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Sleep and circadian rhythms in the acute phase of moderate to severe traumatic brain injury

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Résumé

Les traumatismes craniocérébraux (TCC) sont la principale cause d'invalidité chez les jeunes adultes, engendrant d'importantes séquelles cognitives, physiologiques et comportementales. Les perturbations du cycle veille-sommeil sont parmi les symptômes les plus persistants à la suite d'un TCC et pourraient nuire à la récupération. En effet, le sommeil est nécessaire à l'apprentissage, la plasticité cérébrale et la génération de nouveaux neurones dans le cerveau adulte. Les observations cliniques suggèrent que ces perturbations apparaissent dès les premières semaines suivant le TCC et pourraient suggérer une altération de l'horloge circadienne. Cependant, aucune étude n'a encore documenté comment les perturbations du cycle veille-sommeil émergent et évoluent dans la phase aiguë du TCC, ni leur association à la récupération fonctionnelle et cognitive à court-terme.

Conséquemment, cette thèse vise à caractériser le sommeil et les rythmes circadiens des patients hospitalisés avec un TCC modéré ou sévère et déterminer si les perturbations du cycle veille-sommeil sont causées par un dérèglement de l'horloge circadienne. Pour ce faire, nous avons utilisé des mesures objectives et quantitatives de sommeil et des rythmes circadiens, incluant l'actigraphie, la polysomnographie (PSG) et la mélatonine, dès la phase d'éveil aux soins intensif. Afin de comprendre le rôle du TCC dans ces perturbations, nous avons comparé les patients TCC à des patients hospitalisés avec blessures orthopédiques graves, sans TCC. Ce protocole a mené à cinq articles de recherche.

En premier lieu, nous démontrons que le cycle veille-sommeil des patients TCC est sévèrement perturbé, mais s'améliore chez 50% d'entre eux au cours de leur séjour hospitalier. Les patients avec une amélioration de la consolidation du cycle veille-sommeil ont un meilleur fonctionnement cognitif et fonctionnel au congé de l'hôpital. Ensuite, dans une étude de cas, nous démontrons qu'un patient TCC peut avoir un cycle veille-sommeil complètement différent dans un même environnement, selon son stade de récupération. Notre troisième article confirme que la consolidation du cycle veille-sommeil évolue en synchronie avec la récupération de la conscience et des fonctions cognitives dans la phase aiguë du TCC.

Notre quatrième article compare le sommeil des patients TCC à celui des blessés orthopédiques graves, sans TCC, en utilisant un système de PSG ambulatoire au chevet. Nous démontrons que, contrairement à notre hypothèse, le sommeil des patients TCC comprend tous les éléments et stades d'un sommeil normal. Cependant, ces patients s'endorment plus tôt et ont un sommeil de plus longue durée, mais plus fragmenté, que les patients sans TCC. Dans les deux groupes, le sommeil est de mauvaise qualité, reflétant probablement l'effet de facteurs non-spécifiques associés avec les blessures physiques et l'environnement hospitalier. Conséquemment, la PSG en phase aiguë permet difficilement de distinguer les patients TCC des patients sans TCC.

Notre dernier article confirme que les patients avec TCC ont une consolidation du cycle veille-sommeil et une qualité de sommeil nocturne inférieures à celles des patients sans TCC, ce qui confirme le rôle du TCC dans les perturbations du cycle veille-sommeil. Cependant, malgré ces perturbations plus sévères, les patients TCC ont un rythme normal de la mélatonine et celui-ci n'est pas associé aux perturbations observées. Cet article suggère que des mécanismes neuronaux autres que l'horloge circadienne seraient responsables des perturbations du cycle veille-sommeil à la suite d'un TCC.

Cette thèse est la première à évaluer le sommeil et le fonctionnement de l'horloge circadienne de patients hospitalisés avec un TCC modéré ou sévère ayant atteint la stabilité médicale. En isolant le rôle du TCC de celui du traumatisme physique et du milieu hospitalier, ces études contribuent à comprendre les caractéristiques, les conséquences et la pathophysiologie des perturbations du cycle veille-sommeil à la suite d'un TCC, ouvrant la voie à de possibles interventions visant à améliorer le sommeil et optimiser la récupération.

Mots-clés : traumatisme craniocérébral, sommeil, rythmes circadiens, mélatonine, actigraphie, polysomnographie, soins aigus, récupération, conscience, cognition

Abstract

Traumatic brain injuries (TBI) are the leading cause of disability among young adults, causing debilitating cognitive, psychological and behavioural impairments. Sleep-wake disturbances (SWD) are among the most persistent sequelae following TBI, and could impede recovery. Indeed, sleep is essential to learning, plasticity and neurogenesis. Clinical observations suggest that these disturbances arise in the first weeks following injury, and could suggest a circadian disturbance. However, no study has yet documented how SWD arise and evolve in the acute phase of TBI, or how they are associated to short-term cognitive and functional recovery.

Consequently, this thesis aims to characterize the sleep and circadian rhythms of patients hospitalized with moderate or severe TBI, and determine whether SWD are caused by a deregulation of the circadian clock. To achieve this goal, we used objective and quantitative measures of sleep and circadian rhythms including actigraphy, polysomnography (PSG), and melatonin, beginning in the awakening stage in the Intensive Care Unit. In order to understand the specific role of TBI on SWD, we compared TBI patients to other hospitalized trauma patients, without TBI. Our comprehensive study protocol led to five research articles.

First, we show that the sleep-wake cycle of TBI patients is severely disturbed, but improves for 50% of patients during their hospital stay. Patients whose sleep-wake cycle consolidation improves have better cognitive and functional outcome at hospital discharge. Then, in a single case study, we demonstrate how a patient can have drastically different sleep-wake patterns in the same environment, according to recovery stage. In our third research article, we show that the consolidation of sleep and wake states evolves synchronously with the recovery of consciousness and cognition in the acute phase of TBI.

Our fourth article compares the sleep of TBI patients to that of non-TBI trauma patients using ambulatory PSG at bedside. Contrary to our hypothesis, TBI patients have normal sleep elements and normal proportions of each sleep stages. However, they have earlier sleep onset and longer nighttime sleep duration, but with greater fragmentation, than

non-TBI patients. In both groups, sleep quality is poor, which most likely reflects non-specific factors associated with the physical trauma and hospital environment. Therefore, PSG reveals little information able to distinguish TBI patients from other non-TBI trauma patients at this stage post-injury.

Our final article shows that TBI patients have poorer sleep-wake cycle consolidation and nighttime sleep quality than non-TBI patients, confirming the role of the TBI in altering sleep and wake states. However, despite having more severe SWD, TBI patients have a normal melatonin rhythm, and this rhythm is not associated with the observed SWD. This article suggests that neural mechanisms other than the circadian clock may be responsible for post-TBI SWD.

This thesis is the first to investigate the sleep and circadian clock of hospitalized moderate to severe TBI patients who are medically stable. By isolating the role of the injured brain from that of overall trauma and the hospital setting, these studies contribute to understanding the characteristics, consequences and pathophysiology of post-TBI SWD, unlocking the possibility to design interventions aiming to improve sleep and optimize recovery.

Keywords: traumatic brain injury, sleep, circadian rhythms, melatonin, actigraphy, polysomnography, acute care, recovery, consciousness, cognition

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List of acronyms

ACTH: adreno-corticotropic hormone

ADL: activities of daily living

aMT6s: 6-sulfatoxymelatonin

ANCOVA: analysis of covariance

ANOVA: analysis of variance

AR1: autoregressive

ARAS: ascending reticular activating system

BADS: Behavioral Assessment of the Dysexecutive Syndrome

BCAA: branched chain amino acid

CASE: Cognitive Assessment Scale for the Elderly

CBT: cognitive behavioural therapy

CO: cerebral oedema

CS: compound symmetry

CSF: cerebrospinal fluid

CT: computed tomography

DAI: diffuse axonal injury

DAR: daytime activity ratio

DelRS-R98: Delirium Rating Scale – Revised-98

D-KEFS: Delis-Kaplan Executive Function System

DRS: Disability Rating Scale

DSM-IV: Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders

EDH: extradural hematoma

EDS: excessive daytime sleepiness

EEG: electroencephalography

EMG: electromyography

EOG: electrooculography

ER: emergency room

ESS: Epworth Sleepiness Scale

FOSQ: Functional Outcome Sleep Questionnaire

FSH: follicle-stimulating hormone

GABA: *gamma*-Aminobutyric acid

GCS: Glasgow Coma Scale

GH: growth hormone

GOAT: Galveston Orientation and Amnesia Test

ICP: intracranial pressure

ICSD: International Classification of Sleep Disorders

ICU: Intensive Care Unit

ID: identification

IL-1β: Interleukin 1 beta

ISS: Injury Severity Score

LH: luteinizing hormone

LOS: length of stay

MCS: minimally conscious state

MLS: midline shift

MMSE: Mini Mental State Examination

MRI: magnetic resonance imaging

mNRA: messenger ribonucleic acid

MSLT: Multiple Sleep Latency Test

mTBI: mild traumatic brain injury

MVA: motor vehicle accident

MVPT: Motor-Free Visual Perception Test

MWT: Multiple Wakefulness Test

NREM: non-rapid eye movement

NS: non significant

OI: orthopaedic injury

OSA: obstructive sleep apnea

OSCI: orthopaedic and/or spinal cord injury

PRL: prolactin

PSG: polysomnography

PSH: Paroxysmal Sympathetic Hyperactivity

PTA: post-traumatic amnesia

REM: rapid eye movement

RHD: radial head luxation

RLA: Rancho Los Amigos scale of cognitive functioning

SAH: subarachnoid hemorrhage

SCI: spinal cord injury

SCN: suprachiasmatic nucleus

SD: standard deviation

SDH: subdural hematoma

SEM: strander error of the mean

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

SWA: slow-wave activity

SWD: sleep-wake disturbances

SWS: slow-wave sleep

TBI: traumatic brain injury

TIL: Summary Therapy Intensity Level

TNF-α: tumor necrosis factor alpha

TSH: thyroid-stimulating hormone

VLPO: ventrolateral preoptic nucleus

WAIS: Wechsler Adult Intelligence Scale

WASO: wake after sleep onset

WMS: Wechsler Memory Scale

List of abbreviations

a.k.a.: also known as

cum.: cumulative

e.g.: such as (*exempli gratia)*

etc. : *Et cætera*

F: female

Fig.: Figure

fx: fracture

g: gram

h: hour

hrs: hours

i.e.: that is (*id est)*

L: left

M: male

mg: miligrams

min: minute

ml: milileter

mmHg: milimeters of mercury

n.a.: non-applicable

nd: number

ng: nanogram

ng/ml: nanogram per milileter

R: right

yo: years old

À mon fils Liam, né pendant mes études doctorales.
Souviens-toi de travailler fort pour atteindre tes rêves, de profiter du parcours qui te mènera à tes réalisations et de faire le plus de bien possible autour de toi.

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Chapter I: Introduction and theoretical background

1. General introduction

The hospital environment, in which activity only ceases partially during nighttime, is not conducive to uninterrupted sleep. The care necessary to ensure the health and well-being of patients comes with noise, light, and interventions around the clock. It is therefore not surprising that one of the most stressful experiences of hospitalized patients is their chronic lack of sleep (Novaes et al., 1999; Simini, 1999; Nelson et al., 2001; Park et al., 2014; Beltrami et al., 2015). Unfortunately, despite being a central preoccupation of hospital patients, sleep is often neglected and dismissed as less important than direct medical care and interventions. When we know that sleep is essential to survival of critical illness, optimal health and recovery (Tembo & Parker, 2009), we can wonder what impact sleep disturbances have on the recovery of hospitalized patients. Indeed, poor sleep hinders recovery by lowering the ability to resist infection, by causing or exacerbating neurological problems such as delirium, and prolonging the duration of mechanical ventilation and stay in the Intensive Care Unit (ICU) (Parthasarathy & Tobin, 2004).

The importance of sleep in patients hospitalized with moderate to severe traumatic brain injury (TBI) is especially crucial when considering the role of sleep in learning and neuronal plasticity (Smith, 1996; Walker, 2004; Wilson, 2002; Walker & Stickgold, 2006; Diekelman & Born, 2010), as well as for the generation of new neurons in the adult brain (Roman et al., 2005; Mirescu et al., 2006; Guzman-Marin et al., 2007; Meerlo et al., 2009). Indeed, TBI destroys brain structures and connections that need regeneration. Clinical observations in the acute care setting suggest that sleep-wake disturbances (SWD) appear in the first weeks after TBI, during which patients experience insomnia, inability to stay awake for a few consecutive hours during the day and/or altered sleep-wake cycles, which could point to a disturbance in circadian rhythms. SWD in the acute post-traumatic period probably impede brain recovery, and may contribute to short-term and long-term cognitive, physical, and neurobehavioral impairments resulting from TBI. What is more, SWD, including fatigue, insomnia and hypersomnia, are among the most persistent and debilitating symptoms following TBI (Castriotta et al., 2007; Cantor et al., 2008). Although SWD are reported by at

least 50% of TBI patients in the chronic stage post-injury (Castriotta et al., 2007; Cantor et al., 2008), little is known about their origin, evolution, and consequences.

These preoccupations led us to investigate sleep and circadian rhythms in the acute phase of moderate to severe TBI. More specifically, this thesis aims to characterize SWD in the acute phase, while patients are still hospitalized, to appraise the impact of SWD on short-term cognitive and functional recovery, and to investigate whether these disturbances arise due to a disturbance in the circadian clock. Since sleep is a modifiable behaviour, it is an important therapeutic target with the potential to optimize recovery.

2. Traumatic Brain Injury

Moderate to severe TBI is the principal cause of mortality and lifelong disability among young adults in industrialized countries (Kraus & Chu, 2005; Langlois, Rutland-Brown & Wald, 2006; Roozenbeek, Mass & Menon, 2013). Patients who suffer moderate to severe TBI require an extensive period of hospitalization in the ICU to survive their injury, and generally require several weeks to months of intensive rehabilitation. Ultimately, TBI results in short- and long-term cognitive, psychological and behavioural impairments that interfere with the return to a normal and productive life.

2.1. Characteristics and diagnostic criteria

TBI is an alteration in brain function, or other evidence of brain pathology, caused by an external force (Menon et al., 2010). An alteration in brain function is defined by one of the following signs: a period of decreased level of consciousness, an alteration in mental state at the time of injury (e.g. confusion, disorientation), a loss of memory for events immediately before (retrograde amnesia) or after the injury (post-traumatic amnesia, or PTA), and neurological deficits (e.g. loss of balance, weakness, aphasia, change in vision). Other evidence of brain pathology may include visual, neuroradiological, or laboratory confirmation of brain damage.

The diagnosis of TBI involves an assessment of severity, generally carried out using the Glasgow Coma Scale (GCS), which assesses verbal, ocular and motor functions, immediately following injury (Teasdale & Jennett, 1974). Globally, mild TBI (mTBI) is characterized by a short loss of consciousness (< 30 min), a GCS score between 13 and 15 and a short PTA (< 24 h). Moderate TBI is typically associated with a loss of consciousness of 30 min to 24 h, a GCS between 9 and 12, and PTA of 1 to 14 days. Severe TBI is generally characterized by a loss of consciousness of more than 24 h, a GCS between 3 and 8 and a PTA that persists for several weeks. As opposed to mTBI, patients having suffered a moderate or severe TBI have an extensive loss of consciousness and generally require hospitalization in the ICU to survive their injury. This thesis will focus on moderate to severe TBI.

Varying definitions have been used to describe TBI in the past, which has led to heterogeneity in epidemiological studies. Internationally, the estimated annual incidence of TBI is 295 per 100,000 (Nguyen et al., 2016). In industrialized countries, the annual incidence of moderate and severe TBI is estimated at around 1.2/1000 individuals (Kraus et al., 2005). Though moderate and severe TBI account for approximately 10% of all TBI, they contribute to the majority of deaths, disability and TBI-related costs (McGarry et al., 2002). The most frequent causes of injury are motor-vehicle accidents, falls, assault, recreational injuries, and work accidents (Zygun et al., 2005; Rutland-Brown et al., 2006). Teenagers and young adult males (15-24 years old) have an increased risk of sustaining TBI, while other risk factors include low economic status, low education, and alcohol or drug addiction (Bruns & Hauser, 2003; Nguyen et al., 2016).

2.2. Pathophysiology

Brain lesions resulting from TBI occur in two different time periods. The primary insults occur in the few seconds that follow the TBI and result from the applied biomechanical forces of the injury, including the acceleration, deceleration, and rotational forces concurrent with or secondary to the direct trauma (Greve & Zinc, 2009). They cause focal lesions (i.e. intracranial hematoma, skull fracture, contusions, lacerations) or diffuse axonal injuries. Secondary insults, which are caused by the biomolecular and physiological changes induced

by the primary insult, arise in the hours and days following the initial injury (Raghupathi, 2004; Gennarelli & Graham, 2005; Greve & Zinc, 2009; Petroni et al., 2010; Sandsmark, 2016). Elevated intracranial pressure (ICP) (a.k.a. intracranial hypertension) is the most common form of secondary insult, but others include the production of free radicals, mitochondrial dysfunction, and an inflammatory cascade that ultimately leads to the degeneration of neurons, glial cells, and axons (Holmin et al, 1995). These secondary insults are thus the determining factors in the morbidity and mortality of patients who survive the initial injury (Greve & Zinc, 2009). The long-term damages that arise following moderate to severe TBI are characterized by axonal degeneration throughout the brain (Bendlin et al., 2008; Greenberg et al., 2008; Kumar et al., 2009; Perlbag et al., 2009; Kumar et al., 2010; Kinnunen et al., 2011; Dinkel et al., 2013), and brain atrophy, particularly in the hippocampus and frontal and temporal cortices, as well as the thalamus, basal forebrain, hypothalamus, pituitary stalk, caudate nucleus, and insula (Gale et al., 2005; Gennarelli & Graham, 2005; Salmond et al., 2005; Tasker et al., 2005; Bendlin et al., 2008; Slawik et al., 2009).

2.3. Functional and cognitive consequences of moderate to severe TBI

TBI leads to varying degrees of symptoms and handicaps, depending on mechanism and severity of the injury. In addition to causing both short- and long-term impairments, such as cognitive, behavioural and psychological alterations, TBI also increases the risk of developing psychiatric and neurodegenerative disorders (Vaishnavi, Rao & Fann, 2009; Masel & DeWitt, 2010; Bhalerao et al., 2013), and has been associated with shortened lifespan (Masel & DeWitt, 2010). As such, TBI is no longer considered an event, but a progressive, chronic and heterogeneous disease process (Masel & DeWitt, 2010; Maas, 2016).

In approximately 50% of patients, severe cognitive deficits persist into the chronic phase (Selassie et al., 2008). The most prevalent are attention deficits (Salmond et al., 2005; Salmond et al., 2006; Mathias & Wheaton, 2007), memory impairments (Levin et al., 1988; Curtiss et al., 2001), and executive dysfunctions (i.e. planning, initiation, inhibition, problem solving, mental flexibility, and self-monitoring) (McDonald, Flashman & Saykin, 2002; Spikman & Van der Naalt, 2010). These deficits lead to a reduction in independence and

difficulties regaining a productive lifestyle (Shames et al., 2007). Factors contributing to more severe cognitive deficits include the severity of diffuse axonal injury, the duration of PTA, the extent of cerebral atrophy, and age (Katz & Alexander, 1994).

The period comprising hospitalization and acute rehabilitation following TBI loosely represents the acute and post-acute phases. It is estimated that 85% of cognitive recovery takes place within the first 6-months following TBI (Lippert-Gruner, Lefering & Svestkova, 2007), which suggests that the acute and post-acute phases have an undeniable impact on the long-term functionality and quality of life of patients. Factors that hinder recovery in the first weeks post-injury could determine the course of overall recovery and outcome. This thesis will focus on the hospitalization period of the acute phase.

2.4. The acute phase of TBI

Immediately following the initial injury, most moderate to severe TBI patients are hospitalized in the ICU for several hours to several weeks. This period is marked by an alteration in consciousness, and patients are generally under continuous sedation for several days. Once they reach the awakening stage, patients generally present agitation, confusion, and PTA (Trzepacz & Kennedy, 2005). Neurobehavioural impairments such as impulsivity, irritability, desinhibition, mutism, and apathy can also be observed to varying degrees (Riggio & Wong, 2009). As level of consciousness gradually improves over time, patients may transition through different consciousness levels, transiently or persistently, including unresponsive wake syndrome (UWS; previously known as vegetative state) and minimally conscious state (MCS).

The post-ICU period begins when a patient has reached medical stability, has moved beyond the awakening stage, and has been transferred to a regular or neurological ward within the hospital. Patients generally present impairments in arousal and alertness, reduced information processing speed, impaired memory and executive dysfunctions, impaired language, and reduced self-awareness (McCullagh & Feinstein, 2005). The extent of functional and cognitive deficits observed during this stage is highly variable among patients

and depends on several factors, including the severity of diffuse axonal injury, the location of focal lesions, the duration of PTA, age, level of education, and other pre-existing conditions (de Guise et al., 2005; LeBlanc et al., 2006; de Guise et al., 2006; de Guise LeBlanc et al., 2009; Kosch et al., 2010). Patients can remain agitated and disoriented throughout this stage, as some remain in PTA when they are discharged from the hospital and admitted to internal rehabilitation centers. Only a minority of moderate to severe TBI patients are discharged without being sent to acute internal rehabilitation.

Overall, the ICU and post-ICU stages post-injury are challenging research settings, given the fluctuating medical and cognitive states of patients. Most studies having investigated the physiological effects of TBI have taken place prior to the awakening stage, when patients are still mechanically ventilated and continuously sedated, or during the chronic stage of injury.

3. Sleep

3.1. Normal sleep

Sleep is an active and reversible physiological state, which is essential for survival and healthy functioning of the organism (Banks & Dinges, 2007). While the function of sleep is not fully understood, early hypotheses suggest that sleep serves a function of restoration, by restoring depleted energy (Oswald, 1980), and a function of energy conservation (Walker & Berger, 1980). Recent hypotheses link sleep with metabolic waste clearance in the brain (Xie et al. 2013) and synaptic homeostasis (Tononi & Cirelli, 2003; Tononi & Cirelli, 2006), highlighting the role of sleep in learning and plasticity. Though the function of sleep remains somewhat enigmatic, the effects of sleep loss reveal its undeniable role in the maintenance of a healthy body and brain. Indeed, partial or chronic sleep loss causes a range of neurobehavioural and cognitive deficits, as well as endocrine, metabolic, cardiovascular, immune, and inflammatory alterations that hinder general health (Dinges et al., 1994; Spiegel, Leproult & Van Cauter, 1999; Spiegel, Sheridan & Van de Cauter, 2002; Shamsuzzaman et al. 2002; Banks & Dinges, 2007; Goel et al., 2009; Mullington et al., 2009).

Sleep is comprised of various stages that have measurable behavioural and physiological traits, which reflect their underlying functional mechanisms. Polysomnography (PSG) is the most widely used tool to measure sleep, and includes electroencephalography (EEG), electrooculography (EOG), and electromyography (EMG). While EEG is the measurement of the brain's electrical activity, EOG and EMG measure eye movements and the muscular activity on the chin, respectively. The identification of sleep stages is carried out according to standardized criteria based on the visual analysis of these physiological parameters (Iber, Ancoli-Israel & Quan, 2007).

Sleep architecture is the structural organization of sleep. Sleep stages can be divided into two main categories: rapid eye movement (REM) and non-rapid eye movement (NREM), or slow-wave sleep (SWS). Some bodily movements can accompany NREM, but eye movements are rare. NREM sleep can be divided into three stages that reflect the degree of neuronal synchrony, spanning from lighter sleep (N1 and N2) to deep sleep (N3), where neuronal synchrony is at its peak and slow waves predominate the EEG. REM sleep is the primary stage during which dreaming occurs. It distinguishes itself from NREM sleep through three main characteristics: desynchronized EEG activity, rapid eye movements, and nearly complete muscle atonia, which prevents the enactment of dreams (Siegel, 2011). In the course of one night, the human adult alternates between sleep stages in cycles of approximately 90-100 min in duration. Though stage N3 is most present at the beginning of the night, REM sleep becomes increasingly prevalent as the night progresses.

Although PSG is the gold standard for measuring sleep, it is difficult to use to record sleep and wake states over several consecutive days. Being cumbersome, is it also poorly tolerated by patients hospitalized in critical care and/or in a state of confusion or agitation. Actigraphy is the most-utilized alternative to PSG. The activity monitor, or actigraph, is a small watch-like device worn on the wrist, which records physical motion in all directions, with a sensitivity of 0.05g. Motion is subsequently converted into an electrical signal, which is digitally integrated to derive an activity count (i.e. sum of activity) for each 1-min epoch (Paquet, Kawinska & Carrier, 2007). Actigraphy can easily be used in a hospital setting. With its low invasiveness and cost, it enables the long-term measurement of the rest-activity cycle

in a clinical setting, and is recognized as an indirect measure of the sleep-wake cycle (Martin & Hakim, 2011). The ability of actigraphy to record the rest-activity cycle continuously for up to several weeks makes it an ideal tool to estimate when sleep and wake arise, how they are distributed over the 24 h day, and how they evolve over the course of several days or weeks. In fact, actigraphy has been successfully used in various clinical populations (Martin & Hakim, 2011).

3.2. Sleep in acute care in non-TBI patients

The acute care setting is not favourable to optimal sleep. Studies on patients hospitalized in the ICU, without TBI, have shown that the sleep-wake cycle and sleep quality are severely altered. In fact, approximately 50% of sleep takes places during the day, and up to 96% of sleep is spent in stages N1 and N2, suggesting a drastic reduction or absence of SWS (N3) (Cooper et al., 2000; Gabor et al., 2003; Friese et al., 2007; Gehlbach et al., 2012). The consequences of sleep disturbances in the ICU are probably similar to the effects of chronic sleep restriction in healthy subjects: for example, they may lead to a decrease in cognitive functioning, a slowing of glucose metabolism, the activation of the hypothalamic-pituitary-adrenal axis and an increase in the inflammatory response (Kamdar, Needham, & Collop, 2012).

For a detailed description of normal sleep, sleep in the hospital setting, and the impact of poor sleep on cognitive and functional outcome of TBI patients in hospital and rehabilitation settings, refer to article 1 (Chapter 1, section 5).

3.3. Sleep in the acute and chronic stages of TBI

Little is known about the nature and evolution of SWD after a TBI, and very few studies have documented SWD in acute settings. The earliest studies investigating sleep following moderate-severe TBI took place in rehabilitation centers, using actigraphy and nurse assessments, and found a high prevalence of sleep disturbances, associated with the resolution of PTA (Makley et al., 2008, Makley et al., 2009) In the ICU, observations by clinical staff suggest that these disturbances are present as early as the awakening stage post-injury, while

patients are still in the ICU. However, no study has yet objectively characterized this phenomenon and its impact on acute recovery.

In order for natural sleep and the sleep-wake cycle to be accurately measured in acute TBI, patients need to have minimally reached a stage where they are able to awaken spontaneously. According to international diagnostic guidelines, sleep-wake cycles among patients with severely altered levels of consciousness (e.g. UWS, MCS) are assessed mainly by means of observation, through the identification of periods of eye-opening and eye-closure (Cruse et al., 2013). Indeed, the return of a sleep-wake cycle is assumed to arise once patients reach UWS. However, little empirical evidence exists to support the existence of normal sleep among patients in UWS. In fact, one study showed that the EEG of patients in UWS remains unchanged between periods of eye-opening and eye-closure despite the preservation of "behavioural sleep" (Landsness et al., 2011), highligthing the unreliability of behavioural assesment for the measure of sleep among UWS patients. In patients having reached MCS however, several EEG characteristics of normal sleep are present, including an alteration between REM and NREM sleep (Landness et al., 2011). Therefore, there remains a lack of consensus as to what sleep objectively is, and how it may vary, among patients whose level of consciousness is severely altered. Moreover, the use of automatic sleep scoring can be misleading at this stage of recovery, given the presence of slower baseline EEG in brain-damaged patients (Landsness et al., 2011).

SWD remain present into the chronic phase post-injury in over 50% of patients (Parcell et al., 2006, Ouellet, Beaulieu-Bonneau, & Morin, 2006; Gosselin et al., 2009; Wiseman-Hakes et al., 2009; Kempf et al., 2010; Beaulieu-Bonneau & Morin, 2012). The most prevalent include excessive daytime sleepiness, insomnia, and hypersomnia (Ouellet, Beaulieu-Bonneau & Morin, 2006; Castriotta et al., 2007; Kempf et al., 2010). For a detailed description of SWD following TBI, refer to article 2 (Chapter 1, section 5). This article provides a narrative review of SWD assessed both subjectively and objectively, spanning all levels of severity and phases post-injury.

4. Circadian rhythms

4.1. Processes of sleep regulation

The sleep-wake cycle is regulated by an interaction of the circadian and homeostatic processes (Borbély, 1982). The circadian process involves the rhythmic variation of sleep and wake propensity over 24 h, while the homeostatic process represents the accumulation of sleep pressure during wakefulness, reflected by the amount of EEG slow-wave activity (SWA) during NREM sleep (Achermann et al., 1993; Robillard et al., 2010), and its dissipation during the sleep period (Borbély, 1982). As homeostatic sleep pressure increases with hours spent awake, the circadian wake signal also increases to counterbalance the homeostatic process, reaching its peak approximately 2 h prior to bedtime, which enables us to stay awake during the evening. During nighttime, homeostatic pressure dissipates during sleep, which decreases sleep need as the night progresses. Conversely, the circadian sleep signal reaches its peak approximately 2 h prior to wake time, which enables sleep to be sustained until morning. Therefore, the interaction of these two processes enables the consolidation of wake during the daytime and sleep during nighttime (Borbély & Acherman, 1992; Dijk & Czeisler, 1994; Dijk & Czeisler, 1995), which will henceforth be referred to as a consolidated sleep-wake cycle.

4.2. The circadian system

The importance of the circadian system extends far beyond its implication in sleep-wake regulation. In humans, as in nearly all living organisms, a multitude of biological activities (e.g. hormone secretion, cognitive performance, metabolic functions, muscular strength, cell division) oscillate over a 24 h period and are directly controlled by the endogenous circadian master clock (Takahashi & Zatz, 1982; Moore, 1997; Gronfier, 2009). This master circadian clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Although circadian rhythms are generated endogenously, they are sensitive to the environment, enabling synchronization of the organism to the environmental day. Given that the endogenous period of the circadian clock generally differs slightly from 24 h in humans (Czeisler & Buxton, 2011), this synchronization is crucial to the proper functioning of

the organism in relation to the 24 h day. It enables physiological, cognitive and behavioural functions associated with activity to take place during the daytime, and those associated to rest to occur during nighttime (Czeisler et al., 1999). The main synchronizer of the circadian system is the light-dark cycle, which reaches the SCN through a monosynaptic retino-hypothalamic tract (Takahashi & Zatz, 1982; Moore, 1997; Gronfier, 2009). Non-photic stimuli, such as social interaction and the timing of meals, have also been shown to have some influence on circadian rhythms (Stephan, 2002; Challet et al., 2003; Mistlberger & Skene, 2005).

The rest-activity cycle is the most commonly and most easily measured marker of overall circadian functioning, as it is strongly correlated to the sleep-wake cycle (Barion & Zee, 2007; Martin & Hakim, 2011). However, markers that best reflect the timing of the master circadian clock are those that have a strong endogenous drive. In humans, these include body temperature, melatonin production, and cortisol production, though they may be affected by environment and behaviour when these are not properly controlled. The measurement of these rhythms enables the characterization of the phase (i.e. a specific point within a cycle), period (i.e. a complete cycle, or the elapsed time between successive occurrences of a particular phase), and amplitude (i.e. range of values within a cycle) of the circadian signal (Lemmer & Portaluppi, 1997; Dunlap, Loros, & DeCoursey, 2003; Wirz-Justice, 2007; Czeisler & Gooley, 2007; Mistlberger & Rusak, 2011).

Melatonin production is the best available marker of internal timing of the master circadian clock, given that the timing of onset and offset of melatonin production is tightly controlled by the SCN and that its temporal profile is relatively unaffected by sleep or wake when the environment is constant (Arendt, 2005). Melatonin is a hormone secreted by the pineal gland during the biological night. Its production is driven by the SCN via a multi-synaptic pathway involving the spinal cord and sympathetic nervous system (Teclemariam-Mesbah et al., 1999). Given that melatonin's principal synchronizer is the light-dark cycle, its production is highly sensitive to light exposure. In fact, melatonin production can be suppressed by exposure to light, partially or completely, depending on the spectrum and intensity of light exposure, as well as its duration (Duffy & Wright, 2005). When the master

circadian clock is properly aligned with the environmental day-night cycle, melatonin levels are elevated in blood, urine and saliva during nighttime, and nearly undectable during the daytime. In healthy individuals, the timing and amplitude of the melatonin rhythm are akin to a hormonal fingerprint, with little variation from day to day, or even week to week, even in the absence of controlled conditions (Arendt, 1988; Klerman et al., 2002; Arendt, 2005). Changes in amplitude and timing can therefore be a powerful indicator of circadian disruption. Though melatonin amplitude varies widely between indivuals, greater amplitude is generally considered to reflect a robust circadian rhythm (Arendt, 2005). However, many factors downstream from the master clock can affect the level of a particular behavioral or physiologic variable, including melatonin (Mitslberger & Rusak, 2011). The timing and duration of melatonin production are thus critical features when using melatonin production as a marker of circadian output.

4.3. Circadian rhythms after TBI

One of the possible factors contributing to SWD following TBI is a disruption of the master circadian clock. In fact, the first manifestation of circadian deregulation is a decline in the consolidation of the sleep-wake cycle, marked by an increase in the daytime sleep, a decrease in nighttime sleep, and an increase in sleep fragmentation (Dijk & Czeisler, 1994; Barion & Zee, 2007). Circadian deregulation occurs when the master clock is no longer synchronized to the environmental day, or when the master clock's signal is too weak to properly entrain the peripheral clocks located in other regions of the body and brain (Barion & Zee, 2007).

Few studies have investigated the circadian rhythms of acute TBI patients. In a study performed in 11 patients with neurological injury (including three TBI patients), an absence of circadian rhythm was found for plasma melatonin, plasma cortisol and body temperature (Paul & Lemmer, 2007). When results were compared with critically ill patients without neurological injury, circadian rhythm disturbances were more pronounced in patients with neurological injury than in patients without neurological injury. Another study showed a reduction in serum melatonin levels in addition to a disrupted diurnal melatonin rhythm in 8

TBI patients in the ICU, and these alterations were correlated with TBI severity (Paparrigopoulos et al., 2006). An absence of cortisol circadian rhythm was also found in 10 TBI patients using microdialysis, a well-established sampling technique in neurocritically ill patients, which measures analyte concentrations from extracellular fluid in tissue (Llompart-Pou et al., 2010). A fourth study measured serum melatonin levels every 6 h for the first 7 days post-ICU admission in three patient groups: severe TBI, non-TBI trauma, and ICU without trauma or TBI, with the aim to assess the effects of both TBI and the ICU environment on melatonin (Seifman et al., 2014). No group differences were found for mean concentrations of melatonin, but all ICU groups had decreased melatonin concentrations when compared to healthy control subjects. The authors concluded that both TBI and ICU conditions probably affect melatonin production. Taken together, these results suggest that brain injury may be in part responsible for impaired circadian rhythms in the ICU. Indeed, cerebral lesions in the suprachiasmatic region may contribute to changes in circadian rhythms. However, all of these articles had infrequent measures of circadian markers (every 2, 3, 6 and 8 h), as opposed to hourly measures, making it difficult to characterize melatonin rhythm. More importantly, all of these studies were conducted among mechanically ventilated patients who were under continuous sedation, which could potentially alter circadian function (Dispersyn et al., 2008; Gelbach et al., 2012; Korompeli et al., 2017).

The repercussions of disturbed circadian rhythms on acute TBI patients are thus twofold: 1) given the role of circadian rhythms in the proper functioning of the organism, disturbed circadian rhythms can have deleterious effects on overall health by slowing processes of recovery; 2) given the role of sleep in health and recovery, disturbed circadian rhythms can exacerbate TBI sequelae and hinder recovery by deteriorating sleep timing and quality. However, the link between circadian rhythms and SWD in acute TBI has yet to be established.

5. Review articles

In order to more accurately determine the objectives and hypotheses of this thesis, we carried out a review of the current scientific literature, which led to the following two articles.

Article 1: The impact of poor sleep on cognition and activities of daily living after traumatic brain injury: a review

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Contribution: For this article, I conducted the review of the literature, drafted and critically revised the manuscript.

Abstract

Background: Patients frequently report sleep disruptions or insomnia during their hospital stay, particularly after a traumatic brain injury (TBI). The consequences of these sleep disturbances on everyday activities are not well documented and are therefore not considered in the evaluation of independence in activities of daily living (ADLs). The goal of this narrative review is to explore the consequences of poor sleep quality on cognition and ADLs in the acute and subacute stages of a moderate and severe TBI, when patients are in acute care or inpatient rehabilitation.

Methods: We will present an overview of normal sleep and its role in cognitive functioning, and then present the findings of studies that have investigated sleep characteristics in hospital settings and the consequences of sleep disturbances on ADLs.

Results: During hospitalisation, TBI patients present severe sleep disturbances such as insomnia and sleep fragmentation, which are probably influenced by both the medical condition and the hospital or rehabilitation environment. Sleep disruption is associated with several cognitive deficits, including attention, memory and executive function impairments. Poor quality and/or insufficient quantity of sleep in acute TBI probably affect general functioning and ADLs calling for these cognitive functions.

Conclusions and significance: The cognitive impairments present following TBI are probably exacerbated by poor sleep quality and sleep deprivation during hospitalisation, which in turn impact ADLs among this population. Healthcare personnel should further consider sleep disturbances among people with TBI and a sleep protocol should be established.

Keywords: traumatic brain injury, sleep, activities of daily living, cognition, critical care

1. Introduction

Every year in the United States, at least 1.4 million individuals suffer a traumatic brain injury (TBI), and the most high-risk individuals are young adults, particularly men, aged 15 to 24 (Langlois-Oman, Kraus, Zaloshnja & Miller, 2011). In 23 European countries, incidence of hospital admissions for traumatic brain injury are estimated at 235 per 100,000 people (Tagliaferri, Compagnone, Korsic, Servadei & Kraus, 2006), while incidence rates reach 350 and 325 per 100,000 in Brazil and South Africa, respectively (Roozenbeek, Maas & Menon, 2013). In Australia, a rate of 107 TBI-related hospital stays per 100,000 people was reported in 2004-2005, peaking at 300 per 100,000 among 15- to 24-year-olds (Australian Institute of Health and Welfare, 2007). Occupational therapy interventions in acute care consist of evaluating the repercussions of physical, cognitive and behavioural deficits on independence in everyday activities, and their link with decisions about discharge destination as well as the patient's potential for rehabilitation. Severe sleep-wake cycle disturbances documented in acute and subacute TBI (Duclos et al., 2013; Makley et al., 2009; Nakase-Richardson et al., 2013) probably influence cognitive functioning, particularly learning ability, which by extension impact the patient's ability to demonstrate optimal levels of functioning in everyday activities. Surprisingly, few studies have examined sleep difficulties and their impact on activities of daily living (ADL) among patients with acute TBI. Consequently, the influence of sleep on general functioning is often not considered when making clinical recommendations on the basis of ADL evaluation results. The aim of this narrative review is to explore the impact of poor sleep quality and sleep deprivation on cognition and ADLs among individuals with moderate and severe TBI, primarily during acute hospitalisation and early inpatient rehabilitation following TBI. We will first present an overview of normal sleep architecture and its role in cognitive functioning. We will then present the findings of studies that have investigated sleep characteristics in hospital settings and the consequences of sleep disturbances on ADLs. Finally, we will describe protocols aimed at improving sleep-wake cycles and the specific role of occupational therapists in their implementation.

1.1 Introduction to normal sleep

Sleep is composed of slow-wave sleep stages and of the paradoxical sleep stage (see Figure 1 for a schematic representation of a normal night of sleep). Slow-wave sleep is divided into three stages, namely stages N1 and N2, which are light sleep, and N3, also known as stages 3 and 4, or deep sleep (Carskadon & Dement, 2011; Iber, Ancoli-Israel, & Quan, 2007; Roehrs, 2005). These three stages are also referred to as non-rapid eye movement (NREM) sleep. Paradoxical sleep, also known as rapid eye movement (REM) sleep, has a similar electroencephalographic (EEG) activity as wakefulness and is characterised by muscle atonia and marked eye movements. Paradoxical sleep is the primary stage during which dreaming occurs. In the course of one night, the sleeper alternates between the various sleep stages in cycles of 90 to 100 minutes. There are on average four to six cycles per night. At the beginning of the night, stage N3 is the most present of all sleep stages, while stage N2 and REM sleep are the most prevalent stages towards the end of the night.

Whereas adolescents (ages 13-17) generally require 9 hours of sleep, adults sleep an average of 7-8 hours per night (Foley, Ancoli-Israel, Britz, & Walsh, 2004; Mindell, Owens & Carskadon, 1999). Total sleep time decreases with age, whereas the quantity of light sleep increases progressively (Carrier, Monk, Buysse, & Kupfer, 1997; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). It has also been shown that the decline of deep sleep begins around ages 36-50 (Van Cauter, Leproult, & Plat, 2000). Sleep can be objectively and quantitatively measured by polysomnography (PSG), which minimally includes electroencephalography, electrooculography and electromyography in order to identify each sleep stage. Aside from PSG, other methods are used to evaluate sleep quality, such as actigraphy, an accelerometer that measures movement and is used to monitor the rest-activity cycle, supervision by the nursing staff (when studies occur in hospital settings), and questionnaires.

Figure 1. Sleep architecture of a healthy adult subject

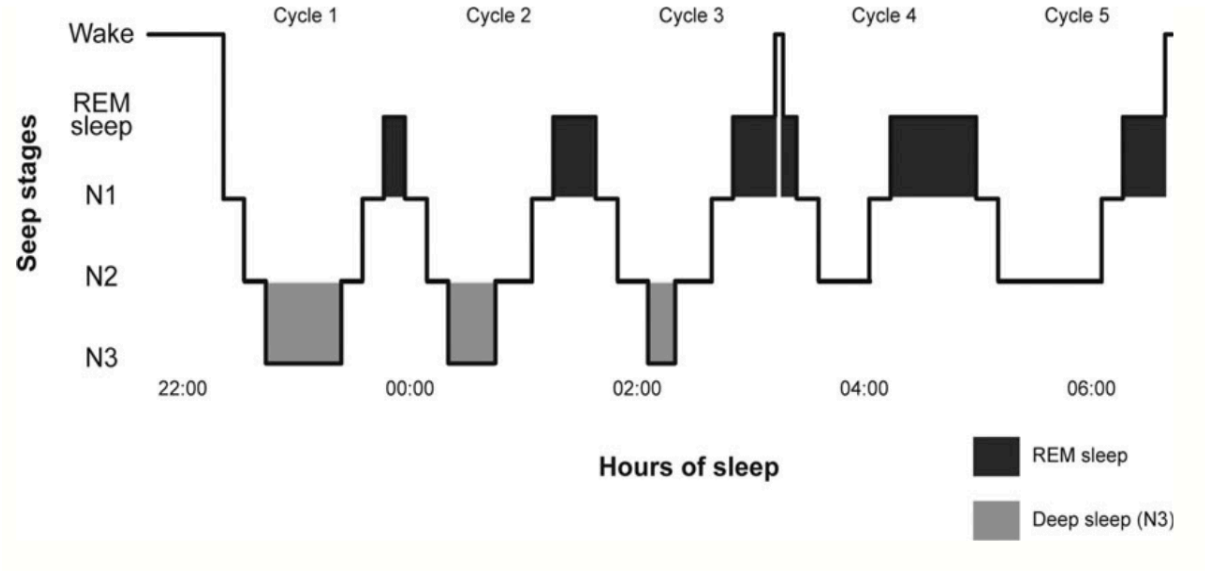

Figure 1 depicts the sleep architecture of a healthy adult subject. Sleep occurs in consecutive cycles of approximately 90 minutes, characterised by varying proportions of N1, N2, N3, and rapid eye movement (REM) sleep. Stage N3, or deep sleep, occurs mainly in the first sleep cycles, diminishing in proportion as the sleep period advances. Conversely, the proportion of REM sleep increases throughout the night, and is mainly present during later sleep cycles.

1.2. Role of sleep in cognition

It is well established that sleep deprivation affects cognitive performance and this is not only true for acute total sleep deprivation, but also for chronic and partial sleep loss (Goel, Rao, Durmer, & Dinges, 2009). Among the cognitive domains that are simultaneously most affected by poor sleep or sleep loss and most important for ADLs, we find attention, memory, and executive functions (Chee & Choo, 2004; Choo, Lee, Venkatraman, Sheu, & Chee, 2005; Diekelman & Born, 2010; Dinges, 1992; Goel, Rao, Durmer, & Dinges, 2009; Harrison & Horne, 2000; Jones & Harrison, 2001; Mu et al., 2005; Tomasi et al, 2009; Walker & Stickgold, 2006). In this section, we will briefly describe the influence of poor sleep or sleep loss on these specific cognitive domains, within a healthy population.

1.2.1 Attention

Attention is generally defined by its different components, which include vigilance, sustained attention, selective attention, alternating attention, and divided attention (Sohlberg & Mateer, 1987). Most studies have documented the influence of sleep deprivation on vigilance and sustained attention. It has been observed that sleep deprivation leads to behavioural changes characterised by a general slowing of reaction times, an increased number of errors (omission and commission) on tasks requiring detection of randomly occurring stimuli, and an increased time-on-task effect, which means that performance worsens across the course of a cognitive task (see Lim & Dinges, 2008 for a review). These behavioural effects of sleep deprivation are not only observed for acute and complete sleep deprivation, but are also observed following partial sleep deprivation. For example, in a study where sleep was restricted to three hours per night for seven days, performance on the vigilance task was affected, with subjects presenting a high rate of omissions when compared to a non-sleep deprived group (Fafrowicz et al., 2010).

1.2.2. Memory

Two types of memory were found to be very sensitive to poor sleep, namely episodic memory, which refers to the capacity to store and retrieve memories that are associated to a specific time and place, and procedural memory, which enables retention of learned connections between stimuli and responses (Tulving, 1983).

Episodic memory is affected by poor sleep in two ways. Firstly, poor sleep impedes learning of verbal and non-verbal material if learning is preceded by a night of poor sleep (i.e. learning after the night of poor sleep). This has been observed among students, since the consequences of sleep deprivation among this chronically sleep deprived population include learning deficits and inferior academic performances (Curcio, Ferrara, & De Gennaro, 2006). Among healthy subjects and individuals presenting insomnia, a link between total sleep deprivation preceding learning and the presence of memory encoding deficits has also been observed (Fortier-Brochu, Beaulieu-Bonneau, Ivers, & Morin, 2012; Yoo, Hu, Gujar, Jolesz, & Walker, 2007). Secondly, poor sleep also impedes learning if learning is followed by a night

of poor sleep (i.e. learning prior to a night of poor sleep). In fact, several studies showed the crucial role of sleep in memory consolidation and cerebral plasticity (Atienza, Cantero, & Stickgold, 2004; Smith, 1996; Walker, 2004; Walker & Stickgold, 2006; Walker, Stickgold, Gaab, & Schlaug, 2005; Wilson, 2002). As an example, one study showed that performance on a visual discrimination task was maximally improved 48-96 hours after initial training, even without practice, but only if subjects could sleep within 30 hours of training (Stickgold, James, & Hobson, 2000). Another study, using learning of synthetic speech, showed that word identification accuracy on the post-test, which took place 12 hours after pre-test, improved by 18.7 ± 1.6 percentage points if the 12-hour interval included sleep, whereas it improved by only 10.1 ± 2.0 percentage points when no sleep was present between pre-test and post-test. Overall, this study showed that speech recognition performance immediately following training was significantly improved, that it subsequently degraded over the span of a day's retention interval, but completely recovered following sleep (Fenn, Nusbaum, & Margolish, 2003).

As for procedural memory, several studies have shown that performance is improved when a post-learning sleep period is present (Albouy et al., 2013; Barakat et al., 2012; Fischer, Hallschmid, Elsner, & Born, 2002; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). Indeed, studies have demonstrated that a sleep episode following a period of practice of given motor sequences increases the speed of performance by 20% and 33.5%, and reduces the error by 30.1% on the specific motor sequence learned (Fischer, Hallschmid, Elsner, & Born, 2002).

1.2.3. Executive functions

Executive functions represent an ensemble of cognitive processes involved in goal-oriented behaviour, including abilities related to planning, organisation, problem-solving, inhibition, working memory, judgment, flexibility of thought, and verbal fluency (Alvarez & Emory, 2006). They enable one to plan, to coordinate a complete series of actions while considering alternatives, to control and update actions when necessary, and to eliminate elements of distraction while paying attention to the task at hand (inhibition) (Welsh & Pennington, 1988; Welsh, Pennington, & Groisser, 1991).

Numerous studies have investigated the impact of poor sleep on executive functions, particularly with regards to judgment, perseveration, impulsivity of behaviour, inhibition of distracting elements, planning of tasks, and word generation (for reviews, see Goel, Rao, Durmer, & Dinges, 2009; Harrison & Horne, 2000; Jones & Harrison, 2001; Killgore, 2010; Reynolds & Banks, 2010). These studies have shown that sleep deprivation does not increase impulsivity among healthy subjects (Acheson, Richards, & de Wit, 2007; Sagaspe, Charles, Taillard, Bioulac, & Philip, 2003). However, according to studies carried out among people suffering from sleep apnea, partial sleep deprivation leads to perseveration and to a decline in mental flexibility during tasks. This affects both the ability to adequately use cognitive functions in order to have good judgement, and the performance on tasks of verbal fluency and planning (Bedard, Montplaisir, Malo, Richer, & Rouleau, 1993; Bedard, Montplaisir, Richer, Rouleau, & Malo, 1991; Olsen, Lawrence, Bottarini, & Pises, 1977). Though no studies have specifically examined this in TBI, we can hypothesise that individuals with neurological vulnerability, such as those with moderate and severe TBI, would be more sensitive to the impact of sleep loss on executive functions.

1.3. Sleep in hospital settings

Sleep deprivation is one of the most frequent complaints among hospitalised individuals, particularly in the intensive care unit (ICU), where 61% of people mention suffering from sleep deprivation (Simini, 1999). According to studies performed with non-TBI ICU patients, sleep disturbance is the second most stressful aspect of hospitalisation (Freedman, Gazendam, Levan, Pack, & Schwab, 2001; Nelson et al., 2001; Richards & Bairnsfather, 1988). PSG studies showed that sleep is lighter and more fragmented in critically ill patients than among the general population (Broughton & Baron, 1978; Beecroft et al., 2008; Cooper et al., 2000; Friese et al., 2007; Gabor et al., 2003; Gehlbach et al., 2012; Kavey & Ahshuler, 1979). In fact, stage N1, which usually represents less than 5% of the night, accounts for approximately 60% of the sleep of ICU patients. As for stage N2, contradictory results are reported: certain studies report normal or higher proportions, while others report a decreased proportion. (Friese et al., 2007; Gabor et al., 2003) However, a significant reduction

is clearly present for stage N3, while paradoxical sleep is often significantly reduced or absent (Friese et al. 2007; Gabor et al., 2003; Gehlbach et al., 2012; Kavey & Ahshuler, 2003).

More recently, sleep in hospital and inpatient rehabilitation settings was specifically investigated among patients with TBI (Duclos et al., 2013; Makley et al., 2009; Makley et al., 2008; Nakase-Richardson et al., 2013). A recent study using actigraphy in a hospital setting has shown that in the acute phase of TBI, patients experience rest-activity cycle disturbances, which globally improve over time (Duclos et al., 2013). In fact, among the 16 patients studied, only 3 (18.8%) had a consolidated rest-activity cycle while in ICU. This is defined as sustained periods of activity during the day and sustained periods of rest during the night. Overall, this study showed that of all days of actigraphy recording in the ICU, only 28.6% days showed a consolidated rest-activity cycle, whereas this proportion increased to 61.1% on the regular units. In the subacute phase of TBI, a study carried out using actigraphy in a rehabilitation unit showed that sleep-wake cycle was altered in 68% of patients (Makley et al., 2009). These patients with sleep-wake cycle disturbances had longer stays in both acute and rehabilitation settings, implying that sleep-wake disturbances may be associated with more severe injury (Makley et al., 2008). Another study showed that, based on item 1 of the Delirium Rating Scale-revised-98 (Trzepacz et al., 2001), mild to severe sleep disturbances were present among 84% of TBI patients (mainly severe) upon admission to a rehabilitation hospital, and persisted for 66% of patients one month post-injury. Results also showed that the presence of such sleep disturbances at one month post-injury was a significant predictor of' the duration of post-traumatic amnesia (Nakase-Richardson et al., 2013).

Many factors may account for the poor sleep of hospitalised patients, particularly in the ICU environment. Indeed, several sources of noise are present, including alarms and conversations among employees, preventing patients from sleeping well (Freedman, Gazendam, Levan, Pack, & Schwab, 2001; Freedman, Kotzer, & Schwab, 1999; Friese et al., 2007; Gabor et al., 2003; Hilton, 1976; Persson Waye, Elmenhorst, Croy, & Pedersen, 2013; Richardson, Allsop, Coghill, & Turncock, 2007) In fact, Cohen et al. (1992) found that difficulty initiating and maintaining sleep was highly reported (81.2%) in hospitalised TBI patients, and that 36% of patients reporting these sleep disturbances identified the hospital

environment as an important causal factor. Receiving 24-hour care also makes sleep more difficult (Freedman, Kotzer, & Schwab, 1999; Tamburri, DiBrienza, Zozula, & Redeker, 2004). Furthermore, the loss of light/dark circadian cues due to constant lighting, as well as being bedridden and in a constant horizontal posture, are all factors that promote daytime sleep (Gabor et al., 2003). In fact, an abnormal distribution of sleep over a 24-hour period, marked by a proportion of daytime sleep around 50%, was observed in non-TBI critically ill patients (Freedman, Gazendam, Levan, Pack, & Schwab, 2001). Moreover, several drugs used as sedatives or analgesics, such as benzodiazepines, opiates, anticonvulsants and antipsychotics, influence sleep characteristics (Borbely, Mattmann, Loepfe, Strauch, & Lehmann, 1985; Bourne & Mills, 2004; Cronin, Keifer, King, & Bixler, 2001; Gimenez et al., 2007; Wilson & Argyropoulos, 2005).

Overall, 80% of patients presenting sleep problems report feeling fatigued, which may have a significant impact on ADLs (Ouellet, Beaulieu-Bonneau, & Morin, 2006). Other factors specific to patients with TBI may also contribute to sleep disturbances in hospital and inpatient rehabilitation settings. Recent studies indicate that 95% of people in the acute phase of moderate to severe TBI have an abnormally low rate of hypocretin-1, a neuropeptide involved in the waking state (Baumann et al., 2005; Baumann, Werth, Stocker, Ludwig, & Bassetti, 2007). This abnormal rate is associated with fatigue and daytime sleepiness, and could reflect hypothalamic damage. Others have suggested that patients who have suffered TBI and present metabolic, endocrine and neurological dysfunctions (i.e. cerebral lesions) run a higher risk of presenting a poorer sleep quality (Breed, Flanagan, & Watson, 2004). One study carried out at least one year post-injury found an association between neuroendocrine abnormalities and fatigue after TBI, showing that at least one pituitary axis was abnormal among 90% of TBI patients. More specifically, an association between higher growth hormone levels and greater fatigue was found (Bushnik, Engaldner, & Katznelson, 2007).

Other variables that might be associated with increased sleep disturbances are pre and post-TBI psychiatric and psychological factors. Sleep disturbances can be related to the presence of depression and anxiety, which are both highly prevalent after TBI (Ouellet, Beaulieu-Bonneau, & Morin, 2006; Parcell, Ponsford, Rajaratnem, & Redman, 2006). Rao

and colleagues (2008) found that insomnia in the acute period following TBI (within 3 months) was closely tied to the appearance of an anxiety disorder. Furthermore, people with TBI can suffer from acute post-traumatic stress disorder, a mental disorder that can manifest itself following a psychologically traumatising event, and can lead to an alteration of sleep and a decrease of slow-wave sleep (American Psychiatric Association, 2013; Bryant, Marosszeky, Crooks, & Gurka, 2000; Germain, 2013; Yetkin, Aydin, & Ozgen, 2010).

Changes in life habits and routines may also play a role in the development of sleep disturbance, although still little research has addressed these factors. For example, due to severe, persistent and debilitating fatigue, TBI survivors are prone to sleep or stay in bed for large amounts of time either because they feel an increased need for sleep, or rest, or because they lack activities (e.g. routine of getting up for work) (Ouellet, Beaulieu-Bonneau, & Morin, 2006). This may be particularly true in the acute phase after the accident, when rest is intuitively thought to promote recovery. Unfortunately though, excessive time spent in bed, sleeping or resting, may actually contribute to creating problems in nocturnal sleep by affecting the macrostructure of night-time sleep (Morin, 1993).

1.4. Impact of poor sleep on functional outcome

Poor sleep or sleep loss can affect ADLs and other functional measures evaluated by occupational therapists. Associations between sleep-wake disturbances and general functioning or daily activities have been investigated among TBI patients (Duclos et al., 2013; Worthington & Melia, 2006). In the study by Duclos and colleagues (2013), absence of a 24-hour sleep-wake cycle during the hospital stay (mean delay of actigraphy start after TBI: 18.0 ± 13.3 days) was associated with lower functioning, as measured with the Disability Rating Scale (Rappaport, Hall, Hopkins, Belleza, & Cope, 1982) and persistent post-traumatic amnesia at hospital discharge in patients with moderate to severe TBI. In rehabilitation centers, Worthington and Melia found that aggressions (related to staff trying to get the person up in the morning), missing out on opportunities for orientation and hygiene programmes in the morning, failing to attend medical appointments and an inability to stay awake during activities were associated with sleep and arousal disturbances (Worthington & Melia, 2006). Considering the role of sleep in cognition, poor sleep can also affect a patient's results on tests

of cognitive screening that are often performed in the context of the occupational therapist's evaluation, such as the ″Mini-mental state examination″(MMSE), the Cognitive Assessment Scale for the Elderly (CASE), as well as results on tests used to evaluate driving capacities (e.g.: ″Trail making″ A et B, ″Motor-free visual perception test″(MVPT)) (Colarusso & Hammill, 2003; Folstein, Folstein, & McHugh, 1975; Geneau, 1996; Lezak, Howieson, & Loring, 2004). According to what has been previously reported regarding the impact of sleep on cognition, deficits presented by patients hospitalised secondary to a TBI on these tests could possibly be, at least in part, attenuated if they had better sleep.

Other studies have been carried out among healthy subjects, as well as among subjects suffering from sleep disorders, and poor sleep quality and/or sleep deprivation have consistently been shown to be significantly associated with general functioning and ADL. More specifically, according to Weaver et al. (1997), the activities most thought to be influenced by disrupted sleep and excessive daytime sleepiness are activities that provide minimal external stimulation and that unmask or possibly increase sleepiness such as driving or passive vigilance. Activities that are considered in the Functional Outcome Sleep Questionnaire (FOSQ) they developed to examine the repercussions of excessive daytime sleepiness include: taking care of financial affairs and paperwork, finishing a meal, maintaining a phone conversation, watching television, working on a hobby, remembering things and concentrating on things. Several studies among various populations (e.g. sleep apnea, narcolepsy, non-restorative sleep, pulmonary fibrosis, heart failure) have used the questionnaire developed by Weaver and found that links between disrupted sleep, excessive daytime sleepiness and poorer performance in these activities (Banhiran et al., 2012; Carmona-Bernal et al., 2008; Chasens, Sereika, Houze, & Strollon, 2011; Mermigkis et al., 2013; Riegel et al., 2012; Su, Liu, Panjapornpon, Andrews, & Foldvary-Schaefer, 2012; Teixeira, Faccenda, & Douglas, 2004; Weaver 2001; Zhang et al., 2013).

In studies carried out using the SF-36 questionnaire, which assesses functional health and well-being through the evaluation of several health domains, physical and social functioning, as well as mental health, functional health and well-being were more affected in individuals with sleep disorders than in individuals who slept normally (Lee et al., 2009;

Ware, Snow, Kosinski, & Gandek, 1993). Accordingly, it has been shown that subjects suffering from insomnia had a poor quality of life, both physically and mentally, and presented a reduced productivity at work as well as alterations of their ADLs (Bolge, Doan, Kannan, & Baran, 2009). More recently, studies performed among elderly subjects have shown that poor sleep and daytime sleepiness predict poorer functional recovery rates during inpatient rehabilitation, as well as greater functional decline (Frohnhofen, Popp, Frohnhofen, & Fulda, 2013; Spira et al., 2012).

The importance of ADL evaluations in acute TBI patients cannot be underestimated as they are generally used to recommend discharge needs or rehabilitation potential. When significant sleep deprivation is present, results obtained with ADL measures could reflect the negative effects of sleep deprivation and therefore inadequately influence clinical decisions. Hence, occupational therapy evaluations of ADL ability would need to nuance test results when sleep deprivation is known to have occurred during the night prior to these evaluations.

2. Protocols to improve sleep in hospital and rehabilitation centers

2.1. Modifying the environment to improve sleep

Considering that some factors impeding good sleep quality and duration can be modified, the following section will present protocols aimed at improving sleep-wake cycles, as well as the specific role of occupational therapists in their implementation. Environment is a major cause of sleep disturbances in hospital settings. Fortunately, some environmental factors can be modified. It has been shown that noise is among the factors that interfere the most with sleep in the hospital (Cohen, Oksenberg, Snir, Stern, & Grosswasser, 1992; Freedman, Gazendam, Levan, Pack, & Schwab, 2001). Having patients use ear plugs and minimizing staff interventions during periods of napping or during the night would enable patients to have more restorative sleep (Richardson, Allsop, Coghill, & Turncock, 2007; Topf, 1992; Topf & Davis, 1993). These methods have been tested among ICU patients and improved sleep was observed (Le Guen, Nicolas-Robin, Lebard, Arnulf, & Langeron, 2014; Richardson, Allstop, Coghill, & Turncock, 2007;Wallace, Robins, Alvord, & Walker, 1999).

Sleep and wake states can also greatly benefit from light during the day and darkness during the night. In fact, the main circadian biological clock, located in the hypothalamus, is normally synchronized to the environmental 24-hour day, mainly by exposure to the light-dark cycle (Czeisler & Gooley, 2007; Dumont & Beaulieu, 2007; Takahashi & Zatz, 1982; Moore, 1997). The sleep-wake cycle is dependent on this circadian biological clock. Light therapy has been shown to be beneficial in synchronizing the circadian clock, improving sleep quality, mood and cognitive performance, (see Munch & Bromundt, 2012 for a review) and has also been found effective in improving sleep and cognitive function among the institutionalised elderly, with or without dementia (Riemersma-van der Lek et al., 2008; Sloane et al., 2007; Van Someren, Kessler, Mirmiran, & Swaab, 1997). More recently, blue light therapy was shows to significantly improve fatigue and drowsiness among chronic TBI patients who reported sleep and wake disturbances (Sinclair, Ponsford, Taffe, Lockley, & Rajaratnam, 2013). Based on these findings, we could hypothesize that light therapy during acute and post-acute TBI could favour more robust sleep-wake rhythms, though this has not been formally investigated.

2.2. Naps to improve cognitive functioning

It has been shown that a nap of 20 to 30 minutes can reduce fatigue and increase cognitive performances for several hours among healthy subjects (Lovato & Lack, 2010). The early afternoon is the time of day during which a nap is most beneficial. A protocol comprising the addition of a daily rest period of approximately 30 minutes following lunch could be established in order to further preserve the cognitive functions of TBI patients. To date, no study investigating the effects of naps in a neurological population has been performed and the potential benefits of naps on cognitive functioning and ADL is not known. It is thus recommended that a case-by-case approach, with constant monitoring on the efficacy and negative consequences of various durations and timings of daytime naps, be used. However, considering the important sleep loss that most patients experience during their hospital stay, professionals such as occupational therapists, may be encouraged to interchange, when possible, treatment sessions between patients when a scheduled patient is taking a nap. It could also be important to ensure that patients are allowed to have rest periods between

various interventions. Most behavioural sleep medicine experts agree that late naps (i.e. taken later than 3:00 PM) may interfere with nighttime sleep (Morin, 2004). Although patients feeling either fatigued or sleepy may want to take a nap after the evening meal, occupational therapists, in collaboration with specialists in recreational activities and/or nurses may contribute to finding alternative activities in order for patients to maintain alertness before bed.

2.3. Interventions to improve insomnia

For patients suffering from insomnia, the implementation of behavioural recommendations such as Stimulus Control or Sleep Restriction (or restriction of time in bed) may be useful (Ouellet & Morin, 2004; Ouellet & Morin, 2007). These procedures have a very large evidence-base in the general population for primary insomnia, and are increasingly disseminated in populations with diverse health conditions by non-sleep specialists (Manber et al., 2012). The goal of Sleep Restriction is to consolidate sleep and promote deeper and more continuous sleep through the night by limiting the time spent in bed to the actual sleep time. A sleep window is prescribed and kept consistent for at least 1-2 weeks at first, then is adjusted (increased or decreased) depending on sleep efficiency. Stimulus Control consists of a set of instructions (e.g. keep 1 hour before bed to relax, reserve bed and bedroom for sleep only, go to bed only when sleepy, limit daytime napping, get out of bed if unable to sleep after 15-20 minutes). Largely based on self-management principles, these techniques could nonetheless be used with hospitalised patients if healthcare professionals supply a minimum of structure and guidance. In an acute care or rehabilitation setting, occupational therapists could be instrumental to the implementation of such behavioural interventions for sleep. For example, occupational therapists could assist patients in finding appropriate activities in order to maintain a prescribed sleep window and follow Stimulus Control instructions. The following could be implemented by occupational therapists: activities in the evening to counteract sleepiness or the habit of going to bed too early (in line with Sleep Restriction); activities to promote a smooth transition between waking activities and sleep and activities in the morning to avoid staying in bed too long and to increase the motivation for getting out of bed and starting the day (in line with Stimulus Control recommendations); activities during the night to distract from worrying, rumination or intrusive thoughts (in line with cognitive and relaxation-

based techniques); activities to avoid smoking before bedtime or during nocturnal awakenings (in line with Sleep Hygiene education); and activities to promote rest during the day without necessarily sleeping (napping), especially late during the day (in line with Stimulus Control recommendations).

The support of nurse colleagues and other professionals (e.g. educators, recreational activities specialists) would be critical to the application of, and adherence to, the various protocols to improve sleep. As such, occupational therapists could have an influential role in raising awareness among the clinical personnel about the impacts of poor sleep and its consequences on the ADLs of people with TBI. The applicability and efficacy of these abovementioned interventions nevertheless need to be investigated among this clinical population and setting. In the meantime, caution and close follow-ups are warranted when any type of intervention is initiated.

3. Limits

Though the focus of this review was to discuss the impact of sleep on cognition and activities of daily living, we did not discuss the effects of medications, particularly sedatives and analgesics, on sleep. Such medications are often administered to TBI patients in acute care and could be responsible, at least in part, for modifications in sleep and wake.

4. Conclusions

This literature review has shown that TBI causes changes in sleep that have repercussions on everyday activities. Lack or loss of sleep has a direct impact on cognition, which in turn has a direct impact on independence in ADL. Loss of sleep or poor sleep can directly limit ADL independence and also amplify other deficits. In acute and post-acute care, this must be considered in two ways. First, the timing of functional assessments should ideally attempt to be scheduled at times of optimal wakefulness. Moreover, interventions should be put into place to limit, to the extent deemed possible, poor sleep and its repercussions on everyday activities.

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Article 2: Sleep and wake disturbances following traumatic brain injury

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Abstract

Traumatic brain injury (TBI) is a major health concern in industrialised countries. Sleep and wake disturbances are among the most persistent and disabling sequelae after TBI. Yet, despite the widespread complaints of post-TBI sleep and wake disturbances, studies on their etiology, pathophysiology, and treatments remain inconclusive. This narrative review aims to summarise the current state of knowledge regarding the nature of sleep and wake disturbances following TBI, both subjective and objective, spanning all levels of severity and phases post-injury. A second goal is to outline the various causes of post-TBI sleep-wake disturbances. Globally, although sleep-wake complaints are reported in all studies and across all levels of severity, consensus regarding the objective nature of these disturbances is not unanimous and varies widely across studies. In order to optimize recovery in TBI survivors, further studies are required to shed light on the complexity and heterogeneity of post-TBI sleep and wake disturbances, and to fully grasp the best timing and approach for intervention.

Keywords: traumatic brain injury, sleep, sleep-wake disturbances, insomnia, hypersomnia, circadian rhythms

1. Introduction

Traumatic brain injury (TBI) is the leading cause of mortality and invalidity among young adults in industrialized countries, with an incidence estimated at over 600 per 100 000 individuals [1,2]. This high incidence represents a major public health concern since TBI often results in long-term physical, cognitive and psychological sequelae that interfere with general functioning and return to work or school.

Sleep-wake disturbances, particularly fatigue, insomnia and hypersomnia, are among the most prevalent and persistent sequelea reported after TBI [3,4]. They have been consistently reported among TBI survivors across all levels of severity, from the acute stage to several years post-injury [5-7]. Yet, the pathophysiology of post-traumatic sleep-wake disturbances is still poorly understood.

The purpose of this narrative review is to describe and appraise the current state of knowledge regarding sleep-wake disturbances following TBI across all levels of severities, spanning the continuum of recovery from the acute stage (first weeks post-injury) to the chronic stage, including years post-injury. A second goal is also to describe the possible causes of sleep-wake disturbances following TBI, as well as pharmacologic and non-pharmacologic treatment options for the management of sleep-wake disturbances post-injury. Finally, the importance of sleep for cognitive and functional recovery will be discussed, and general directions for future study perspectives will be provided.

For the purpose of this literature review, the acute phase of TBI refers to the first 6 months post-injury, which constitutes the period immediately following TBI and the early phase of recovery. The chronic phase of TBI will refer to the period following the acute phase, spanning from 6 months to several years post-injury, regardless of the presence of symptoms.

2. Diagnosis and general consequences of TBI

Traumatic brain injury occurs when an external force causes an alteration in brain functions such as decreased level of consciousness, loss of memory, neurological deficits or any alteration in mental state at the time of the injury [8]. The diagnosis of TBI necessarily

involves a severity assessment [9]. Globally, mild TBI (mTBI) is characterized by a short loss of consciousness (< 30 min), and/or a short post-traumatic amnesia (< 24 h), a Glasgow Coma Scale (GCS) score [10] between 13 and 15 [1]. Sports-related brain injuries with an alteration in mental state are generally referred to as "concussion". Moderate and severe TBI are typically associated with longer loss of consciousness, a GCS score equal or lower than 12, and PTA longer than 24 h. No hospital admission is generally required for mTBI, while moderate and severe TBI often necessitate hospitalisation in the intensive care unit due to the presence of cerebral haemorrhages, contusions and intracranial hypertension [11].

The most frequent causes of TBI are motor-vehicle accidents, falls, assault, recreational and sport-related injuries, and work accidents [12,13]. The principal factors known to increase the risk of sustaining a TBI are age (15-24 years old) and gender (male); other factors are alcohol or drug addiction, low socioeconomic status, and low education [14].

The extent of functional and cognitive deficits observed in the acute period is highly variable among TBI patients and depends on several factors, such as location of focal lesions [15,16], severity of diffuse axonal injury, length of PTA [15,17], age[16, 18], education [16], and preexisting conditions [19]. Despite the variability of deficits, they can be categorized in relation to their influence on cognition, social behaviors, psychological status, and somatic symptoms.

In fact, arousal and alertness impairments, reduced information processing speed, impaired memory, executive dysfunctions, impaired communication, and reduced self-awareness are among the most frequent cognitive deficits observed [20]. Neurobehavioral impairments such as impulsivity, irritability, disinhibition, mutism, confusion and confabulatory communication, and apathy can be observed, particularly in those with more severe injuries and or in the acute stage of injury [21]. Psychological sequelae, such as irritability, anxiety, and depressed mood can be observed in ≥50% of individuals in the first 6 months following severe TBI [22]. These affective symptoms remain prevalent among 16-48% of patients over the two years post-injury, and are reported at many years post injury (>10yrs) in those with chronic sleep-wake disorders [23]. Finally, somatic symptoms, such as

headache, dizziness, but also perturbation in sleep are often reported in the hours following TBI [22] and these symptoms remain present in 23-65% of patients two years after TBI onset.

Recovery from symptoms usually takes place within 1 to 3 months in mTBI, while 85% of the improvement in functioning occurs in the first six months and improvement continues until one year after moderate to severe TBI [24]. Unfortunately, impairments in these symptoms, including in those related to sleep disturbances, persist over one year in 50% of moderate-severe TBI patients [25], affecting their autonomy, productivity, and their quality of life [26].

3. Sleep disturbances following TBI

3.1. Changes in sleep quality and quantity

Complaints of sleep loss and poor sleep quality are common following TBI. These comprise complaints of difficulties initiating and maintaining sleep, frequent arousals, and early awakenings. In the following section, prevalence of poor sleep quality and related polysomnographic findings will be described for mTBI and for the moderate-severe TBI population separately. For each TBI severity population, results for the acute and chronic phases will be reported.

3.1.1. Acute stage of mTBI

According to Chaput et al. [27], sleep complaints are present in the first days and weeks following mTBI. In fact, 13.3% of the 443 patients included in their study reported sleep complaints on the Rivermead post-concussion symptom assessment questionnaire 10 days post-injury, while this proportion increased to 33.5% at 6 weeks post-injury. Interestingly, patients with sleep complaints at 10 days post-injury were 2.9 times more likely to experience sleep difficulties at 6 weeks post-injury and were more likely to suffer from irritability, depressive symptoms, and headaches at both 10 days and 6 weeks post-injury, suggesting that acute sleep complaints predict psychological and somatic symptoms among individuals with mTBI. Poor sleep quality was also reported after sports-related concussions where athletes who had suffered at least one concussion (4.4±3.8 months since injury)

complained of worst sleep quality, more severe sleep disturbances and poorer daytime functioning on the Pittsburgh Sleep Quality Index when compared with healthy control athletes [28].

Although a high proportion of patients have sleep complaints in the acute phase of their mTBI, heterogeneous results were obtained on objective measures of sleep such as polysomnography (PSG). In fact, several authors found no differences in sleep macroarchitecture between mTBI patients and controls in the acute stage of the injury [28-30].

Conversely, studies looking at sleep microarchitecture have found promising results. In fact, Rao et al. [29] showed that mTBI patients within 1 week of injury had abnormalities in sleep EEG power spectral analyses when compared to matched controls. More specifically, mTBI patients had lower delta power, but higher alpha and beta power in non-rapid eye movement (NREM) sleep. A more recent study conducted by Khoury et al. [31] compared 24 mTBI patients (45 ± 22.7 days post-injury) with post-traumatic sleep complaints to 18 controls on quantitative EEG during sleep. Overall, results showed that patients reported a worse sleep quality for their in-laboratory sleep recording compared with control subjects. Moreover, mTBI patients had significantly longer sleep latency (17.8 ± 15.3 min vs. 8.9 ± 5.7 min), which was within normal range (<20 min) despite their complaints of poor sleep, and lower sleep efficiency (89.2 ± 7.5% vs. 93.7 ± 5.7%). Lower delta in REM sleep and higher beta and gamma power in NREM sleep were also observed among the mTBI group compared to the control group, and pain was the main factor associated with abnormal EEG power during sleep. This microarchitecture sleep pattern characterised by reduced power of low frequency bands and increased power of high frequency bands may represent hyperarousal among mTBI individuals and was previously documented among insomniac patients [32].

3.1.2. Chronic stage of mTBI

Subjective sleep complaints have also been widely documented in long-term mTBI, the most pervasive of which are insomnia, sleep fragmentation, and early morning awakenings. [3,33,34] Beetar et al. [33] conducted a retrospective chart review in order to compare the incidence of sleep complaints in symptomatic mTBI. The study included 202 TBI patients

(127 mild and 75 moderate-severe) 23.9 ± 21.2 months post-injury, who were compared to a group of non-TBI neurologic patients. Insomnia complaints were reported by 65.3% of all mTBI patients. Overall, insomnia complaints were significantly more prevalent in the TBI group compared with the non-TBI neurologic patients (56.4% vs. 30.9%), and more frequent among mTBI than moderate-severe TBI (65.4% vs. 41.3%). Sleep complaints were still present in 23.7% of mTBI patients at least five years post-injury. In another study aiming to delineate which factors predict suboptimal outcome after TBI, Clinchot et al. [34] found that approximately 75% of the 145 mTBI patients included in their study reported sleep disturbances one year post-injury, the most common of which was waking up too early. Globally, these studies indicate that complaints of poor sleep are found in approximately 65-75% of chronic mTBI patients.

With the conflicts in Afghanistan and Iraq, the military population has recently sparked the interest of TBI researchers, even though the mechanism of injury often differs from that of TBI in civilians. One study [35] evaluated 116 soldiers with combat-related blunt and blast TBI (84.5% mild) 16.1 ± 11.5 months post-injury using directed questioning regarding sleep complaints. Nearly all (97.4%) participants reported sleep complaints. More specifically, poor sleep quality was reported by 81.9% of participants, and 54.3% reported sleep fragmentation. According to the study by Bryan [36], the incidence of insomnia increased with TBI frequency in the military population, from 5.6% for no TBIs, 20.4% for single TBI, and 50.0% for multiple TBIs.

In the chronic phase of mTBI, studies that have objectively measured sleep through PSG have generally been able to corroborate the pervasive self-reported complaints of disturbed sleep identified in the abovementioned studies. More specifically, studies using PSG have shown that those with mTBI and persistent symptoms have less efficient sleep, shorter REM onset latency, longer sleep onset latency, shorter total sleep time, a decrease in REM sleep and an increase in stage N2 sleep, when compared to healthy age- and sex-matched controls [37,38]. In the abovementioned study performed among soldiers [35], PSG findings revealed sleep fragmentation, with an average sleep efficiency of 86.3% ± 12.1% and a mean

total arousal index of 17.7± 11.5 events per hour. Insomnia was present in 55.2% of their subjects based on DSM-IV diagnostic criteria.

Importantly however, to our knowledge, there have not been any studies to date that have objectively investigated the sleep of all those with mTBI; current studies are limited to recruitment of participants with self-reported sleep complaints. Such a study would be invaluable in order to elucidate on the role of mTBI in generating structural sleep changes, and on the factors associated with the presence and absence of sleep complaints.

3.1.3. Acute stage of moderate and severe TBI

Clinical observations in acute care settings suggest that sleep disturbances appear in the first weeks after TBI, where patients present insomnia, an inability to stay awake for a few consecutive hours during the day, and/or altered sleep-wake cycles. To date, a few studies have investigated acute sleep-wake disturbances during the period of hospitalisation, including in the intensive care unit (ICU), regular units of trauma center and in rehabilitation centers during the early period of rehabilitation. A recent study conducted by our group aimed to measure the rest-activity cycle when patients were hospitalised in the intensive care unit and regular wards, looking specifically at the consolidation of rest and activity periods, or patients' ability to sustain activity during the day and rest during the night [39]. Using 10-day actigraphy recordings in 16 TBI patients, the study showed severe fragmentation of the rest-activity cycle, reflecting fragmentation of sleep and wake episodes. Using a ratio of daytime activity to 24h activity ≥80% to denote rest-activity cycle consolidation, we were able to show that the rest-activity cycle was consolidated only 46.6% of all days, but that a significant linear trend of improvement was found over time. Worse sleep-wake cycle consolidation and evolution were associated with higher TBI severity, and longer duration of ICU and hospital stay. Patients with more rapid return to a consolidated rest-activity cycle were more likely to emerge from PTA and to have lower disability at hospital discharge. Another preliminary study conducted by our group compared the sleep architecture of 6 moderate-severe TBI (4 males; 25±11.3 yrs) during their hospital stay to that of 11 healthy controls (7 males; 25±10.5 yrs) [40]. The TBI patients underwent 24-h bedside ambulatory PSG, while controls underwent in-laboratory PSG. Our results indicated that TBI patients had more fragmented

sleep characterised by greater total wake duration, (159±104.7 min on average as compared to 53.7±47.0 for controls) and a higher number of arousals (49.7±35.4 on average as compared to 20.2±7.8 for control subjects). Sleep efficiency for those with TBI was 74±15.9% (on average) in comparison to 88±9.3% for controls.

Studies carried out during early rehabilitation also point to a high prevalence of sleep-wake disturbances. One research group conducted a prospective observational study of 31 patients with moderate-severe TBI admitted to an inpatient rehabilitation unit, and found that 68% had disturbed nighttime sleep, defined as two or more hours awake during the night, as measured by hourly nurse observations [41]. This same group conducted another study in which they used actigraphy on 14 moderate-severe TBI patients for the duration of their stay in a rehabilitation unit, between 9 to 23 days post-injury [42]. Overall, 78% of patients had a mean 1-week sleep efficiency that was severely impaired (≤ 63%). Patients who had cleared PTA prior to rehabilitation admission had significantly better sleep efficiency than patients with ongoing PTA. Nakase-Richardson et al. [43] conducted a prospective observational study on primarily severe TBI patients, using item one of the Delirium Rating Scale-Revised-98 (DelRS-R98) to classify the severity of sleep-wake cycle disturbance as none, mild, moderate, or severe. Results showed that mild to severe sleep disturbances were present among 84% of patients upon admission to a rehabilitation hospital, and persisted for 66% of patients one month post-injury. The presence of sleep disturbance at one month post-injury had a significant predictive value on the duration of PTA.

3.1.4. Chronic Moderate-Severe TBI

Studies investigating subjective sleep complaints in the chronic phase of moderate-severe TBI patients point to frequent complaints of TBI-induced changes in sleep quality [3,34,44-48], changes in bedtime[47,48], longer sleep onset latency [46-48], more nocturnal awakenings [47], and symptoms of insomnia [3,49]. Overall, subjectively-reported sleep changes have been reported in 42 to 80% of TBI patients, though perception of one's condition may be altered by persistent cognitive deficits among this population, leading to and underreporting of complaints [34,45-48]. In a meta-analysis of 1706 TBI survivors documented across 21 studies utilizing both objective and self-report measures, Mathias and

Alvaro [50] reported that TBI survivors were likely to suffer from insomnia (observed in 50% of TBI patients), difficulty maintaining sleep (50%), poor sleep efficiency (49%), early morning awakenings (38%), difficulty with sleep initiation (36%) and nightmares (27%).

Studies that have used PSG to objectively measure sleep in chronic moderate-severe TBI patients have shown impaired sleep efficiency [44,51], an increase in slow wave sleep [52], and excessive nocturnal awakenings [51,53]. Interestingly, Mathias and Alvaro [2012] reported that objective sleep measures identified more sleep-wake problems than self-report measures on problems with sleep maintenance, sleep efficiency, and awakening [50].

Ouellet et al. [3] used a detailed questionnaire to assess the sleep quality and fatigue of 452 community-based TBI patients (all severity; 83.2% moderate-severe). Over 50% of patients reported symptoms of insomnia, and 29.4% fulfilled the diagnostic criteria for an insomnia syndrome. In a cross-sectional study including 121 TBI survivors 2 years post-injury, Cantor et al. [49] found a similar prevalence of insomnia syndrome (24%) using the DSM-IV and ICSD diagnostic criteria. Since these patients were not recruited from a sleep clinic or according to the presence of sleep complaints, these results suggest that a high proportion of TBI patients have sleep problems but do not consult a sleep clinic, leaving these problems untreated.

Although studies that have utilized objective sleep measures have also identified various sleep disturbances in moderate-severe TBI patients, one study reported no significant differences on PSG variables between 22 moderate and severe TBI survivors tested 53.0 ± 37.1 months post-injury compared to 22 controls [54]. However, patients in this particular study were community-based participants who were not consulting a sleep clinic, as opposed to most other PSG studies on moderate-severe TBI patients. Because time since injury ranged from 1 to 11 years, the authors suggested that objectively-measured sleep alterations could become gradually attenuated over time, which could explain why their study showed no significant differences between TBI patients and controls. Another study sought to compare subjective sleep complaints to objective measures in 14 TBI patients 21 months post-injury on average with an insomnia complaint and 14 healthy controls [53]. Even though significant differences were found on all subjective sleep measures, no PSG variables were significantly

different between groups. These findings highlight an important issue for consideration when comparing research across the literature, as some studies recruit on the basis of self-report of sleep problems, or those seeking help for sleep problems, while others, such as the study by Beaulieu-Bonneau [54], do not.

3.2. Hypersomnia and excessive daytime sleepiness

Hypersomnia, or increased sleep need per 24-h, is a widespread condition following TBI that is often associated with excessive daytime sleepiness (EDS), though EDS may be a result of insomnia or poor nocturnal sleep. One study group has suggested that pleiosomnia, or an increased need for sleep of at least 2 hours per 24-h, was a more accurate term to reflect an increased pressure to sleep following TBI [52]. In the following section, hypersomnia and EDS are presented for mild and moderate-severe TBI separately.

3.2.1. Mild TBI

Watson et al. [55] used the Sickness Impact Profile, a detailed health status questionnaire that measures behavioral changes due to illness, to assess sleepiness at one month post-injury, for which they evaluated 348 TBI patients (78% mild TBI), 132 non-cranial trauma controls, and 102 trauma-fee controls. The study showed that at one month post-injury, a significantly greater proportion of TBI subjects (55%) endorsed one or more sleepiness items of this questionnaire, as opposed to non-cranial trauma controls (41%) and trauma-free controls (3%). A greater number of TBI subjects endorsed each of the four sleepiness items than did both control groups. Among the military population, complaints of EDS were identified as being widely pervasive, and reported by 85.2% of participants [35].

Despite this high prevalence of daytime sleepiness, very few studies investigated hypersomnia and EDS using objective measures among the mTBI population. One study used the Multiple Sleep Latency Test (MSLT) to compare the sleepiness mTBI patients (12 months to 21 years post-injury) who had been referred to a sleep lab to that of healthy matched controls. The MSLT tests for excessive daytime sleepiness by measuring sleep latency during five scheduled daytime naps, each separated by two hours of wake. The authors were able to

confirm patients' complaints and showed that mTBI patients had significantly greater number of sleep entrance episodes, and a significantly shorter time to fall asleep [38].

Gosselin et al. [28] examined the spectral analysis of the waking EEG in 11 concussed athletes as compared to healthy control athletes. Their results showed increased delta and reduced alpha EEG activity during wakefulness, while no modifications were found during sleep despite the high frequency of poor sleep quality complaints, suggesting that sport-related concussions are associated with wakefulness dysfunctions rather than sleep disturbances per se. The authors proposed that this waking EEG pattern may represent impaired vigilance among concussed athletes.

3.2.2. Moderate-severe TBI

Studies carried out one to three months post-injury have shown that daytime sleepiness is highly present following moderate-severe TBI [55,56]. While Watson et al. [55] found that greater sleepiness was associated with greater TBI severity, Rao et al. found no such association [56]. Studies investigating subjective daytime complaints in the chronic phase of moderate-severe TBI patients point to more frequent and longer daytime napping [48,54,57], and EDS [30,48,51,57,58].

Among studies that have recruited patients with sleep complaints, the study conducted by Verma et al. [51] showed that 30 of the 60 TBI patients (60% moderate-severe according to the Global Assessment of Functioning scale) reported hypersomnia as their presenting complaint. Overall, 28 patients had an elevated Epworth Sleepiness Scale (ESS) score higher than 11, pointing to EDS. Of these 28 participants who underwent MSLT, 15 had a mean sleep onset latency <5 min, confirming their complaints. Sommerauer et al. [52] conducted a case-control study compared 36 consecutively admitted TBI patients (13 mild; 23 moderate-severe) who reported pleiosomnia, defined as an increase need for sleep of at least 2h per 24h, to healthy controls, using detailed history, sleep logs, actigraphy, nocturnal PSG, and the MSLT. They found that EDS was highly prevalent (42%), as was the number of patients taking daytime naps (47%). The authors also found that nocturnal total sleep time was increased in

TBI patients, though patients underestimated their need for sleep. This finding led the authors to conclude that pleiosomnia may be even more frequent than previously reported.

Other studies that have recruited their TBI patients from the community, without considering the presence of sleep complaints, and yet have also found daytime sleepiness [4,30]. Baumann et al. [30], who evaluated 65 patients 6 months post-injury, and Castriotta et al. [4], who evaluated 87 TBI patients (8% mild; 59% moderate-severe; remaining TBI of unknown severity) 64.3 ±117.7 months post-injury, both used PSG, and MSLT to assess objective sleepiness in TBI patients. In their studies Baumann et al. [30] and Castriotta et al. [4], found that hypersomnia was present in 25 and 11%, respectively. Using a criteria of sleep latency <5 min on the MSLT to represent EDS, Baumann et al. [30] also showed that 25% of the study sample had objective EDS, compared to 1-6% in the general population [59]. This prevalence of objective daytime sleepiness was close to that of subjective daytime sleepiness, as measured by the ESS, which was found in 28% of the sample. Twelve patients (18%) reported regular daytime napping (≥3 per week). Though Baumann et al. [30] found that hypersomnia was associated with severe TBI, Castriotta et al. [4] found no association between daytime sleepiness and injury severity or time since injury.

Despite several studies having highlighted the increase in EDS following TBI, the previously mentioned study by Beaulieu-Bonneau [54] revealed no significant differences on objective sleepiness, as measured by MSLT, between 22 moderate and severe TBI survivors tested 53.0 ± 37.1 months post-injury and 22 matched controls.

4. Other sleep-wake disorders common following TBI

Overall, studies that have objectively measured sleep using PSG have also found other sleep disorders in chronic moderate-severe TBI. Among them, the study by Verma et al. [51], included 60 TBI patients (40% mild, 60% moderate-severe; 3 months to 2 years post-injury) consulting in a sleep clinic and the following sleep disorders have been observed: hypoxia (observed in 70% of patients), periodic leg movement during sleep (35%), REM sleep behaviour disorder or increased electromyogram tone during REM sleep (13%), and sleep-onset REM periods, often associated to narcolepsy (5.5%). Parasomnia were diagnosed in 16

patients (25%) and comprised acting out dreams (8%), sleepwalking (8%), nightmares (7%), sleep paralysis (5%), nocturnal enuresis (5%), cataplexy (3%) and nocturnal eating (3%) [51].

Other studies have recruited their TBI patients in community, without considering the presence of sleep complaints, have also shown that several sleep disorders were present following TBI. When using PSG among those TBI patients (all severity) 64.3 ±117.7 months post-injury, Castriotta et al. [4] found abnormal sleep in 46% of the study sample, which included obstructive sleep apnea (OSA) (23%), hypersomnia (11%), periodic leg movements in sleep (7%), and narcolepsy (6%). Among soldiers with TBI, 34.5% had OSA syndrome [35].

4. Pathophysiology of sleep-wake disturbances following TBI

The pathophysiology of post-traumatic sleep-wake disturbances still remains unclear but can possibly be explained by a complex interaction between several physiological, environment, and psychological factors.

4.1. Brain lesions and brain dysfunctions

Abnormal neuroimaging results, mostly from computed tomography scanning, are found in approximately 5 to 10% of mTBI patients [22] and in up to 90% of patients with severe TBI [60]. Traumatic brain injury also results in more subtle brain damage characterised by decreased synaptic density, and axonal and dendritic degeneration [61]. The cortical and subcortical structures and networks involved in sleep, wake, and circadian rhythmicity may be impaired or damaged in a proportion of TBI patients and possibly explain part of the sleep-wake disturbances observed in this population, but no study specifically assessed this association yet.

Baumann [30] found that in 43% of his study sample, potential causes of sleep and wake disturbances could not be explained by any other factor than the TBI itself (all severity). The possible factors that were considered were sleep-related breathing or movement disorders, narcolepsy or behaviourally induced insufficiency sleep syndrome, substance abuse, demographic characteristics, residual clinical symptoms, or other TBI characteristics.

Furthermore, it has been shown that patients in the acute phase of moderate to severe TBI have abnormally low levels of hypocretin-1 levels in their cerebrospinal fluid [30,62]. Hypocretin-1 (orexin A) is an excitatory neuropeptide produced by the hypothalamus, which is involved in the regulation of arousal. Involvement of the hypocretin system in the acute sleep-wake disturbances of TBI patients is possible, and could be linked to hypersomnia. However, based on currently available research, the hypocretin system may not necessarily explain the high prevalence of chronic sleep-wake disturbances, including insomnia as return to normal values of hypocretin has been observed 6 months post-TBI. Further research is needed to elucidate the underlying pathophysiological mechanisms of chronic sleep-wake disturbances of varying diagnoses (i.e. insomnia, hypersomnia, fragmented sleep, increased sleep need, pleiosomnia).

4.2. Circadian rhythm disturbances

One factor that may contribute to sleep-wake disturbances is altered circadian rhythms. The circadian clock, located in the suprachiasmatic nucleus of the hypothalamus, is primarily synchronised to the 24-h environmental day by the light-dark cycle [63,64]. Circadian disruption occurs when the main biological clock, located in the hypothalamus, is not synchronised to the 24-h day and/or when it produces a circadian signal too weak to entrain properly the peripheral clocks located in other regions of the brain and body. One of the most obvious manifestations of circadian disruption is a decreased consolidation and abnormal timing of the sleep-wake cycle [65].

Sleep-wake disturbances reported by mTBI patients in the chronic phase of injury may be caused by circadian rhythm dysfunctions that can be manifested as advanced or delayed phase syndrome. Concordant with this hypothesis, Ayalon et al. [66] used actigraphy, salivary melatonin, oral temperature measurement and PSG, to evaluate 42 patients with mTBI and insomnia. The authors founds that 15 (36%) had circadian rhythm sleep disorders (8 had a delayed sleep phase syndrome and 7 displayed an irregular sleep–wake pattern).

Alterations in daily rhythms have also been found in chronic moderate and severe TBI, where patients showed decreased evening melatonin production [44,67]. Decreased melatonin

secretion, however, was not found in another study performed in 10 TBI patients 516 ± 124.04 days post-injury and 10 age- and sex-matched controls [68].

Moreover, the immune response triggered by the TBI itself, and possibly other injuries that may accompany it, could contribute to circadian dysregulation following injury. Indeed, increasing evidence points to a bidirectional communication between circadian physiology and immune function [69].

Clock genes may also be dysregulated following TBI. An animal study conducted by Boone et al. [70] found that male rats exposed to fluid-percussion TBI had altered circadian gene expression in both the suprachiasmatic nucleus (SCN) and hippocampus, when compared to sham surgery rats. *Bmal1* and *Cry1*, both key clock genes, were dysregulated, as was the daily rhythm of locomotor activity, which persistently showed reduced activity in the TBI group, coinciding with the dysregulation of clock genes in the SCN and hippocampus. The authors suggested that a disturbance in the transcriptional-translation feedback loops that modulate circadian timing could be induced by TBI.

During the hospitalisation period following TBI, the hospital environment itself may favour the loss of light/dark circadian cues due to constant lighting [71], which can influence the circadian clock. The fact that patients are bedridden in a constant horizontal posture may also promote daytime sleep, which in turn, also influences nocturnal sleep. A few studies have investigated the circadian rhythms of acute TBI patients hospitalised in the intensive care unit, all of which have pointed to major circadian anomalies, which suggest that brain injury may aggravate circadian rhythms disturbances found among critically ill patients [72-74]. A prospective clinical study conducted by Paul and Lemmer [72] showed an absence of 24-h variation in well-documented markers of circadian rhythms, namely body temperature, plasmatic melatonin and cortisol, heart rate, blood pressure, and spontaneous motor activity in 24 critically ill analgo-sedated patients. The observed circadian rhythm disturbances were more pronounced in the 11 patients with severe brain injury (including 3 moderate-severe TBI patients, 7 patients with subarachnoid hemorrhage following the rupture of an intracerebral aneurysm, and 1 patient with hypoxic brain injury) than in patients without a brain injury. To

our knowledge, no study has specifically sought out to investigate circadian alterations in the acute phase of mTBI.

4.3. Endocrine dysfunction

Endocrine dysfunctions are also common following TBI, especially for endocrine functions emerging from the pituitary, and reported as varying from 15% to as high as 90% among moderate-severe TBI patients 2 weeks to several years post-injury [75,76]. These disturbances include hypopituitarism, impaired growth hormone release, hypo/hyperthyroidism, hypothalamic gonadism, and abnormal adrenocortical function. Endrocrine disturbances may be associated with sleep-wake disturbances and fatigue following TBI, as some endocrine changes, such as growth hormone (GH) deficiency and altered cortisol levels, are known to have specific effects on sleep architecture. To test for endocrine dysfunctions, routine blood tests can be carried out to assess hormone levels of the pituitary gland, particularly those of the anterior pituitary (e.g. somatotrophins, corticotropins, thyrotrophins, lactotrophins and gonadotropins), most commonly found to be altered following TBI (see Table 1).

4.4. Impact of the hospital environment

In the acute phase post-injury, hospitalised TBI patients are confronted by environmental conditions that are unfavourable to adequate sleep and circadian rhythmicity. Many factors may account for the poor sleep of hospitalised patients, particularly in the ICU environment, where several sources of noise are present, including alarms and conversations from healthcare personnel [77]. In fact, Friese et al. [78] indicated that 36% of hospitalised TBI patients with sleep complaints pointed out the hospital environment as an important causal factor. Receiving 24-hour care has also been shown to make sleep more difficult [79]. Being under the effects of sedatives, analgesics, narcotics, anticonvulsants and antipsychotics may also influence sleep characteristics [80]. As previously mentioned, the loss of light-dark circadian cues due to constant lighting may also be an environmental factor highly responsible for sleep-wake and circadian disturbances.

4.5. Anxiety and depression

Anxiety and depression have been shown to be highly prevalent after TBI and to have a negative impact on sleep [3,23,46,47,67]. Furthermore, those with TBI can suffer from acute post-traumatic stress disorder, a mental disorder that can manifest itself following a psychologically traumatizing event, and can lead to an alteration of sleep and a decrease of slow-wave sleep [81]. Huang et al. [45] recently examined risk factors associated with persistent sleep complaints following TBI (all severity). The authors subdivided the 25 patients with persistent sleep complaints into two groups, comparing those with sleep complaints at 6 and 12 months to those with complaints at 12 months only. The group with complaints at 6 and 12 months had higher levels of depression and post-traumatic distress at both 6- and 12-months post-injury. Conversely, Rao et al. [56] reported that based on structured clinical interview, the presence of insomnia in the acute period following TBI was related to heightened anxiety. With regards to TBI, depression has been associated with reports of sleep changes and worse sleep quality, as well as an increase in nighttime awakenings (subjective and objective) [47,31]. Though anxiety and depression can alter sleep and wake, these studies do not suggest that sleep-wake disturbances are only driven by these effects, but that they may rather occur in parallel.

4.6. Pain

Pain is another factor to which sleep disturbances have been partly attributed in several studies [3,31,33,46,48,67,82]. In fact, Beetar et al. [33] showed that when patients with pain complaints were removed from his study sample, the prevalence of insomnia complaints was reduced by nearly half, plummeting from 69% to 38.6%. A recent study linked pain with an increase in rapid EEG frequency bands mostly during REM and slow wave sleep in mTBI (45 ± 22.7 days post-injury) with pain [31]. TBI patients without pain did not exhibit rapid EEG frequency bands, suggesting that pain may explain, at least in part, poor sleep in this population.

5. Management of sleep-wake disturbances

5.1. Modifying the hospital and early rehabilitation environments to improve sleep

Since the environment may increase sleep disturbances in the hospital setting, some environmental factors may be easily modified to promote sleep. For example, providing patients with ear plugs and eye masks, or minimizing staff interventions at night and during naps could enable patients to have a more restorative sleep [77].

Among individuals with circadian disorders (i.e. phase advance or delay), light therapy has been shown to adjust the circadian clock to the environment [83], and has been recognized by the American Academy of Sleep Medicine [84]. Light therapy has previously been used among in the ICU among non-TBI patients, and has been shown not only to improve patients' circadian rhythms, and lead to a swifter recovery [85], but the efficiency of this intervention needs to be evaluated among acute TBI patients.

5.2. Interventions to improve insomnia

Prior to treating insomnia, the clinician should screen for other sleep disorders (e.g. restless leg syndrome) as well as medical (e.g. acute and chronic pain) or psychiatric conditions (e.g. anxiety, depression, and posttraumatic stress disorder) that may be associated with, or underlie insomnia (see Table 1).

Table 1. Screening and interventions for post-TBI insomnia and hypersomnia (list not exhaustive).

	Insomnia	Hypersomnia
SCREENING	*Insomnia and hypersomnia may be caused or exacerbated by the following conditions, which should be ruled out.*	
Medical history	A particular attention should be paid to: - Acute/chronic pain - Current (or withdrawal from) medication and dosage	A particular attention should be paid to: - Neurodegenerative diseases - Current medication and dosage - Weight gain - Brain lesions
Neuropsychiatric evaluation	- Anxiety - Acute/chronic stress - Depression (and other mood disorders) - Posttraumatic stress disorder - Substance abuse disorders	- Depression (and other mood disorders) - Substance abuse disorders
Sleep disorders	- Restless leg syndrome - Sleep breathing disorders (apnea, sleep maintenance insomnia) - Circadian rhythm disorders (phase advance or delay)	- Sleep breathing disorders (apnea) - Narcolepsy - Kleine-Levine syndrome - Behaviorally induced insufficient sleep syndrome - Circadian rhythm disorders (phase advance or delay)
Blood tests	- Endocrine (pituitary) function o Somatotrophins (growth hormone (GH)) o Corticotropins (adrenocorticotropic hormone (ACTH), beta-endorphin) o Thyrotrophins (thyroid-stimulating hormone (TSH)) o Lactotrophins (prolactin (PRL)) o Gonadotropins (luteinizing hormone (LH), follicle-stimulating hormone (FSH))	
INTERVENTIONS	*If sleep-wake disturbances are associated to another psychiatric or medical condition, this condition should also be treated.*	
Modifications of the hospital environment	- Ear plugs - Eye mask - Minimizing staff interventions during nighttime/naps - Light therapy or exposure to natural light in the morning (hypersomnia)	
Non-pharmacological	- Sleep hygiene o Regular bed/wake times o Avoiding lengthy daytime naps (more than 60 minutes) o Avoiding daytime naps after 3:00 PM o Avoiding coffee and alcohol 4 to 6 hours prior to bedtime o Avoiding strenuous exercise at least one hour prior to bedtime o Avoiding stimulant activities at least one hour prior to bedtime (video games, suspense movies) o Avoiding nicotine in the hours prior to bedtime or during awakenings in the night o Avoiding light and noise in the bedroom during the night o Using the bed only for sleep or sexual activities	

	○ Going to bed only when ready to sleep - Light therapy in the morning (hypersomnia) - Cognitive behavioral therapy (insomnia)	
Pharmacological	- Benzodiazepine sedative-hypnotics - Non-benzodiazepine sedative-hypnotics - Melatonin	- Modafinil - Amphetamine-based psychostimulants - Methylphenidate-based psychotimulants - Non-psychostimulants (Atomoxetine, Guanfacine) - Amantadine

Prescription and over-the-counter pharmacologic interventions are the most common and accessible treatments for insomnia. However, although pharmacologic interventions have been effective in treating sleep disturbances in healthy individuals, it has been consistently reported that benzodiazepines, the most frequently prescribed sleep agent used to treat insomnia, and GABA-agonists result in cognitive impairment when plasma levels are at their peak [86]. There also exists some evidence suggesting that benzodiazepines produce residual effects on cognition, whereas some have shown the GABA agonists may have detrimental effects on neuroplasticity [86]. Moreover, the side-effects of sedative-hypnotic sleep-agents, such as the Z-drugs, include daytime drowsiness, as well as cognitive and psychomotor impairments, all of which are likely to add to the burden of TBI sequelea [87].

Conversely, the use of oral melatonin by critically ill patients has also been shown to improve sleep duration and efficiency [88]. Additionally, melatonin has been shown to have remarkable antioxidant properties, preserves mitochondrial homeostasis, may protect against neurodegenerative processes, and combat free radical damage in the brain, therefore acting as a therapeutic agent in the treatment of cerebral oedema following TBI [89]. However, there appears to be no study that has specifically assessed the efficiency of melatonin to improve sleep and circadian rhythms in TBI patients.

Cognitive behavioral therapy (CBT), including behavioral interventions such as Stimulus Control or Sleep Restriction (restriction of time in bed), has been shown to be efficient in improving the sleep efficiency, reducing sleep onset latency, and reducing the

number of nocturnal awakenings, of mild to severe TBI patients suffering from insomnia [90,91]. Strong evidence supports the use of CBT for primary insomnia in the general population, and this intervention is being increasingly disseminated in populations with diverse health conditions by non-sleep specialists.

When used in a small sample of patients with TBI (unspecified severity; n = 12; 2.2 ± 1.3 years post-injury) and insomnia complaints, acupuncture has also been shown to have a beneficial effect on perception of insomnia severity and improved cognitive functioning, though acupuncture had no effect on sleep time, as measured by actigraphy [92].

5.3. Interventions to improve hypersomnia

Prior to treating hypersomnia, as with insomnia, the clinician should screen for medical and psychiatric conditions that may be associated with, or underlie hypersomnia (see Table 1). If sleep comorbidities (e.g. sleep breathing disorders (apnea), periodic limb movement in sleep, and narcolepsy) emerge, usual treatment for these conditions is recommended.

Pharmacological treatments used in the management of hypersomnia include modafinil, amphetamine-based psychostimulants, methylphenidate-based psychostimulants, non-psychostimulants, and amantadine, though studies on their effectiveness remain inconclusive with regards to post-TBI hypersomnia. For example, while Jha et al. [93] found no difference between modafinil and placebo, Kaiser et al. [94] observed a decrease in post-TBI daytime sleepiness, as measured by the ESS, the Maintenance of Wakefulness Test (MWT), and the amount of time spent awake according to actigraphy. Wiseman-Hakes et al. [57] reported that a methylphenidate-based psychostimulant was successful in improving day-time alertness and cognitive performance in a case study evaluation of an individual with severe TBI and post traumatic hypersomnia.

6. Conclusions and study perspectives

The goal of this review was to describe the current state of knowledge on sleep-wake disturbances and circadian rhythm alterations following TBI. We aimed to describe the

possible causes of these alterations, and explore the pharmacologic and non-pharmacologic treatment options to treat them.

Sleep disturbances have been shown to exacerbate trauma related cognitive, communication and mood impairments, as well as pain, and compromise the recovery process [23,57]. Memory and new learning are often impaired following TBI of all severities, and the importance of sleep in hippocampal function, learning and the formation of memory in humans has been confirmed by imaging studies [93]. From a more general perspective, partial or chronic sleep restriction has negative repercussions for behavioral, cognitive, inflammatory, immune, cardiovascular, metabolic, and endocrine functions [96-100]. Taken together, these results suggest that acute and chronic sleep restriction and/or fragmentation in TBI survivors can hinder processes of physical, psychological and cognitive recovery, and lead to a reduction in learning capabilities, neural plasticity, and neurogenesis. Interestingly, Wiseman-Hakes et al. [23] reported functional, as well as clinically and statistically significant improvements in sustained and divided attention, working memory, speed of language processing and mood in response to individualized treatment of post-trauma onset sleep-wake disorders in adults (including sleep hygiene recommendations, pharmacological interventions and/or apnea treatment with follow-up).

Further studies should investigate how these sleep-wake and circadian disturbances originate and evolve, and whether measures can be taken to prevent them. Various treatment options should be further investigated, particularly in the acute phase where recovery is most crucial for the optimisation of patient functionality and quality of life.

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6. Current gaps in the literature

Although SWD are among the most persistent sequelae following TBI, and there is mounting evidence that they impede recovery and exacerbate trauma-related impairments, no study has yet documented how SWD arise and evolve in the acute phase of TBI. Moreover, no study has measured the association between SWD and short-term cognitive and functional recovery. Finally, given the implication of the circadian system in sleep-wake regulation, and the vulnerability of the master circadian clock to brain injury, the functioning of the circadian system must also be assessed to elucidate the pathophysiology of post-TBI SWD.

Firstly, we need objective measures of the sleep-wake cycle in acute TBI in order to verify whether clinical observations can be confirmed. The sleep-wake cycle of acute TBI patients must also be compared to that of other hospitalized patients, without TBI, in order to isolate the role of the brain injury from possible environmental and medical confounds.

Secondly, given the role of sleep in brain function, and because TBI may injure brain regions implicated in sleep-wake regulation, we need to understand whether recovery or cognitive and neurological functions is linked with recovery of the sleep-wake cycle.

Thirdly, we need to verify whether sleep architecture is preserved in acute non-sedated TBI patients, and to compare TBI patients to other hospitalized patients to, once more, isolate the role of the brain injury.

Finally, we need to verify whether the SWD of acute moderate to severe TBI patients are due to an abnormal circadian clock signal.

By contributing to a better understanding of how SWD originate and evolve in acute TBI, as well as their short-term consequences, this thesis could lead to new clinical procedures favouring better sleep and circadian rhythms during the hospital stay, in order to optimize recovery and improve quality of life.

7. Objectives and hypotheses

The general aim of this thesis is to characterize the sleep and circadian rhythms in patients hospitalized with moderate or severe TBI, and determine whether SWD are caused by circadian deregulation. To achieve this goal, we use objective and quantitative measures of sleep and circadian rhythms including actigraphy, PSG, as well as melatonin rhythm in urine, beginning in the awakening stage in the ICU, and continuing during the post-ICU hospital stay. In order to understand the specific role of TBI on SWD, we compare our TBI patients to other hospitalized trauma patients, without TBI.

The objectives of this thesis are achieved through one comprehensive research protocol, carried out from 2010 to 2016, leading to five research articles:

7.1. Articles 3 and 4

Given that the sleep-wake cycle of moderate to severe TBI patients has never been measured during the acute hospital stay, Article 3 aims to characterize the sleep-wake cycle of moderate to severe TBI patients, during the ICU and post-ICU phases. Our goal is to obtain objective data to appraise the features, severity, and evolution of SWD. Moreover, we investigate whether SWD are associated with clinical characteristics and/or functional and cognitive outcome measures at hospital discharge. We hypothesize that patients will exhibit a severely disturbed sleep-wake cycle that will improve over time. Our second hypothesis is that poorer sleep-wake cycle consolidation will be associated with more severe TBI and poorer outcomes at hospital discharge.

Article 4 aims to characterize the SWD of a single patient, hospitalized for severe TBI. We monitor this patient's sleep-wake cycle using actigraphy during his acute hospitalization phase and again during the subacute (post-acute) stage, when the patient is readmitted to our hospital for paranoid delusions, five days following initial discharge. This Case Report provides us with a unique opportunity to follow-up on our actigraphy measures in a patient with severe neuropsychiatric sequelae.

7.2. Article 5

Article 5 aims to further explore the relationship between acute SWD and cognitive outcome in the acute phase. More specifically, we use actigraphy to assess the day-to-day evolution of the sleep-wake cycle and the recovery of consciousness and cognitive functions. Finally, we assess the temporal directionality of this association in order to understand which improves first. We hypothesize that the consolidation of sleep-wake states will increase with improving consciousness and cognition, as they depend on overall brain integrity.

7.3. Article 6

Given that PSG is the gold standard for measuring sleep, Article 6 aims to determine the feasibility of using PSG to assess sleep quality and architecture of TBI patients in the post-ICU phase. To achieve this goal, we perform one night of ambulatory PSG at the bedside. We also aim to explore associations between clinical and sleep characteristics, to understand what aspects of the injury and treatment were associated with patients' sleep. In this study, we compare the sleep of TBI patients to that of non-TBI trauma patients. Given the effects of the hospital environment on sleep, and considering the structural, biochemical and pathophysiological changes that occur during the acute phase post-TBI, we expect to observe significant modifications in sleep stages and architecture in our TBI group. We also expect TBI patients to have a longer nighttime sleep period, but with greater sleep fragmentation.

7.4. Article 7

In our final article (Article 7), we first aim to explore whether the brain injury itself has an impact on the sleep-wake cycle. As such, we isolate the effects of the brain injury from that of the hospital environment by comparing the sleep-wake cycle of TBI patients to that of non-TBI trauma patients, hospitalized in a similar environment. Subsequently, our goal is to determine whether the observed SWD may be due to an alteration in the circadian clock signal. We therefore compare the melatonin rhythms of TBI and non-TBI patients to see if TBI patients have an altered melatonin production. Finally, we assess whether the profile of melatonin production, which reflects the proper functioning of the master circadian clock, could explain sleep-wake disturbances observed among TBI patients during their hospital stay.

This is the study that truly enables us to draw the link between SWD and the functioning of the circadian system.

Collectively, these articles are the first to investigate the sleep and circadian rhythms of hospitalized moderate to severe TBI patients who are medically stable and no longer mechanically ventilated or continuously sedated. These studies lay the groundwork for understanding the characteristics, consequences and pathophysiology of post-TBI SWD, and isolate the role of the injured brain from that of overall trauma and the hospital setting. This thesis has a direct translational impact on clinical practice and draws attention to the importance of monitoring sleep in acute TBI, unlocking the possibility to design interventions aiming to improve sleep and optimize recovery.

Chapter II: Methodology and Results

1. Overview of research protocol

Moderate to severe TBI patients were recruited from Hôpital du Sacré-Cœur de Montréal, a level-1 trauma center, between January 2010 and May 2016. TBI severity was assessed upon admission to the emergency room, prior to intubation, using the GCS (Teasdale & Jennett, 1974). TBI patients were included if they had a GCS score between 3 and 12 and/or received a diagnosis of moderate or severe TBI from the neurosurgeon.

Given they have a similar demographic profile and have injuries severe enough to require an extensive medical care and medication, patients having suffered severe orthopaedic and/or spinal cord injuries, without TBI (non-TBI), were tested as the control group. These non-TBI patients were recruited from Hôpital du Sacré-Coeur de Montréal between January 2012 and January 2016. Severe orthopaedic injury was defined as a complex traumatic injury, such as multiple fractures with or without damage to peripheral nerves or to the vascular system, which necessitates intervention by a specialized multidisciplinary team.

Patients were excluded if they were younger than 16 or older than 65 years old, given that major changes to sleep quality and architecture, as well as to circadian rhythms (i.e. phase and amplitude), take place with aging (Bliwise, 2011). Patients were also excluded if they were quadriplegic; had a history of substance abuse, had a diagnosed psychiatric, neurological or sleep disorder prior to injury; suffered any damage to both eyes or the optic nerve (modifying light perception); or if they had a prior history of TBI. The study was approved by the ethics committee of Hôpital du Sacré-Coeur de Montréal.

TBI patients were screened during their stay in the ICU, and were approached once they had been determined likely to survive their injuries. The majority of TBI patients were unable to provide written and informed consent at the time of recruitment given their medical condition and state of consciousness. Written consent for participation was therefore obtained from their families. Non-TBI patients were either approached during their stay in the ICU or regular units, and they provided written consent for their participation.

Patients began study measures once they had reached medical stability (i.e. no longer had elevated ICP and/or hemodynamic instability, were extubated, had no fever or active infection), and continuous sedation had ceased for at least 24 h.

Given that the patients included in the five research articles were tested within one comprehensive research protocol, all were subjected to the same inclusion and exclusion criteria. Overall, 43 TBI and 35 non-TBI patients were tested. Among the TBI patients, 13 (30.2%) were included in only one article, 13 (30.2%) were included in two articles, 11 (25.6%) were included in three articles, and six (14.0%) were included in four articles. More specifically, all patients included in Article 3 were also included in Articles 5 and 7, constituting 53.5% and 20.8% of the study samples of these articles, respectively. Among non-TBI patients, all were included in Article 7, six (17.1%) of which were also included in Article 6.

1.1. Actigraphy

Once patients had reached a score ≥3 on the Rancho Los Amigos scale of cognitive functioning (RLA) (Hagen et al., 1972), indicative of some physical reactivity to internal and external stimuli, they began wearing a wrist actigraph (Actiwatch-L or Actiwatch-Spectrum, Philips Healthcae, Andover, MA) on a non-paralyzed arm for up to two weeks. Data were uploaded into dedicated software (Actiware 5.0), and activity counts were derived per 1-min epoch.

1.2. Melatonin

Urine was collected from the urinary catheter of patients every hour for 25 h, as soon as consent was obtained and patients were medically stable. The hourly concentration of 6-sulfatoxymelatonin (aMT6s), melatonin's principal metabolite, was calculated using the Bühlmann ELISA (ALPCO Diagnostics).

Though some patients began urine collections and actigraphy measures concurrently, some had their urine collected prior to the start of actigraphy, given they were not sufficiently

reactive for actigraphy to be efficacious when urine collections took place (for a general timeline of study measures, refer to Figure 1 below).

1.3. Polysomnography

Some patients underwent a bedside PSG recording during their stay in the neurological or orthopaedic unit. PSG generally took place toward the end of the actigraphy recording period, when TBI patients were less agitated and better able to tolerate the PSG materials. PSG was recorded using a 32-channel Siesta system (Compumedics Limited, Charlotte, North Carolina, USA). Electrode installation was done at the bedside by experienced electrophysiology technicians. PSG comprised four EEG leads (F4, C3, C4, O2) with a linked opposite mastoid reference (Iber, Ancoli-Israel et al., 2007), left and right EOG, and EMG. An oronasal thermistor was used to monitor respiration, and a transcutaneous finger pulse oximeter was used to measure oxygen saturation.

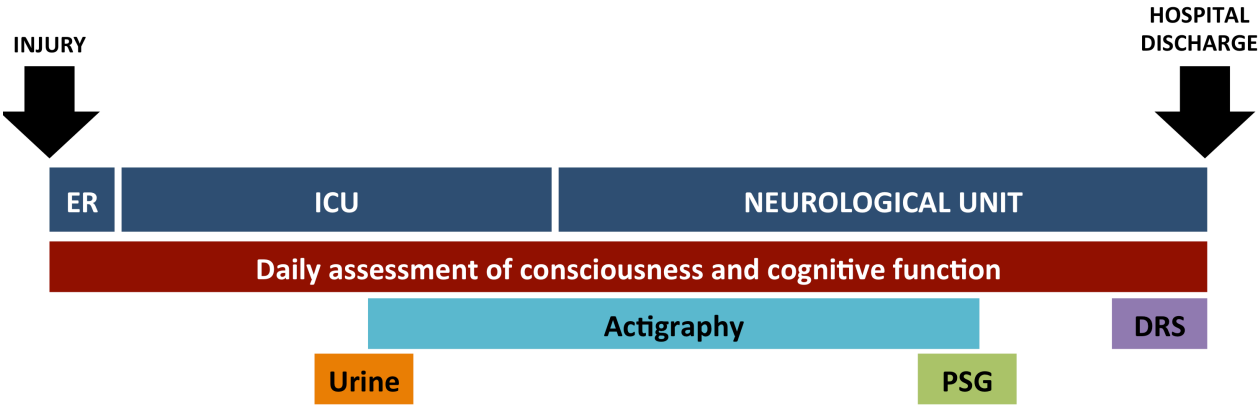
1.4. Measures of consciousness, cognition, and functional outcome

Assessment of consciousness and cognitive function was carried out daily by occupational therapists, using the Rancho Los Amigos scale of cognitive functioning (RLA) (Hagen et a., 1972). The RLA is a behavioural rating scale developed specifically to monitor the stages of recovery in the adult TBI population (Dowling, 1985). Administered at bedside, the RLA evaluates level of awareness to the environment, response to stimuli, ability to follow command, confusion, attention, and the appropriateness of verbalization and motor actions. Though the RLA is not the gold standard measure of consciousness assessment, it is included in the routine assessment of TBI patients at Hôpital du Sacré-Coeur de Montréal, and was therefore already collected by occupational therapists for clinical purposes prior to the start of the study.

PTA was assessed by occupational therapists using the Galveston Orientation and Amnesia Test (GOAT) (Levin et al., 1979) on a daily basis, once patient reached a minimal GCS score of 9, enabling assessment with the GOAT. Emergence from PTA was designated as the first of two consecutive days with a GOAT score ≥76.

The Disability Rating Scale (DRS) score was calculated within the last 72 h prior to hospital discharge by occupational therapists (Rappaport et al., 1982). The DRS is a 29-point scale, for which absence of disability is scored 0 and extreme vegetative state is scored 29.

Figure 1. Timeline of study measures in relation to injury and stages of hospitalization.



ER: Emergency Room; ICU: Intensive Care Unit; PSG: polysomnography; DRS: Disability Rating Scale

Article 3: Rest-activity cycle disturbances in the acute phase of moderate to severe traumatic brain injury

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Contribution: For this article, I recruited the patients, acquired the data, participated in the analysis and interpretation of the data, drafted and critically revised the manuscript.

ABSTRACT

Background Sleep-wake disturbances are among the most persistent sequelae after traumatic brain injury (TBI) and probably arise during the hospital stay following TBI. These disturbances are characterized by difficulties sleeping at night and staying awake during the day.

Objective The aim of the present study was to document rest-activity cycle consolidation in acute moderate/severe TBI using actigraphy, and to assess its association with injury severity and outcome.

Methods Sixteen hospitalized patients (27.1±11.3 years) with moderate/severe TBI wore actigraphs for 10 days, starting in the intensive care unit when continuous sedation was discontinued and patients had reached medical stability. Activity counts were summed for daytime (7:00-21:59) and nighttime periods (22:00-6:59). Ratio of daytime period activity to total 24-h activity was used to quantify rest-activity cycle consolidation. An analysis of variance was carried out to characterize the evolution of the daytime activity ratio over the recording period.

Results Rest-activity cycle was consolidated only 46.6% of all days, however a significant linear trend of improvement was observed over time. TBI severity, intensive care unit and hospital lengths of stay were associated with poorer rest-activity cycle consolidation and evolution. Patients with more rapid return to consolidated rest-activity cycle were more likely to have cleared post-traumatic amnesia and to have lower disability at hospital discharge.

Conclusions Patients with acute moderate/severe TBI had an altered rest-activity cycle, probably reflecting severe fragmentation of sleep and wake episodes, which globally improved over time. A faster return to rest-activity cycle consolidation may predict enhanced brain recovery.

Key words: traumatic brain injury, sleep, circadian rhythms, actigraphy, intensive care

Introduction

Sleep disturbances are among the most persistent and disabling sequelae after traumatic brain injury (TBI), reported by over 50% of patients[1-6] and are known to compromise recovery in chronic TBI.[7] These disturbances are characterized by difficulties sleeping at night and staying awake during the day.[2,8-11] Although sleep-wake disturbances are common in TBI patients, little is known about their origin and evolution. They probably appear in the first days after injury, when patients are hospitalized in the intensive care unit (ICU). A recent study carried out in the post-acute phase of TBI reported that mild to severe sleep-wake disturbances were present among 84% of patients upon rehabilitation admission, and persisted for 66% of patients one-month post-injury.[12] Although no sleep studies have been performed among TBI patients in the ICU, previous ICU studies in non-TBI patients have shown that both sleep-wake cycle and sleep architecture are highly disturbed,[13-14] with a large proportion of sleep occurring during the day and up to 96% of total sleep spent in the lighter, less restorative sleep stages (stages 1 and 2).[15-16]

Sleep disturbances in the ICU are likely to have the same deleterious effects as chronic sleep restriction in healthy subjects on cognition, blood pressure,[17] glucose metabolism,[18] activation of the hypothalamic-pituitary-adrenal axis, and inflammatory response.[19- 21] The lack of deep sleep can have severe consequences during early rehabilitation of patients with TBI by slowing processes of physical recovery and exacerbating cognitive and neurobehavioral impairments, especially hippocampal-dependent memory processes.[22] Thus, there is a critical need to understand the nature and evolution of sleep disturbances in acute moderate to severe TBI, from the ICU to hospitalization in regular wards.

Polysomnography is the gold standard for measuring sleep architecture; however, it does not enable long-term measurement and is poorly tolerated by highly monitored or confused patients. An interesting alternative is wrist actigraphy, a valuable instrument to measure long-term rest-activity cycle in a clinical setting. In healthy subjects, rest-activity cycle has been strongly correlated with the sleep-wake cycle, and is often used as an indirect measure of the sleep-wake cycle.[23] Indeed, because of its low invasiveness and cost, actigraphy has been successfully used among different clinical populations.[24-27]

The aim of the present study was to document rest-activity cycle consolidation during the acute phase of moderate and severe TBI using actigraphy recordings. Moreover, this study aimed to explore the clinical characteristics and outcome measures correlated with prolonged absence of rest-activity cycle consolidation. We hypothesized that patients would exhibit a severely disturbed rest-activity cycle that would improve over time. Our second hypothesis was that poorer rest-activity cycle consolidation would be associated with more severe TBI and poorer outcome at hospital discharge.

Methods

Subjects

The study comprised 16 hospitalized patients (mean age 27.1±11.3 years) with moderate or severe TBI recruited from Hôpital du Sacré-Coeur de Montréal, a level 1 trauma centre (see Table 1 for patient characteristics). The study was approved by the hospital ethics committee. Consent for participation was obtained from patients' families. Patients who eventually became cognitively able to provide informed consent for themselves were asked to sign a consent form for study protocol to continue.

Inclusion/Exclusion criteria

TBI was defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force.[28] TBI severity was assessed upon emergency room admission using the Glasgow Coma Scale (GCS)[29] and was reassessed thirty-minutes later to provide a post-reanimation index of TBI severity. Patients were included if they had a GCS score of 3-12 upon emergency room admission and had to be hospitalized in ICU. One subject with a GCS score of 14 at emergency room admission was included, as he subsequently suffered elevated intracranial pressure (ICP), rapidly dropped to a GCS of 3 and received a diagnosis of severe TBI.

Patients were excluded if non-fluent in French or English before injury, if they were quadriplegic, had a history of substance abuse, psychiatric or neurological disorders, or had diagnosed sleep disorders. Such information was obtained from patients' families through

psychosocial assessments carried out by the ICU social worker and were confirmed by research assistants. Patients were also excluded for pregnancy, incarceration, homelessness, or if they suffered any damage to both eyes, or the optic nerve (modifying light perception).

Protocol

Clinical variables

Injury severity. Length of ICU stay, hospital length of stay, duration of continuous sedation/analgesia, number of days with elevated ICP (>20mmHg), Marshall[30] and Rotterdam[31] scores, as well at the Summary Therapy Intensity Level (TIL)[32] were documented for each day in the ICU. Cumulative administered dose of sedative and analgesic medication (lorazepam, midazolam, propofol, morphine, hydromorphones, and fentanyl) in ICU was calculated according to the previously described method.[33] Sedative, analgesic, antiepileptic and neuroleptic medications were also noted for all days of actigraphy recording that took place in the regular units (see Supplementary materials for details).

Cognitive and functional outcome. Cognitive and behavioural functions were assessed daily by occupational therapists using the Rancho Los Amigos (RLA) scale[34] and the Galveston Orientation and Amnesia Test (GOAT).[35] Duration of post-traumatic amnesia (PTA) was calculated from the day the patient reached a GCS score of 9, as suggested in the standard GOAT protocol.[35] Emergence from PTA was designated as the first of 2 consecutive days with a GOAT score ≥76. Since 6 patients were still in PTA at hospital discharge and no PTA duration could be documented for them, no analyses were performed on PTA duration. Rather, patients were divided according to presence or resolution of PTA at discharge. The Disability Rating Scale (DRS)[36] score at discharge (last 72-h of hospitalization) was calculated by the occupational therapist. The DRS is a 29-point scale, for which absence of disability is 0 and extreme vegetative state is 29, commonly used among the moderate-severe TBI population.

Table 1. Demographic and clinical characteristics of patients

ID #	Age	Sex	Mechanism of injury	GCS (ER/30min post-admission)	Neuroimaging results	Marshall Score	Rotterdam Score	Days with elevated ICP	Peak TIL score	Cum. ICU dose analgo-sedation (g)	Days in ICU	LOS	PTA at discharge (Y/N)	DRS at discharge	Orientation at discharge	Start of protocol (days post-injury)
1	29	M	MVA	9/6	Fronto-parietal SDH (L), CO, temporal contusion (L), 8mm MLS	3	4	13	18	68.8	38	51	Y	13	Internal	30
2	23	M	MVA	3/3	Thalamic contusion (R), SAH, ventricular hemorrhage (R)	2	3	0	3	22.1	24	36	N	7	Internal	17
3	21	M	MVA	14/-	Epidural hemorrhage, CO, laceration of meningeal artery, multiple traumatic lesions, fronto-temporal fx (R) with SDH, ventricular collapse	6	3	14	22	137.3	40	56	N	6	External	28
4	55	M	Fall from moving vehicle	11/-	Traumatic SDH (L), frontal and temporal SAH (L), diffuse cerebral lesions,	5	4	3	15	31.4	15	32	N	7	Internal	13

					frontal intraparenchymal contusion (L)											
5	20	M	MVA	11/11	Bilateral SDH	2	3	0	4	0.1	13	26	N	6	External	8
6	17	F	MVA	4/7	Intraparenchymal hemorrhage, SAH, CO, probable PSH, contusion	3	4	6	12	14.6	40	54	Y	14	Internal	11
7	29	M	MVA	7/7	Fronto-temporal parenchymal contusion (L), SAH	2	2	3	13	17.4	13	26	N	8	Internal	7
8	17	M	MVA	6/6	Diffuse CO, multiple SDH, temporal EDH (L)	6	3	16	18	42.1	52	64	N	11	Internal	27
9	47	M	Fall	6/3	No traumatic anomalies	1	2	0	4	5.2	5	11	N	5	External	4
10	26	F	MVA	7/7	EDH, SAH, open temporo-parietal fx (L)	2	2	0	6	4.8	7	22	N	5	Internal	8
11	23	M	Hit by car	3/4	EDH, SAH, open temporo-parietal fx (L) Decerebration, fronto-temporal SDH (L) with 4mm MLS, parenchymal hematoma of cerebellum (L) and mesencephalon (R), RHL, open	2	3	9	16	61.4	40	87	Y	16	Internal	52

					comminuted fx medial orbital wall (L), probable PSH											
12	21	F	MVA	6/6	Convex SDH, 5mm MLS, contusion, fx orbital floor, ventricular hernia	2	3	14	13	77.9	38	56	Y	13	Internal	26
13	20	M	MVA	3/3	SDH, frontal SAH (L)	2	3	0	5	4.9	24	68	Y	10	Internal	17
14	43	M	Fall	3/3	SAH, parietal SDH (L), temporal contusion (R)	2	3	13	19	82.8	27	54	Y	10	Internal	31
15	17	M	MVA	7/7	Frontal SDH (R), frontal SAH (L), periorbital oedema (R), frontoparietal skull fracture (R), slight MLS	2	3	0	3	5.4	5	13	N	5	External	4
16	18	M	MVA	5/7	Temporal and parietotemporal contusions (L)	1	2	0	4	2.8	5	13	N	8	External	5

CO – cerebral oedema, DRS – Disability Rating Scale, EDH - extradural hematoma, fx - fracture, GCS - Glasgow Coma Scale, ICP – intracranial pressure, ICU – intensive care unit, L – left, LOS – length of stay, MLS - midline shift, MVA - motor vehicle accident, PSH - Paroxysmal Sympathetic Hyperactivity, PTA – post-traumatic amnesia, R – right, RHL - radial head luxation, SAH - subarachnoid hemorrhage, SDH - subdural hematoma, TIL – Therapy Intensity Level,

Actigraphy

Patients wore a wrist actigraph (Actiwatch-2, MiniMitter Philips Healthcare, Andover, MA, USA) on a non-paralyzed arm during hospitalization. The actigraph is a small, watch-like device that contains an accelerometer, which records physical motion in all directions with a sensitivity of 0.05g. Motion is then converted to an electric signal, which is digitally integrated to derive an activity count per 1-minute epochs.

Data was acquired during hospitalization, beginning in ICU for most patients and continuing throughout hospitalization in regular wards. Actigraphy recording began when continuous sedation and analgesia had ceased for at least 24-h. By that stage, patients were no longer intubated and had reached a level of medical stability defined by the absence of elevated ICP, of hemodynamic instability, and of fever or active infections. Moreover, the actigraph was installed only once patients reached a RLA score ≥III, indicative of a more apparent physical reactivity to internal and external stimuli.

Approximately every 3 days, data were uploaded into dedicated software (Actiware 5.0). Removal of the actigraph for data uploads took on average 7.9±6.2 minutes, during which time wrist activity was not recorded.

Data analyses

Due to the absence of a consolidated 24-h rest-activity cycle on most recording days, the cosinor analysis, which is typically used to quantify the rest-activity cycle,[37] would have led to non-valid results. In the present study, rest-activity cycle consolidation was thus estimated with the ratio of daytime activity to total 24-h activity. For each 24-h day and for each subject, the activity counts were summed separately for daytime (07:00-21:59) and nighttime (22:00-6:59) periods. Nighttime was defined according to the schedule of the hospital unit, and was characterized by lower levels of activity and light. Total 24-h activity (07:00-06:59) was the sum of the daytime and nighttime periods. Each 1-min epoch during which no recording took place (due to actigraph removal for data uploads) was attributed the average activity count of the period (daytime or night-time) during which the actigraph was

removed. The percentage of total 24-h activity occurring in the daytime was calculated to obtain the daytime activity ratio [daytime activity ratio = (daytime activity/24-h activity) x100]. A ratio of 50% indicated a level of activity evenly distributed across daytime and nighttime periods, whereas a ratio of 100% indicated that all activity occurred during daytime. According to our preliminary analyses, a daytime activity ratio of 80% was chosen to designate an adequate consolidation of the rest-activity cycle, synchronised to the day-night cycle. Five variables were used to evaluate the state and evolution of rest-activity cycle consolidation: mean daytime activity ratio for the total recording period, daytime activity ratio averaged over the first and last 48-h of recording, percentage of improvement between first and last 48-h of recording, and number of days with daytime activity ratio ≥80%.

Actiware 5.0 automatically scored a minute of recording as "moving" according to a threshold value of ≥10 activity counts per epoch. The quantity of minutes of moving was then calculated for each day of recording, for each patient. Minutes during which the actigraph was removed for data uploads were scored as "moving", since the actigraph was removed only when subjects were not resting.

Statistical analyses

A within-subject ANOVA with *Time* as the repeated factor was carried out to compare the daytime activity ratio over the 10 days of recording. This analysis was only carried out on patients who had 10 days of recording. All other analyses included all 16 patients. Paired t-tests on daytime activity ratio were also performed to compare the first and last 48-h of actigraphy recording. To test our second hypothesis, a series of Pearson correlations were conducted between actigraphic variables and each variable of injury severity and outcome. Sub-groups of patients with and without PTA at hospital discharge were compared using independent samples t-tests. Exploratory testing of each sub-group's improvement of rest-activity cycle consolidation was performed using an ANOVA with one repeated measure (time). If not otherwise mentioned, the data are presented as mean ± standard deviation, Significance was set at $p<0.05$.

Results

Figures 1 and A show the actigraphy recordings of all patients. Patients began wearing the actigraph 18±13.3 days post-injury and a delay of 13.9±13 days was observed between the last day of actigraphy recording and hospital discharge. Details on patients' clinical characteristics and actigraphy recordings are presented in the Results section of Supplementary materials.

Consolidation of the rest-activity cycle in acute TBI

When all patients (n=16) and all days of recording (n=148) were considered, daytime activity represented 75.1±13.7% of total activity. Overall, the criteria of ≥80% daytime activity, representing a consolidation of the rest-activity cycle, was met only in 69 (46.6%) of all days of recording. Cycle consolidation was present during only 18 of 63 days (28.6%) in ICU, but increased to 52 of 85 days (61.1%) in regular wards. In the 3 patients who recovered rapidly and had less than 10 days of actigraphic recording, most days (93.3%) showed ≥80% daytime activity, suggesting that the ≥80% criteria was valid, although arbitrary.

Figure 1 shows the actigraphy recordings of four patients, which are an adequate representation of all patients tested. Two general patterns of rest-activity cycle were observed. The first pattern, represented by patients #2 and 12, was observed in 8 patients and illustrates a continuous absence of rest-activity cycle consolidation over all days of recording. Several of these patients also had only brief periods of consolidated rest over the 24-h, as shown by the brief periods during which the actigraph was not active. The second pattern, illustrated by the actigrams of patients #3 and 10, was observed in 8 patients and depicts an improvement in the consolidation of the rest-activity cycle over the 10 days or recording.

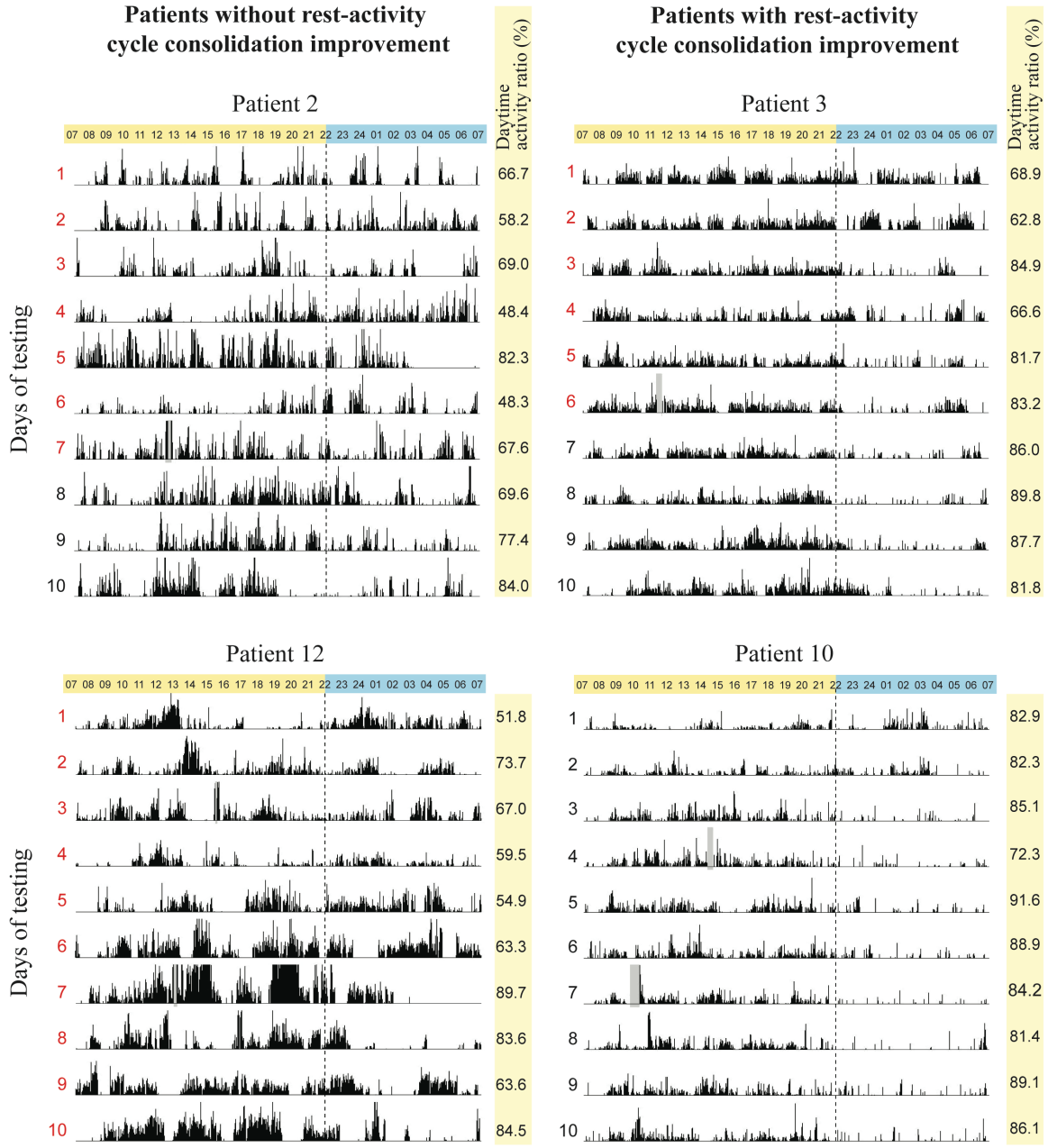

Figure 1. **Examples of actigraphy recordings.** Examples of 10-day actigraphy results from 4 representative patients. Each of the 10 days is represented on a separate line, from 07:00 to 07:00 h. Total activity counts for each minute of recording is illustrated by vertical dark lines. The same scale of 0 to 1000 activity counts was used for all subjects and all days of recording. Hours included in the Day period (07:00 to 22:00) are shown in yellow and those included in the night period (22:00 to 07:00) are in blue at the top of each graph. Daily percentages of daytime activity on total 24-h activity are indicated on the right side of each actigram. Periods with no recording are represented by grey rectangles. Days when the recording took place in ICU are in red.

During the first 48-h of actigraphy, only 4 patients (25%) showed a consolidated rest-activity cycle, however this evolved to being present in 10 patients (62.5%) during the last 48-h of recording. Furthermore, only 3 patients (18.8%) reached a daytime activity ratio ≥80% while in ICU. Average daytime activity ratio of the first 48-h of recording was 70.8±10.1%, increasing to 79.1±13.7% for the last 48-h, thus showing a significant improvement of 9.3±11.3% between the beginning and end of recording ($t(30)=-2.1$, $p<0.05$). Of the 12 patients with 10 days of actigraphy, a significant linear trend of improvement was observed from day 1 to day 10 ($F(1,11)=11.92$, $p<0.01$, see Figure 2).When patients were considered individually, improvement from the first to last 48-h of actigraphy was quite diverse, ranging from -22.39% to 26.97%.

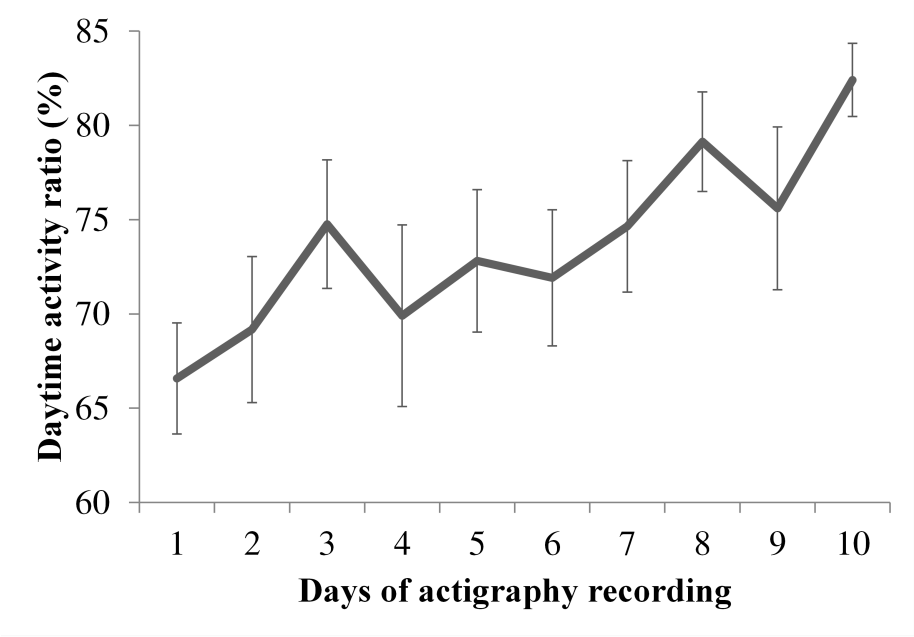

Figure 2: Evolution of the consolidation of rest-activity cycle over ten days. Evolution of the mean (± SEM) daytime activity ratio in the 12 patients having 10 days of recording. The linear trend of improvement was statistically significant ($p< 0.01$).

On average, patients had 827.2±233.2 min scored "moving" per 24-h (57.4% per day) during the first 48-h of recording, and 845.8±166.0 min per 24-h (58.7% per day) during the last 48-h of recording. The percentage of time moving per 24 h is provided for each patient and for each day of recording in Supplementary Table 1.

Association between rest-activity cycle and clinical variables

Table 2 presents the Pearson correlation coefficients showing the associations between rest-activity variables and clinical variables. Better or improving rest-activity cycle consolidation was associated with higher GCS at admission, a shorter ICU stay, and a shorter hospital stay. The daytime activity ratio of the first 48-h of actigraphy was not related to any variable of injury severity or outcome. The Marshall and Rotterdam scores, peak TIL score, number of days of elevated ICP, and cumulative ICU dose of analgosedation were not significantly associated with any rest-activity variable.

Better rest-activity cycle consolidation was associated with lower disability at discharge (Figure 3). More specifically, a higher daytime activity ratio for the total recording period, a higher daytime activity ratio in the last 48-h of recording, a higher percentage of improvement from the first to last 48-h, and a higher number of days with rest-activity cycle consolidation were associated with lower DRS scores (r values ranging from -0.53 to -0.69, p's<0.05).

Table 2. Pearson correlation coefficients between rest-activity cycle and clinical variables

Actigraphy variables	GCS	Marshall	Rotterdam	Peak TIL	Days elevated ICP	Cum. ICU dose analgosedation	Length ICU stay	Total length hospital stay	DRS at discharge
Mean daytime ratio for total recording period	0.33	0.04	-0.27	-0.39	-0.40	-0.33	-0.59*	-0.67**	-0.68**
Mean daytime ratio for first 48-h	-0.17	-0.25	-0.33	-0.43	-0.35	-0.41	-0.38	-0.30	-0.23
Mean daytime ratio for last 48-h	0.39	0.09	-0.19	-0.30	-0.22	-0.16	-0.50*	-0.69**	-0.74**
Improvement of daytime ratio between first and last 48-h	0.53*	0.28	0.06	-0.01	0.04	-0.15	-0.23	-0.48	-0.58*
No. days with consolidated rest-activity cycle (≥80%)	0.56*	0.25	-0.13	-0.19	-0.26	-0.11	-0.47	-0.54*	-0.67**

*: $p<0.05$; **: $p<0.01$

GCS - Glasgow Coma Scale, TIL – Therapy Intensity Level, ICP – intracranial pressure, ICU – intensive care unit, DRS – Disability Rating Scale

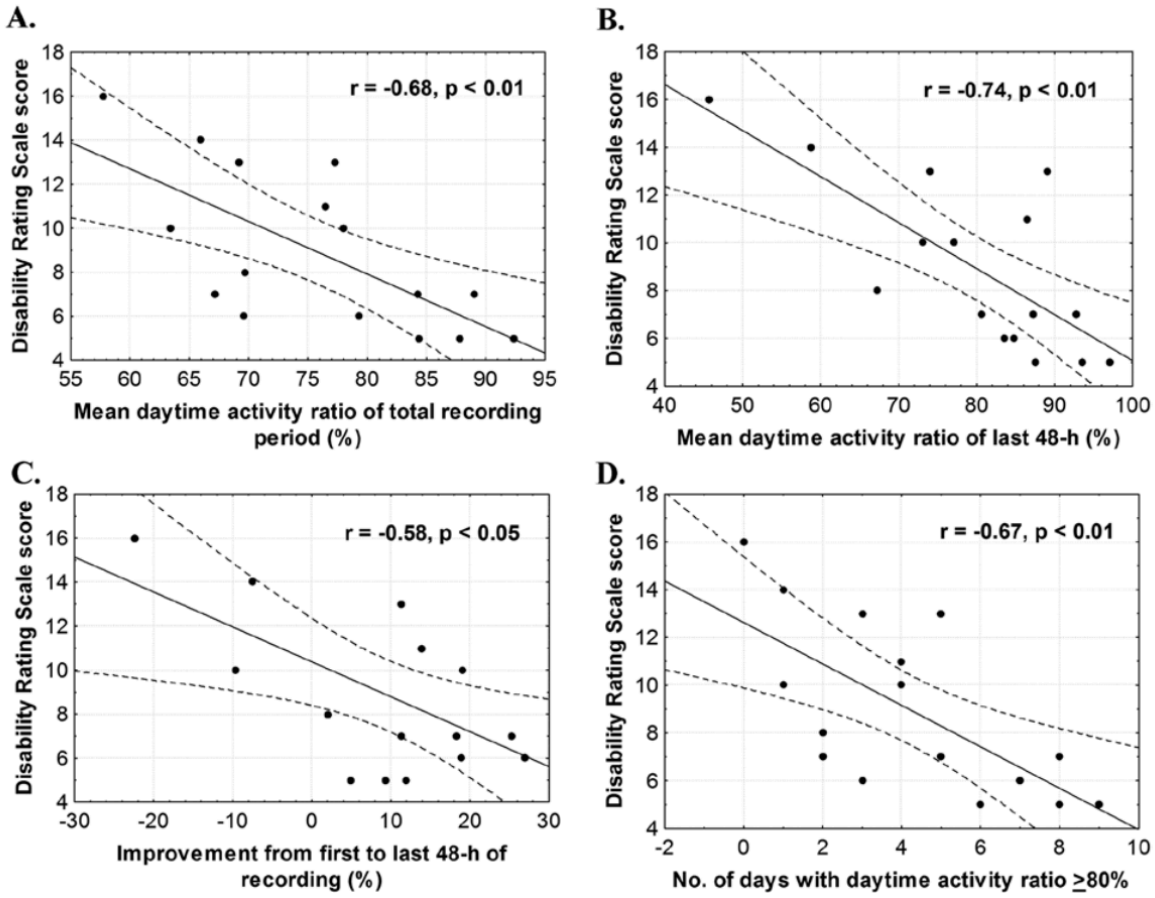

Figure 3: Illustration of the significant Pearson correlations between the daytime activity ratio and the score on the Disability Rating Scale (DRS) at discharge. 3A. Negative correlation between the daytime activity ratio averaged over the total recording period and the DRS at discharge. 3B. Negative correlation between the daytime activity ratio averaged over the last 48-h of actigraphy recording and the DRS at discharge. 3C. Negative correlation between the percentage of improvement between the first and last 48-h of recording and the DRS at discharge. 3D. Negative correlation between the number of days with a daytime activity ratio ≥80% and the DRS at discharge. Dashed lines represent the 95% confidence intervals.

Table 3 shows the actigraphy results of patient sub-groups divided according to presence or absence of PTA at hospital discharge. Patients no longer in PTA at discharge had significantly higher daytime activity ratio over the total recording period, higher daytime activity ratio in the last 48-h of recording, greater improvement between the first and last 48-h of recording, and more days of consolidated rest-activity cycle (t and p values detailed in

Table 3). Moreover, the only actigraphy measure that did not differ between groups was the daytime activity ratio of the first 48-h of recording. Therefore, the 2 sub-groups were very similar during the first 48-h of recording, however the patients no longer in PTA at discharge showed significantly greater improvement over time. The ANOVA performed over the 10 days of recording confirmed a significant evolution of consolidation of the rest-activity cycle in patients no longer in PTA at discharge [$F(1,6)=8.85$, $p<0.05$]; this evolution was not significant in patients still in PTA at discharge [$F(1,4)=2.61$, $p=0.18$]. When compared on variables of injury severity and outcome, patients still in PTA at discharge had a longer ICU stay (33.5±6.9 vs. 17.9±16.2 days, $t(14)=2.2$, $p<0.05$), a longer hospital stay (61.7±13.8 vs. 34.1±17.7 days, $t(14)=3.7$, $p<0.01$) and a higher DRS score at discharge (12.4±2.5 vs. 6.7±1.8, $t(13)=5$, $p<0.001$).

Table 3. Association between PTA upon discharge and variables of actigraphy compared between sub-groups of patients with (n=6) and without (n=10) post-traumatic amnesia (PTA) at discharge.

Actigraphy variables	PTA at discharge	No PTA at discharge	t-value	p value
Mean daytime ratio for total recording period (%)	68.6 ± 8.0 [57.7,79.0] [§]	80.01 ± 8.97 [67.15,92.34]	-2.6	.022*
Mean daytime ratio for first 48-h (%)	69.3 ± 9.3 [58.0,82.8]	71.79 ± 10.86 [56.50,87.74]	-0.5	.645
Mean daytime ratio for last 48-h (%)	69.6± 15.2 [45.7,89.0]	86.09 ± 8.30 [67.20,97.06]	-2.8	.013*
Improvement of daytime ratio between first and last 48-h (%)	0.4 ± 16.0 [-22.4,19.1]	14.30 ± 8.13 [2.06,26.97]	-2.3	.034*
No. days with consolidated rest-activity cycle (≥80%)	2.3 ± 2.0 [1,5]	5.40 ± 2.60 [2,9]	-2.5	.026*

[§]: Ranges; *: $p<0.05$

Discussion

Poor circadian rest-activity cycle consolidation in acute TBI

Our aim was to characterize the quality and evolution of the rest-activity cycle in acute moderate to severe TBI. We found that rest-activity cycle consolidation was predominantly absent during the first days of actigraphy recording, but globally improved over time during their hospital stay. In fact, when a daytime activity ratio ≥80% was used as a threshold for adequate rest-activity cycle consolidation, consolidation was observed for 28.1% of days in the first 48h, while this percentage increased to 68.8% the last 48h of recording. Two distinct patterns of evolution of the rest-activity cycle were observed: 50% of patients showed an absence of rest-activity cycle consolidation throughout the recording period, while the other 50% had reached a daytime activity ratio ≥80% by the last 48-h of recording.

This absence of rest-activity cycle consolidation is likely associated with fragmentation of both sleep and wake episodes. The number of minutes moving was similar during the first and last 48-h of recording and covered nearly 60% of the day. This observation suggests that the absence of consolidation of the rest-activity cycle was not caused by constant rest, but rather reflects the dispersion of activity bouts all over the 24-h. Since actigraphy has not been validated with polysomnography in this bed-ridden population, it cannot be concluded that the absence of activity represents sleep. However, the presence of activity over the 24-h shows that the rest episodes were highly fragmented by intervening activity bouts, thereby possibly preventing the occurrence of any deep sleep episodes of significant duration.

Association between consolidation of the rest-activity cycle, injury severity and recovery

This study revealed significant associations between TBI severity and the rest-activity cycle. More precisely, less severe TBI was associated with greater improvement between the first and last 48-h of activity recording, and with more days of consolidated rest-activity cycle. Shorter lengths of ICU and hospital stay were associated with a higher average daytime activity ratio over all days of recording, and with a higher average daytime activity ratio in the last 48-h of recording. A shorter duration of total hospital stay was also associated with more

days of consolidation of the rest-activity cycle. Although these results will need to be confirmed in a larger sample, they do point to the role of TBI in the persistence of rest-activity cycle disturbances in acute care.

Our study also revealed significant associations between the rest-activity cycle and outcome at hospital discharge. First, we found that patients no longer in PTA at discharge had better rest-activity consolidation over the total recording period and during the last 48-h of recording, had greater improvement of rest-activity consolidation between the first and last 48-h of recording, and had more days of consolidated rest-activity cycle. Moreover, patients with a more rapid return to a consolidated rest-activity cycle over the 10 days of actigraphy were more likely to clear PTA before hospital discharge. Similar results were also found for disability severity, where patients with better rest-activity cycle consolidation and with greater improvement of cycle consolidation showed lower DRS scores at discharge. These associations between rest-activity cycle consolidation and outcome at hospital discharge were observed even if there was an average delay of 13.9 ± 13 days between the last day of recording and hospital discharge, suggesting that the degree of rest-activity cycle consolidation is associated with cerebral recovery and may predict short-term outcome in acute TBI.

An association between sleep and PTA has already been reported among 14 TBI patients in a rehabilitation setting, where patients who had cleared PTA before admission to the rehabilitation centre showed better sleep efficiency, as measured with wrist actigraphy, compared to patients with ongoing PTA.[11] These results point to a close link between sleep consolidation and cognitive functioning, but it is currently difficult to establish a causal relationship in the context of TBI. In fact, considering that sleep has a crucial role in memory consolidation, learning, cerebral plasticity, and neurogenesis,[38-39] sleep fragmentation may, probably by preventing the apparition of deep sleep,[22] impede PTA resolution in patients with TBI. However, it is also possible that structural brain damage simultaneously affects memory and sleep, either through dissociated or common pathways. In the latter case, PTA and rest-activity cycle consolidation, or increased sleep efficiency, may occur simultaneously when brain recovers sufficiently to allow both sleep consolidation and PTA resolution.

Possible causes of the lack of consolidation of the rest-activity cycle

The rest-activity cycle is the most easily observed manifestation of endogenous circadian rhythms.[40] The main circadian biological clock, located in the hypothalamus, generates an oscillation of about 24-h that is normally synchronized to the environmental 24-h day, mainly by exposure to the light-dark cycle, but also by regular timing of social contacts, food intake, etc. In humans, the endogenous circadian clock synchronizes physiological, cognitive and behavioural functions such that those associated with activity happen in the daytime while those associated with rest and sleep occur during the night. Circadian disruption occurs when the main biological clock is not synchronized to the 24-h day and/or when it produces a circadian signal too weak to entrain properly the peripheral clocks located in other regions of the brain and body. The first manifestation of circadian disruption is a decreased consolidation and abnormal timing of the rest-activity cycle, and sleep-wake disorders.[41] The ICU is devoid of regular day-night environmental cues, and the ICU stay is associated with severe medical conditions, analgesia and sedation, all known to affect the temporal structure of circadian rhythms and induce circadian desynchrony.[42-43] The fact that there was no correlation between the number of minutes moving per 24-h and the daytime activity ratio in our patients suggests that the daytime activity ratio was not affected by the quantity of activity, but rather measures the circadian organization of activity and rest periods. Although a low daytime activity ratio could also signal a poor timing of consolidated sleep, such as sleep that occurs with a phase advance (e.g., 19:00 to 3:00) or phase delay (e.g., 3:00 to 11:00), visual inspection of actigraphy data suggests that it was not the case of our patients. When patients had a low daytime activity ratio, they rather had fragmented rest and activity dispersed over 24-h. The concurrent measure of robust circadian markers would be necessary to assess the contribution of circadian disruption to the decreased consolidation of the rest-activity cycle in TBI patients.

TBI itself could be responsible, at least in part, for altered circadian rest-activity rhythm. In a previous study, ICU patients with neurological injury showed more severe circadian rhythm disturbances than patients without neurological injury.[44] Due to our small sample size, it is currently not possible to understand the role of specific TBI characteristics,

such as location of brain lesions, however we can hypothesize that patients with brain injury in hypothalamic regions, for example, will be at greater risk of circadian rhythm disturbances.

Actigraphy in a hospital setting

It has been shown that actigraphy underestimates wakefulness,[45-47] particularly when subjects lie immobile in bed in a nonsleeping state,[48] and especially among a critically ill population.[49] Therefore, the already short rest episodes observed on actigraphy recordings probably overestimates the quantity of sleep our patients actually experienced.

A daytime activity ratio ≥80% was used to designate the presence of rest-activity cycle consolidation. Since subjects frequently reached a ratio above 85-90% in the last days of recording, 80% was a conservative threshold to denote an acceptable rest-activity rhythm. The significant association of this threshold of consolidation with GCS and outcome supports its usefulness as a measure of rhythmicity within this patient population and setting.

Study limitations

Although the rest-activity cycle has been strongly correlated with the sleep-wake cycle among healthy subjects,[23] such an association has not been formally validated among subjects hospitalized in critical care. Due to its small number of patients, our study serves as an exploratory initiative aiming to understand the nature of sleep and rest-activity cycle disturbances in the acute phase of moderate-severe TBI. Therefore, the use of actigraphy and the parameters chosen to analyse the data collected during the acute phase of the moderate-severe TBI population will need to be formally validated in a larger cohort and compared with concurrent polysomnography recordings.

Conclusions

This study is the first initiative aiming to understand the nature and evolution of sleep and circadian rhythm disturbances in acute moderate to severe TBI. Despite the difficulties encountered in a hospital setting, our study demonstrates that is it possible to effectively use actigraphy to assess the rest-activity cycle, even in acute care. Although a larger sample will be needed to perform a formal validation, the associations found between the rest-activity

cycle and variables of outcome at hospital discharge suggest that actigraphy could become an important clinical tool for the monitoring and prognosis of TBI patients.

Our data revealed severe disturbances of the rest-activity cycle in the acute phase of moderate-severe TBI. Such disturbances had not previously been systematically documented and quantified for an extended period of time among this population. The lack of consolidation of the rest-activity cycle was associated with rest episodes of very short duration, not compatible with the occurrence of the deepest stages of sleep. Considering the role of sleep in cerebral plasticity and neurogenesis, sleep disturbances in acute TBI may impede short and long-term cognitive and neuronal recovery in this population. Efforts to restore circadian synchrony while patients are hospitalized may help to prevent the development of chronic sleep and wake disturbances and to optimise recovery.

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Competing interests None.

Ethics approval Ethics approval was provided by the Ethics Committee of Hôpital du Sacré-Coeur de Montréal.

Provenance and peer review Not commissioned; externally peer reviewed

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Supplementary note

Results

Clinical characteristics of the patients

On average, patients spent 23.8±15.3 days in the ICU and were hospitalized for a total of 41.8±22.7 days. Nine patients (56.3%) had elevated ICP: of those 9 patients, elevated ICP was present for 10.1±5.0 days. Five patients did not have their ICP monitored, either because criteria for insertion were not met or because it was not clinically indicated.

Of all 85 days of recording in the regular units, sedative, analgesic, antiepileptic or neuroleptic medications were given on a total of 16 days to 6 different patients. Two patients received sedatives: one patient (patient #1) received a 1mg dose of midazolam per day for two days, while another (patient #2) received a single 1 mg dose of lorazepam. Four patients (patients #2, 10, 11 and 15) received an average daily dose of 2.65±1.27 mg of hydromorphone for 2.5±1 days. One patient (patient #5) received a single 200 mg dose of phenytoin (antiepileptic). Finally, one patient (patient #2) received neuroleptic medication: a single 1mg dose of haloperidol and 4 daily 15 mg doses of olanzapine.

Actigraphy recording

Most patients (12/16) were hospitalized in the ICU at the beginning of actigraphy recording. The 4 other patients started the actigraphy recording 1 (patients #10 and 16), 4 (patient #14) and 18 (patient #11) days after ICU discharge. Ten days of actigraphy were recorded for 12 of the 16 patients. Three patients (patients #9, 15 and 16) recovered rapidly and left the hospital after only 6, 8, and 6 days of actigraphy recording respectively. Another patient (patient #11) wore the actigraph 8 full days, though the days were non-consecutive due to discomfort and medical interventions, as were the ten days of recording for Patient 6. In both cases of non-consecutive recordings, there was no difference in the rest-activity cycle consolidation between the beginning and the end of the interruption.

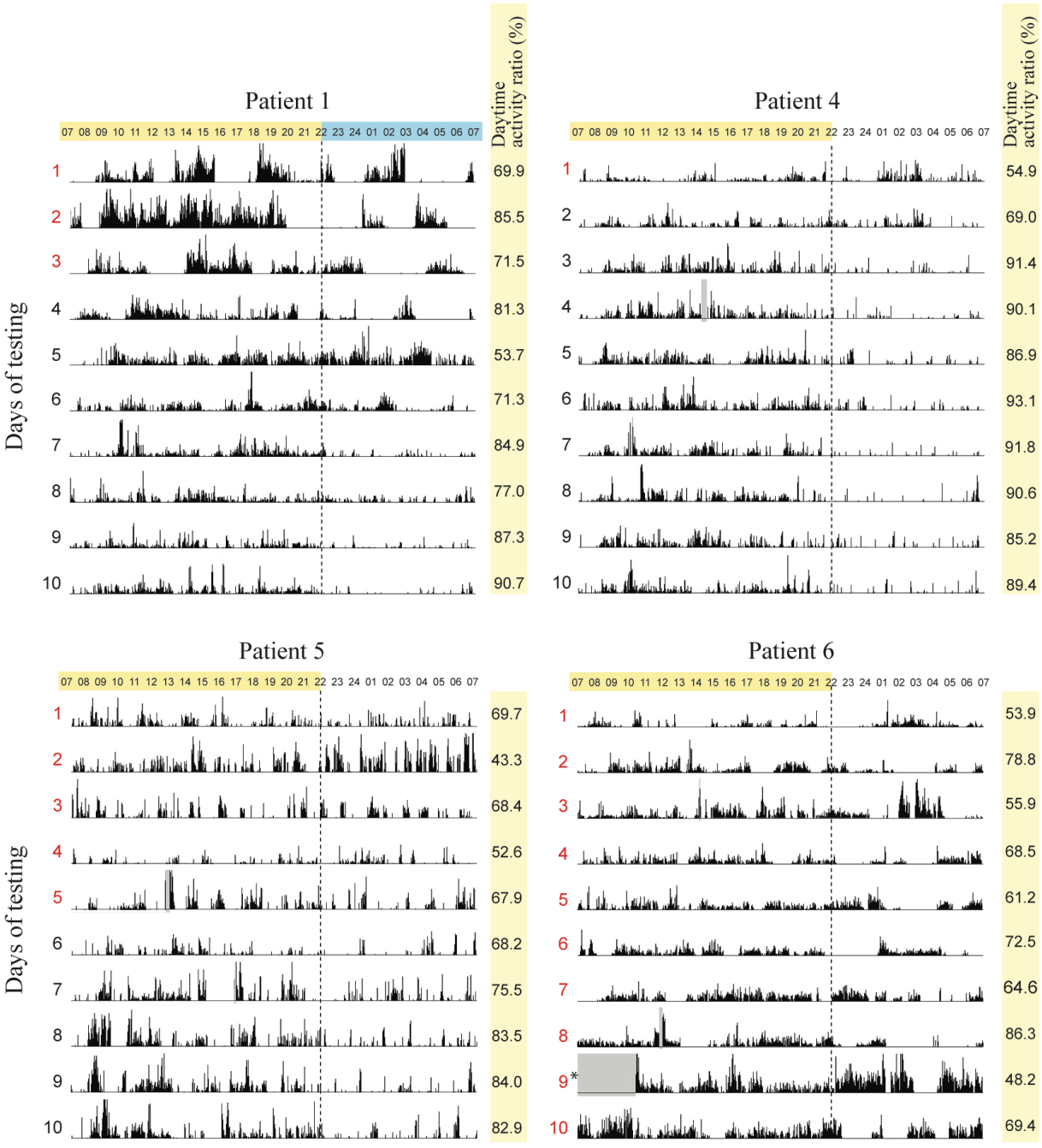
We carried out t-tests for independent samples in order to compare patients whose first 48-h of recording was in the ICU (n = 9) to those who were transferred to regular units prior to

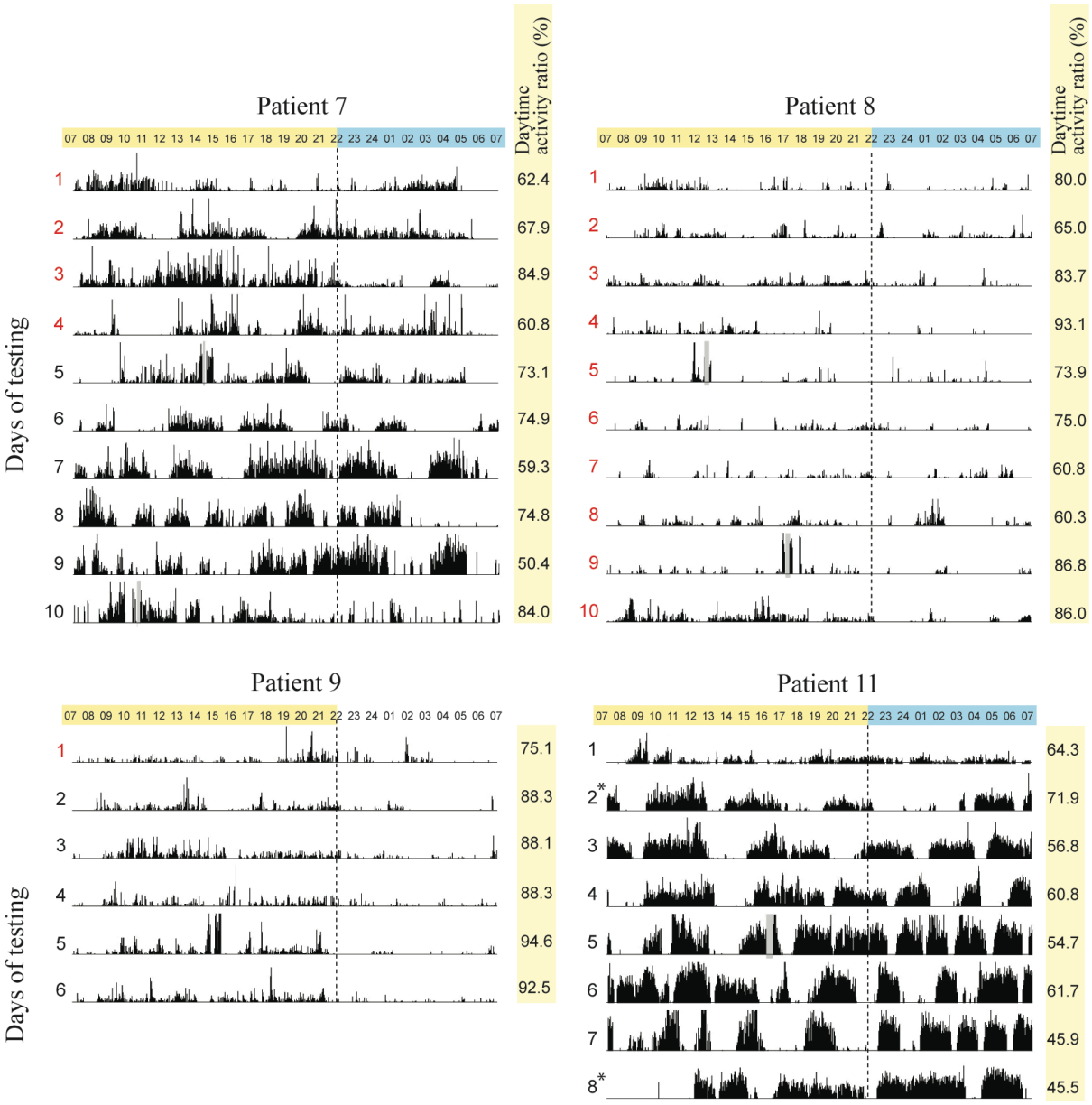
or during the first 48-h of actigraphy recording (n = 7). There was no significant difference between these groups on any of the 5 actigraphy variables (p-values between 0.16 and 0.88). The fact that there was no significant difference on actigraphy variables between patients whose first 48-h of recording was in the ICU and those who were transferred to regular units prior to or during the first 48-h of actigraphy recording suggests that our actigraphy results were not influenced by the location of the patients at the start of actigraphy recording.

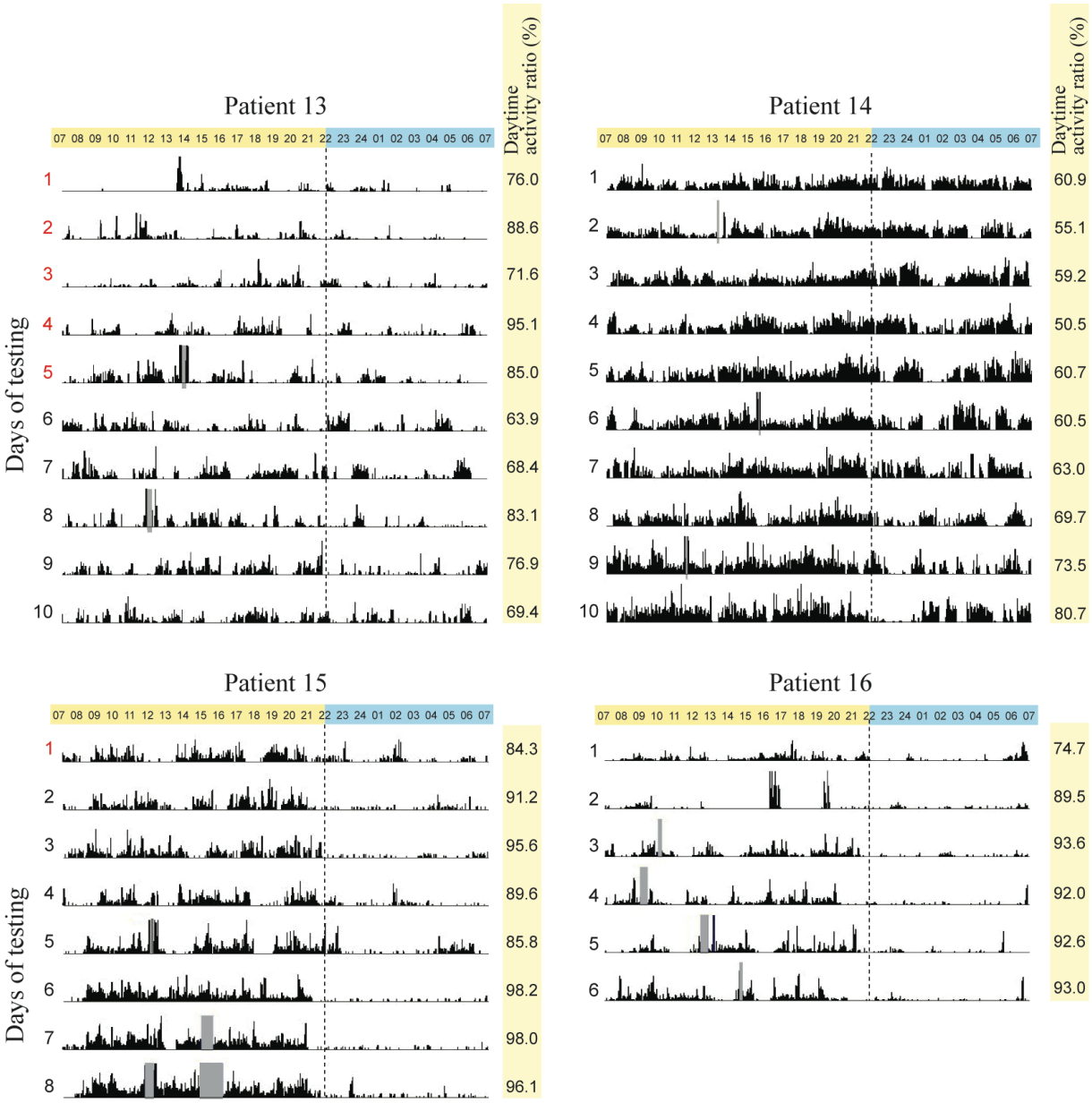
Figure Legends for Supplementary Materials

Supplementary Figures A1, A2, and A3. Individual actigraphy recordings

Actigraphy results from all patients, except those already presented in Figure 1. Each of the 10 days is represented on a separate line, from 07:00 to 07:00 h. The number of activity counts for each minute of recording is illustrated by vertical dark lines. The same scale of 0 to 1000 activity counts was used for all subjects and all days of recording. Hours included in the daytime period (07:00 to 22:00) are shown in yellow and those included in the nighttime period (22:00 to 07:00) are in blue at the top of each graph. The daily daytime activity ratio (%) is indicated on the right side of each actigram. Periods with no recording are represented by grey rectangles. Days where the recording took place in ICU are in red. The start of a non-consecutive day of recording is labelled by an asterisk.


Patient 1
Patient 4
Patient 5
Patient 6
Days of testing
Daytime activity ratio (%)
07 08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 01 02 03 04 05 06 07
1 69.9
2 85.5
3 71.5
4 81.3
5 53.7
6 71.3
7 84.9
8 77.0
9 87.3
10 90.7
1 54.9
2 69.0
3 91.4
4 90.1
5 86.9
6 93.1
7 91.8
8 90.6
9 85.2
10 89.4
1 69.7
2 43.3
3 68.4
4 52.6
5 67.9
6 68.2
7 75.5
8 83.5
9 84.0
10 82.9
1 53.9
2 78.8
3 55.9
4 68.5
5 61.2
6 72.5
7 64.6
8 86.3
9* 48.2
10 69.4


Patient 7
Patient 8
Patient 9
Patient 11
Days of testing
Daytime activity ratio (%)
07 08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 01 02 03 04 05 06 07
1 62.4
2 67.9
3 84.9
4 60.8
5 73.1
6 74.9
7 59.3
8 74.8
9 50.4
10 84.0
1 80.0
2 65.0
3 83.7
4 93.1
5 73.9
6 75.0
7 60.8
8 60.3
9 86.8
10 86.0
1 75.1
2 88.3
3 88.1
4 88.3
5 94.6
6 92.5
1 64.3
2* 71.9
3 56.8
4 60.8
5 54.7
6 61.7
7 45.9
8* 45.5


Patient 13
Patient 14
Patient 15
Patient 16
Days of testing
Daytime activity ratio (%)
07 08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 01 02 03 04 05 06 07
1 76.0
2 88.6
3 71.6
4 95.1
5 85.0
6 63.9
7 68.4
8 83.1
9 76.9
10 69.4
1 60.9
2 55.1
3 59.2
4 50.5
5 60.7
6 60.5
7 63.0
8 69.7
9 73.5
10 80.7
1 84.3
2 91.2
3 95.6
4 89.6
5 85.8
6 98.2
7 98.0
8 96.1
1 74.7
2 89.5
3 93.6
4 92.0
5 92.6
6 93.0

Supplementary Table A1. Total fraction of time moving (%) as scored by the Actiware program with a threshold of ≥10 activity counts per minute.

	Fraction of time moving per 24-h (%)									
Patient	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**
1	57.6%	65.4%	64.9%	58.7%	78.1%	61.7%	61.5%	70.0%	60.3%	57.9%
2	51.6%	69.3%	51.0%	69.8%	69.4%	50.5%	68.1%	69.6%	60.8%	52.1%
3	39.9%	80.4%	62.2%	73.6%	60.2%	76.1%	41.4%	67.3%	48.5%	74.2%
4	55.9%	56.6%	53.1%	57.6%	55.4%	60.7%	50.5%	51.9%	54.5%	52.9%
5	53.7%	60.0%	42.2%	36.4%	45.3%	35.0%	50.8%	49.2%	49.5%	52.2%
6	59.5%	66.2%	74.4%	68.0%	72.7%	65.2%	69.9%	64.9%	74.2%	73.6%
7	62.6%	78.4%	78.8%	64.5%	64.3%	52.1%	72.5%	58.5%	65.3%	52.4%
8	41.6%	54.2%	58.4%	27.3%	22.4%	29.1%	35.6%	44.6%	27.2%	61.9%
9	41.9%	44.4%	57.8%	55.1%	49.4%	55.8%	---	---	---	---
10	53.7%	55.8%	54.7%	31.9%	50.9%	52.5%	54.2%	62.4%	55.6%	58.2%
11	81.1%	61.9%	77.8%	71.9%	76.3%	77.2%	66.3%	67.8%	---	---
12	66.8%	69.8%	71.8%	55.9%	68.4%	74.4%	64.8%	57.1%	75.9%	60.1%
13	27.1%	34.7%	37.8%	40.5%	45.8%	50.5%	52.2%	38.0%	47.8%	49.2%
14	90.4%	87.1%	87.0%	89.0%	84.4%	85.1%	84.4%	85.3%	77.4%	81.9%
15	55.6%	49.8%	56.5%	51.0%	59.1%	59.3%	57.7%	65.1%	---	---
16	44.4%	20.8%	46.5%	44.0%	46.9%	47.6%	---	---	---	---

Article 4: Evolution of severe sleep-wake cycle disturbances following traumatic brain injury: A case study in both acute and subacute phases post-injury

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Contribution: For this article, I recruited the patient, acquired the data, participated in the analysis and interpretation of the data, drafted and critically revised the manuscript.

ABSTRACT

Background: Sleep-wake disturbances are frequently reported following traumatic brain injury (TBI), but they remain poorly documented in the acute stage of injury. Little is known about their origin and evolution.

Case presentation: This study presents the case of a patient in the acute phase of a severe TBI. The patient was injured at work when falling 12 m into a mine and was hospitalized in the regular units of a level 1 trauma centre. From days 31 to 45 post-injury, once he had reached a level of medical stability and continuous analgosedation had been ceased, his sleep-wake cycle was monitored using actigraphy. Results showed significant sleep-wake disturbances and severe sleep deprivation. Indeed, the patient had an average nighttime sleep efficiency of 32.7 ± 15.4%, and only an average of 4.8 ± 1.3 hrs of sleep per 24-hr period. After hospital discharge to the rehabilitation centre, where he remained for 5 days, the patient was then readmitted to the same neurological unit for paranoid delusions. During his second hospital stay, actigraphy recordings resumed from days 69 to 75 post-injury. A major improvement in his sleep-wake cycle was observed during this second stay, with an average nighttime sleep efficiency of 96.3 ± 0.9% and an average of 14.1 ± 0.9 hrs of sleep per 24-hr period.

Conclusion: This study is the first to extensively document sleep-wake disturbances in both the acute and subacute phases of severe TBI. Results show that prolonged sleep deprivation can be observed after TBI, and suggests that the hospital environment only partially contributes to sleep-wake disturbances. Continuous actigraphic monitoring may prove to be a useful clinical tool in the monitoring of patients hospitalized after severe TBI in order to detect severe sleep deprivation requiring intervention. The direct impact of sleep-wake disturbances on physiological and cognitive recovery is not well understood within this population, but is worth investigating and improving.

Keywords: traumatic brain injury, sleep disorders, actigraphy, circadian rhythms, neurocritical care, neuropsychiatry

BACKGROUND

Chronic sleep-wake disturbances, such as insomnia and hypersomnia, are among the most widely-reported sequelea following traumatic brain injury (TBI), and have been documented across all levels of TBI severity, until several years post-injury [1]. Less attention has been paid to sleep-wake disturbances that occur in the first weeks post-injury. This might be explained by the challenges of performing sleep studies in an acute care setting, where most patients are confused and are not able to evaluate their own sleep quality.

A first group of studies that aimed at documenting sleep disturbances in post-acute TBI used nurse observations in individuals admitted to rehabilitation centres. One study found that of 31 patients, 21 (68%) had two or more hours awake during the night [2]. Similarly, a second study showed that mild to severe sleep disturbances were present among 84% of TBI patients upon rehabilitation admission, and persisted for 66% of patients one month post-injury [3]. This research group used item one of the Delirium Rating Scale-Revised-98 to classify the severity of sleep-wake cycle disturbance as none, mild, moderate, or severe.

With the aim of using more objective methods to document the sleep-wake cycle of patients in the acute and post-acute phases of moderate-severe TBI, a second group of studies used actigraphy, which measures physical motion over time, to derive a rest-activity pattern. It has been shown that the rest-activity cycle measured with actigraphy strongly correlates with the sleep-wake cycle [4]; consequently, the rest-activity cycle derived from actigraphy is often referred to as the sleep-wake cycle. Within this context, a study carried out during early rehabilitation found that 11 of 14 moderate-severe TBI patients had an average 1-week sleep efficiency lower than 63%, pointing to pervasive sleep-wake disturbances [5]. More recently, Gardani and colleagues evaluated 30 patients with chronic severe TBI in an inpatient rehabilitation setting, using actigraphy and self-report measures [6]. The authors found that 67% of patients had sleep-wake cycle disturbances, 50% of which met diagnostic criteria for a sleep disorder, according to the International Classification of Sleep Disorders (2nd edition). Additionally, we recently used 10-day actigraphy recordings with 16 TBI patients hospitalized in a level 1 trauma centre in order to quantify the clustering of activity during the daytime and

of rest during the nighttime as an estimate of their sleep-wake cycle consolidation. We found that patients had a poor sleep-wake cycle consolidation, which gradually improved over time [7]. However, using a threshold of ≥80% of all 24-h activity occurring in the daytime, only half of the patients reached an acceptable sleep-wake cycle consolidation during the recording period. Patients who reached an acceptable sleep-wake cycle consolidation (≥80%) were more likely to emerge from posttraumatic amnesia (PTA) and to have lower disability at hospital discharge.

Despite the high prevalence of acute and subacute sleep-wake disturbances in TBI patients, their aetiology is not well understood. Furthermore, no study has yet documented the sleep-wake cycle during both the acute and subacute phases of TBI, while the patient was hospitalized in the same environment, which is of interest given that the hospital environment itself may be a contributing factor to disturbed sleep and wake. The aim of this article is to document the case of one of our TBI patients from the abovementioned study [7], who suffered severe sleep-wake cycle disturbances during his acute hospital stay. Since this patient was readmitted five days post-discharge and wore the actigraph during his second hospital stay, his case enables us to document the evolution of his sleep-wake cycle over time and to juxtapose the sleep-wake cycle recorded during two different hospital stays in a similar environment, during the acute (measured days 31-45 days post-injury, starting 4 days following discharge from the ICU) and subacute (measured days 69-75 post-injury) phases.

CASE PRESENTATION

Biographical History

LC is a 43-year-old right-handed Caucasian male, who resides with his spouse and two teenage daughters. Prior to his injury, LC was in good physical health, had no previous history of TBI, chronic disease, drug or alcohol abuse, or psychiatric, neurological or sleep disorders.

Injury

LC suffered a severe TBI when falling 12 m into a well of a mine during work hours. LC lost consciousness, had an initial Glasgow Coma Scale (GCS) score of 6 [8], and was

immediately transported by ambulance to the nearest hospital, located approximately 160 km from the site of injury. Upon arrival at the regional hospital, his GCS score was 8. Following clinical evaluation, he was immediately transferred by ambulance to a level 1 trauma centre located over 500 km from the site of injury. A level 1 trauma centre provides the highest level of surgical and specialized care to trauma patients, is comprised of a full range of equipment and specialists dedicated to the care of patients having suffered TBI or orthopaedic injuries, and generally receives the most severe cases within a large geographical area.

First admission

LC was admitted to the trauma centre approximately 15 hours after injury. His GCS score was 3 (intubated) upon admission to the Emergency Room, and he was taken to the Intensive Care Unit (ICU). A computed tomography (CT) scan revealed diffuse subarachnoid haemorrhage in the left hemisphere, left parieto-occipital subdural hematoma, right temporal intraparenchymal hematoma (3 cm), intrapeduncular, left intrapontine and temporal petechiae, as well as left frontal and right parieto-occipital contusions (see Figure 1). His Marshall score was 2 [9], and his Rotterdam score was also 2 [10]. LC also suffered multiple facial fractures, a C4 cervical fracture, D6, D8 and D12 thoracic fractures, a fracture of the left 9^{th} rib, a spleen laceration, a pseudo-aneurysm of the aorta (4 mm), and a left pneumothorax.

LC was hospitalized in the ICU for 27 days. Overall, he was under continuous sedation for 16 days, during which time he received an average daily dose of 4.79 ± 2.33 g of propofol, and 6.2 ± 2.2 mg of fentanyl. During 11 of those 16 days of continuous sedation, LC also received an average daily dose of 0.55 ± 0.25 mg of midazolam. He was intubated 25 days, had elevated intracranial pressure (≥ 20 mmHg) during 13 days with a peak at 46.3 ± 14 mmHg, and had on average 7.3 ± 14 episodes of elevated intracranial pressure per day.

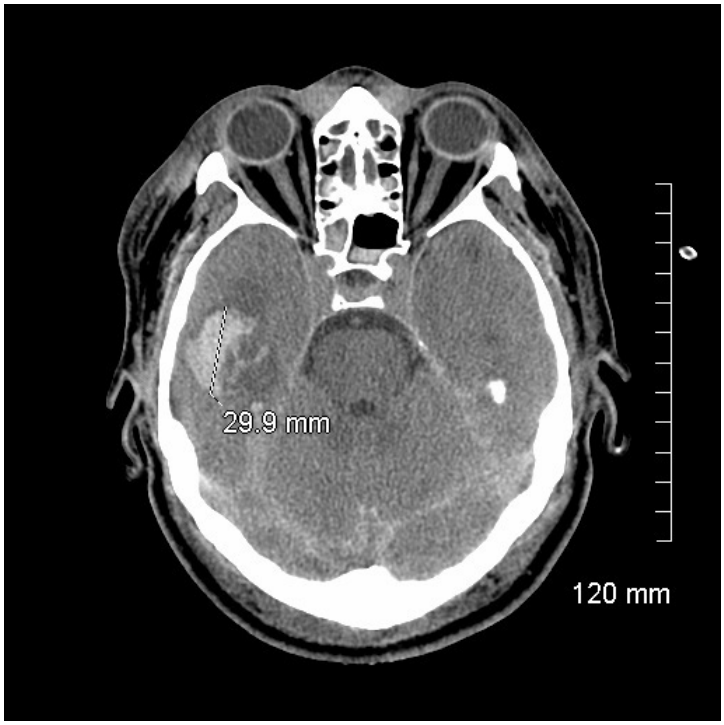

Figure 1. CT scan at admission. Initial CT scan taken at admission, showing right temporal parenchymal hematoma, diffuse subarachnoid haemorrhage in the left hemisphere, and diffuse axonal injury.

LC began responding to simple orders 15 days post-injury, when sedation was interrupted briefly to assess his level of response, and he opened his eyes 16 days post-injury. Subsequent to ICU discharge (27 days post-injury), LC was transferred to a six-patient room in the neurological ward. LC suffered akinetic mutism and moderate-severe oropharyngeal dysphagia throughout the first 46 days post-injury, and he then began to whisper, reaching a normal voice level 2 days prior to hospital discharge. At this point, he could walk unassisted and was fully functional in all bed and chair transfers.

LC was discharged from the trauma centre 55 days post-injury and admitted to a 200-bed inpatient rehabilitation centre, specialized in the care of TBI, orthopaedic injuries and neurology. Within the 72 hours prior to hospital discharge, LC had a score of 10 out of 29 on the Disability Rating Scale [11], reflecting confused communication ability, partial cognitive disability for grooming, a markedly dependent level of functioning (mental, emotional, or

social), and a non-competitive level of employability. The neurological examination carried out 8 days prior to hospital discharge (47 days post-injury) yielded a score of 5 on the Neurological Outcome Scale for Traumatic Brain Injury without the supplemental items [12]. Deficits arose when LC was asked the current month and his age, which he both answered incorrectly, as well as when asked to identify odours or name objects for stimulus cards. This could either be the result of mild to moderate aphasia, or PTA, which would account for an inability to recall the words associated to various stimuli. Due to persistent akinetic mutism throughout most of the hospitalization period, neuropsychological evaluations were only carried out during the second hospital stay.

Second admission

Five days after his admission to the inpatient rehabilitation centre, LC was readmitted to the trauma centre by ambulance for persecutory paranoid delusion, as per clinical observations at the inpatient rehabilitation centre, and remained hospitalized for 43 days in a two-patient room of the same neurological ward on which he had previously been hospitalized.

During this second hospital stay, LC continuously suffered retrograde and anterograde memory deficits with confabulations, severe temporal and spatial disorientation, verbal desinhibition, distrusting and suspicious behaviour, paranoia, and anosognosia. LC's condition was attributed the diagnosis of post-TBI psychotic disorder. Neuropsychological evaluation carried out on days 87 and 89 post-injury showed severe dysfunctions in all cognitive domains (see Table 1).

LC was discharged 43 days after this second admission (102 days post-injury), and was readmitted to the inpatient rehabilitation centre. The occupational therapy report from LC's final evaluation, carried out 1 week prior to this second discharge, described him as completely dependent for domestic activities of daily living (for timeline of injury and hospital stays, see Figure 2).

Given his lengthy second admission, his psychiatric complications and persistent cognitive and functional sequelea, LC's case does not represent one of typical post-TBI recovery, but rather depicts a slower and complexified recovery process.

Table 1. Scores on Neuropsychological Tests carried out 87 and 89 days post-injury (second hospital stay)

Tests	
Mini-Mental State Examination	17**
Boston Naming Test (abbreviated form of 30 items)	3**
Semantic verbal fluency (*Animal*s *90* s)	
- total (errors)	13 (9)**
Phonological verbal fluency (*P* & *F* 90 s)	
- total (errors)	8 (8)**
Category switching verbal fluency D-KEFS	
- total (errors)	0 (2)**
Writing to dictation	Dysorthographia 6/10
Clock Drawing (Rouleau scoring system)	Conceptual deficits and planning difficulties
Copy of the House	Normal
Mesulam Cancellation task	
- time in s	123**
Trail making test	
- part A (time in s)	78**
- part B (time in s)	215**
Mental Control WMS-III	20*
Longest Digit span forward WMS-IV	4*
Longest Digit span backward WMS-IV	3*
Logical memory (first story) WMS-IV	
- immediate free recall	3**
- delayed free recall	0**
Hopkins verbal learning test	
- total immediate free recall	13**

- delayed free recall	0**
Victoria Stroop test – interference	
- time in s	51**
- errors	5**
Matrix Reasoning WAIS-IV	12*
Key Search BADS	9

BADS: Behavioural Assessment of the Dysexecutive Syndrome ; D-KEFS: Delis–Kaplan Executive Function System ; WAIS: Wechsler Adult Intelligence Scale ; WMS: Wechsler Memory Scale

** ≥ 1 ≤ 2 standard deviations away from expected mean for age and/or years of education and/or gender, according to the standards of each test*

*** > 2 standard deviations away from expected mean for age and/or years of education and/or gender, according to the standards of each test*

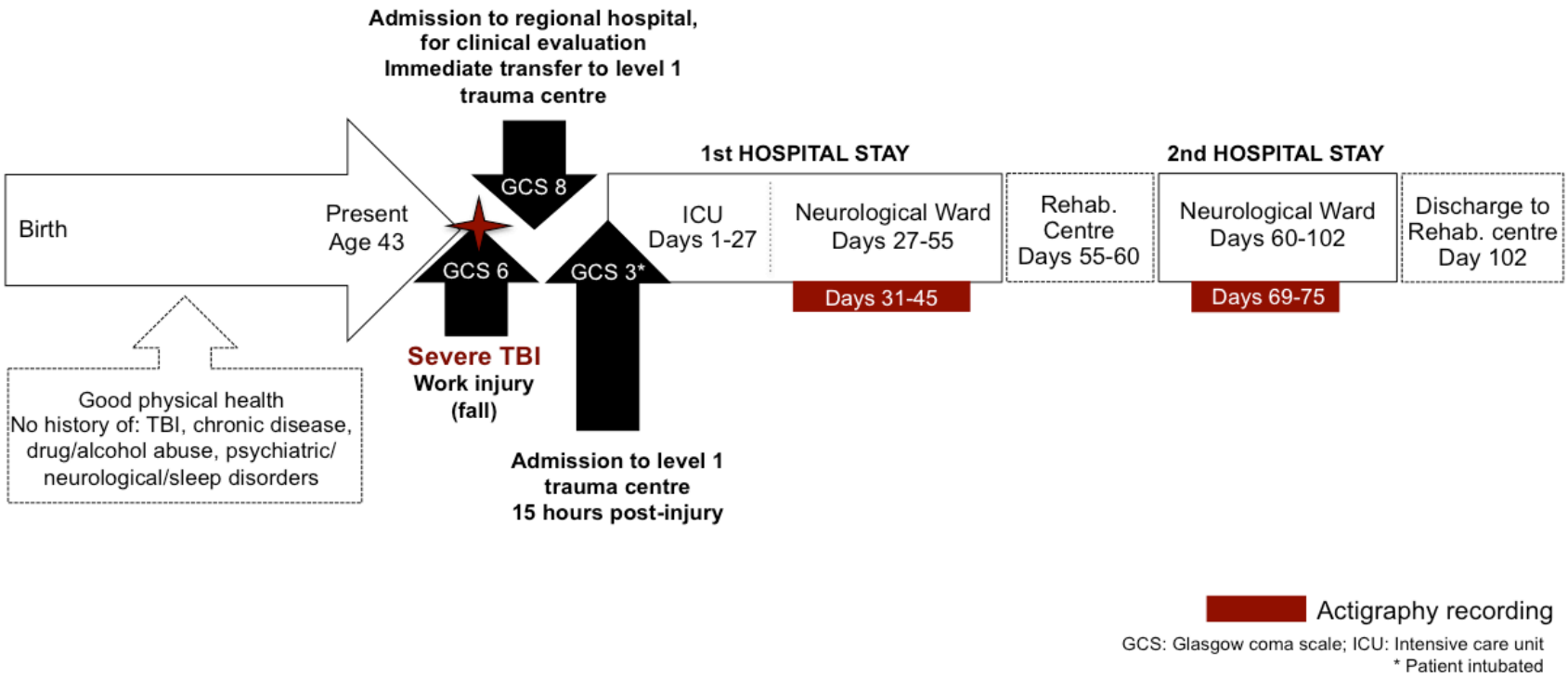

Figure 2. Timeline of injury, hospital stays and actigraphy. Timeline of relevant injury information, admissions and transfers, detailing the first and second hospital stays in the level 1 trauma centre, during which actigraphy monitoring took place.

METHODS

Actigraphy protocol

LC was recruited as part of a larger longitudinal study taking place at *Hôpital du Sacré-Coeur de Montréal*, which was approved by the hospital ethics committee. Consent for participation was obtained from LC's spouse, since he was unable to provide informed consent on his own.

LC wore a wrist actigraph on his non-dominant (left) arm during his first and second hospital stays (Actiwatch-2 during the first stay, and Actiwatch Spectrum during the second stay; MiniMitter Philips Healthcare, Andover, MA, USA). The actigraph is a small, watch-like device that contains an accelerometer, which records physical motion in all directions with a sensitivity of 0.05 g. Motion is then converted to an electric signal, which is digitally integrated to derive an activity count per 1-min epochs. During the first hospital stay, the actigraphy recording began 31 days following the injury, 4 days after discharge from the ICU. Continuous intravenous or subcutaneous administration of a sedative drug was ceased 11 days prior to the start of actigraphic recording. LC was no longer intubated and had reached a level of medical stability defined by the absence of elevated intracranial pressure, of hemodynamic instability, and of fever or active infections. When the actigraph was installed, LC had also reached a Rancho Los Amigos score of IV, indicative of a confused/agitated state [13]. LC could follow simple commands for motor action inconsistently and with delay, would turn his head when his name was called. Data was acquired for 15 days during hospitalization in the regular unit, during which time he received no sedatives or analgesics. Approximately every 3 days, data were uploaded into dedicated software (Actiware 5.0).

During the second hospital stay, LC wore the actigraph for seven days, beginning 69 days post-injury. During this recording period, LC received a daily dose of 3 mg of lorazepam (1 mg at 8:30 hrs, 17:00 hrs, and 22:00 hrs).

Data analyses

For each day the actigraph was worn, each minute of recording was scored as "sleep" or "wake" using the automatic scoring system of the dedicated software (Actiware 5.0). A particular 1-min epoch was scored as wake by comparing the activity counts of this epoch to those immediately surrounding it. The threshold chosen to score a 1-min epoch as wake was > 20 activity counts per minute. A smaller number yielded to a score of sleep. For each epoch the actigraph was not worn, due to the removal of the actigraph for data downloads or bathing, the epoch was scored as wake since the patient was awake in both contexts.

A sleep bout was defined as a period of 5 or more consecutive epochs scored as sleep by Actiware 5.0. To reduce the artificial fragmentation of rest periods, isolated 1-min epochs scored as wake were manually converted to sleep, similar to the smoothing method suggested by Sitnick et al. [14].

Sleep efficiency was calculated for the nocturnal period (22:00 hrs to 6:59 hrs), and was defined as [(number of epochs scored as sleep / total number of nocturnal epochs)*100].

Sleep-wake cycle consolidation, or the clustering of activity during the daytime and of rest during the nighttime, was estimated with the ratio of daytime activity to total 24-hr activity, as previously described [7]. Briefly, for each 24-hr period, the activity counts were summed separately for daytime (07:00 hrs -21:59 hrs) and nighttime (22:00 hrs - 6:59 hrs) periods. Total 24-hr activity (07:00 hrs - 06:59 hrs) was the sum of the daytime and nighttime periods. The percentage of total 24-hr activity occurring in the daytime was calculated to obtain the daytime activity ratio [daytime activity ratio = (daytime activity/24-hr activity) x100].

Statistical analyses

Descriptive statistics (mean and standard deviation) were computed for the total quantity of sleep per 24-hr period, mean duration of daytime and nighttime sleep bouts ("sleep bout duration"), the nocturnal sleep efficiency, and the daytime activity ratio. Student's t-tests

were carried out to assess differences in these results between the first and second hospital stays.

RESULTS

The actigraphy recordings for the first and second hospital stays are presented in Figure 3. During the first hospital stay, high levels of activity were dispersed throughout 24-hr periods for most of the 15 days of recording, and very brief periods of sleep are observed. As for the second hospital stay, prolonged periods of sleep are observed, mostly during nighttime.

Total quantity of sleep per 24-hr period

During the actigraphy recording of the first hospital stay, LC had an average of 4.8 ± 1.3 hrs of sleep per 24-hr period, which significantly increased to 14.1 ± 0.9 hrs during the second hospital stay ($t(20) = -16.8$, $p < 0.001$) (see Figure 3).

Duration of sleep bouts

During the first hospital stay, sleep bouts had an average duration of 14.9 ± 11.9 min and the longest sleep bout over the 15 days of actigraphy was 97 min (occurring at 22:39 hrs on day 41 post-injury). During the second stay, sleep bouts were on average 38.4 ± 59.0 min, which represents a significant improvement compared to the first hospital stay ($t(400)=-6.2$, $p < 0.001$). The longest sleep bout started at 21:16 hrs on day 72 post-injury and was of 342 min in duration. During the night, averaged sleep bout was significantly longer during the second hospital stay, increasing from 16.6 ± 13.7 min in the first stay to 90.1 ± 88.6 min in the second stay ($t(192) = -9.9$, $p < 0.001$). The average duration of daytime sleep bouts also increased from the first to the second hospital stay, from 12.5 ± 8.3 min to 17.9 ± 17.3 min ($t(206) = -2.9$, $p = 0.005$).

Sleep efficiency

Nocturnal sleep efficiency increased significantly from the first to the second hospital stay (32.7 ± 15.4% vs. 96.3 ± 0.9%, $t(20) = -10.27$, $p < 0.001$).

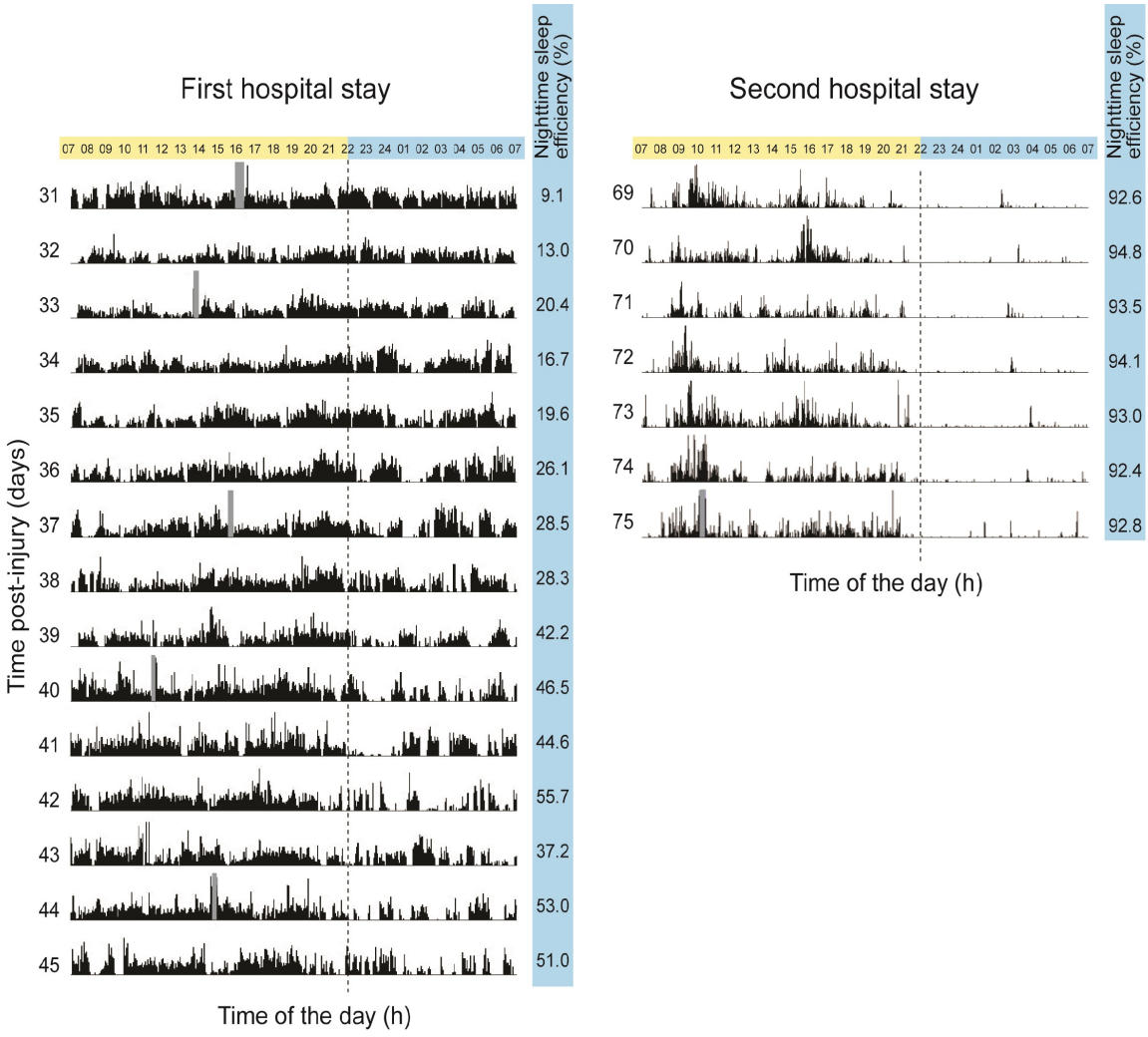

Figure 3. Actigraphy recordings of the first and second hospital stays. Each of the 15 and 7 days of recording are represented on a separate line, from 07:00 to 07:00 hrs. Total activity counts for each minute of recording is illustrated by vertical dark lines. The same scale of 0 to 1000 activity counts was used for all days of both hospital stays. Hours included in the day period (07:00 to 22:00 hrs) are shown in yellow and those included in the night period (22:00 to 07:00 hrs) are in blue at the top of each graph. The number on the left of each day of recording corresponds to the day post-injury. Nocturnal sleep efficiency is indicated on the right column of each actigram.

Rest-activity cycle consolidation

When all days of recording were considered for each hospital stay, daytime activity ratio was 67.8 ± 9.8% during the first hospital stay, and 96.2 ± 1.0% during the second hospital stay, which represents a significant improvement in sleep-wake cycle consolidation ($t20) = -7.53, p < 0.001$)).

CONCLUSIONS

We presented the case of a 43-year old male, who suffered significant sleep-wake disturbances in the first 3 months post-TBI. LC's first hospital stay was marked by an average of only 4.8 ± 1.3 h of sleep per 24-hr for the 15 days of recording. Importantly, this short sleep duration measured with actigraphy probably overestimates the quantity of sleep LC actually experienced. In fact, actigraphy is known to underestimate wakefulness [15-18], particularly when individuals lie in bed immobile but awake [19], and especially among a critically ill population [20]. On the other hand, it is not impossible that LC may have slept during periods of motor activity. However, the recorded levels of activity were very high (see Figure 3), suggesting that if sleep did occur, it was agitated and most likely not restful. Taken together, our results suggest severe and persistent sleep deprivation during the first hospital stay.

Aside from sleep deprivation, this study also suggests that LC suffered severe sleep fragmentation. The patient was not able to stay asleep for a long period of time (mean nighttime sleep bout duration of 16.6 ± 13.7 min), and the mean sleep efficiency of 32.7% measured during the first hospital stay was well below the 85% mark that is generally considered pathological [21]. Altogether, these results demonstrate that sleep was highly disturbed during the first hospital stay. Such a pattern of sleep is most likely incompatible with the deeper sleep stages associated with recovery, although this cannot be confirmed with actigraphy measures alone.

When LC's sleep-wake cycle was re-evaluated during the second hospital stay, LC was able to have significantly longer periods of continuous bouts of sleep, especially during the night. Sleep efficiency improved significantly, increasing from 32.7 ± 15.4% to 96.3 ± 0.9%. Total quantity of sleep per 24-hr period also increased from 4.8 ± 1.3 hrs during the first stay

to 14.1 ± 0.9 hrs during the second stay. Moreover, periods of activity were mainly concentrated during the daytime (daytime activity ratio of 96.2 ± 1.0%), suggesting the presence of a well-consolidated sleep-wake cycle. During the second hospital stay, LC's sleep pattern may be more closely aligned with hypersomnia, which is reported in approximately 10-30% of TBI patients in the post-acute and chronic phases of injury [1,22].

During the actigraphy recording of his first hospital stay, LC was hospitalized in the neurological ward, in a room of 6 patients, and was re-hospitalized in the same ward during his second hospital stay, in a two-patient room. In this ward, hallway lights are generally turned on from 7:00 hrs to 22:00 hrs, and the hospital personnel attempts to keep noise and light levels as low as possible between 22:00 hrs and 7:00 hrs. Considering the significant improvement in sleep-wake cycle consolidation during the second hospital stay, despite LC being hospitalized in the same ward, this case study suggests that the hospital environment cannot entirely account for the sleep deprivation and sleep disturbances occurring in patients with TBI.

Being under the effects of sedatives, analgesics, narcotics, anticonvulsants and antipsychotics may also influence sleep characteristics during acute hospitalization following TBI [23]. Furthermore, withdrawal from such medications may also influence sleep and wake. As LC was discharged from the ICU only 4 days prior to the start of actigraphy, the sleep-wake cycle measured during his first hospital stay may have been influenced by withdrawal from the sedatives and analgesics administered while he was in the ICU. Conversely, improvements in sleep-wake cycle consolidation during the second hospital stay, including longer nighttime sleep periods, could partially be due to the effect of lorazepam, as LC was not taking analgosedative medication during the 15 days of actigraphy recording of his first stay. However, since equal (1 mg) doses were administered three times daily (8:30 hrs, 17:00 hrs, 22:00 hrs) during the second stay, and not exclusively prior to bedtime, LC's consolidated daytime wakefulness and nighttime sleep cannot be due solely to the effect of medication.

Pain may also be an important contributing factor to sleep disturbances following TBI. LC had multiple fractures, which most likely generated significant pain. In the chronic phase of TBI (all severities), pain is known to negatively influence sleep [24-27], as early as the

post-acute period [28]. Among ICU patients without TBI, pain has also been associated to sleep disturbances [29-31]. The influence of pain on LC's sleep may have been stronger during the first hospital stay, as pain may have gradually subsided with time, though no pain evaluations were systematically carried out due to akinetic mutism.

Clinical implications

This case report is the first to extensively document sleep-wake disturbances in both the acute and subacute phases of severe TBI. Indeed, this was the only case we encountered of a patient being readmitted shortly after discharge, providing us with a unique opportunity to follow-up on our actigraphy measures. This successive monitoring of LC's sleep-wake cycle, while in the same hospital ward, distinguishes the present study from previously published TBI sleep studies [2,3,5,6], including our own [7]. Results revealed the presence of severe sleep deprivation and the absence of normal 24-h sleep-wake organisation during the acute phase after a severe traumatic brain injury. Severe sleep deprivation is bound to have negative consequences on physical, psychological and cognitive recovery following TBI. Indeed, post-TBI sleep disturbances have been shown to heighten cognitive, mood and communication impairments, in addition to intensifying pain and compromising recovery [32,33]. In a more general manner, partial or chronic sleep deprivation has been shown to negatively impact cognitive, behavioural, immune, inflammatory, cardiovascular, endocrine and metabolic functions [34-38]. In the case of LC, severe and persistent sleep deprivation and fragmentation, as well as the severe disturbance of the sleep-wake cycle in the first hospital stay, may have contributed to the psychiatric condition having led to his second hospital admission. Indeed, sleep and circadian disturbances are associated to mental health and psychiatric symptoms and disorders [39-41], while sleep deprivation has been associated with psychotic symptomatology [42].

The sleep deprivation experienced by LC was much more severe and prolonged and than that of other moderate-severe TBI evaluated within our larger study [7]. Interestingly, the case of LC differs from previously observed cases of TBI patients for whom improved sleep and wake seem to coincide with improved cognitive functions in the weeks following injury [5,7,43] Rather, LC had persistent PTA, cognitive deficits and psychiatric symptoms, despite

significant improvement of sleep-wake cycle consolidation from the first to the second hospital stay. This may suggest that severe and prolonged sleep deprivation in acute TBI could possibly exacerbate cerebral damage and have persistent effects on cognitive sequelea and recovery.

No sleep medication was given to LC during the actigraphy recording period of the first hospital stay, during which he was suffering from severe sleep deprivation, probably because he was not able to communicate his sleep problem. Systematic monitoring of sleep by observation are difficult to conduct and quite time-consuming. It is therefore rarely included in the nursing care, especially in patients in such severe medical conditions. Actigraphy may be particularly useful among patients with confusion or communication deficits, as it objectively identifies sleep patterns and may contribute to providing timely and adequate treatment if sleep disturbances arise. The sleep disturbances experienced by LC could probably have been attenuated, though the means through which sleep can be facilitated within this population still need to be further investigated.

This report highlights the importance of monitoring the sleep-wake cycle in acute care, as it may inform or influence patient recovery, though more studies are needed to define this relationship and determine whether it is causal or bidirectional. Even though actigraphy cannot distinguish rest from sleep, it remains a useful tool for the prolonged measurement of sleep-wake disturbances in a hospital setting, even among patients who may lack the cognitive capacity to identify and/or report sleep-wake problems to healthcare personnel.

Limitations

One limitation to this study is that no magnetic resonance imaging (MRI) was performed. Given its superior spatial resolution compared with CT [44], MRI would have enabled a more precise detection of alterations in cortical and subcortical structures and networks involved in the regulation of sleep and wake. However, with the CT scan at admission, we were still able to detect petechiae within the pons, which is a region highly involved in sleep-wake regulation [45,46].

List of abbreviations

CT – computed tomography

GCS – Glasgow coma scale

ICU – Intensive Care Unit

MRI – magnetic resonance imagine

PTA – posttraumatic amnesia

TBI – traumatic brain injury

Ethics approval and consent to participate

This study was approved by the ethics committee of Hôpital du Sacré-Cœur de Montréal, named *Comité d'éthique de la recherche et de l'évaluation des technologies de la santé* (protocol no. 2011-690).

Written and informed consent for study participation was provided by the patient's wife. A copy of the written consent is available for review by the Editor of this journal.

Consent for publication

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

The raw actigraphy data supporting the conclusions of this article are included (as supplementary materials).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

C. Duclos: recruited the patient, acquired the data, participated in the analysis and interpretation of the data, drafted and critically revised the manuscript.

M. Dumont: contributed to the conception and design of the study, contributed to interpreting the data, drafting and critically revising the manuscript.

M-J. Potvin: acquired data, participated in the interpretation of data, and critically revised the manuscript.

A. Desautels: contributed to the conception of the study, interpretation of data, and critically revised the manuscript.

D. Gilbert: contributed to the interpretation of data and critically revised the manuscript

DK. Menon: contributed to the conception and design of the study, interpretation of data, and critically revised the manuscript.

F. Bernard: contributed to the conception and design of the study, interpretation of data, and critically revised the manuscript.

N. Gosselin**:** led the conception and design of the study, obtained funding for the study, substantially contributed to analysis and interpretation of data, and was involved in drafting and rcritically evising the manuscript.

All authors have given final approval of the version to be published and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Article 5: Parallel recovery of consciousness and sleep in acute traumatic brain injury

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Contribution: For this article, I recruited the patients, acquired the data, participated in the analysis and interpretation of the data, drafted and critically revised 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.

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.

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

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).

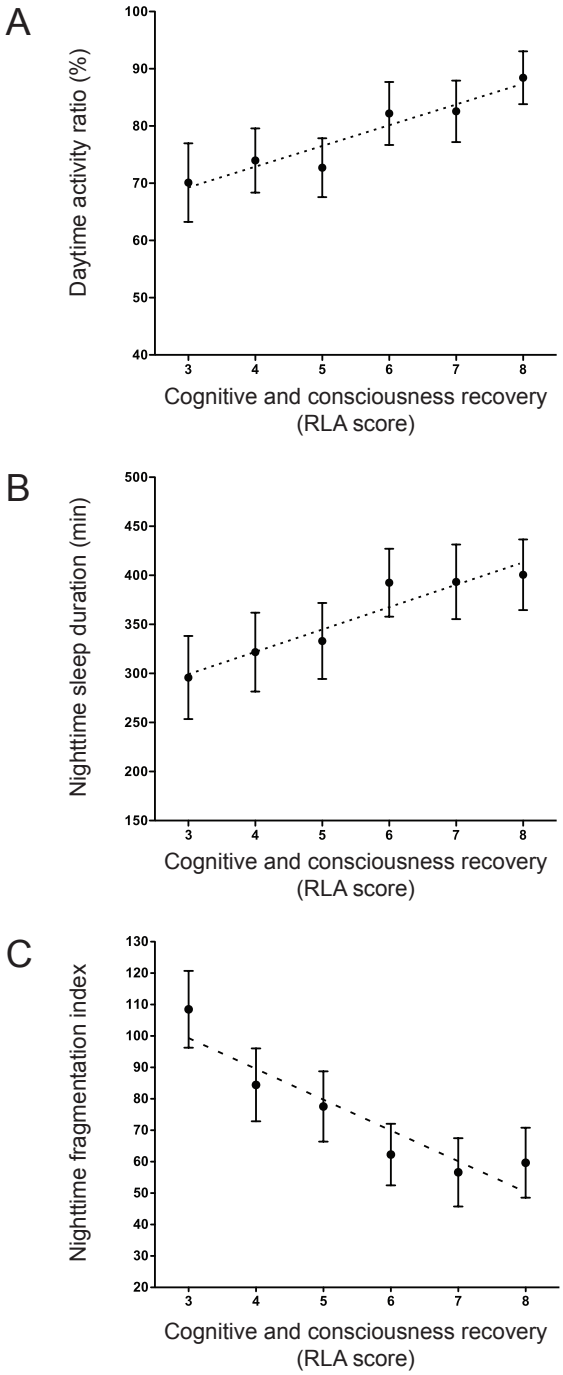

Figure 1. Association between cognitive and consciousness recovery and the sleep-wake cycle. Parallel evolution of the Rancho Los Amigos scale of cognitive functioning score and (A) daytime activity ratio; (B) nighttime sleep duration; and (C) fragmentation index in the 30 patients assessed over 233 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 for (A) ($p < 0.001$), (B) ($p = 0.002$), and (C) ($p < 0.001$).

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.

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

	Actigraphic variables	**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		

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).

Clinical implications

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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Article 6: Sleep in the acute phase of severe traumatic brain injury: A snapshot of polysomnography

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Contribution: For this article, I recruited the patients, acquired the data, participated in the analysis and interpretation of the data, and critically revised the manuscript.

Abstract

Background/Objectives: The onset of pervasive sleep-wake disturbances associated with traumatic brain injury (TBI) is poorly understood. This study aimed at a) determining the feasibility of using polysomnography in patients in the acute, hospitalized stage of severe TBI; and to b) explore sleep quality and sleep architecture during this stage of recovery, compared to patients with other traumatic injuries.

Methods: A Cross-sectional case-control design was used. We examined the sleep of seven patients with severe TBI (17-47 years old; 20.3 ± 15.0 days post-injury) and six patients with orthopaedic and/or spinal cord injuries (OSCI, 19-58 years old; 16.9 ± 4.9 days post-injury). One night of ambulatory polysomnography was performed at bedside.

Results: Compared to OSCI patients, TBI patients showed a significantly longer duration of nocturnal sleep and earlier nighttime sleep onset. Sleep efficiency was low and comparable in both groups. All sleep stages were observed in both groups with normal proportions according to age.

Conclusion: Patients in the acute stage of severe TBI exhibit increased sleep duration and earlier sleep onset, suggesting that the injured brain enhances sleep need and/or decreases the ability to maintain wakefulness. As poor sleep efficiency could compromise brain recovery, further studies should investigate whether strategies known to optimize sleep in healthy individuals are efficacious in acute TBI. While there are several inherent challenges, polysomnography is a useful means of examining sleep in the early stage of recovery in patients with severe TBI.

Keywords: traumatic brain injury, sleep, polysomnography, orthopaedic injury, acute care

Introduction

Sleep-wake disturbances are common across the continuum of recovery following traumatic brain injury (TBI),[1-3] however their onset is still poorly understood. Using actigraphy in an acute care setting, we have shown that these disturbances emerge in the early stage after moderate- severe TBI, evidenced by non-consolidated daytime activity and nighttime rest.[4] Rest fragmentation and prolonged rest duration were also identified using actigraphy among mild to severe TBI patients within 24 hours of being admitted to a neurosurgical ward.[5]

In addition to the effects of the hospital environment on sleep, and considering the major structural, biochemical and pathophysiological changes that occur during the acute phase of severe TBI, including diffuse axonal injury, focal lesions, elevated intracranial pressure, hypoxemia, reduced metabolism, apoptosis, and inflammation,[6] we predict that significant modifications to sleep stages and architecture may occur. In accordance with this hypothesis, recent rodent models of TBI have reported an increase in the amount of sleep, reduction in wakefulness, and more transitions between sleep and wakefulness in the first hours post-injury.[7-10] However, no alterations in the amount of rapid eye movement (REM) or non-REM (NREM) sleep were observed, suggesting that acute TBI decreases the ability to maintain prolonged wakefulness rather than altering the proportion of each sleep stage.

While several studies have investigated sleep using polysomnography (PSG) in the chronic stages of TBI, to our knowledge, no prior study has utilized PSG with electroencephalography (EEG), electrooculography (EOG) and chin electromyography (EMG) to examine sleep stages and architecture during the acute stage of severe TBI in non-sedated patients. This may be due to the challenges of performing PSG recordings in this population, when most patients are confused and agitated. However, contrary to other methods used to assess sleep in hospital settings, namely actigraphy and nurse assessment, PSG leads to more accurate measurements of sleep quality and is the only method to identify sleep stages.[11,12] Thus, PSG recording in acute TBI would allow for an improved understanding of the emergence of sleep-wake disturbances.

In the present study, we conducted bedside PSG in seven non-sedated patients hospitalized with acute (< 45 days post-injury), severe TBI and six patients with severe orthopaedic or spinal cord injuries (OSCI) without TBI to compare the sleep of patients hospitalized with similar medical condition severity, within a similar environment. We utilized EEG, EOG, and chin EMG to objectively measure sleep stages and architecture at bedside.

The aim of this research was to determine the feasibility of using PSG recordings with this acute patient population and to explore sleep quality and sleep macroarchitecture via PSG, in the acute, hospitalized stage of severe TBI. We also aimed to explore associations between injury characteristics and PSG variables. Based on animal studies and our previous actigraphy study,[4] we hypothesized that in comparison to those with OSCI, severe TBI patients would have an increased amount of sleep, reductions in wakefulness, and greater fragmentation of their sleep during the night.

Methods

Participants

A cross-sectional case-control design was used. The present study was performed in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement for case-control studies.[13] Potential TBI participants and their families were approached in the Intensive Care Unit (ICU) of the *Hôpital du Sacré-Cœur de Montreal*, a tertiary Trauma Center, from June 2009 to January 2014. Seven patients with severe TBI (range: 17 – 47 years old; 4 males) were recruited (see Figure 1 for flow diagram) and compared to six patients with severe OSCI (range 19 – 58 years old; 3 males). Five TBI patients in the present study were included in a previous study reporting actigraphy data only.[4] TBI was defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force.[14] TBI severity was assessed upon emergency room admission using the Glasgow Coma Scale (GCS)[15] and reassessed thirty minutes later to provide a post-reanimation score. Patients in the TBI group were included if they had a GCS score of 3 to 8 on both assessments. See Table 1 for demographic and injury characteristics.

Inclusion Criteria: Age 16-59 years; extubated, normal intracranial pressure and no active or suspected infection at time of data collection; continuous intravenous sedation and analgesia discontinued for a minimum of 48 h; remaining in the tertiary trauma center long enough to complete the study.

Exclusion criteria (both groups): Pre-injury history of diagnosed psychiatric or neurologic disorders (including previous TBI), sleep disorders, substance abuse, or disease known to affect sleep and/or circadian rhythms; pregnancy; severe eye injuries that would modify perceived light; inability to tolerate research materials; temporary skull bone flap removal. Because of a peri-ocular laceration, one OSCI patient was initially suspected of having a mild TBI, however he did not reach the criteria for a diagnosis of mild TBI, as he had a normal brain computed tomography (CT) scan, no confusion or disorientation was observed and he had an initial GCS score of 15, and was therefore, not excluded.

The study received ethics approval from the hospital ethics committee. Consent to participate was provided by the patients' family member in all TBI cases. Patients who eventually became cognitively able to provide informed consent for themselves during data collection were asked to sign a consent form for study protocol to continue. OSCI participants were able to provide their own consent.

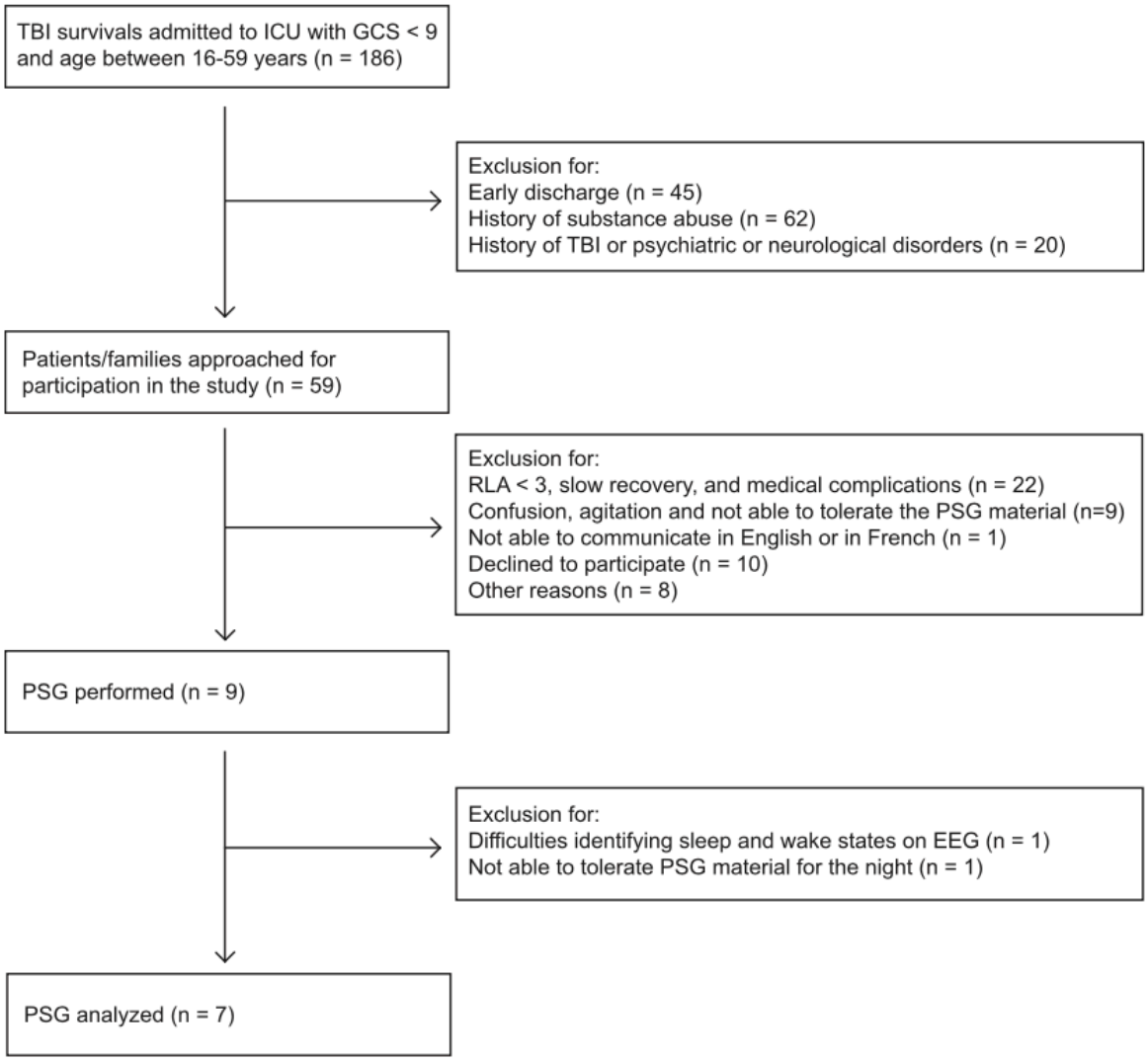

Figure 1. Flow diagram representing TBI patient recruitment. A total of 186 TBI survivors aged between 16 and 59 years old and with a Glasgow Coma Scale score < 9 were admitted to the Hôpital du Sacré-Coeur de Montréal's intensive care unit from June 2009 to January 2014. 59 patients or families when approached for their participation in the study and 9 polysomnographic recordings were performed, but only 7 were suitable for analysis.

Table 1. Demographic and clinical characteristics for patients with moderate-severe traumatic brain injury (TBI group) and patients with orthopaedic or spinal cord injuries (OSCI group)

ID	Sex/ Age	Type of injury	Initial GCS	CT scan	ICU LOS (days)	Hospital LOS (days)	Time between trauma and PSG (days)	Time between ICU discharge and PSG (days)	RLA at the time of PSG recording	PTA at hospital discharge	Medications during PSG
TBI											
1	F/20	TBI/OI	3	Normal	5	34	7	2	VII	No	Hydromorphone (Dilaudid 1 mg at 03:25 and 06:25)
2	M/23	TBI/OI /SCI	3	Thalamic contusion (R), Frontal SAH (L), Ventricular haemorrhage (R), Diffuse oedema	24	36	30	6	VII	No	Hydromorphone (Dilaudid 1 mg at 20:15); Mirtazapine (Remeron 15 mg at 22:00)
3	M/47	TBI	6	Normal	5	11	7	2	VI	No	None
4	F/26	TBI/OI	7	Frontal (L) and parietal (R) SAH, Open temporoparietal fracture (L)	7	22	12	5	VIII	No	Piperacillin and tazobactam (Tazocin 3375mg at 21:00 and 03:00)
5	M/20	TBI/OI	3	Frontoparietal (L) and tentorial incisura SDH, Parietal SAH (L), Occipital intraventribular haemorrhage, Diffuse oedema	24	68	31	7	III	Yes	Amantadine (Symmetrel 150 mg at 22:00)

6	M/17	TBI/OI	7	Frontal and temporal SDH (R), Fronto-insular SAH (L), Frontolateral petechiae (L), Diffuse oedema	5	13	10	5	VII	No	Methylphenidate (Concerta 63 mg at 8:30)
7	F/18	TBI/OI	5	Diffuse oedema, Sylvian fissure SAH (L), Multiple frontal, temporal (L) and subcortical (L) white matter contusions, DAI	33	59	45	12	V	Yes	Amantadine (Symmetrel 150 mg at 22:00)
OSCI											
8	M/19	SCI	15	Normal	4	22	9	5	VIII	No	Hydromorphone (Dilaudid 2 mg at 21:10 and 23:35); Pregablin (Lyrica 25 mg at 21:00)
9	F/24	OI/SCI	15	No CT scan performed	0	16	13	NA	VIII	No	Pregablin (Lyrica 75 mg at 22:00)
10	M/26	SCI	15	Normal	4	19	16	8	VIII	No	Hydromorphone (Dilaudid 4 mg every 3 h); Pregablin (Lyrica 100 mg at 22:00)
11	F/58	OI	15	Normal	15	53	20	5	VIII	No	Morphine (Statex 15 mg, 18:00 and 22:00; 10 mg at 02:00 and 06:00)

13	F/50	OI	15	Normal	0	33	25	NA	VIII	No	Hydromorphone (Dilaudid 2 mg at 17:00, 21:00, and 1:30)
14	M/22	SCI	15	Normal	0	16	14	NA	VIII	No	Morphine (Statex 10 mg at 20:45, 03:40 and 07:00), Pregabalin (Lyrica 50 mg at 22:00)

TBI: Traumatic brain injury; OSCI: orthopaedic and spinal cord injury; OI: Orthopaedic injury; SCI: Spinal cord injury; GCS: Glasgow Coma Scale score; R: Right; L: Left; SAH: Subarachnoid haemorrhage; SDH: Subdural haemorrhage; DAI: Diffuse axonal injury; ICU: Intensive care unit; LOS: Length of stay; PSG: Polysomnography; RLA: Rancho Los Amigos; PTA: Post-traumatic amnesia.

Study protocol and data analyses

Clinical variables: We documented GCS, brain CT scan results, length of ICU stay, hospital length of stay, and Marshall score.[16] CT scans were interpreted by a neuroradiologist (D.G.). Cumulative administered dose of sedative and analgesic medication (lorazepam, midazolam, propofol, morphine, and fentanyl) in ICU was calculated according to the previously described method.[17] As per standard clinical protocol, daily assessments of cognitive function were performed by occupational therapists using the Rancho Los Amigos (RLA) scale.[18] Post-traumatic amnesia (PTA) at discharge was evaluated with the Galveston Orientation and Amnesia Test (GOAT).[19]

Polysomnography: PSG's were recorded for at least 16 continuous hours, starting between 13:14 and 18:46, using a 32-channel Siesta system (Compumedics Limited, Charlotte, NC, USA). PSG's for both groups were performed in regular neurologic or orthopaedic units following discharge from ICU. Electrode installation was done at bedside by two experienced and registered medical electrophysiology technologists. PSG comprised at least three EEG leads (C3, C4, O2) with a mastoid (M1) reference, left and right EOG, and chin EMG. Participants were able to move around when able, since the PSG recording system was ambulatory. A trained research assistant stayed next to the patient room throughout the recording to observe the online PSG, and a registered medical electrophysiology technologist was on call and available in the hospital during the PSG to replace electrodes if needed.

Since no restrictions were placed on when patients were permitted to sleep, the sleep period was thus defined as the longest period of sleep during the night. Visual inspection of PSG data revealed that all participants began their first period of continuous nocturnal sleep (>10 min) between 20:11 and 00:19, and the end of their sleep period occurred between 06:22 and 08:47 (see Table 2). Any period of sleep that occurred following an awakening longer than 15 min, and later than 06:30 was considered a nap and thus not included within the nighttime sleep period.

All PSG recordings were reviewed by a neurologist with a specific training in sleep medicine and with several years of experience in a sleep clinic (A.D.). Sleep stages and events

were scored according to the American Academy of Sleep Medicine Manual [20] by a trained medical electrophysiology technologist with a strong expertise in sleep. The following variables were derived: sleep period duration, beginning and end of the sleep period, total sleep time, sleep efficiency (percentage of time asleep during the sleep period), amount of wake after sleep onset, number of awakenings, microarousal index (number of microarousal/h), minutes and percentages of each sleep stage and REM sleep latency. Sleep variables were calculated for the nocturnal sleep period.

Statistical analyses

All results are reported with descriptive statistics using means, standard deviations and medians. Given our small sample, non-parametric tests were used. Mann-Whitney U tests were performed to compare the groups for clinical and sleep variables. Additionally, Spearman correlations were run between PSG variables and clinical characteristics. Correlations were conducted on data from all participants (TBI and OSCI), except for variables specific to TBI (e.g. GCS, RLA). Significance was set at $p < 0.05$.

Results

Clinical characteristics of our sample

Demographic and clinical characteristics of the TBI and OSCI groups are presented in Table 1. The TBI group included 7 patients (3 females; 24.4 ± 10.4 years old, median: 20 years old) and the OSCI group comprised 6 patients (3 females; 33.2 ± 16.5 years old, median: 25 years old). No significant group difference was found for age and sex. The average initial GCS in the TBI group was 4.9 ± 1.9 (median: 5, range: 3-7) at the emergency room, which corresponds to severe TBI criteria. Among the seven TBI patients, six also had severe orthopaedic injuries. Although pain was not operationally evaluated during the PSG recording, two TBI patients and all OSCI patients were taking analgesic medication. Brain CT scan findings were classified according to Marshall score,[16] with two TBI patients having a score of I (no visible pathology) and five having a score ranging from II (diffuse injury) to IV (any lesion surgically evacuated) (detailed neuroimaging findings are presented in Table 1). RLA scores at the time of PSG are presented in Table 1 in order to provide a gross measure of

cognitive function for the TBI group. The RLA levels ranged from III (Localized response only: patient responds specifically and inconsistently with delays to stimuli, but may follow simple commands for motor action) to VIII (Purposeful, appropriate response: patient oriented, responds to environment but abstract reasoning abilities decreased). No group difference was found for the time between injury and PSG recording (TBI: 20.3 ± 15.0 days, median: 12 days; OSCI: 16.0 ± 5.0 days, median: 15.5 days), time between ICU discharge and PSG (TBI: 5.6 ± 3.4, median: 5 days; OSCI: 5.5 ± 5.9, median: 5 days) or hospital length of stay (TBI: 34.7 ± 22.0, median 34 days; OSCI: 26.5 ± 14.4, median: 20.5 days).

Polysomnography

Table 2 presents individual PSG results. The duration of sleep periods was longer in the TBI group compared to the OSCI group (TBI: 10:23 ± 00:32, median: 10:31; OSCI: 08:32 ± 01:12, median: 08:11, $U(11) = 6.0$, $Z = 2.07$, $p < 0.05$), with an earlier sleep onset for the TBI than the OSCI group (TBI: 20:57 ± 00:42, median: 20:49, OSCI: 22:43 ± 00:54, median: 22:32, $U(11) = 2.0$, $Z = -2.7$ $p < 0.01$). However, the end of their sleep periods occurred at a similar time. Within the sleep period, TBI patients had a longer sleep duration than OSCI patients (TBI: 08:15 ± 00:49, median: 08:20; OSCI: 06:59 ± 01:09, median: 06:41, $U(11) = 6.0$, $Z = 2.07$, $p < 0.05$). Long duration of awakening after sleep onset and poor sleep efficiency were observed for both groups with no significant group differences. No group difference was found for arousal variables or microarousal index. All sleep stages were present in all patients from both groups and we were able to identify all elements of sleep, such as sleep spindles, k-complexes and sleep stages in all participants. When the percentage of each sleep stage was considered, very similar sleep architecture was observed between the two groups for N1, N2, N3 and REM sleep.

Variables associated with polysomnographic characteristics

No significant correlation was found between clinical characteristics (e.g. initial GCS, ICU length of stay, delay between injury and PSG) and sleep variables. Cumulative dose of analgesic and sedative medication received during the ICU stay was also not associated with any PSG variables.

Table 2. Polysomnographic results for patients with severe TBI and patients with OSCI

ID	Sleep period beginning (hrs:min)	Sleep period end (hrs:min)	Sleep period duration (hrs:min)	Sleep duration within sleep period (hrs:min)	WASO (hrs:min)	Nb. of arousals	Sleep efficiency (%)	Stage N1 (%)	Stage N2 (%)	Stage N3 (%)	REM sleep (%)	Micro-arousal index (nb./h)
TBI												
1	21:13	08:24	11:11	08:56	02:14	28	80.0	9.9	57.3	20.2	12.6	5.8
2	20:11	06:42	10:31	08:20	02:10	44	79.3	5.6	29.0	40.9	24.6	6.7
3	22:11	08:47	10:34	07:36	02:55	64	72.0	16.9	54.0	17.7	11.4	6.4
4	19:56	07:12	10:30	08:43	01:46	23	83.1	9.2	40.4	30.2	20.2	3.8
5	20:49	06:42	09:52	07:15	02:37	58	73.5	13.3	56.8	10.8	19.1	2.5
6	21:23	06:53	09:30	09:26	00:04	6	99.3	2.7	45.2	34.1	18.0	1.7
7	20:13	06:48	10:34	07:31	02:50	28	71.2	8.6	49.2	26.9	15.3	4.3
OSCI												
8	21:51	08:40	10:49	09:16	01:33	50	85.6	22.3	34.1	32.7	10.9	4.1
9	23:07	07:09	08:02	06:53	01:02	25	85.6	3.1	52.7	34.7	9.4	1.6
10	00:19	07:53	07:34	06:51	00:42	21	90.6	7.5	63.3	15.8	13.4	3.8
11	22:20	06:42	08:21	06:22	01:58	36	76.3	14.8	63.5	4.2	17.5	7.8
12	22:44	06:22	07:38	06:31	01:07	16	85.4	6.4	52.7	16.9	24.0	5.4
13	21:58	06:47	08:48	06:02	02:32	19	68.6	10.9	50.3	22.5	16.3	1.5
TBI (mean ± SD)	**20:57 ± 00:42**	**07:21 ± 0:52**	**10:23 ± 00:32**	**08:15 ± 00:49**	**02:05 ± 00:58**	**35.9 ± 20.5**	**79.8 ± 9.7**	**9.5 ± 4.7**	**47.4 ± 10.2**	**25.8 ± 10.3**	**17.3 ± 4.6**	**4.5 ± 2.0**
OSCI (mean ± SD)	**22:43 ± 00:54**	**07:15 ± 0:51**	**08:32 ± 01:12**	**06:59 ± 01:09**	**01:29 ± 00:40**	**27.8 ± 12.9**	**82.0 ± 8.1**	**10.8 ± 6.8**	**52.8 ± 10.8**	**21.1 ± 11.5**	**15.3 ± 5.3**	**4.0 ± 2.4**
U-value	**2.0**	**NS**	**6.0**	**6.0**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**
p-value	**<0.01**	**NS**	**<0.05**	**<0.05**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**

TBI: Traumatic brain injury; OSCI: Orthopaedic and spinal cord injury; hrs: hours; min: minutes; nb: number; WASO: Wake after sleep onset; REM: Rapid eye movement; SD: Standard deviation; NS: non significant.

Discussion

This study demonstrates the feasibility of measuring sleep via PSG in acute severe TBI patients. Although the findings of this study must be considered as preliminary, we observed that, in comparison to a control group of OSCI patients without moderate-severe TBI, patients with severe TBI had longer nocturnal sleep duration and earlier nighttime sleep onset during their hospital stay.

Feasibility and usefulness of PSG in acute care

The small sample within the present study is representative of the challenges of performing PSG in acute TBI patients. Some patients are unable to tolerate the materials, and/or may be confused or agitated, which limits the feasibility of PSG in the acute stage. On the other hand, patients with a more rapid recovery are better able to tolerate the study materials, however, their fast recovery is then associated with a much smaller window of time between the cessation of continuous sedation and hospital discharge, making it very difficult to conduct a 24-h PSG.

However, despite these challenges, the use of PSG during the acute phase of severe TBI is feasible, and has been able to provide new information regarding sleep during this very early stage post injury. In fact, we found that despite their fragmented sleep, TBI patients had normal elements of sleep, such as sleep spindles, k-complexes, and normal proportions of each sleep stages. These findings contrast with previous sleep studies performed in sedated non-TBI patients in whom up to 96% of total sleep was spent in stages N1 and N2 (Cooper et al., 2000; Gehlbach et al., 2012). The present study also allowed for documentation of the exact amount of sleep in TBI patients, which was higher than that of OSCI patients. Although other techniques such as actigraphy and nurse assessment can give an approximation of sleep duration, only PSG can document exact sleep duration, particularly when sleep is fragmented. It would also have been of interest to evaluate sleep with PSG in the confused/agitated state, during which an absence of rest-activity cycle consolidation was documented by actigraphy.[4] However, PSG is not feasible during this stage, due to posttraumatic agitation and intolerance

to the materials. Thus, for the stage of very early recovery, actigraphy remains the best tool to study sleep-wake patterns.

Excessive sleep need or an inability to maintain wakefulness?

It is possible that the preliminary finding of an earlier sleep onset and an increased sleep duration in acute TBI be explained by an enhanced sleep need secondary to the brain injury. Consistent with this hypothesis, a recent rodent model reported an acute increase in sleep duration immediately following TBI. [8] Findings among humans also show that excessive sleep need is observed in approximately 22% of mild to severe TBI patients reporting chronic sleep-wake disturbances,[21] however, an excessive sleep need has not previously been documented among acute TBI patients. The role of sleep in neuroplasticity and neurogenesis is well recognized [22,23] and it is possible that some aspects of sleep may be critical for brain recovery following TBI and thus may be driving an increased need for sleep. This warrants further investigation.

Conversely, it is also possible that the increased sleep duration and early sleep onset observed in the present study be reflective of an inability to maintain wakefulness rather than an excessive sleep need. This interpretation has been proposed among several animal models of TBI [7,10,24] and a decrease in hypocretin-1 (orexin) neuron activation, a neuropeptide involved in the arousal system, has been reported in mice one month after injury.[7,24] In humans, a large decrease in cerebrospinal fluid levels of hypocretin-1[25] and a loss of histaminergic neurons in the tuberomammillary nucleus, a major arousal-promoting nucleus located in the posterior hypothalamus, has also been found following severe TBI. [26] These observations suggest that impaired neurotransmitter signaling may be a contributing factor to a decreased ability to maintain wakefulness, resulting in increased sleep duration and earlier sleep onset among our patients.

Sleep deprivation hypothesis

Factors other than the brain injury itself may explain the hypothetical increased sleep need or the inability to maintain wakefulness. The hospital environment (e.g. noise, light, activities) in itself may explain in part the poor sleep efficiency we observed for both TBI and

OSCI patients. Severe sleep abnormalities have been reported in critically ill non-TBI patients in the ICU,[27-29] with up to 96 % of actual sleep time spent in the lighter stages of sleep. Moreover, the previous actigraphy study conducted by our group showed an absence of well-consolidated rest periods among TBI patients hospitalized in the ICU.[4] Thus, a significant sleep debt is likely to have accumulated while our patients were in the ICU, which may be one contributing factor to our finding. However, the average interval between ICU discharge and PSG recording was similar across the two groups of subjects. It is possible that the TBI patients experienced greater sleep deprivation during their stay in ICU than those with OSCI and thus may have accumulated a greater sleep debt, however this was not measured in the current study.

Medications

Almost all patients were being administered medications that are reported to cause varying degrees of sleep modifications in healthy subjects,[30] including analgesics. Some of these medications (amantadine, piperacillin and tazobactam, and hydromorphone) have been reported to cause insomnia, while mirtazapine is known to increase total sleep time, and pregabalin and mirtazapine decrease number of awakenings in healthy subjects. Morphine is reported to decrease N3 sleep and increase N2, though it is not reported to modify total sleep time.[31] Opioid medication is known to influence sleep with suppression of REM sleep and slow wave sleep followed by a subsequent rebound.[32,33] It is difficult to specifically delineate sleep modifications that may be related to or a result of medication in our sample. However the increased sleep duration observed in the TBI patients cannot be explained by mirtazapine, as only one patient was taking this medication.

Limitations of the study

Given the specific nature of this study, the challenges of recruiting among severely injured patients and thus our small sample size, our findings are preliminary and further research is needed with larger samples in order to generalize these results to those patients with severe TBI in the acute post-agitation stage.

There may also be some limitations regarding the use of OSCI patients as the comparison group. This group differed from the TBI group in terms of pain and analgesic medications administered during the PSG. Moreover, severe orthopaedic injury or SCI may lead to acute sleep-wake disturbances. Nevertheless, OSCI patients likely remain the best control group for TBI patients, as both groups include young adults who were healthy prior to their injury, which is not the case for most of critically ill patients.

Finally, we recognize the possible and likely confound of pain amongst both groups in relation to sleep. The OSCI group received more pain medication than the TBI group, most likely due to higher levels of cognitive functioning and awareness. Given the length of our PSG and the terminal half-life analgesic (ex. 2.3 h for hydromorphone), we recognize that pain levels likely would have fluctuated throughout the PSG recordings. Future studies would benefit from the addition of a simple visual analog pain scale for those patients able to complete it.

Conclusion

Consistent with our hypothesis, sleep was fragmented with low sleep efficiency indicative of poor sleep quality. Similar results were also found among the comparison group of OSCI patients and likely reflect non-specific factors associated with the traumatic experience and the hospital environment. However, the results of this preliminary study demonstrate that an earlier sleep onset and increased sleep duration for those patients with severe TBI are the primary differences in sleep identified between the two groups.

A possible interpretation may be that the brain damage associated with severe TBI results in either an increased sleep need or a difficulty maintaining wakefulness. This interpretation is consistent with high levels of sleepiness frequently reported among TBI patients.[34] Improving sleep quality during the acute stage of TBI with consideration of pharmacological and environmental factors may optimize recovery of the brain itself and improve the ability to maintain optimal levels of arousal and wakefulness for cognitive recovery.

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Article 7: Sleep-wake cycle deregulation but normal circadian clock signal in acute traumatic brain injury

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Contribution: For this article, I recruited the patients, acquired the data, participated in the analysis and interpretation of the data, drafted and critically revised the manuscript.

Abstract

Hospitalized patients with moderate-severe traumatic brain injury (TBI) have a deregulated sleep-wake cycle, which could be related to circadian dysfunction caused by the brain injury. This study aimed to determine whether sleep-wake disturbances observed in hospitalized TBI patients are comparable to those observed in patients with traumatic injuries other than TBI. Moreover, we tested the hypothesis that deregulated sleep-wake cycles were associated with a weaker circadian clock signal. To achieve these goals, we compared the sleep-wake cycle and melatonin rhythms of moderate-severe TBI patients to that of trauma patients without TBI (non-TBI), and evaluated the association between melatonin and the sleep-wake cycle in TBI patients. Forty-two moderate-severe TBI (31.1±14.0 yo; 29 men) and 35 non-TBI patients (34.3±15.2 yo; 24 men) wore wrist actigraphs for 9.4±4.2 days, starting 19.3±12.6 days post-injury. The daytime activity ratio was used to quantify sleep-wake cycle consolidation, and nighttime sleep duration and fragmentation index were calculated as measures of nighttime sleep quality. Of these 77 patients, 17 TBI (30.3±13.3 yo; 14 men) and 15 non-TBI patients (31.1±13.7 yo; 12 men) had their urine collected every hour for 25h, starting 18.3±12.3 days post-injury. Concentration of urinary 6-sulfatoxymelatonin was calculated to obtain total 24h excretion, melatonin secretion onset, offset, and duration. A cosinor analysis was carried out to determine whether a significant rhythm was present, and to assess rhythm amplitude and acrophase. We compared groups on actigraphy and melatonin variables using Student's t-tests. We investigated associations between melatonin and actigraphy variables using Pearson's correlations. Statistical significance was set at $P<0.01$. We found that TBI patients had poorer daytime activity ratio (TBI: 77.5±9.4%; non-TBI: 84.6±6.9%, $t(75)=-3.69$, $P<0.001$), shorter nighttime sleep duration (TBI: 353.5±96.6 min; non-TBI: 421.2±72.2 min, $t(75)=-3.24$, $P<0.01$), and higher fragmentation index (TBI: 72.2±30.0; non-TBI: 53.5±23.6, $t(75)=2.68$, $P<0.01$). However, a melatonin rhythm was present in TBI patients, and no group differences were found on any of the melatonin variables. No associations were found between melatonin and actigraphy variables in TBI patients. This study shows that moderate-severe TBI patients have more serious sleep-wake disturbances than other trauma patients without TBI, suggesting that the brain injury itself has an influence on the sleep-wake cycle. However, these sleep-wake disturbances are not due to an impaired circadian clock signal. Neural mechanisms other

than the circadian system may be responsible for post-TBI sleep-wake disturbances. Since sleep is a modifiable behavior, it may be a promising target to improve recovery.

Introduction

Sleep could have important benefits on a traumatically injured brain, particularly in the acute stage when the brain needs regeneration. In fact, sleep increases synaptic plasticity, neurogenesis, neurotoxic waste clearance, and decreases neuroinflammation, and oxidative stress (Smith, 1996; Walker & Stickgold, 2006; Meerlo et al., 2009; Diekelman and Born, 2010; Xie et al., 2013; Clark and Vissel, 2014; Tononi and Cirelli, 2014; Kreutzman et al., 2015; Fernandes et al., 2015; Villafuerte et al., 2015; Zielinski et al., 2016). To fulfill its recuperative functions, sleep must be continuous and has to occur within a well-organized sleep-wake cycle (Fuller et al., 2006). However, non-sedated patients with TBI have a complete absence of the 24 h sleep-wake cycle following discharge from the intensive care unit (ICU), and only 50% regain their ability to maintain longer periods of daytime wakefulness and nighttime sleep during their hospital stay (Duclos et al., 2014; Duclos et al., 2016).

The exact causes of sleep-wake disturbances observed in acute and post-acute TBI are still unknown. Environmental factors and factors associated with critical care, such as pain and the use of sedative and analgesics, are the most obvious suspects (Drouot et al., 2008; Pisani et al., 2015). As these factors are common to all hospitalized patients with severe trauma, the comparison between patients with moderate to severe TBI and patients with severe traumatic injuries but no TBI (e.g. orthopedic injuries) may help to identify the specific contribution of brain injury to sleep-wake disturbances.

The circadian clock located in the suprachiasmatic nuclei may also contribute to sleep-wake disturbances observed after TBI. This clock generates rhythms of about 24 h for all physiological and behavioral functions, including sleep timing. It synchronizes itself with the environmental day-night cycle (Klerman, 2005). Light captured by the retina follows the monosynaptic retino-hypothalamic tract to reach the suprachiasmatic nuclei (Moore & Eichler, 1976). A robust and well-synchronized circadian signal will usually translate to a well-consolidated sleep-wake cycle, with a main sleep episode at night and a long, sustained period of time awake during the day (Dijk and Czeisler, 1994; Dijk and Czeisler, 1995). Conversely, misalignment between internal circadian time and sleep timing results in decreased

consolidation of the sleep-wake cycle, as shown by fragmented nighttime sleep and by excessive sleepiness and naps during daytime (Dijk and Von Schantz, 2005; Barion and Zee, 2007). These perturbations characterize the sleep-wake pattern that was documented in patients hospitalized with acute moderate and severe TBI (Duclos et al., 2014; Duclos et al., 2016; Duclos et al., 2017).

The brain injury itself may disrupt the circadian clock and decrease the strength of the circadian output. An indirect marker of circadian output is the measure of melatonin production by the pineal gland (Arendt, 2005). When the circadian clock is correctly synchronized to the external day-night cycle, melatonin production shows elevated levels during the night and is almost undetectable during the day. The timing of onset and offset of production is tightly controlled by the suprachiasmatic nuclei, which makes the measurement of melatonin a recognized marker of the internal clock activity (Arendt, 2005). The few studies that have investigated the melatonin rhythms of TBI patients hospitalized in the ICU reported decreased melatonin production and a disturbed melatonin rhythm (Paparrigopoulos et al., 2006; Paul and Lemmer, 2007; Seifman et al., 2014). However, all of these studies had infrequent measures of melatonin (every 2, 3, and 6 h), as opposed to hourly measures, making it difficult to identify phase advances or delays. Moreover, all of these studies were conducted among mechanically ventilated patients who were under continuous sedation, which could directly alter circadian function (Dispersyn et al., 2008; Gehlbach et al., 2012; Korompeli et al., 2017).

The present study aimed at testing two hypotheses: 1) the cerebral insult contributes to the sleep-wake disturbances observed in hospitalized TBI patients; and 2) a circadian disruption is associated with the observed sleep-wake cycle disturbances in moderate-severe TBI patients. To achieve these goals, we first tested whether TBI patients in the acute phase post-injury have more severe sleep-wake disturbances than patients with severe traumatic injuries, without TBI, hospitalized in the same environment. Secondly, we compared the melatonin rhythm of TBI patients to that of other trauma patients, without TBI, and assessed whether an abnormal circadian rhythm of melatonin production was associated with the sleep-wake disturbances observed among TBI patients during their hospital stay.

Materials and Methods

Study Design

Sleep-wake cycle consolidation, nighttime sleep quality, and melatonin circadian rhythm were assessed in moderate-severe TBI patients, no longer mechanically ventilated or continuously sedated, and compared to that of other trauma patients without TBI, hospitalized in a similar environment.

Patients

Moderate and severe TBI patients were recruited from Hôpital du Sacré-Coeur de Montréal, a level-1 trauma centre affiliated to the Université de Montréal, between January 2010 and June 2016. TBI was defined as an alteration in brain function or other evidence of brain pathology caused by an external force (Menon *et al*., 2010), and TBI severity was assessed upon emergency department admission, prior to intubation, using the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974). TBI patients were included if they were hospitalized in the ICU for their TBI.

Patients having suffered severe orthopaedic and/or spinal cord injuries, without TBI, were tested as part of our control group given they have a similar demographic profile and have injuries severe enough to require extensive medical care and medication. Non-TBI patients were recruited from Hôpital du Sacré-Coeur de Montréal, between January 2012 and January 2016. Severe orthopaedic injury was defined as a complex traumatic injury, such as multiple fractures with or without damage to peripheral nerves or to the vascular system, which necessitates intervention by a specialized multidisciplinary team. Although it is difficult to completely rule out mild TBI in patients with orthopaedic and spinal cord injury, no patient from the non-TBI group had evidence of TBI on the CT scan. All patients had a GCS of 14 or 15 in the emergency department, except one intoxicated patient who had a GCS of 8 upon admission, due to elevated blood alcohol levels and a mandibular fracture that made verbal assessment of the GCS unfeasible. Her CT scan was normal and she was judged by the treating physician to be exempt from TBI. In the majority of cases, a GCS of 14 was obtained

when the verbal or motor response was altered due to peripheral lesions (upper body injuries and/or facial fractures) rather than brain injury.

In order to characterize our study sample, mechanism of injury, Injury Severity Score (ISS) (Baker et al., 1974), GCS score at emergency department admission, ICU and hospital lengths of stay were calculated for all patients. Cumulative dose of sedatives and analgesics (lorazepam, midazolam, propofol, morphine, hydromorphones, and fentanyl) administered in the ICU was calculated according to the previously described method (Ely et al., 2004), and fentanyl was converted to morphine-equivalent dose (Ely et al., 2004). For TBI patients only, number of days with elevated intracranial pressure (>20 mm Hg), as well as Marshall and Rotterdam scores (Marshall *et al*., 1992; Mass *et al*., 2005) were calculated. Patients were excluded if they were younger than 16 or older than 65 years old; were quadriplegic; had a history of substance abuse, had a diagnosed psychiatric, neurological or sleep disorder prior to injury; suffered any damage to both eyes or the optic nerve (modifying light perception); or if they had a prior history of TBI. Consent for participation was obtained from patients' families, and the study was approved by the hospital ethics committee.

Measures

Overview of research protocol

We recruited 42 consecutive TBI and 35 consecutive non-TBI patients who fit the inclusion criteria, were hospitalized sufficiently long to participate, and for whom consent for participation was provided (see Table 1 for demographic and clinical characteristics). In the TBI group, mechanisms of injury were motor vehicle accident (n = 29), fall (n = 8), recreational/sports injury (n = 4), and blow to the head (n = 1). Twenty-two patients (52.4%) had elevated intracranial pressure during their ICU stay, of an average duration of 8.5 ± 5.3 days. Mechanisms of injury in the non-TBI group were motor vehicle accident (n = 20), fall (n = 8), being crushed by a heavy object (n = 4), and recreational/sports injury (n = 3). Thirty patients of the TBI group were also included as participants in one, two or three previous publications aiming at different questions (Duclos et al., 2014; Wiseman-Hakes et al., 2016; Duclos et al., 2017).

Table 1. Demographic and clinical characteristics of total sample

	TBI (n = 42)	Non-TBI (n = 35)	t-value or X^2	P-value
Age	31.1 ± 14.0	34.3 ± 15.2	-0.095	0.3444
Sex (Men/Women)	29/13	24/11	0.002	0.9642
GCS at admission	7.8 ± 3.4	14.7 ± 1.2	11.474	<0.000001
Injury Severity Score	30.4 ± 10.6	19.8 ± 8.9	4.556	<0.0001
Cumulative dose of sedatives and analgesics administered in ICU (g)	31.2 ± 34.1	2.2 ± 4.3	4.041	<0.001
Length of ICU stay (days)	21.4 ± 13.7	4.8 ± 4.3	6.872	<0.000001
Hospital length of stay (days)	41.5 ± 24.8	25.3 ± 13.4	3.507	<0.001
Marshall score	2.7 ± 1.4	n.a.	n.a.	n.a.
Rotterdam score	3.1 ± 1.2	n.a.	n.a.	n.a.
Length of actigraphy recording (days)	10.2 ± 4.6	8.5 ± 3.6	1.81	0.0741
Start of actigraphy recording (days post-injury)	20.6 ± 13.0	11.8 ± 8.0	3.55	<0.001

GCS: Glasgow Coma Scale; ICU: intensive care unit

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 on regular neurological/orthopaedic wards. As described in a previous study (Duclos et al., 2014), actigraphy recording began when continuous sedation and analgesia had ceased for at least 24 h, and once patients reached a score ≥3 on the Rancho Los Amigos scale (Hagen et al., 1972), indicative of apparent physical reactivity to internal

and external stimuli. At this stage, patients had reached medical stability, defined by the absence of mechanical ventilation, fever, active infections, hemodynamic instability, and elevated intracranial pressure. With its low invasiveness, actigraphy enables the long-term measurement of the rest-activity cycle, and is recognized as an indirect measure of the sleep-wake cycle (Martin & Hakim, 2011).

Melatonin production was estimated in a subset of patients using the urinary excretion of 6-sulphatoxymelatonin (aMT6s), melatonin's main metabolite (Arendt, 2005). Urine was collected for 25 h, either prior to or during the period of actigraphy recording. On average, actigraphy recording began 2.8 ± 4.4 days following urine collections in TBI patients, as their Rancho Los Amigos scale of cognitive functioning score (i.e. level of movement and physical reactivity to internal and external stimuli) was too low to start any earlier (Hagen et al., 1972).

Sleep-wake assessments

Continuous actigraphy recordings lasted between 3 and 20 days. On average, patients wore the actigraph for 9.5 ± 4.2 days with no difference between groups (Table 1). Actigraphic recordings started 16.7 ± 11.8 days post-injury; this delay was shorter for the non-TBI than the TBI group (Table 1). Data were uploaded into dedicated software (Actiware 5.0) and activity counts were derived per 1 min epoch. For all days of actigraphy recording, activity counts were summed for the daytime (7:00-21:59) and for nighttime (22:00-6:59). Daytime and nighttime were identified according to the light/dark schedule of the hospital. Three variables were derived from actigraphic recordings, as previously described (Duclos et al., 2017). We measured consolidation of the 24 h sleep-wake cycle using the daytime activity ratio (DAR). The DAR represents the percentage of total 24 h activity occurring in the daytime [(daytime activity/24 h activity)x100]. The two variables used to assess nighttime sleep quality were 1) nighttime sleep duration, which is the number of minutes scored as sleep during the nighttime period (22:00-6:59); and 2) nighttime fragmentation index, which is an index of restlessness strongly correlated with the arousal index, as measured by polysomnography (Wang, Wong et al., 2008).

Assessment of melatonin rhythm

The entire contents of the urinary catheter was collected every hour and, after measuring total volume, a small quantity of urine was frozen at -20°C in 5 ml aliquots. Concentration of aMT6s (in ng/mL) was calculated in duplicate using Bühlmann ELISA kits (ALPCO Diagnostics). The kit used had a minimum detection limit of 1.5 ng/ml, an intra-assay precision of 7.1% and an inter-assay precision of 11.9%. The aMT6s data was used to calculate total 24 h excretion (ng). The onset and offset of melatonin secretion were estimated by the time of the sample at which the aMT6s concentration exceeded the average of the three preceding (onset) or following (offset) samples by 100% (Lushington et al., 1996; Benhaberou-Brun et al., 1999). Duration of melatonin secretion was defined as the interval between onset and offset. A cosinor analysis (Monk and Fort, 1983) was also carried out to quantify amplitude (difference between estimated peak value and estimated mean value, in ng/mL) and acrophase (clock time of the estimated peak value, in h) of the rhythm.

Statistical Analyses

Using Student's t-tests, TBI and non-TBI groups were compared on all variables assessed with actigraphy and aMT6s excretion. Chi-square statistics were used to compare nominal data. Bivariate correlation analyses were carried out using Pearson's correlation coefficient to assess associations between actigraphy and aMT6s variables in TBI patients. Given multiple comparisons, statistical significance was set at $P < 0.01$.

Results

Sleep-wake cycle and nighttime sleep quality assessed with actigraphy

Globally, the TBI group showed more altered sleep-wake cycle compared to the non-TBI group (see Table 2 for actigraphy results and Fig. 1 for typical actigrams of 4 TBI patients and 4 non-TBI patients).

Daytime activity ratio: Patients in the TBI group had lower DAR than those in the non-TBI group ($P < 0.001$), reflecting that their sleep and wake periods were more randomly dispersed throughout the day and night. When a threshold of 80% was used to denote a

consolidated sleep-wake cycle (Duclos et al., 2014), TBI patients also had significantly more days with a DAR < 80 % than non-TBI patients ($P < 0.0001$).

Nighttime (22:00-6:59) sleep duration: Patients in the TBI group had shorter nighttime sleep duration than the non-TBI group ($P < 0.01$). Sleep duration was as 5.9 ± 1.6 h in TBI patients, while non-TBI patients had a nighttime sleep duration of 7.0 ± 1.2 h.

Nighttime fragmentation index: TBI patients had a higher fragmentation index than non-TBI patients ($P < 0.01$), suggesting that their sleep was more restless.

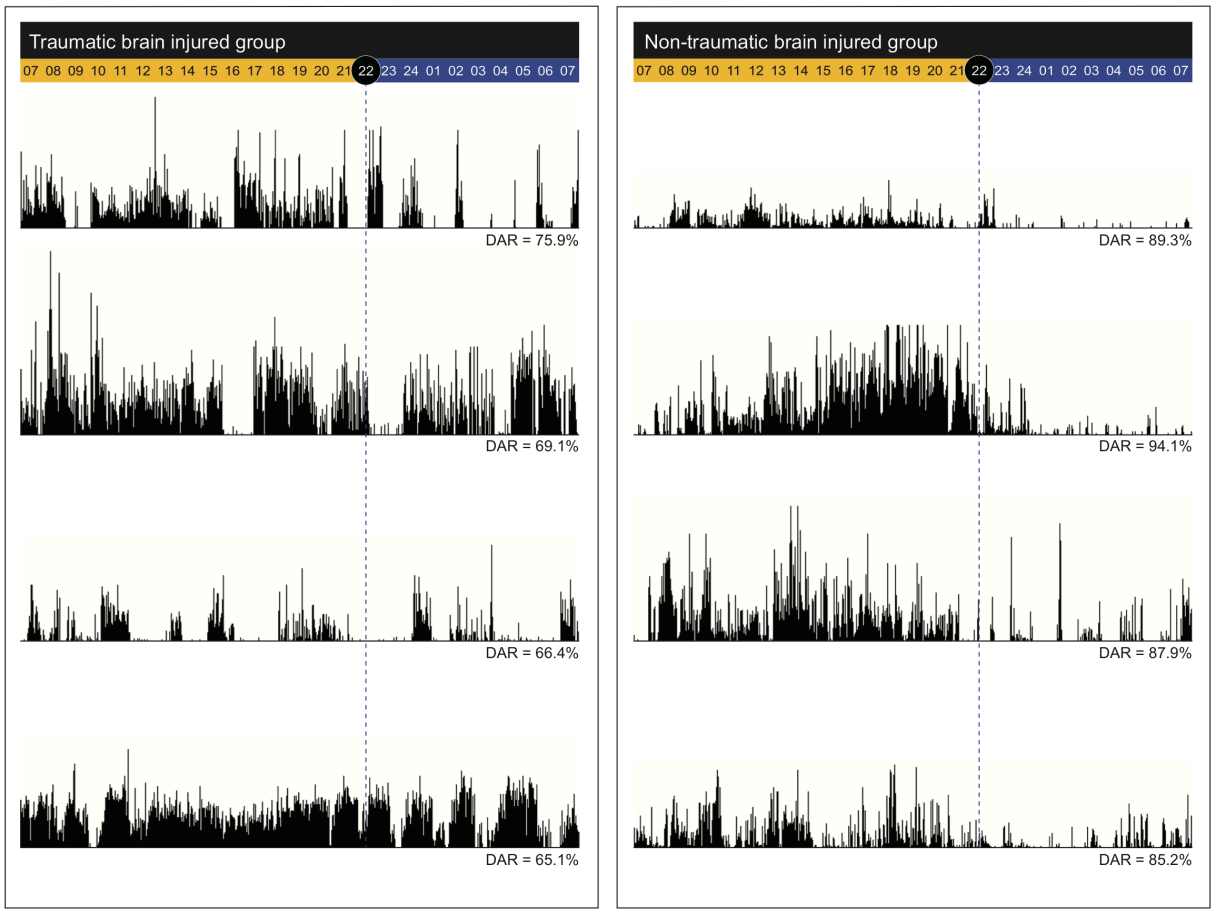

Figure 1. Example of actograms of TBI and non-TBI patients. Examples of typical actigraphic findings of four TBI patients (left panel) and four non-TBI patients (right panel). Total activity counts for each minute of recording are illustrated by vertical dark lines, on a scale of 0 to 1,000 activity counts. Daytime hours (07:00–22:00 hours) are shown in yellow and nighttime hours (22:00–07:00 hours) in blue. Daily daytime activity ratios (DAR) are indicated at the bottom of each actogram.

Table 2. Sleep-wake cycle and nighttime sleep characteristics (mean ± SD) in patients with (TBI) or without (non-TBI) traumatic brain injury

Actigraphy variables	TBI (n = 42)	Non-TBI (n = 35)	t-value	P-value
Mean DAR (%)	77.5 ± 9.4	84.6 ± 6.9	-3.690	<0.001
Days with DAR<80% (no.)	5.0 ± 4.0	1.7 ± 2.2	4.394	<0.0001
Mean nighttime sleep duration (min)	353.5 ± 96.6	421.2 ± 72.6	-3.236	0.0019
Mean fragmentation index	72.2 ± 30.0	53.5 ± 23.6	2.843	0.0059

DAR: Daytime activity ratio.

Melatonin rhythm estimated with aMT6s excretion

Of all participants recruited, 18 TBI and 16 non-TBI patients wore a urinary catheter when the study began and took part in urine collections. Urine collection took place 18.3 ± 12.3 days post-injury (TBI: 23.3 ± 14.1 days post-injury; Non-TBI: 12.5 ± 6.4 days post-injury). One TBI patient and one non-TBI patient were excluded from analyses because of missing data on many samples (see Supplementary Table 1 for demographic and clinical characteristics of patients who were included in melatonin analyses). When compared to TBI patients who did not take part in urine collections, TBI patients who took part in urine collections had more days of elevated intracranial pressure (7.3 ± 6.4 vs. 2.5 ± 4.2; $t(40) = -2.912$, $P < 0.01$). No differences were found for age, sex, GCS, cumulative dose of sedatives and analgesics administered in ICU, duration of ICU stay and hospital length of stay. Non-TBI patients who took part in urine collections did not differ from other non-TBI patients with regards to age, sex, cumulative dose of sedatives and analgesics administered in ICU, as well as ICU and hospital lengths of stay.

Hourly concentration of aMT6s excretion indicated the presence of a significant 24-h rhythm of melatonin production in both groups (Fig. 2). As shown in Table 3, there was no significant difference on any descriptive variables, including timing of secretion (onset, offset and acrophase), total excretion and estimated amplitude. None of the aMT6s variables was associated with sleep-wake variables in TBI patients, including the DAR, number of days with a DAR < 80 %, nighttime sleep duration and fragmentation index, as measured by actigraphy. These associations were still non-significant even when correlations were restricted to the first 72 h following urine collection (this analysis was possible in 10 patients).

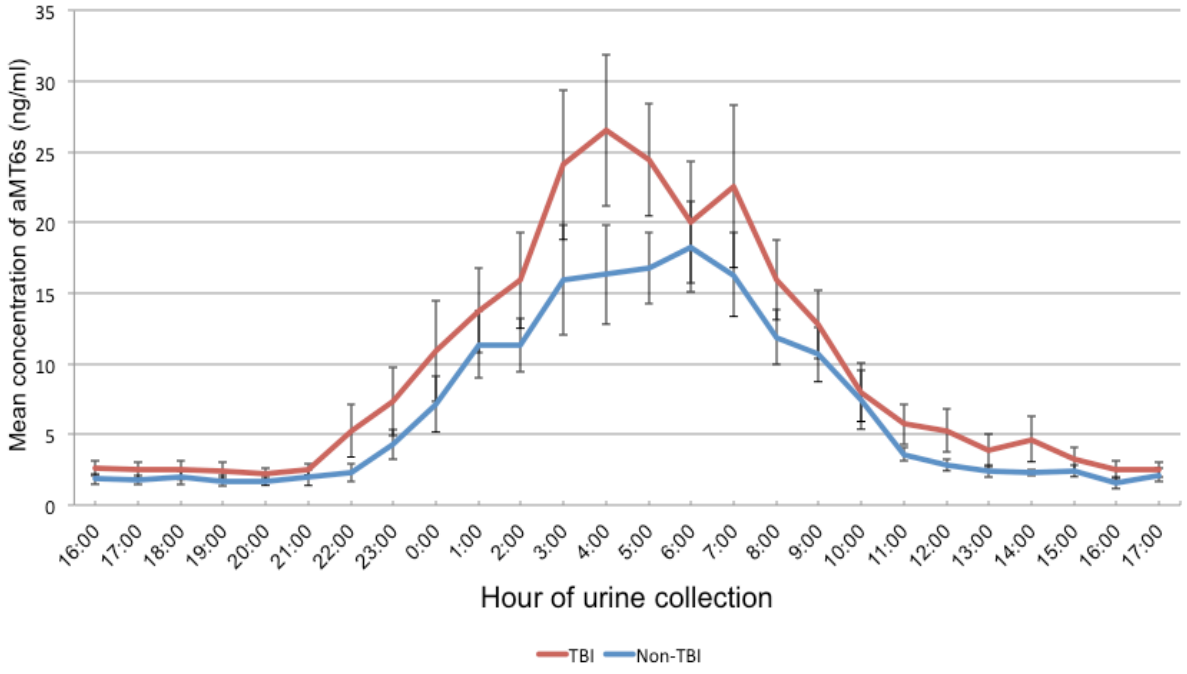

Figure 2. Rhythm of 6-sulfatoxymelatonin excretion of TBI and non-TBI patients. Profiles of urinary excretion of 6-sulphatoxymelatonin (aMT6s) over 25 h in TBI patients (in red) and non-TBI patients (in blue). Data points represent group means ± SEM. There was no significant group difference at any hour.

Table 3. Characteristics (mean ± SD) of 6-sulfatoxymelatonin (aMT6s) excretion and of circadian estimates for TBI and non-TBI groups

aMT6s excretion	TBI (n = 17)	Non-TBI (n = 15)	t-value	P-value
Total 24 h excretion (ng)	14371.5 ± 9934.2	13117.9 ± 5547.7	0.430	0.6706
Onset (h:min)	23:25 ± 2:22	23:40 ± 1:50	-0.336	0.7391
Offset (h:min)	8:07 ± 2:51	7:36 ± 1:41	0.615	0.5432
Duration of secretion (h)	8.7 ± 2.8	7.9 ± 2.0	0.894	0.3784
Circadian amplitude (ng/mL)	12.0 ± 7.5	8.2 ± 4.5	1.737	0.0927
Circadian acrophase (h:min)	5:08 ± 2:14	5:16 ± 1:32	-0.185	0.8541

Post-hoc analyses

Our TBI group had more severe overall injury than the non-TBI group, as denoted by clinical variables: higher ISS, longer ICU stay, longer hospital length of stay, and a higher cumulative dose of sedatives and analgesics administered in ICU. Some of these clinical variables were associated to sleep-wake variables in our TBI group, as measured by actigraphy. In fact, higher ISS was associated to a greater number of days with DAR < 80 % ($r = 0.415$, $p = 0.009$); and longer ICU stay was associated with a greater number of days with DAR < 80 % ($r = 0.485$, $p = 0.001$), shorter nighttime sleep duration ($r = -0.410$, $p = 0.007$), and higher fragmentation index ($r = 0.432$, $p = 0.004$).

A *post hoc* univariate ANCOVA with "ISS" as a covariate revealed that our group effects (TBI vs. non-TBI) were still significant, or nearly so, for our four actigraphy variables (P-values: DAR = 0.009, days with DAR < 80 % = 0.009; mean nighttime sleep duration = 0.003; fragmentation index = 0.018). A second univariate ANCOVA with "duration of ICU

stay" as a covariate revealed that our group effects (TBI vs. non-TBI) were no longer significant for any of our four actigraphy variables.

Discussion

This study assessed whether TBI specifically contributes to the sleep-wake disturbances observed in hospitalized patients, and tested whether circadian disruption is present and associated with the observed sleep-wake cycle disturbances in TBI patients. Using actigraphy, we showed that TBI patients have weaker sleep-wake cycle consolidation, as well as shorter and more restless nighttime sleep than non-TBI patients, hospitalized in a similar environment. Despite having a more disturbed sleep-wake cycle, TBI patients have a rhythm of melatonin production comparable to that of non-TBI patients, in both timing and amplitude. Finally, our study showed that characteristics of the melatonin rhythm are not associated to the sleep-wake disturbances observed in TBI patients during their hospital stay. Our study is the first to assess melatonin rhythm in hospitalized TBI-patients who are not mechanically ventilated and under continuous sedation, and also the first to use a hospitalized trauma population as a control group to compare sleep-wake and melatonin data, thus controlling for environmental and pharmacological factors influencing sleep.

Despite severe trauma and hospital environment, non-TBI patients had a nighttime sleep that was more sustained and of longer duration than TBI patients. Their sleep-wake cycle was also more consolidated. Therefore, our results suggest a direct or indirect role of the injured brain in the acute sleep-wake disturbances of TBI patients.

Surprisingly, we found that TBI patients had a normal circadian rhythm of melatonin production despite an absence of 24 h sleep-wake cycle. Both timing and amplitude were similar to those of non-TBI patients who did not have the same sleep-wake disturbances. In fact, the majority of patients were within the normal range of 24 h aMT6s excretion for healthy adults (Malhberg et al., 2006). Moreover, the timing of melatonin production reflected a normal circadian phase in relation to nocturnal sleep (Tzischinsky et al., 1993). This finding clearly excludes the possibility that the brain injury impairs the generation of a normal circadian signal by the hypothalamic circadian clock. Furthermore, the absence of correlation

shows that the circadian timing or amplitude was not related either to nighttime sleep variables or to sleep-wake cycle consolidation.

Contrary to the results of the present study, previous studies systematically found a disruption in melatonin secretion (Paparrigopoulos et al., 2006; Paul and Lemmer, 2007; Seifman et al., 2014). This discrepancy between our results and previous studies may be due to the fact that patients in previous studies were tested in the first days post-injury, were receiving continuous sedation and analgesia at the time of testing, and were mechanically ventilated. Conversely, our study measured the sleep-wake cycle and melatonin rhythm in the waking stage after TBI, being close to the injury itself but enabling the assessment of a more naturally occurring sleep-wake cycle and melatonin rhythm than in past studies, but doing so in the acute phase. Moreover, quantifying urinary concentration of aMT6s on an hourly basis also provided us with the ability to assess melatonin phase, which previous acute studies were unable to do.

Some studies have shed light on wakefulness disturbances following TBI, which may contribute to the sleep-wake cycle disturbances observed in our study. One hypothesis suggests a deficiency in wake-promoting neurotransmitters, namely hypocretin-1 and histamine. Findings from fatal TBI in humans showed a loss of both histaminergic and hypocretin neurons in the hypothalamus (Baumann et al., 2009; Valko et al., 2015). In patients having survived TBI, reduced hypocretin-1 cerebrospinal fluid (CSF) levels were observed 1-4 days post-injury (Baumann et al., 2005), with a return to normal values after 6 months (Baumann et al, 2007). Patients with moderate to severe TBI, and those who reported sleepiness, had the lowest hypocretin-1 levels. A second hypothesis suggests that a disconnection in the ascending reticular activating system (ARAS), a brain pathway that is key in regulating wakefulness, could also cause disruptions of wakefulness. As most ARAS regions, namely the pons, the hypothalamus and the thalamus, are vulnerable to TBI (Crompton, 1971; Edlow et al., 2013; Delano-Wood et al., 2015), disconnection in the ARAS could have a direct impact on TBI patients' ability to remain awake for extensive periods of time, therefore leading to frequent short bouts of sleep. Two recent cases of mild TBI support this hypothesis (Jang & Kwon, 2016), showing that lesions of the pontine reticular formation

and the intralaminar thalamic nucleus were associated with post-traumatic hypersomnia and fatigue in the chronic phase post-injury. In another case of a mild TBI patient with excessive sleepiness 10 weeks post-injury, which had worsened by 16 months post-injury (Jang & Kwon, 2017), no significant abnormality was found in the dorsal and ventral lower ARAS 10 weeks post-injury, but these regions showed thinning and partial tearing 16 months post-injury, with concurrent aggravation of the ARAS and daytime sleepiness. Further studies are required to assess the contribution of wakefulness disruptions to acute sleep-wake disturbances.

Although no statistically significant differences were found between our groups, TBI patients had a mean amplitude of the melatonin rhythm nearly twice a high as that of non-TBI patients. A recent study in acute pediatric TBI showed an increase in melatonin production in sedated and mechanically ventilated TBI pediatric patients, when compared to other critically ill children, without TBI, hospitalized in pediatric ICU (Marseglia et al., 2017). Serum melatonin levels were assessed every 3 to 4 h between 22:00 and 12:00. This difference was even more pronounced when TBI patients were compared to values reported in the literature for healthy children of similar age. The authors explained this increase in melatonin levels as a possible response to oxidative stress and/or inflammation due to TBI. Another study investigated the link between melatonin levels and markers of oxidative stress in adults with severe TBI and hospitalized in the ICU, in the first 10 days post-injury (Seifman et al., 2008). The authors found that melatonin levels in the CSF increased over time and were positively associated with isoprostane CSF levels, a compound produced in response to free radicals. Interestingly, melatonin has antioxidant properties by stimulating antioxidant enzymes and upregulating mRNA levels of superoxide dismutase (Rodriguez et al., 2004). It also reduces neuroinflammation and apoptosis in mice (Zhao et al., 2015). Given the oxidative and inflammatory processes triggered by TBI (Rodriguez-Rodriguez et al., 2014), melatonin production may be increased in the acute phases post-injury as a defense mechanism. Conversely, increased melatonin production in the TBI patients could be evidence of a normal hypothalamic-pineal circuit trying to normalize sleep and circadian patterns, but not succeeding as downstream processes are disrupted. The aforementioned effects of melatonin are probably dependent on overall brain function. Future studies should aim to assess whether

this increase is specific to the TBI in the acute phase, and whether melatonin administration has any effect on sleep-wake patterns or neuroinflammation.

Limitations

Although our groups were well matched in terms of age, sex, and absence of pre-existing neurological, psychiatric, or sleep disorders, the non-TBI group had lower ISS, shorter ICU stay, and a lower cumulative dose of sedatives and analgesics administered in ICU compared to the TBI group. These group differences we expected given the nature of their injuries. Higher ISS and longer ICU stay were both correlated with poorer sleep in the TBI group, suggesting that more complex TBI/injuries are linked with more altered sleep-wake cycles. When we statistically controlled for ISS and duration of ICU stay, we found that it was not possible to isolate the effect of the TBI from the effect of duration of ICU stay. Although an ideal control group would match the clinical characteristics of our targeted patients, the very nature and demographics of moderate-severe TBI patients make this difficult to attain. What can be drawn from these associations between clinical and sleep-wake variables is that injury severity and treatment intensity/duration are associated with more sleep-wake disturbances. Whether they are due to the TBI itself or to longer ICU stay duration remains to be determined. Dissociating the TBI from concomitant injuries, the ICU environment and the treatment intensity remains an important challenge in understanding the direct role of the TBI in acute sleep-wake disturbances.

Unfortunately, we were not able to assess melatonin and actigraphy simultaneously in all patients, given the limitations imposed by actigraphy, which requires a minimal level of physical activity and reactivity to the environment. However, when this occurred, melatonin measures began 2.8 ± 4.4 days prior to actigraphy recording. This suggests that melatonin production was unlikely to have become disturbed once actigraphy started, given that melatonin disturbances have generally been reported closer to injury, when patients are still continuously sedated and mechanically ventilated (Paparrigopoulos et al., 2006; Paul and Lemmer, 2007; Seifman et al., 2014).

Clinical impacts

Using actigraphy, this study showed that hospitalized moderate to severe TBI patients have poorer sleep-wake cycle consolidation, shorter nighttime sleep duration and more sleep fragmentation than other hospitalized trauma patients without TBI. These results point to the role of TBI in altering sleep and wake. Despite severe sleep-wake disturbances, TBI patients have a robust melatonin rhythm, which was not associated to the observed sleep-wake disturbances during the hospital stay. Although many factors could influence the sleep-wake cycle of hospitalized TBI survivors, our study suggests that neural mechanisms other than the circadian system may be responsible for post-TBI sleep-wake disturbances. Impacts of presenting such a poor sleep in the acute and post-acute stages of TBI on neuronal, cognitive and functional recovery are still emerging, but tend to show that sleep loss and poor brain recovery are associated (Holcomb et al. 2016; Duclos et al., 2017). Since sleep is a modifiable behavior, it could be a promising target to optimize recovery after TBI.

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Supplementary Material

Supplementary Table 1. Demographic and clinical characteristics of sub-sample patients of who were included in melatonin analyses

	TBI (n = 17)	Non-TBI (n = 15)	t-value or X^2	P-value
Age	30.3 ± 13.3	31.1 ± 13.7	-0.176	0.8617
Sex	14 men; 3 women	12 men; 3 women	0.029	0.8649
GCS at admission	6.7 ± 3.2	14.9 ± 0.4	-9.815	<0.000001
Injury Severity Score	32.1 ± 10.3	22.8 ± 8.0	2.757	0.0100
Cumulative dose of sedatives and analgesics administered in ICU (g)	39.3 ± 31.3	0.86 ± 0.14	4.045	0.0004
Length of ICU stay (days)	26.7 ± 13.5	5.3 ± 3.6	5.934	<0.00001
Hospital length of stay (days)	50.9 ± 21.2	26.8 ± 11.9	3.890	0.0005
Actigraphy recording (days)	12.4 ± 3.4	10.1 ± 2.7	2.024	0.0523
Start of actigraphy recording (days post-injury)	24.9 ± 13.5	11.6 ± 6.0	3435	0.0018
Start of urine collection (days post-injury)	23.3 ± 14.1	12.5 ± 6.4	2.725	0.0106

GCS: Glasgow Coma Scale; ICU: Intensive Care Unit

Chapter III: General Discussion

1. Overall study conclusions

SWD are among the most persistent and disabling consequences of TBI, and they impact both the outcome and the quality of life of survivors. Though clinical observations suggest they arise early following injury, their nature, origin and evolution had not been previously investigated. The principal objective of this thesis was to characterize the sleep and circadian rhythms of hospitalized patients with moderate to severe TBI, and investigate the associations between SWD and short-term neurological and cognitive recovery. By comparing TBI patients to other hospitalized trauma patients, without TBI, we isolated the effect of the brain injury on sleep and circadian rhythms from that of the hospital environment and other trauma-related factors. This thesis contributes to the preliminary understanding of acute post-TBI SWD and their potential implications, on which further research can build in order to improve sleep and optimize recovery.

The first two articles of this thesis (Articles 1 & 2) reviewed the introductory concepts of sleep. Article 1 described normal sleep and its role in cognitive functioning, exposed the characteristics of sleep in the hospital setting, and outlined the consequences of sleep disturbances on functional outcome in the context of TBI. Article 2 surveyed the literature and current state of knowledge with regards to sleep-wake disturbances following TBI of all severities, in both acute and chronic stages. These articles described the importance of sleep following TBI, and laid the groundwork for understanding the current gaps in the literature, highlighting the necessity of objective sleep-wake measures in acute TBI, while patients are hospitalized and no longer continuously sedated.

In Article 3, we characterized the quality and evolution of the sleep-wake cycle of TBI patients, which had not been previously done. We found that the sleep-wake cycle was severely disturbed, but improved for 50% of patients during their hospital stay. Patients whose sleep-wake cycle consolidation improved had lower disability and had emerged from PTA at hospital discharge. This article highlighted the probable association between sleep and recovery in the acute phase post-injury. Furthermore, we developed a new analytic approach, the DAR, to characterize the sleep-wake cycle in a context where the circadian sleep-wake

cycle is absent and where no standard approach can be used. Finally, we showed that measuring the sleep-wake cycle with actigraphy is possible in this population, even in an acute care setting.

Article 4 exposed the case of a severe TBI patient we were able to assess during two consecutive hospital stays, representing both the acute and subacute phases post-injury. This patient had severe sleep deprivation and fragmentation, as well as an absence of a consolidated sleep-wake cycle during his first hospital stay. The sleep deprivation experienced by this patient was much more severe and prolonged and than that of other TBI patients evaluated in Article 3, and may have contributed to the subsequent psychiatric condition having led to his re-hospitalization. In fact, this patient had persistent PTA, cognitive deficits and psychiatric symptoms, despite significant improvements in sleep-wake cycle consolidation from his first to his second hospital stay. This case demonstrates how a patient can have drastically different sleep-wake patterns in the same environment, according to recovery stage.

Article 5 showed that the consolidation of sleep and wake states evolves synchronously with the recovery of consciousness and cognition in the acute phase of TBI. By assessing the day-to-day evolution of consciousness, cognitive function and the sleep-wake cycle, we found that they all evolved in parallel. This association sheds light on the pathophysiology of post-TBI SWD, suggesting that alterations in consciousness are strongly associated to sleep, and therefore, that the hospital environment only partly accounts for post-TBI SWD. Although we were not able to identify a causal relationship between sleep and the recovery of consciousness and cognition, this article suggests that assessing the sleep-wake cycle in acute TBI could be a useful clinical tool to monitor overall neurological evolution and recovery.

In Article 6, we performed one night of ambulatory PSG at the bedside in both TBI and non-TBI trauma patients. Though we expected to find significant alterations in sleep stages and architecture in our TBI group, TBI patients had normal elements of sleep, such as sleep spindles, k-complexes, and normal proportions of each sleep stages. However, TBI patients had earlier sleep onset and longer nighttime sleep duration, but with greater fragmentation, than non-TBI patients. In both groups, sleep was fragmented, with low sleep efficiency, reflecting poor sleep quality, which most likely reflects non-specific factors associated with

the physical trauma and hospital environment. Although this article demonstrated the feasibility of assessing sleep with PSG in the acute phase of TBI, PSG at this stage post-injury reveals little information able to distinguish TBI patients from other non-TBI trauma patients. This gold-standard method for measuring sleep is only feasible when patients are no longer in a confused/agitated state, given their intolerance to study materials during PTA, which restricts the use of PSG to a later phase, closer to hospital discharge. At this stage, the sleep-wake cycle has already improved for most patients, as shown in Article 3. For the early recovery stages, and because it enables a longitudinal assessment of the sleep-wake cycle, actigraphy remains the best tool to study sleep-wake patterns in acute TBI.

Article 7 showed that TBI patients have poorer sleep-wake cycle consolidation and nighttime sleep quality than other hospitalized trauma patients, without TBI, hospitalized in the same environment. These results confirm the role of TBI in altering sleep and wake states. Contrary to our main hypothesis that SWD were caused by a deregulation of the master circadian clock, this article points in a different direction: despite having more severe SWD, TBI patients have melatonin circadian rhythm, and this rhythm is not associated with the observed SWD. This enables us to conclude that neural mechanisms other than the circadian system may be responsible for post-TBI SWD.

The following sections will highlight the implications of our findings, possible causal factors, and potential confounding factors in relation of the findings presented in this thesis. Moreover, measures to improve sleep and wake and future research priorities will be proposed.

2. Brain mechansims that could explain acute sleep-wake disturbances

2.1. Disruption of sleep- and wake-regulatory pathways

Given that the recovery of a 24 h sleep-wake cycle is associated with improvements in consciousness and cognition, a possible interpretation may be that brain damage associated

with TBI, such as focal lesions or diffuse axonal injury, disrupts the pathways that regulate sleep and/or wakefulness.

Wakefulness is promoted by an ascending reticular activating system (ARAS), which connects the reticular formation of the pons to cortex through of two major branches: one dorsal branch innervating the thalamus, and another, the ventral branch, extending into the forebrain and posterior hypothalamus and comprising cholinergic, noradrenergic, serotoninergic, dopaminergic, and histaminergic neurons in the pedunculopontine and laterodorsal tegmental nucleus, locus coeruleus, dorsal and median raphe nucleus, and tuberomammillary nucleus, respectively (Schwartz & Roth, 2008). Wakefulness occurs when a strong activation from the pons reaches the cortex. Conversely, sleep is mainly induced by the activation of GABA-ergic neurons of the ventrolateral preoptic nucleus (VLPO) of the hypothalamus, the dorsal raphe nucleus, the periaqueductual gray, and the locus coeruleus (Zielinski, McKenna & McCarley, 2016) that inhibit this activation from the pons.

Many regions of the ARAS, particularly the pons, the hypothalamus and the thalamus, are vulnerable to TBI (Edlow et al., 2013; Delano-Wood et al., 2015; Crompton, 1971). Recent cases of mild TBI support this hypothesis, showing that lesions and thinning of the dorsal and ventral lower ARAS are associated to hypersomnia, daytime sleepiness and fatigue in the chronic phase post-injury (Jang & Kwon, 2016; Jang & Kwon, 2017). Damage to one or more of the structures involved in the ARAS could, for example, reduce TBI patients' ability to remain awake for extensive periods of time. Concordant with this hypothesis, rodent models of both acute and chronic TBI have previously shown that mice having sustained TBI spend more time in NREM sleep during their active phase and have difficulties sustaining consolidated wake (Willie et al., 2012; Lim et al., 2013; Skopin et al., 2015; Sabir et al., 2015). This inability to maintain wakefulness was present even when sleep architecture was normal, suggesting that alterations of wakefulness mechanisms independent of sleep quality may be involved. Overall, this indicates a strong likelihood of wakefulness, rather than sleep disturbance.

Unfortunately, most of the damage induced by TBI may go unnoticed in routine brain imaging. Most mTBI patients, and even some moderate-severe TBI patients, do not exhibit

abnormal findings on CT scans, yet suffer important symptoms, including persistent SWD (Hou et al., 2013). One of the challenges of characterizing the extent of structural brain damage TBI survivors is the difficulty in carrying out MRIs in the acute phase post-injury. Future studies should aim to use MRI to assess the integrity of brain structures implicated in the initiation and maintenance of sleep and wake.

2.2. Impairment of neurotransmitters involved in sleep-wake regulation

Some studies have pointed to an alteration in wake-promoting neurostransmitter systems, namely orexin (a.k.a. hypocretin) neurons of the lateral hypothalamus and histaminergic neurons of the tuberomammillary nucleus, as a possible explanation for post-TBI SWD disturbances. Glutamate also seems to contribute to sleep-wake changes and as well as cognitive function, and could offer potentially insightful information into the association between the recovery of the sleep-wake cycle and cognitive function.

Orexin and Histamine

Orexin is a wake-promoting neuropeptide known to promote wakefulness and stabilize the sleep-wake cycle (Thomasy et al., 2017). Orexin receptors are located in the locus coeruleus, tuberomamillary nucleus, the median raphe nucleus and reticular formation, and they most likely upregulate monoaminergic neuronal populations (Schwartz & Roth, 2008).

A recent mouse study of mild to moderate TBI showed that at 15 days post-injury, wakefulness was decreased and NREM sleep was increased, while a severity-dependent reduction in orexin and cholinergic neurons was observed (Thomasy et al., 2017). Conversely, levels of melanin-concentrating hormone neurons, which have sleep-promoting effect, were unaltered. The authors concluded that TBI reduces the ability to maintain wakefulness, and that this effect is mainly mediated by a reduction in orexin-producing neurons. Other rodent studies have also reported decreased levels of hypothalamic orexin (Willie et al., 2012) and decreased orexin neuronal activation during wakefulness (Lim et al., 2013). A recent study in rats reported fewer histaminergic neurons in the tubermammilary nucleus following TBI, and the number of histaminergic-producing neurons inversely correlated to the quantity of sleep

per 24 h period (Noain et al., 2017). These animal studies point to a dysfunction of both orexin and histamine following TBI.

In humans, fatal TBI has been associated with a loss of histaminergic and orexin neurons in the hypothalamus (Baumann et al., 2009; Valko et al., 2015), while reduced levels of orexin-A (hypocretin-1) have been observed in the CSF of TBI survivors in the first four days post-injury (Baumann et al., 2005). However, the TBI patients studied four days post-injury may have still been under continuous sedation, though this was not specified in the article (Baumann et al., 2005), and this could influence the activity of orexin neurons. Indeed, anesthetic-induced unconsciousness may result from the interaction of anesthetics with the neural circuits that regulate sleep and wake (Brown, Lydic & Schiff, 2010), suggesting that anesthetics could have a direct influence on the activity of orexin neurons. Orexin and histamine levels may therefore be more severely depleted in TBI patients unable to emerge from coma, or in the early stages of consciousness recovery.

The sleep-wake pattern observed in our acute TBI patients may not fully reflect a wakefulness disturbance, especially in the first days of actigraphy recording. In fact, in these first days of recording, patients experience high levels of activity/wakefulness, during both day and night, interspersed with brief periods of rest/sleep. This pattern of sleep and wake fragmentation may not necessarily coincide with an inability to intiate wakefulness, but could signal a deficiency in the maintenance of wakefulness.

Glutamate

Given the association between recovery of the sleep-wake cycle and cognitive function in acute TBI, as we have shown in this thesis, glutamate could have an important influence on both, and may partly explain their association.

Glutamate in an excitatory neurotransmitter known to regulate the sleep-wake cycle, but also has a crucial role in learning and memory through its contribution to synaptic transmission and plasticity (McEntee & Crook, 1993; Riedel, Platt & Micheau, 2003). Emerging data suggest that lowered glutamate levels may contribute to both decreased wakefulness and cognitive dysfunction following TBI. Studies have shown decreased levels of

endogenous branched chain amino acids (BCAAs), which are required for *de novo* cerebral glutamate synthesis (Sandsmark, Eliott & Lim, 2017), following TBI in humans (Sharma, Lawrence & Hutchison, 2017). A recent mouse study also reported decreased glutamate levels within the presynaptic terminals synapsing onto orexin neurons in the hypothalamus one week post-TBI (De Luche et al., 2015), suggesting decreased excitatory inputs onto the orexinergic system (Sandsmark, Eliott & Lim, 2017). Decreased glutamate levels may therefore comprise orexin neuron function following TBI.

Glutamate plays an essential role in the regulation of REM sleep, activating the principal EEG components of REM sleep through projection to the basal forebrain, and sending spinal projections that regulate REM sleep atonia (Lu et al., 2006). The role of glutamate in the REM-on/REM-off switch suggests that alterations in glutamate levels could alter sleep architecture, in addition to modifying EEG activity and compromising muscle atonia during REM sleep. Conversely, our PSG results suggest unaltered proportions of REM and NREM sleep in hospitalized TBI patients, when compared to other trauma patients without TBI. This unaltered sleep architecture suggests a certain preservation of glutamate levels, at least sufficiently to maintain the REM-on/REM-off switch. However, given that sleep architecture was not measured earlier following injury, it is possible glutamate levels renormalized once patients reached a level of consciousness and cognitive functioning sufficient to enable PSG recording.

2.3. Defective switching mechanism between sleep and wake

The interaction between the VLPO and the ARAS acts as an "on-off" switch, regulating sleep and wakefulness and promoting rapid and clear transitions between both states (Saper, Scammell & Lu, 2005). Any interruption in these circuits, such as lesions or axonal injury, can disrupt the "on-off" switch, blurring the distinction between sleep and wake. An individual with a faulty "on-off" switch will therefore drift slowly and frequently back and forth between both states, spending much time in an in-between state, in which arousal is not optimal and sleep is not fully initiated (Saper et al., 2010). A defective switching mechanism is also hypothesized to cause to an intrusion of sleep elements into wakefulness, and of wakefulness elements into sleep (Schwartz & Roth, 2008). Such intrusions have been

documented following TBI in both humans and mice, such as presence of delta activity during wakefulness (Gosselin et al., 2009; Modarres et al., 2016), or enhanced beta power during NREM sleep (Arbour et al., 2015).

The VLPO and orexin neurons both play a central role in the switching mechanisms between sleep and wake. VLPO lesions will not only reduce sleep duration, but will reduce the stability of both sleep and wake, resulting in frequent transitions (Lu et al., 2000). In fact, damage to the VLPO is more susceptible to causing sleep-wake fragmentation than lesions to arousal cell groups (monoaminergic and cholinergic) (Saper et al., 2010). Conversely, orexin neurons seem to be required to anchor the "on-off" switch of sleep and wakefulness (Saper et al., 2005). A decrease of orexin neurons can lead to faulty switching between states, and poor maintenance of both states (Saper, Chou & Scammell, 2001). In fact, orexin knockout mice have normal duration of sleep and wake per hour, when compared to wildtype mice, but have very brief sleep and wake bouts, with much more frequent transitions between states (Mochizuki et al., 2004). Moreover, the fragmentation of sleep and wakefulness is not a consequence of altered sleep homeostatis or poor circadian control, as these knockout mice are able to maintain similar sleep-wake behaviour during constant darkness, and have normal recovery sleep following sleep deprivation. Overall, the sleep-wake cycle described in the case of VLPO lesions and decreased orexin closely resembles the sleep-wake pattern observed in our acute TBI patients, and may suggest that a defective switching mechanism between sleep and wakefulness is responsible for the observed SWD.

2.4. Disturbance in the homeostatic process of sleep regulation

Post-TBI SWD could be induced by a disturbance in the sleep homeostatic process (Borbély, 1982). A disturbance in the homeostatic process could comprise alterations in the speed at which sleep pressure, quantified through the amount of SWA during NREM sleep (Achermann et al., 1993; Robillard et al., 2010), accumulates during wakefulness and/or dissipates during sleep. In a recent mouse model of acute mTBI, researchers found an increased quantity but decreased global coherence of EEG slow wave counts during enforced wakefulness, which they take to signal a deregulation of the homeostat of sleep and wake post-TBI (Modarres et al., 2016).

An injured brain may require to provide a high level of effort, in the form of higher neuronal activity, to rebuild damaged cells and synapses. Considering that the need for sleep is directly correlated with the level of neuronal activity (Kattler, Dijk & Borbély, 1994), patients may experience a faster buildup of sleep need. Importantly, sleep homeostatic regulation may not be restricted to a global brain phenomenon, but may have local features, related to how various brain regions are solicited during wakefulness (Krueger & Obal, 1993). In fact, increased solicitation of specific brain regions has been associated with increased SWA in these regions (Kattler et al., 1994), reflecting that a greater recovery, in the form of synaptic downscaling, is needed (Tononi & Cirelli, 2006; Tononi & Cirelli, 2014). Acute TBI patients do seem to have short and fragmented periods of sleep and wake throughout the day (Articles 3, 4, 5, 7), which, if taken to signal an inability to maintain wakefulness, may suggest increased sleep pressure. However, the fact that daytime sleep is also not sustained for very long periods seems contrary to what would be expected if sleep pressure was, in fact, elevated. In our PSG study (Article 6), TBI patients showed a significantly longer duration of nocturnal sleep and earlier nighttime sleep onset, which may reflect an intensified sleep pressure. However, we cannot specifically draw such conclusions given that SWA was not measured.

The presence of increased delta activity during wake (Modarres et al., 2016; Gosselin et al., 2009) could also reflect the intrusion of sleep-like elements into wakefulness, either as a result of a defective "on-off" switch regulating sleep and wake, as previously mentioned, or of a local deregulation of homeostatic sleep pressure. Evidence in rats suggests that the brain can have local bouts of sleep during wakefulness, in which populations of neurons can suddenly go "offline" (Vyazovskiy et al. 2011). This phenomenon of local sleep could also explain EEG slowing during wakefulness (Modarres et al., 2016), driven by an imbalance of local neuronal solicitations during wake and/or by local brain damage. Identifying the regions from which EEG slowing originates during wakefulness could provide powerful insight into brain functioning, and may help infer the location and extent of brain damage.

Future studies should aim to investigate whether a dysregulation of the homeostatic drive contributes to the observed SWD in acute TBI. Namely, it would be interesting to assess the temporal and topographical dynamics of SWA buildup and dissipation. However, the

challenge of using PSG and/or EEG early in the acute phase, and at different time points during the recovery of consciousness remains substantial.

2.5. Inflammation

Is it possible that the inflammatory cascade that follows TBI contributes to acute sleep alterations, and as inflammation resolves, such alterations improve. Compelling evidence points to a possible link between inflammation and SWD.

Acute inflammatory response occurring after TBI results in the secretion of mediators of inflammation, known to increase sleepiness and the duration of SWS. More specifically, proinflammatory cytokines have also been shown to modulate sleep. In rodent studies, an injection of Interleukin 1 beta (IL-1β) or Tumor necrosis factor alpha (TNF-α) increases NREM sleep duration and suppress REM sleep in a dose-dependent fashion (Fang, Wang & Krueger, 1998; Terao et al., 1998; Kubota et al., 2002; Krueger, 2008; Imeri & Opp, 2009). Conversely, animal models also show that inhibition of IL-1β and TNF-α decreases spontaneous NREM sleep (Opp & Krueger, 1991; Opp & Krueger, 1994; Takahashi et al., 1995; Takahashi et al., 1996). Antibodies of IL-1β (i.e. anti-IL-1β) inhibit sleep rebound following sleep deprivation in rats, suggesting a potential role for IL-1β in the homeostatic regulation of sleep (Opp & Krueger, 1994). Moreover, the increase of TNF-α following TBI could influence sleep through its action on orexin and melatonin, as TNF-α temporarily inhibits melatonin synthesis in the rat (Fernandes et al., 2006), and suppresses the neuronal activity of orexin by degrading the mRNA of its precursor (Zhan et al., 2011). It has also been shown that knockout mice for both receptors of TNF-α have higher levels of orexin mRNA than wild type mice (Kapas et al., 2008).

In summary, the principal components of the inflammatory response following TBI seem capable of inducing an increase in NREM sleep, a decrease in REM sleep and a modulation of SWA. Despite the compelling link between inflammation and sleep, only one study has suggested an association between IL-1β and increased sleep duration in the hour following mTBI in the mouse (Rowe et al., 2014). Though our PSG study revealed no specific differences in sleep architecture among our TBI population, our control group of non-

TBI trauma patients probably also experienced similar inflammatory processes in relation to their injuries, making it difficult to draw any specific conclusions on the association between inflammation and sleep in our population. Future studies could aim to assess levels of various inflammatory markers and their possible association with the sleep-wake cycle characteristics in acute TBI.

3. Potential confounding variables

The following section highlights the confounding factors that were most likely present, to some degree, for a majority of the patients tested in this thesis. However, other factors that may arise following TBI or traumatic injuries, including psychological symptoms (e.g. anxiety, depression, post-traumatic stress disorder) and neuroendocrine dysfunction (e.g. hypopituitarism, impaired growth hormone release, hypo/hyperthyroidism, hypothalamic gonadism, and abnormal adrenocortical function) have also been shown to be associated to sleep-wake quality and fatigue (Frieboes et al., 1999; Ouellet, Beaulieu-Bonneau & Morin, 2006; Parcell et al., 2006; Bushnik, Englander & Katznelson, 2007), and should be further investigated in relation to SWD in acute TBI.

3.1. Sedative and analgesic medication

In addition to undergoing a period of continuous sedation in the first days following TBI, nearly all patients included in the articles of this thesis were taking some form of sedative or analgesic at the time of actigraphy recording, or in the days prior. Opioid analgesics, such as morphine, fentanyl and dilaudid, are known to infuence sleep by suppressing REM sleep and SWS (N3), followed by a subsequent rebound (Rosenberg, Rosenberg-Adamsen & Kehlet, 1995; Sucheki, Tiba, & Machado, 2012). Opioids have also been shown to decrease N3 and REM sleep, and increase N2 sleep (Rosenberg et al., 1995; Dimsdale et al., 2007), which could contribute to more frequent awakenings and less restorative sleep if experieced by TBI patients. Other medications given to hospitalized patients, such as psychostimulants and antibiotics, have also been linked to insomnia (e.g. amantadine, piperacillin, tazobactam), while others (e.g. mirtazapine and pregabalin) have been shown to increase the quantity and quality of sleep in healthy populations (Mollayeva & Shapiro, 2013).

Sedatives and analgesics are heavily used in the acute phase of TBI, as soon as patients are admitted to the ICU. In fact, TBI patients are generally continuously sedated for several days, until they reach medical stability. Sedatives and analgesics are used to facilitate mechanical ventilation, prevent agitation, reduce pain, and they most likely improve ICP and cerebral perfusion (Jacobi et al., 2002; Arroliga et al., 2005; Mehta et al., 2006; Mehta, McCullagh & Burry, 2011; Flower & Hellings, 2012; Barr et al., 2013; Burry et al., 2014). Sedatives and analgesics have adverse effects on circadian rhythms, particularly when sedatives are administered at a time other than during the biological night, as they deregulate sleep-wake cycle mechanisms more heavily (Dispersyn et al., 2008). Given that circadian disturbances can hinder proper physiological, behavioural and cognitive functioning (Gronfier et al, 2009), which can slow overall recovery, more studies are needed to evaluate the direct impact of sedatives on circadian function. Human studies that have evaluated the impact of anesthesia on circadian rhythms have done so in hospitalized patients who had recently suffered one or multiple injuries, undergone surgery, or had an active infection. It is therefore difficult to isolate the effects of the anesthetic from that of the physical insults, pain, and medication administered following anesthesia. Indeed, these medical conditions can engender a cascade of circadian disturbances (Dispersyn et al., 2008; Coogan & Wise, 2008). What is more, the loss of circadian synchronizers during the period of anesthesia or heavy sedation (e.g. light-dark cycle, regular meals, postural changes or physical activity, social stimuli) could also further disturb the master circadian clock, independently of medication (Mistlberger & Rusak, 2011).

What remains unclear is whether sedatives share the restorative properties of sleep. A one-hour period of isoflurane anesthesia, during which slow waves are present, has been shown to decrease SWA following sleep deprivation in the rat, when compared to a mock condition (Nelson et al. 2010). This suggests that the slow waves induced by anesthesia may be able to substitute sleep slow waves in the recovery from sleep deprivation. However, isoflurane anesthesia following REM sleep deprivation does not reduce subsequent REM sleep rebound (Mashour et al., 2010). It has previously been shown that prolonged sedation with propofol does not result in increased SWA in the subsequent sleep period, suggesting that propofol anesthesia is not akin to sleep deprivation (Tung & Mendelson, 2004). In fact,

propofol anesthesia generates slow waves similar to those generated in SWS, sharing the same spatial origin and propagation pattern (Murphy et al., 2011). Conversely, dexemdetomidine seems able to generate not only slow waves, but also spindles, as observed in stage N2 sleep (Huupponen et al., 2008; Brown, Purdon & Van Dort, 2011). A rat study has also demonstrated that dexedetomidine exerts its anesthetic effect by activating the endogenous sleep network: by inhibiting the locus coeruleus, the VLPO becomes active and increases the release of GABA, in turn inhibiting activity in the tuberomamillary nucleus (Nelson et al., 2003). Though the way sedatives and analgesics interact with an injured brain to influence sleep and circadian rhythms remains unclear, these studies suggest that the sedative effect of certain molecules could be produced in part by their action on the neuronal circuits generally involved in the initiation and/or maintenance of natural sleep. General anesthesia may even help recovery from sleep deprivation while sleep deprivation may potentiate the anesthetic's effects, highlighting the interconnectivity of anesthesia and sleep (Tung et al., 2003; Tung, Szafran & Mendelson, 2002).

More studies are needed to understand the influence of the various substances administered to TBI patients on sleep-wake physiology and overall recovery. It remains unclear what molecules, particularly which sedatives, are susceptible to promoting a more favourable outcome, and whether promoting nighttime sleep with sedatives can have the same beneficial effects as natural sleep. For example, comparing the effects of propofol treatment to that of Dexmedetomidine on acute SWD and sleep architecture could be interesting given that Dexmedetomidine seems to better replicate natural sleep features than propofol. Moreover, the cumulative effects of such medications on sleep and wake remain nebulous, despite their heavy use in the ICU population.

3.2. Delirium in ICU

Delirium, defined as an alteration in mental status, organized thinking, attention and level of consciousness (American Psychiatric Association, 2013), is reported in 40-90% of ICU patients (Angles et al., 2008; Barr et al., 2013). Delirium typically occurs two to five days post-ICU admission, and lasts one to five days (Burry, Williamson, et al., 2017). In the general ICU population, there is strong evidence that mechanical ventilation, sedative medication,

older age, sepsis, hypertension, dementia, trauma, coma and immobility are risk factors for the development of delirium (Brummel & Girard, 2013; Zaal et al., 2015). In trauma ICU patients, additional risk factors include ISS score, as well as the cumulative dose of opiates and benzodiazepines (Duceppe et al., 2017).

Although SWD are not a diagnostic criterion for delirium, over 75% of delirious patients suffer from sleep changes (Weinhouse et al., 2009). Though delirium was not specifically assessed in our TBI patients, it is possible that some SWD may be due to this condition. However, if delirium did occur in our TBI cohort, it probably did so before we started actigraphy recording, meaning that delirium symptomatology was most likely resolved by the time our sleep-wake measures began. In fact, actigraphy recording began 20.6 ± 13.0 (range: 4-53) days post-admission, and 12.2 ± 9.3 days (range 1-39) after the end of mechanical ventilation and continuous sedation. Moreover, our results show that the observed SWD extend much beyond a one- to five-day period, which is the habitual duration of ICU delirium. Although the hazard ratio of delirium in TBI is 2.01 (Duceppe et al., 2017), one major obstacle in assessing the incidence of delirium following TBI is that detection and classification of delirium in the TBI population are still contested (Trzepacz et al., 2011; Duceppe et al., 2017). The efficacy of detection tools for ICU delirium, such as the Confusion Assessment Method – Intensive Care Unit and the Intensive Care Delirium Screening Checklist, are somewhat questioned in the TBI population (Frenette et al., 2016). It remains difficult to discriminate between delirium and other acute cognitive dysfunction in acute TBI patients, especially given that the lack of consensus around the definition of, and distinction between delirium and PTA following TBI. PTA is often referred to as a confusional state that comprises more than only deficits in memory and orientation. PTA may refer to the period spanning from a coma to episodic memory deficits, but the varying definitions and criteria of both delirium and PTA following TBI make research interpretation difficult (Trzepacz et al., 2011).

Future studies should also aim to assess whether delirium and its residual effects may contribute to post-TBI SWD. More specifically, studies could assess whether TBI patients who have suffered ICU delirium have more severe and persistent SWD in the acute phase.

However, the above-mentioned risk factors for the development of delirium are also factors associated with more severe injury, poorer prognosis and outcome. Though methods to better diagnose delirium in the acute TBI population are still needed, assessing the efficacy of melatonin administration in delirium prevention (Burry, Scales et al., 2017) could shed light on possible mechanisms linking delirium and sleep.

3.3. Pain

Pain has been widely reported as a contributing factor to poor sleep in acute care (Novaes et al., 1999; Nelson et al., 2001; Little et al., 2012; Kamdar et al., 2012; Beltrami et al., 2015). Patients hospitalized with severe injuries suffer fluctuating levels of pain, which may not always be properly relieved, particularly when patients are disoriented, confused, or unable to communicate, as is frequently the case in acute TBI. Therefore, the subjective experience of pain is most likely difficult to appraise in this population. In fact, pain often leads to agitation and acute care, and is erroneously treated with a sedative, rather than analgesics (Brummel et al., 2013). Though our non-TBI patients most likely also experienced intense and prolonged pain during their hospital stay, they were most likely better able to communicate their discomfort and ensure they were adequately relieved.

Since it causes microarousals, or intrusions of wakefulness into NREM sleep, pain can hinder sleep initiation and maintenance, leading to less restorative sleep (Ouellet, Beaulieu-Bonneau & Morin, 2015) One recent study conducted on mTBI patients in the first month post-injury found that patients with moderate-to-severe pain had longer nighttime sleep and more frequent naps than other mTBI patients with mild or no pain, and controls (Suzuki et al., 2017). Mild TBI patients with pain also have greater increase in rapid EEG frequency bands during sleep than those without pain, 1.5 month post-injury, suggesting that pain is associated to poor sleep (Khoury et al., 2013). In the chronic phase of TBI, pain has been identified as a risk factor for poorer reported sleep quality (Beetar, Guilmette & Sparadeo, 1996; Fichtenberg et al., 2000; Guilleminault et al., 2000; Ouellet et al., 2006; Parcell et al., 2006; Ponsford et al., 2012; Ponsford et al., 2013). Pain therefore seems to be associated to poorer sleep quality and greater sleep need following TBI, and should systematically be evaluated in TBI survivors with sleep complaints or a disturbed sleep-wake cycle.

4. How to improve the sleep-wake cycle after TBI

There is currently no sleep intervention for acute TBI that are supported by evidence. There is however several treatment options that should be tested in future research projects.

Importantly, this thesis confirms that melatonin circadian rhythm is present in acute TBI patients, which suggests that the master circadian clock is properly functioning. However, melatonin signal transmission pathways and other downstream processes of the circadian system may be defective following TBI, therefore contributing to sleep-wake disruption. Administering melatonin in the ICU and post-ICU phases of TBI could possibly have a beneficial effect on sleep initiation. Indeed, aside from being a marker of the master clock's ability to generate a normal circadian rhythm, melatonin also has a role in initiating and modulating sleep through its action on melatonin receptors (Liu et al., 2016). Melatonin administration is known to promote sleep onset and maintenance (Cajochen et al., 1996 ; Arendt & Skene, 2005; Zhdanova, 2005), and can be used effectively to entrain non-24 h rhythms (Lewy et al., 2005). If TBI does lead to a decrease in the expression of melatonin receptors, as has been recently shown in a study on rats in the first day following TBI (Osier et al., 2017), perhaps a stronger melatonin signal is necessary to exert the same circadian and hypnotic effects that it normally would in a healthy brain.

Conversely, melatonin analogs, which show higher affinity for melatonin receptors than melatonin itself (Liu et al., 2016), could be investigated in this population. Compounds such as agomelatin, ramelteon, and tasimelteon, have been shown to improve insomnia and non-24 h sleep-wake disorders (Liu et al., 2016; Williams et al., 2016). What is more, evidence suggests a role of melatonin in protecting against apoptosis, ischemia, and neurodegeneration (Tan et al., 2005). These neuroprotective effects may be influenced in part by the activation of melatonin receptors (Liu et al., 2016), which suggests that targeted melatonin analogs could potentially procure these neuroprotective effects. In fact, agomelatin has been shown to induce hippocampal neurogenesis in the adult rat (Banasr et al., 2006). This therapeutic potential for both the sleep-wake cycle and neuroprotection makes melatonin and its analogs worth further investigation in the acute TBI population.

Favouring continuous nighttime sleep through the administration of sedatives could also be beneficial to acute TBI patients. As opposed to benzodiazepines (e.g. flurazepam, lorazepam), which alter sleep architecture and may induce sleep rebound, non-benzodiazepine hypnotics (e.g. zolpidem, zopiclone) may provide the optimal compromise between an optimal therapeutic effect and limited side effects (Ouellet et al., 2015). Conversely, other pharmalogical treatments could be used to stimulate daytime wakefulness in patients who have excessive daytime sleepiness, such as modafinil, psychostimulants, non-psychostimulants (Atomoxetine, Guanfacine), and amantadine. A methylphenidate-based psychostimulant has been shown to improve daytime alertness and cognitive performance in a case study of severe TBI with chronic hypersomnia (Wiseman-Hakes et al. 2011). Another study in chronic TBI showed that modafinil was successful in reducing daytime sleepiness and increasing time spent awake during the daytime, as measured by actigraphy (Kaiser et al., 2010).

The stimulating, rather than chronobiotic, effects of light therapy could also be investigated in the hospital setting. Indeed, although it follows a diurnal pattern, ICU lighting is constantly low, even during the daytime (Fan et al., 2017). Aside from its circadian properties, light has acute stimulating effects on the brain (Phipps-Nelson et al., 2003; Vandewale et al., 2006; Cajochen, 2007). Light modulates human alertness and performance levels in ways that could enhance daytime wake in hospitalized TBI patients and optimize rehabilitation potential in the post-ICU stage. Blue light has been shown to be most effective in increasing alertness and cognitive performance (Cajochen et al., 2007; Munch & Bromundt, 2012). It has also been shown to increase the activity of mood-related brain areas, suggesting a role in improving mood (Vandewalle et al., 2009). Therefore, light therapy during daytime, particularly in the blue spectrum, could improve daytime wake and, in turn, enhance the duration and quality of nighttime sleep.

Adequate pain management is essential to favouring restorative sleep. However, the opioids used to treat pain are associated with suppression of REM and NREM sleep, sleep fragmentation, and even delirium (Beltrami et al., 2015; Brummel et al., 2013). Low doses of opioids seem beneficial to both pain treatment and delirium prevention (Brummet al., 2013; Duceppe et al., 2017), but when opioid analgesics are given in sufficently high doses to sedate,

they once again become a risk factor for delirium (Brummel et al., 2013). Inversely, insufficient pain management increases the risk of delirium (Burry et al., 2017), which can lead to impaired sleep-wake cycle (Weinhouse et al., 2009). Given that patient comfort is essential to sleep quality and delirium prevention (Novaes et al., 1999; Nelson et al., 2001; Little et al., 2012; Kamdar et al., 2012; Beltrami et al., 2015; Brummet al., 2013), a balanced (rather than excessive) administration of analgesic medications is essential.

BCAA supplementation has been recently emerging as a potential therapeutic avenue to improve both SWD and cognitive outcome following TBI. Both human and animal studies have shown that a diet supplemented with BCAAs improves cognitive outcome following TBI (for review, see Sharma et al., 2017), by increasing glutamate synthesis and restoring normal cortical excitability (De Luche et al., 2015; Sandsmark, Eliott & Lim, 2017). One pilot study tested the intravenous administration of BCAAs in severe TBI patients in UWS and MCS during the acute phase post-injury, and found that BCAA administration was associated to improved outcome, as measured by the DRS (Aquilani et al., 2008). Lim and colleagues (2013) showed that a BCAA dietary supplement given to mice in chronic mTBI reinstated orexin neuron activation and improved the ability to sustain wakefulness after a mild sleep deprivation. Though BCAA supplementation therapy is still only emerging and its effects on the sleep-wake cycle in humans has not yet been evaluated, it may have the potential to mitigate SWD and neurocognitive impairments following TBI. However, given the potential neurotoxic effects of glutamate, which can lead to brain swelling and neuronal death (Duhaime, 1994), more studies are required to assess its efficacy and rule out potential negative effects. Further studies are also required to assess ideal dosage and duration of effect (Elkind et al., 2015).

Other measures to improve the sleep-wake cycle of hospitalized TBI patients have been proposed in Articles 1 and 2, and include modifications the hospital environment (e.g. noise reduction, providing eye masks and ear plugs, stronger light/dark contrasts, reducing staff interventions during nighttime, preventing naps in late afternoon of evening), promoting daytime naps to improve cognitive functioning, and other behavioural measures to improve insomnia (e.g. Stimulus Control, Sleep Restriction).

Finally, this thesis confirms that the TBI itself has a role in impairing the sleep-wake cycle, and that the hospital environment and aspects of the overall trauma and critical care are not the sole contributors to sleep-wake disruption. Given that the pathophysiology of these SWD remains unknown, and may be multi-factorial, it remains a challenge to determine the optimal way to improve sleep and wake secondary to the brain insult. If sleep-wake cycle consolidation is dependent on overall neuronal recovery, as suggested in Article 5, it may be difficult to intervene directly in the improvement of sleep and wake until the brain has reached a certain level of recovery.

5. Strengths of the studies presented in this thesis

5.1. Research protocol and patients

This thesis contributes to the understanding of the characteristics and evolution of sleep-wake and circadian pathology following TBI. The research protocol described in this thesis was the first to take place in the acute phase post-injury and on patients who were no longer continuously sedated or mechanically ventilated, enabling the assessment of sleep and circadian measures in a more naturalistic context and eliminating important confounds. The novelty of this research protocol also resides in its longitudinal component, enabling the assessment of the sleep-wake cycle for up to two weeks during the hospital stay. Having concomitant measures of melatonin production, PSG, consciousness and cognitive function provides an evolutive and multifaceted comprehension of the interplay between the sleep-wake cycle, circadian rhythms, and recovery.

The overall study protocol included 43 moderate-severe TBI patients and 35 non-TBI controls, which is a larger patient population than previous circadian studies in acute TBI (Paparrigopoulos et al., 2006; Paul & Lemmer, 2007; Llompart-Pou et al., 2010). We collected a wide range of clinical characteristics (e.g. mechanism of injury, GCS, Marshall and Rotterdam scores, ISS, days of elevated ICP, duration of ICU stay, cumulative ICU doses of sedatives and analgesics, hospital length of stay), measures of recovery (e.g. daily RLA, GOAT, DRS at discharge), actigraphy, PSG, and melatonin data, enabling us to efficiently characterize our participants, as well as their sleep-wake and circadian profiles. What is more,

the hourly sampling of urine over a 25 h period enabled us to better characterize the circadian melatonin rhythm than previous studies with infrequent circadian measures. This large sample size and ample dataset enabled us to identify different patterns of sleep-wake recovery, conduct more sophisticated statistical analyses (e.g. repeated measures ANOVA, mixed model analyses), and reduce the possibility of statistical type I and type II errors.

The use of a control group also addresses the major limitations imposed by the hospital environment and overall trauma. By comparing the sleep-wake and melatonin rhythms of TBI patients to that of other trauma patients without TBI, we were able to isolate, at least partly, the effect of the brain injury on our measures of interest. Applying strict exclusion criteria to our groups also minimized the possibility of observing SWD secondary to other conditions, such as a previous neurological/psychiatric/sleep disorder, withdrawal from drugs or alcohol, and previous TBI. Despite these exclusion criteria, we had a sample of patients representative of the overall moderate-severe TBI population with regards to age, sex, and mechanism of injury.

5.2. Development of novel measures to assess sleep-wake rhythm

In the study of circadian rhythms, the cosinor method is usually used to verify whether a rhythm oscillates over a 24 h period, and to characterize the parameters of this rhythm (Monk & Fort, 1983; Cornelissen, 2014). Given that hospitalized TBI patients have such arrhythmic sleep-wake patterns, we were unable to use this method to characterize the sleep-wake cycle of our patients. More specifically, the cosinor method was unable to distinguish the varying degrees of sleep-wake cycle consolidation, and was therefore unfit to characterize evolution in sleep-wake cycle consolidation within a single patient, or differences between patients. Consequently, this thesis introduces a new method of quantifying sleep-wake cycle consolidation, which we devised to most accurately characterize the sleep-wake cycle of hospitalized TBI patients. The DAR was developed to coincide with the hospital's day-night schedule, which is imposed uniformly to all patients. Although activity levels (i.e. quantity of movement) varied greatly from one patient to the next, the DAR enables a distinction between sleep and wake that is relative to each patient's own level of activity for a given day. Indeed, rather than characterizing sleep and wake states based on thresholds of activity counts per

epoch, the DAR assesses the day-night distribution of rest and activity. In order to ensure that the DAR was not influenced by the overall quantity of activity over the 24 h period, we verified the association between the number of minutes moving per 24 h and the DAR, and no association was found.

6. Limits

One overarching methological limit to this thesis is that the five research articles were based the same sample of participants, tested in a single study protocol. Future studies should therefore aim to replicate the obtained results in another patient cohort.

6.1. Actigraphy as a proxy measure of the sleep-wake cycle

In this thesis, the sleep-wake cycle was measured longitudinally using actigraphy. Actigraphy measures the rest-activity cycle, and is therefore an indirect measure of the sleep-wake cycle. Moreover, it is known to underestimate wakefulness (Blood et al., 1997; Kushida et al., 2001; de Souza et al., 2003; Paquet et al., 2007), especially when individuals lie immobile but awake in their bed and/or during critical illness (Acebo & LeBourgeois, 2006, Beecroft et al., 2008). Even though this is a limit to the method, it suggests that the sleep disturbances measured in our patients may be even more severe than reported in our research articles, which strengthens our conclusions that SWD are severe and widespread in the acute phase of TBI. More specifically, the limits imposed by actigraphy suggest that nighttime sleep duration may be even lower than we reported, though this cannot be confirmed. On the other hand, it is not impossible that patients may have slept during periods of motor activity, but given that activity levels were high in most patients, this seems unlikely. Indeed, muscle tone is absent during REM sleep and very low during NREM sleep (Saper, 2013), except among individuals with REM sleep behaviour disorder (Schenck et al., 1986; Schenck & Mahowald, 2002). Moreover, if sleep did occur during periods of activity, it was most likely not restful. Finally, the inclusion of non-TBI trauma patients, whose sleep-wake cycle was much less disturbed and whose nighttime sleep duration was around seven hours per night, supports the efficacy of actigraphy for measuring sleep and wake in this setting and population.

We currently have a study in preparation, in which we assess the minute-by-minute concordance between actigraphy and ambulatory PSG during the nighttime sleep episode in hospitalized TBI patients and non-TBI patients with severe traumatic injuries. Our preliminary results (TBI: n = 6 TBI; non-TBI: n = 11) suggest that actigraphy in hospitalized trauma patients has an excellent sensitivity (i.e. ability to detect sleep; above 92%) and strong epoch-by-epoch accuracy (above 85%) when compared with ambulatory PSG. The sensitivity and accuracy obtained in our preliminary results are similar to those reported in studies among healthy individuals in normal conditions (Blood et al., 1997; De Souza et al., 2003; Acebo & Le Bourgeois, 2006; Paquet et al., 2007). However, we found that the ability of actigraphy to detect wakefulness was low, reaching only 60%, though it was similar to or higher than what has been observed in previous studies among healthy controls (Blood et al., 1997; De Souza et al., 2003; Paquet et al., 2007). Total sleep time, total wake time and sleep efficiency did not significantly differ between actigraphy and PSG, but actigraphy did underestimate the number of awakenings. Although these results suggest that actigraphy is a valid tool for monitoring sleep and wakefulness in patients hospitalized with acute severe traumatic injuries, a larger validation study is needed to confirm our preliminary findings.

Although actigraphy cannot distinguish rest from sleep, it remains a useful tool for the prolonged measurement of SWD in a hospital setting, and can provide powerful insight into overall recovery, even among patients who may lack the cognitive or communicative ability to identify and/or report sleep-wake problems.

6.2. Weaknesses of the DAR as a measure of sleep-wake cycle consolidation

Given that the DAR was designed to coincide with the hospital's day-night schedule, the DAR could easily be influenced by phase advances or delays (e.g. the sleep period occurring from 19:00 to 3:00, or from 3:00 to 11:00, respectively). However, each actogram was visually inspected to ensure that this was not the case. In our study population and setting, patients who had low DAR were those whose rest and activity periods were fragmented and dispersed over the 24 h period, rather than advanced or delayed. Proper care should be used when using the DAR in other settings and populations, as phase advances or delays should

always be ruled out before the DAR can be taken to reflect the consolidation of the 24 h sleep-wake rhythm.

A DAR of 80% was used as the threshold to designate an acceptable level of sleep-wake cycle consolidation. Before selecting this threshold for use in the articles of this thesis (Articles 3, 4, 5 and 7), various other thresholds (e.g. 70%, 75%, 85%, 90%) were tested and compared among our moderate-severe TBI patients. The 80% threshold was found to be the most capable of distinguishing patients who improved from those who did not, based on visual comparison of patient actogrammes. Patients naturally divided themselves in two groups: those whose DAR remained low throughout the study period, and those whose DAR improved gradually and surpassed the 80% mark for several consecutive days at the end of the recording period. Moreover, since patients were frequently able to reach a ratio above 85-90% in the last days of recording, 80% was a conservative threshold to denote an acceptable sleep-wake cycle consolidation. The 80% threshold therefore naturally emerged as critical point in sleep-wake cycle consoliation, but was not selected based on additional empirical evidence. However, the fact that the 80% threshold was associated to measures of severity and outcome (i.e. GCS, DRS, PTA status at discharge), and that it was easily attained by non-TBI controls, supports its usefulness as a measure of rhythmicity within this population and setting. To refine an optimal sleep-wake consolidation threshold in future studies, ROC curve analyses could be carried out to determine the threshold with optimal sensitivity/specificity, and normative data for sleep-wake consolidation using the DAR could be determined among a large population of healthy adults.

6.3 Limits imposed by polysomnography

The use of PSG in the acute phase of moderate to severe TBI necessarily implies a selection bias. Indeed, given that the PSG recording materials (i.e. EEG, EMG, EOG, oximeter and oronasal thermistor) are somewhat cumbersome, the only TBI patients who tolerated PSG materials were those with improved cognitive function, who were no longer agitated and confused. This translates to PSG having been carried out among the TBI patients who had a more favourable outcome during their hospital stay, and most likely a less severe injury. Moreover, it restricted PSG recordings to a later stage post-injury, once sleep-wake

disturbances had already greatly improved. This selection bias and the timing of PSG recordings may explain why little difference was found in the sleep architecture between our TBI and non-TBI groups. Moreover, it could explain why Article 6 revealed longer nighttime sleep duration in TBI patients, whereas Article 7, carried out earlier in the recovery process, revealed significantly shorter nighttime sleep duration among the TBI group, as assessed by actigraphy.

Despite the challenge in doing so, future studies using PSG and/or EEG should aim for earlier recordings, and include less cooperative patients, who are probably also those exhibiting the most disturbed sleep-wake cycle. Moreover, the abovementioned preliminary actigraphy validation results are from 16.2 ± 11.3 days post-injury (range 7-31) among the TBI group, once patients were sufficiently calm and oriented to tolerate PSG materials. Consequently, assessing the validity of actigraphy for the assessment of sleep and wake during the phase of agitation would also be needed.

6.4. Using the RLA for the assesment of consciousness

In this thesis, the RLA scale was used to assess the level of consciousness and cognitive functioning of TBI patients. Though the Coma Recovery Scale is the gold standard method for the assessment of consciousness (Giacino, Kalmar & Whyte, 2004), it is time-consuming, requires trained examiners, and is therefore difficult to carry out on a day-to-day basis among critically ill patients who are easily fatigued and already highly solicited by medical personnel. Conversely, the RLA is routinely integrated into the clinical assessment of TBI patients, and evaluates some of the same key aspects of consciousness that are used to distinguish between UWS, MCS and emergence from MCS in the Coma Recovery Scale (e.g. response to command, motor action, functional communication and functional object use). The RLA was therefore chosen because of its accessibility and apparent validity within our patient population. However, the assessment of consciousness based on behavioural responsiveness, as is the case for both the RLA and the Coma Recovery Scale, remains problematic. Indeed, the presence of consciousness goes clinically undetected in up to 40% of neurologically-impaired patients who cannot reliably or consistently respond to their environment (Schnakers et al., 2008). Although there is currently no method able to objectively and accurately assess a

patient's level of consciousness at bedside, and behavioural assessments remain the only available option, the use of RLA for the assessment of consciousness it therefore limited by its dependency on patient responsiveness.

6.5. Hospital environment

Although our final article included a control group of non-TBI trauma patients hospitalized in a similar environment, elements of the hospital environment known to influence sleep and/or circadian rhythms and to contribute to ICU-related sleep-wake complaints, such as lighting, noise, and staff interventions, were not investigated (Fan et al., 2017; Gabor et al., 2003; Drouot et al., 2008; Hardin, 2009; Little et al., 2012; Beltrami et al., 2015; Knauert, Haspel & Pisani, 2015; Korompeli et al., 2017). Future studies should carefully monitor such environmental conditions in order to identify modifiable contributors to post-TBI SWD.

7. Future research priorities

7.1. Sleep disturbance, wake disturbance, or faulty switching mechanism?

One question that should be prioritized in the study of SWD in acute TBI is whether these disturbances reflect defective sleep, wakefulness, or switching mechanism between both states. Our PSG study (Article 6), revealed longer sleep time and earlier sleep onset in TBI patients, but no changes in sleep architecture, suggesting that mechanisms that favour sleep initiation and transitions between NREM and REM sleep seem functional. However, in the first days of actigraphy recording, prior to our PSG study, TBI patients seem to have difficulty maintaining both sleep and wakefulness for an extended period of time, which makes it difficult to determine whether it is sleep, wakefulness, or the switching mechanism that is malfunctioning.

Given that orexin plays a central role in both the regulation of wakefulness and the anchoring of the switching mechanism between sleep and wake, it is a crucial neurotransmitter to evaluate in the acute phase of TBI, when patients are no longer continuously sedated. More

specifically, orexin levels in CSF could be compared to actigraphy measures in order to assess their association to SWD, including sleep-wake cycle consolidation, as well as quality/continuity of daytime wakefulness and nighttime sleep. The evolution of orexin levels in the first weeks following injury could also provide insightful information on the mechanisms behind the reconsolidation, or absence of reconsolidation, of a 24 h sleep-wake cycle.

Given that a loss of histaminergic neurons has been found in fatal TBI, histamine levels are also worth investigating in acute TBI. Identifying the specific sleep-wake variables with which histamine levels are associated (e.g. daytime sleep duration, nap frequency) is also essential. The depletion of histamine levels would signal a wakefulness disturbance, and could provide insight into potential therapeutic avenues for clinical trials. Indeed, a new molecule has recently been approved to increase activity of histaminergic neurons, thereby increasing alertness and wakefulness duration (Dauvilliers et al., 2013).

Integrating MRI measures in the acute stage of TBI is also essential to understanding the extent of brain lesions and white matter disconnection in the ARAS, susceptible to explaining fragmentation of wakefulness. Given the role of the hypothalamus in sleep-wake regulation and stability between sleep and wake states, its integrity should also be assessed using MRI.

Assessing the proper functioning of the switching mechanisms between sleep and wake has seldom been done in previous research, but remains an important research question to address with regard to SWD in acute TBI. State space analysis of EEG power spectrum, which uses principal component analysis, has recently been used to enable the visualization of the boundaries between sleep and wake states. This technique enabled the confirmation of sleep-wake instability in an orexin knockout mouse model (Diniz Behn et al., 2010), and among narcoleptic patients (Schoch et al., 2017). This novel methodological approach provides a more dynamic (transitional) description of EEG than visual sleep scoring and spectral analysis, and has proven to be applicable to healthy and pathological sleep in both rodents and humans (Imbach, 2016). Consequently, state space analysis could be a promising method with

which to investigate the integrity of the switching mechanism between sleep and wake in acute TBI.

7.2. Can we improve nighttime sleep quality and optimize recovery?

The effects of pharmacologically-induced nighttime sleep could also be evaluated in acute TBI. Indeed, we have shown that acute TBI patients have shorter nigthtime sleep duration and higher fragmentation than other hospitalized trauma patients, without TBI (Article 7). Moreover, nighttime sleep duration and fragmentation were associated to the recovery of consciousness and cognitive function (Article 5). Although we showed that this evolution was synchronous, sleep is essential to the regeneration of damaged brain structures, and the sleep disruption we documented in TBI patients is bound to have negative effects on overall recovery. Therefore, it remains relevant 1) to verify if sleep duration and quality can be improved through the administration of sedatives, particularly non-benzodiazepines; and 2) to assess the impact of nighttime sedative administration on the recovery of consciousness and cognitive function, and emergence from PTA. Such investigation could provide powerful insight into the therapeutic potential of optimized sleep during the hospital stay of moderate to severe TBI patients.

8. Conclusion

Moderate to severe TBI affects mostly young adults entering the productive years of their lives, and is the main cause of disability in this population. Given that the initial trauma and subsequent brain hypoxia and edema destroy brain structures and connections that need regeneration, sleep is essential to recovery.

In this thesis, we have shown that SWD are present as early as the acute hospitalization phase of moderate to severe TBI, once patients reach medical stability and are no longer continuously sedated. These SWD are characterized by an absence of 24 h sleep-wake cycle, short nighttime sleep duration and excessive sleep fragmentation. These disturbances are attributable to the brain injury itself, rather than exclusively to the hospital environment, as they are more severe than those observed in other hospitalized trauma patients, without TBI.

The recuperation of a 24 h sleep-wake cycle and the improvement of nighttime sleep quality are strong indicators of overall neurological recovery. In fact, their evolution goes hand in hand with recovery of consciousness and cognitive function. Moreover, improvements in SWD over the hospital stay are strongly associated with functional outcomes and PTA at hospital discharge. Contrary to our initial hypothesis, SWD in the acute phase of TBI do not seem to be caused by a disturbance in the master circadian clock. In fact, TBI patients have a circadian melatonin rhythm comparable to that of their non-TBI counterparts, which is within the normal range of 24 h aMT6s excretion for healthy adults.

In a clinical perspective, this thesis highlights the necessity of monitoring the sleep-wake cycle in the acute phase of TBI. Though more studies are needed to assess the directionality or bidirectionality of sleep and recovery following TBI, longitudinal assessment of the sleep-wake cycle through actigraphy could be a useful clinical tool to assess overall neurological recovery in hospitalized TBI patients. Actigraphy could be systematically used in the ICU and neurological units to monitor the progress and recovery of TBI patients. Given that sleep is a modifiable behaviour, efforts to minimize SWD could optimize recovery process, prevent the development of chronic SWD, and ultimately improve quality of life.

In summary, this thesis confirms the presence and severity of SWD in acute moderate to severe TBI, and their association to short-term neurocognitive recovery. Though our results suggest that the master circadian clock is functioning properly, future research should aim to elucidate the pathophysiological mechanisms of acute SWD that could be used as a target for treatment. Given that TBI is a heterogeneous disease process that requires an individualized and multifaceted treatment, elucidating the specific mechanisms responsible for SWD will remain a considerable challenge in this field of research.

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