methods:** This study comprised thirty hospitalized patients (age: 29.1 ± 13.5 years old) with in the acute phase of moderate or severe TBI. Testing started 21.0 ± 13.7 days post-injury. Consciousness level and cognitive functioning were assessed daily with the Rancho Los Amigos scale of cognitive functioning (RLA). Sleep and wake cycle characteristics were estimated with continuous wrist actigraphy. Mixed model analyses were performed on 233 days, with the RLA (fixed effect) and sleep-wake variables (random effects). Linear contrast analyses were performed in order to verify if consolidation of the sleep and wake states improved linearly with increasing RLA score. **Results:** Associations were found between scores on the consciousness/cognitive functioning scale and measures of sleep-wake cycle consolidation ($p < 0.001$), nighttime sleep duration ($p = 0.018$), and nighttime fragmentation index ($p < 0.001$). These associations showed strong linear relationships ($p < 0.01$ for all), revealing that consciousness and cognition improved in parallel with sleep-wake quality. Consolidated 24-h sleep-wake cycle occurred when patients were able to give context-appropriate, goal-directed responses. **Conclusions:** Our results showed that when the brain has not sufficiently recovered a certain level of consciousness, it is also unable to generate a 24-h sleep-wake cycle and consolidated nighttime sleep. This study contributes to elucidating the pathophysiology of severe sleep-wake cycle alterations in the acute phase of moderate to severe TBI.

Abbreviations: AR1 = autoregressive; CS = compound symmetry; DAR = daytime activity ratio; GCS = Glasgow coma scale; ICU = intensive care unit; MCS = minimally conscious state; PTA = posttraumatic amnesia; RLA = Rancho Los Amigos scale of cognitive functioning; TBI = traumatic brain injury.

The following **Nonstandard characters** were inserted using the Symbol gallery of Microsoft Office: ±; =; ≥; ≤; <; >

Introduction

Non-sedated patients in the acute stage of a moderate to severe traumatic brain injury (TBI) have serious alterations of their sleep-wake cycle,[1,2] characterized by short sleep and wake bouts, a few minutes in length, dispersed over the 24 h.[1] Pain, medication, and the hospital environment are possible causes of these sleep-wake disturbances.[3] However, recent experimental models of TBI have shown that the injured brain itself has a direct effect on the sleep-wake cycle by increasing fragmentation of sleep and wake periods.[4-6]

In patients with acute TBI, the reconsolidation of the 24-h sleep-wake cycle predicts emergence from post-traumatic amnesia (PTA) at hospital discharge[1] as well as cognitive impairments in rehabilitation settings.[7,8] Studies on chronic disorders of consciousness also suggest that the circadian variation of the sleep-wake cycle re-emerges with improving consciousness.[9] Overall, these observations point to an intrinsic association between recovery of the sleep-wake cycle, consciousness and cognition following a brain injury. However, we have yet to characterize how the sleep-wake cycle recovers on a day-to-day basis in relation to improving consciousness and higher cognitive functions in acute TBI.

The objective of this study was to verify whether an association exists between the evolution of the sleep-wake cycle and the recovery of consciousness and cognition in acute moderate to severe TBI. A second objective was to determine which improved first, or whether they evolved synchronously. We predicted that the consolidation of sleep-wake states would increase synchronously with improving consciousness and cognition, because they depend on overall brain integrity.

Materials and methods

Patients

We recruited patients from Hôpital du Sacré-Coeur de Montréal, a level-1 trauma center affiliated to the Université de Montréal, between January 2010 and May 2015. We defined TBI as an alteration in brain function or other evidence of brain pathology caused by an external force,[10] and assessed TBI severity upon emergency room admission, prior to intubation, using the Glasgow Coma Scale (GCS).[11] We included patients if they were hospitalized in the intensive care unit (ICU) for their TBI. In order to characterize our study sample, we documented the following for all patients: mechanism of injury, GCS score at emergency room admission, ICU and hospital lengths of stay, number of days with elevated intracranial pressure (>20 mmHg), Marshall and Rotterdam scores,[12,13] which are qualitative CT classification systems, Disability Rating Scale score within 72 h of hospital discharge, [14] and patient orientation at hospital discharge. We obtained written informed consent for study participation from patients' families, and the hospital ethical standards committee on human experimentation approved the study. We excluded patients if they were younger than 16 or older than 65 years old; were quadriplegic; had a history of substance abuse, psychiatric, or neurological disorders; had a diagnosed sleep disorder prior to injury; suffered any damage to both eyes or the optic nerve (modifying light perception); or had a prior history of TBI or concussion.

Experimental Design

During the ICU and post-ICU hospital stay, patients wore an activity monitor to assess their sleep-wake patterns continuously for several days, during which a daily assessment of consciousness and cognition was also carried out.

Assessment of consciousness and cognitive level

We used the Rancho Los Amigos scale of cognitive functioning (RLA),[15] a comprehensive behavioral rating scale developed specifically to monitor the stages of recovery in the adult TBI population,[16] which can be easily administered at bedside. The RLA evaluates key features of consciousness and cognitive functioning, such as level of awareness of the environment, response to stimuli, ability to follow command, confusion, attention, and the appropriateness of verbalization and motor actions. The RLA scale consists of eight hierarchical levels, with Level 1 representing no response and Level 8 representing purposeful and appropriate cognitive function (see Table 1). Duration of RLA assessment ranges from 5 to 40 minutes and is carried out when patients are fully awake and all aspects of the scale are assessable. Trained occupational therapists with experience with the acute TBI population assessed the RLA scale daily on weekdays.

Sleep-wake assessments

Patients wore a wrist actigraph (Actiwatch-L or Actiwatch-Spectrum, Philips Healthcare, Andover, MA) on a non-paralyzed arm starting in the ICU, and continuing throughout hospitalization in regular wards. As described in a previous study,[1] actigraphy recording began when continuous sedation and analgesia had ceased for at least 24 h, and once patients reached a

RLA score ≥3, indicative of a more apparent physical reactivity to internal and external stimuli. With its low invasiveness, actigraphy enables the long-term measurement of the rest-activity cycle, and is recognized as an proxy measure of the sleep-wake cycle.[17]

We measured activity counts per 1-min epoch and derived three variables from actigraphic recordings to estimate sleep-wake quality:

Daytime activity ratio (DAR): We estimated consolidation of the 24-h sleep-wake cycle with the daytime activity ratio (DAR).[1] The DAR represents the percentage of total 24-h activity occurring in the daytime [(daytime activity/24 h activity)x100]. A high DAR reflects a more consolidated sleep-wake cycle, with a high concentration of activity (wake) during the day (7:00-21:59 h) and rest (sleep) during the night (22:00-6:59 h). A DAR ≥80% represents a consolidated 24-h sleep-wake cycle.[1]

Nighttime sleep duration: Given that sleep diaries could not be used, we defined nighttime as the period when light and noise were minimized in the hospital, which was from 22:00-06:59 h. We estimated sleep duration based on periods of inactivity, using the designated actigraphy software (Actiware 5.0) with a medium wake threshold (40 activity counts per minute). The total of 1-min epochs scored as "sleep" between 22:00 and 06:59 h defined nighttime sleep duration.

Nighttime fragmentation index: The dedicated software also computes a nighttime fragmentation index, which is an index of restlessness that reflects the frequency of changes between mobility and immobility, and is correlated to the arousal index, as measured by polysomnography.[18,19] This fragmentation index corresponds to the summed percentage of mobile bouts and immobile bouts of 1 min for the given interval, divided by the total number of immobile bouts of >1 min [(%Mobile Bouts of 1min + %Immobile Bouts of 1min)/ #Immobile Bouts >1min]. A mobile bout is a 1-min epoch with ≥4 activity counts.

Statistical analyses

In order to assess the relationship between consciousness/cognition and consolidation of sleep and wake states on a day-to-day basis, we integrated the RLA score into linear mixed model analyses with DAR, nighttime sleep duration, and fragmentation index, using alternatively autoregressive (AR1) and compound symmetry (CS) covariance structures. The CS structure assumes that variance and covariance of observations of a single patient are homogenous, while the AR1 structure posits that covariance between observations on the same patient comes from the exponential decrease in covariance between observations as they get farther apart in time.[20] We entered the RLA as the fixed effect and the DAR, nighttime sleep duration and fragmentation index as random effects (each in a separate analysis).

In order to verify if consolidation of the sleep and wake states improve linearly with increasing RLA score, we performed linear contrast analyses within the mixed model analyses, for the three variables (DAR, nighttime sleep duration, fragmentation index).

Finally, we performed cross-correlation analyses, which enable the identification of the best-fit lag, in order to determine whether sleep parameters or consciousness and cognitive recovery improved first, or whether they evolved synchronously. We averaged the RLA score and actigraphy variables per day over 10 days, and performed cross-correlation analyses between RLA score and each actigraphy variable separately, with a maximum lag of 3 days (30%), to minimize bias.[21]

We set statistical significance at $p<0.01$ and report only results from the best fitting mixed model, based on the smallest Akaike's Information Criterion.

Control for potentially confounding variables

To ensure that our four variables of interest (i.e. RLA, DAR, nighttime sleep duration, and nighttime fragmentation index) were not indirect measures of time since ICU discharge, and were not influenced by the cumulative dose of sedatives and analgesics received in the ICU, we submitted these variables to Pearson's correlations. We found no association ($r's < 0.45$, n.s. for all). RLA and our three sleep-wake variables were therefore not indirect measures of the passage of time and the natural improvement of patients' overall condition, nor were they influenced by the quantity of sedatives and analgesics received during the patients' ICU stay.

To ensure that reactivity to internal/external stimuli (RLA score) was not simply an indirect measure of daytime sleep duration, we evaluated the association between RLA and duration of daytime sleep using a Pearson's correlation and found no association ($r= 0.06$, $p =0.35$).

Finally, we verified if time of morning increase in lighting (≥10 lux) measured through the Actiwatch differed according to RLA score, and no association was found ($r = 0.105$, $p = 0.122$).

Results

Patient characteristics

We recruited the 30 consecutive patients who fitted our inclusion criteria, were hospitalized sufficiently long to participate in the study, and provided consent for participation. Patients were 29.1 ± 13.5 years old (range: 17-58; 22 men) and the average GCS score at admission was 7.7 ± 3.6 (range: 3-14). Two patients had a GCS score of 14 and one had a GCS of 13 at admission, but received a diagnosis of moderate or severe TBI by the neurosurgeon given they had

decompressive craniectomy. Mechanisms of injury were motor vehicle accident (n=20), fall (n=7), recreational/sports injury (n=2), and blow to the head (n=1). Patients had an average ICU stay of 22.9 ± 14.2 days, and a hospital length of stay of 44.6 ± 21.2 days. Fifteen patients (50%) had elevated intracranial pressure during their ICU stay of an average duration of 10.4 ± 4.6 days. Twenty-eight (93.3%) patients had evidence of traumatic injuries on their initial brain CT scans, and average Marshall and Rotterdam scores were 2.9 ± 1.4 (range: 1-5) and 3.3 ± 1.3 (range: 2-6), respectively. Average score on the Disability Rating Scale was 10.2 ± 4.4 prior to hospital discharge, corresponding to moderate-severe deficits. Overall, 23 patients (76.7%) were transferred to an inpatient rehabilitation center.

Association between level consciousness/cognition and sleep-wake patterns

Patients wore the actigraph for 11.3 ± 4.1 days, starting 21.0 ± 13.7 days post-injury (in ICU for 60% of the patients). Overall, there were 233 days of both actigraphy recording and RLA assessment.

DAR: We observe a strong association between RLA and DAR (see Table 2). Our results showed that an increase in RLA score was associated with a linear improvement in the consolidation of the 24-h sleep-wake cycle, as measured by the DAR (see Fig. 1A). When we used a DAR criterion of ≥ 80% to determine the occurrence of a consolidated sleep-wake cycle,[1] we observed that patients attained a consolidated 24-h sleep-wake cycle when they evolved from a RLA score of 5 (confused, non-purposeful response, but able to answer simple commands) to 6 (goal-directed behavior). Figure 2 shows example of actigraphic findings in relation to RLA scores.

Nighttime sleep duration: We observed a moderate association between RLA score and nighttime sleep duration (trend for significance when the Bonferonni correction was applied), and

an increase in RLA score was associated with a linear improvement in nighttime sleep duration (see Table 2) (see Fig. 1B).

Nighttime fragmentation index: We also found a strong association between RLA score and fragmentation index , such that an increase in RLA score was associated with a linear decrease in nighttime fragmentation index (see Table 2) (see Fig. 1C).

Cross-correlations revealed that the best-fit lag between RLA and DAR was 0 ($R^2 = 0.816$, $p < 0.001$), suggesting that improvements in DAR were simultaneous to that of RLA scores. Cross-correlations with nighttime sleep duration and nighttime fragmentation index were not significant, although a trend for a correlation at lag 0 was observed between RLA and fragmentation index ($r=-0.60$, $p=0.069$).

Discussion

In this study of 30 hospitalized patients in the acute phase of moderate and severe TBI, we demonstrate that the recovery of consciousness and higher cognitive functions occurs in parallel with improvements in consolidation of the sleep-wake cycle, as measured with actigraphy. Increasing consciousness and cognitive functioning was also tightly timed with the increase of the estimated nighttime sleep duration and the decrease in the estimated nighttime fragmentation index. This study establishes a clear link between acute sleep-wake disturbances and recovery of brain functions after TBI. No previous study investigated this temporal association in acute TBI, following emergence from coma. Some research groups showed that the presence of sleep elements measured by electroencephalography (EEG) (i.e. sleep spindles, K-complexes, and rapid eye movement sleep) are associated with level of consciousness, cognition and/or prognosis

in post-traumatic coma, in the subacute phase of brain injuries, and in chronic disorders of consciousness.[22-24] Other studies focused on the presence or absence of a 24-h sleep-wake cycle in chronic disorders of consciousness. For example, a study[25] compared the strength of the circadian rest-activity cycle of patients in chronic unresponsive wake syndrome (RLA score ~2) to that of patients in chronic minimally conscious states (MCS; RLA score ~ 3-5), using 4-day actigraphy, and showed a more robust circadian rhythm of rest-activity in patients in MCS. Our study shows that this parallel improvement continues with further improvement of the cognitive state, and demonstrates the linearity of the relationship. Our results also suggest that in acute TBI, consolidation of a circadian sleep-wake cycle attains an acceptable level (DAR $\geq$ 80%) only when patients emerge from MCS, marked by the capacity for functional communication or functional use of objects (RLA score $\geq$ 6).[26] Prior to this stage of consciousness recovery, sleep and wake states are present, but are fragmented and dispersed throughout the day and night rather than consolidated in a circadian rhythm. Although we cannot confirm the causal relationship between the injured brain and sleep-wake patterns, our results suggests that when the brain has not sufficiently recovered a level of consciousness to sustain both arousal and awareness of one's surroundings, it is also unable to generate consolidated sleep and wake.

Though the linearity of the relationship between RLA and the actigraphy variables is strong, the three sleep-wake variables seem to plateau at RLA scores of 6, 7 and 8. This plateauing may reflect the optimal level of consolidation of the sleep-wake cycle and nocturnal sleep quality that patients can reach in this context, given the limitations of the hospital environment, nursing interventions, and residual pain. Future studies should aim to assess what constitutes "normal" sleep parameters among critically ill patients in the ICU and regular wards without brain injury, to better situate the sleep of TBI patients.

Given that in healthy individuals, sleep restriction negatively affects cognition, particularly memory formation,[27] the inability to consolidate sleep and wake may hinder the recovery of consciousness and cognitive function after TBI. Impaired sleep is hypothesized to impede memory by preventing synaptic homeostasis.[28] Without sleep, the brain is thus less able to encode and consolidate new information in memory. Synaptic plasticity and hippocampal neurogenesis, two crucial processes for recovery following TBI, are also highly sleep-dependent.[29] In this context, poor sleep consolidation may impede cognitive recovery after a brain injury. However, in the present study, cross-correlation analyses suggest a synchronous recovery of sleep quality, cognition and consciousness, rather than a causal relationship. This suggests that in the context of acute TBI, it is most likely overall neuronal recovery that drives the progressive return of consciousness, cognition and sleep.

Strengths and limitations

Actigraphy is a measure of physical motion and therefore indirectly measures sleep and wake through assessment of the rest-activity cycle. Actigraphy is closely correlated to polysomnography in healthy individuals and is well validated for the estimation of sleep parameters across age groups.[17] Moreover, one research team recently showed that actigraphy correlated with polysomnography-measured total sleep time and sleep efficiency among severe TBI inpatients in a rehabilitation setting.[30] Still, results of the present study reflect an indirect measure of sleep and wake, though actigraphy remains the best-suited method for the long-term assessment of sleep-wake cycles within this clinical population.

Results from cross-correlations are sometimes criticized because they tend to overestimate the strength of time-lagged relationships, mainly because of data autocorrelations and intra-

multiplicity.[21] However, given the strength of the cross-correlation analysis between RLA and DAR (r = 0.816) and a moderate autocorrelation (0.5) in our data, we estimate our type I error rate bias to be under 0.10,[21] which is negligible. Moreover, given the high variability of RLA scores and actigraphy data on each day of actigraphy recording, averaging our RLA and actigraphy data per day most likely weakened inter-day differences. Such pooling of data to create averages per day, as required to perform cross-correlation analyses, reduces variability and the number of data points, and may thus explain why no cross-correlation was significant with nighttime sleep duration and fragmentation index (trend for significance only).

Conclusions

This study showed that the consolidation of the sleep and wake states go hand in hand with the recovery of consciousness and cognition in acute TBI, though the directionality (or bidirectionality) of this relationship remains unknown. Insight on the association between neuronal recovery and the sleep-wake cycle could help shed light on the pathophysiology of post-TBI sleep-wake disturbances, which frequently persist up to several years post-injury.[31-35] This association also suggests that assessment of the sleep-wake cycle in acute TBI may be a useful tool for monitoring patient evolution and recovery. Moreover, the possibility of a positive feedback action of improved consolidation of sleep and wake states on consciousness and cognitive recovery may be worthy of further investigation. The role of hospital lighting and noise could be interesting to assess in future studies in order to better appraise their implications in sleep-wake disturbances. However, given that patients in the present study were hospitalized in the same environment but had different sleep-wake cycle consolidation and quality depending on their level of consciousness, it may suggest that environmental factors only partly account for the sleep-wake disturbances observed in hospitalized TBI patients. Results from the present study

could have implications for the development of interventions targeting the sleep-wake cycles and aimed at optimizing functional recovery in both acute and chronic disorders of consciousness.

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Table 1. Rancho Los Amigos scale of cognitive functioning, including the number of days and patients representing each RLA score. (Adapted from previously published article,[36] with permission from the editor)

RLA score	Description	Days (nb.)	Patients (nb.)
1 No response	Patient does not respond to external stimuli and appears asleep.	-	-
2 Generalized	Patient reacts to external stimuli in nonspecific, inconsistent, and nonpurposeful manner with stereotypic and limited responses.	-	-
3 Localized	Patient responds specifically and inconsistently with delays to stimuli, but may follow simple commands for motor action.	26	7
4 Confused-agitated	Patient exhibits bizarre, nonpurposeful, incoherent or inappropriate behaviours, has no short-term recall, attention is short and nonselective.	31	8
5 Confused, innapropriate, nonagitated	Patient gives random, fragmented, and nonpurposeful responses to complex or unstructured stimuli - Simple commands are followed consistently, memory and selective attention are impaired, and new information is not retained.	80	14
6 Confused-appropriate	Patient gives context-appropriate, goal-directed responses, dependent upon external input for direction. There is carry-over for relearned, but not for new tasks, and recent memory problems persist.	37	10
7 Automatic-appropriate	Patient behaves appropriately in familiar settings, performs daily routines automatically, and shows carry-over for new learning at lower than normal rates. Patient initiates social interactions, but judgment remains impaired.	44	10
8 Purposeful-appropriate	Patient oriented and responds to the environment but abstract reasoning abilities are decreased relative to premorbid levels.	15	3

Table 2. Association between sleep-wake patterns and level of consciousness/cognition

		Significance of mixed model p-value	**Linear contrast analysis** p-value
Sleep-wake cycle consolidation			
Daytime activity ratio (%)		0.0005	0.0003
Mean ± SD	77.4 ± 12.3		
Range	41.3-98.2		
Nighttime sleep quality			
Total sleep time (h)		0.018	0.002
Mean ± SD	5.7 ± 2.0		
Range	0.5-8.7		
Fragmentation index		0.00000003	0.000008
Mean ± SD	78.8 ± 39.8		
Range	4.8-199.3		

Figure legends

Figure 1. Association between cognitive and consciousness recovery and the sleep-wake cycle

(A) Parallel evolution of the Rancho Los Amigos scale of cognitive functioning score and daytime activity ratio in the 30 patients assessed over 233 days. Black dots indicate the mean daytime activity ratio per score on the Rancho Los Amigos scale, generated within the mixed model equation, and black bars represent SEM. The linear contrast analysis was statistically significant ($p < 0.001$).

(B) Parallel evolution of the Rancho Los Amigos scale of cognitive functioning score and nighttime sleep duration and in the 30 patients assessed over 233 days. Black dots indicate the mean nighttime sleep duration (min) per score on the Rancho Los Amigos scale, generated within the mixed model equation, and black bars represent SEM. The linear contrast analysis was statistically significant ($p = 0.002$).

(C) Parallel evolution of Rancho Los Amigos scale of cognitive functioning score and nighttime fragmentation index and in the 30 patients assessed over 233 days. Black dots indicate the mean nighttime fragmentation index per score on the Rancho Los Amigos scale, generated within the mixed model equation, and black bars represent SEM. The linear contrast analysis was statistically significant ($p < 0.001$).

Figure 2. Examples of actigraphic findings in relation to RLA scores

Examples of typical actigraphic findings for RLA ranging rom 3 to 5 (left panel), and RLA ranging from 6 to 8 (right panel). Total activity counts for each minute of recording is illustrated by vertical dark lines, on a scale of 0 to 1000 activity counts. Daytime hours (07:00-22:00 h) are

shown in yellow and nighttime hours (22:00-07:00 h) are in blue. Daily Daytime activity ratio (DAR) are inidicated at the bottom of each actogram.