24-h polysomnographic recordings and electrophysiological spectral analyses from a cohort of patients with chronic disorders of consciousness

Raechelle M. Gibson[1,2] · Laura B. Ray[3] · Geoffrey Laforge[1,2] · Adrian M. Owen[1,2,4] · Stuart M. Fogel[3,5]

Abstract

Fourteen patients with severe brain injuries and chronic disorders of consciousness underwent polysomnographic recordings for a 24-h period. Their electrophysiological data were scored using a modified sleep staging system employed in a previous study of similar patients (J Head Trauma Rehabil 30:334–346, 2015). In addition to sleep scoring, the patients' data were compared with a sample of approximately age-matched healthy volunteers in the spectral domain. All patients demonstrated some form of a sleep–wake cycle; however, the integrity of normal sleep features was remarkably heterogenous across individuals, and in some cases, sleep was significantly impoverished. In three patients, these cycles were biphasic and comprised of only alternating periods of wakefulness and sleep-like electrophysiological activity. Two patients demonstrated a sleep–wake cycle that included all sleep stages aside from non-REM stage 3, and another two patients demonstrated a sleep–wake cycle that included all sleep stages aside from REM sleep. The remaining seven patients, which included patients diagnosed as being in a minimally conscious state and patients diagnosed as being in a vegetative state (unresponsive wakefulness syndrome), demonstrated full sleep architecture, including *k*-complexes, REMs, and slow wave sleep. However, three of the patients with full sleep architecture did not generate sleep spindles. Altogether, these findings highlight the heterogeneity of brain function among patients with disorders of consciousness, regardless of their diagnostic category. Polysomnography is a useful tool to complement other behavioural and physiological assessments that characterize the abilities of each patient.

Keywords Sleep · Polysomnography · Vegetative state (unresponsive wakefulness syndrome) · Disorders of consciousness

Introduction

Following a severe head injury, many survivors enter a transient, non-responsive state referred to as coma. While some patients who recover from a comatose state regain awareness, a small number of patients exhibit altered states of awareness for the remainder of their lives. Collectively, these prolonged, altered states of awareness are known as chronic disorders of consciousness [1]. The vegetative state (unresponsive wakefulness syndrome) comprises the absence of voluntary behaviour alongside cycles of eye opening and closing [2]. In contrast, the minimally conscious state is ascribed to patients who demonstrate variable, but reproducible, overt volition, and emergence from a minimally conscious state is indicated when the patient demonstrates reliable voluntary behaviour [3]. Although all patients with chronic disorders of consciousness remain dependent on others for complete care, the vegetative state (unresponsive wakefulness syndrome) is distinct from the other disorders because this condition implies the absence of awareness. In the past 25 years, researchers, clinicians and others interested in patient welfare have exerted increasing efforts to better understand this complex condition of apparent wakefulness without awareness. The study of sleep in these patients may provide insight into the nature of the

✉ Stuart M. Fogel
 sfogel@uottawa.ca

1 The Brain and Mind Institute, Western University, London, Canada

2 Department of Psychology, Western University, London, Canada

3 Sleep Research Unit, The Royal's Institute of Mental Health Research, Ottawa, Canada

4 Department of Physiology and Pharmacology, Western University, London, Canada

5 School of Psychology, University of Ottawa, Ottawa, Canada

underlying neural trauma, as well as the consequences in terms of disruptions to awareness and cognitive capacity.

From a neuroanatomical perspective, sleep–wake cycles occur through the regulation of the thalamus and cerebral cortex by diffuse afferent connections from the ascending reticular activating system [4, 5]. Accordingly, patients with disorders of consciousness who exhibit sleep–wake cycles presumably have intact reticular activating systems [1]. Aside from cyclical regulation, sleep comprises many complex neurological processes associated with a continuum of conscious states. For example, rapid eye movement (REM) sleep is associated with neural activity that closely resembles wakefulness, and healthy sleepers awoken during REM sleep frequently report vivid, structured dreams [6, 7]. In contrast, non-REM sleep is characterized by down-regulation of the cortical interactions associated with consciousness [8–10]. Healthy sleepers awoken during non-REM sleep typically report dreams of a duller sensory and perceptual quality, if they report any dreams at all [11, 12]. From a clinical perspective, sleep integrity has well-documented associations with physical and mental health. For example, insufficient sleep is associated with metabolic disruptions [13] and an increased risk of cardiovascular disease [14]. Moreover, insomnia is a symptom of, and a risk factor for, depression [15]. For patients who are behaviourally non-responsive, sleep thus provides an important window into their otherwise inaccessible subjective experiences and related health outcomes.

The sleep and circadian rhythms of patients with disorders of consciousness have previously been described for clinical purposes. Overall, patients diagnosed as being in a minimally conscious state tend to exhibit more preserved sleep architecture than patients diagnosed as being in a vegetative state (unresponsive wakefulness syndrome) [16–19]. Further, slow wave sleep correlates with more overt signs of awareness in most of these patients [20–23]. The circadian rhythms of patients with chronic disorders of consciousness are quite variable, with reports of periods ranging from 6 to 63 h in one study [24] and 23–26 h in another study [25]. Furthermore, other investigators have reported no circadian rhythmicity at all among these patients [26, 27].

Some variability in the sleep architecture of patients with disorders of consciousness presumably owes to the diffuse and variable brain injury characteristics of these disorders. Other environmental factors, such as bedside noise or premature awakening by caregivers, and medical factors including acute illness, insufficiently managed pain, or postural discomfort, likely further contribute to sleep abnormalities in these patients [28]. From a procedural standpoint, the assessment of sleep architecture in patients with disorders of consciousness is technically challenging because these patients variably exhibit standard electrophysiological sleep criteria. Several studies of sleep in patients with disorders

of consciousness employ custom, adapted sleep staging criteria to overcome this issue, e.g., [19, 29, 30], while others rely upon automated, data-driven approaches, e.g., [18, 31, 32]. Furthermore, patients with disorders of consciousness tend to generate more artefacts than healthy volunteers during physiological recordings, typically owing to involuntary movements, stray electrical noise from bedside equipment, and excessive sweating. Finally, many patients exhibit disruption to the timing and duration of sleep episodes. This warrants the use of 24-h polysomnographic (PSG) recordings in order to fully capture the extent of sleep disruptions.

In this investigation, 24-h polysomnographic recordings from 14 patients with chronic disorders of consciousness are described. Because the convenience sample of patients was heterogeneous with respect to age, the polysomnographic recordings of two separate groups of approximately age-matched volunteers without brain injuries (older and younger adults) are also presented to represent age-related changes in sleep. The sleep data were quantified in the time domain and categorised using customised sleep staging criteria from a previous investigation [33]. In our work, analyses were used to further quantify the data in the frequency domain in line with recent findings concerning spectral profiles of altered conscious states during sedation [34–36]. It was predicted that patients with more overt signs of awareness would demonstrate relatively preserved sleep architecture compared to patients with fewer overt signs of awareness.

Materials and methods

Participants

Patients in this study comprised a convenience sample recruited as part of a larger, on-going research programme concerning perception and cognition following acquired brain injury. Fourteen patients contributed data of sufficient duration and quality for inclusion in the current investigation. The patients ranged in age from 14 to 65 years (median = 53). The diagnosis of each patient was determined according to their best performance during the administration of the coma recovery scale-revised prior to their participation in the sleep study [37].

Demographic and clinical information is presented in Table 1.

The healthy participants in the study comprised older and younger adults recruited for two unrelated investigations. The data used in this study were collected as a baseline screening night for the unrelated investigations. The younger healthy volunteers (n = 17) ranged from 20 to 29 years of age (median = 21 years), while the older healthy volunteers (n = 20) ranged from 30 to 62 years of age (median = 36 years). An initial telephone interview

Table 1 Overview of the patient demographic and clinical data

Patient	Sex/age/interval since ictus (years)	Aetiology	Diagnosis	Coma recovery scale-revised scores						
				Auditory	Visual	Motor	Oromotor	Communication	Arousal	Total
1	Female/65/1.2	Anoxic (cardiac arrest)	Vegetative state (unresponsive wakefulness syndrome)	0	0	2	1	0	1	4
2	Male/27/8.6	Traumatic (sports accident)	Emergence from a minimally conscious state	4	5	6	1	2	3	21
3	Male/40/3.1	Traumatic (motor vehicle accident)	Minimally conscious state	1	3	0	1	0	2	7
4	Female/46/22.2	Traumatic (motor vehicle accident)	Vegetative state (unresponsive wakefulness syndrome)	0	1	2	1	0	2	6
5	Male/55/1.5	Brainstem stroke	Locked-in syndrome	4	5	2	2	2	3	18
6	Male/27/1.3	Traumatic (fall)	Vegetative state (unresponsive wakefulness syndrome)	1	0	2	1	0	1	5
7	Male/23/1.4	Traumatic (motor vehicle accident)	Emergence from a minimally conscious state	3	5	2	2	2	2	16
8	Male/26/9.5	Traumatic (motor vehicle accident)	Vegetative state (unresponsive wakefulness syndrome)	3	5	2	1	0	2	13
9	Male/21/3.7	Anoxic (cardiac arrest)	Vegetative state (unresponsive wakefulness syndrome)	0	1	2	1	0	0	4
10	Female/14/2.9	Anoxic (asphyxia)	Vegetative state (unresponsive wakefulness syndrome)	1	0	2	2	0	2	7
11	Male/31/3.1	Anoxic (cardiac arrest)	Minimally conscious state	2	2	0	1	0	2	7
12	Female/29/8.9	Traumatic (motor vehicle accident)	Minimally conscious state	3	3	1	1	0	2	10
13	Female/28/0.83	Anoxic (asphyxia)	Vegetative state (unresponsive wakefulness syndrome)	1	1	2	1	0	2	7
14	Male/25/3.25	Traumatic (motor vehicle accident)	Vegetative state (unresponsive wakefulness syndrome)	1	1	0	1	0	2	5

was used to exclude participants for atypical sleep patterns (sleep time outside the approximate hours of 10:00 PM to 9:00 AM), shift work, head injury, regular cigarette smoking and excessive alcohol consumption, use of medications known to affect sleep, and history of chronic pain. Participants were required to abstain from drug use, caffeine, nicotine, and alcohol at least 3 days prior to, and throughout the duration of, the study. Participants were also asked to keep consistent sleep routines throughout their participation in the study, which was confirmed by actigraphy and sleep diaries.

During the sleep disorder screening night, standard polysomnographic recordings (including electroencephalogram, EEG; electrooculogram, EOG; and electromyogram, EMG, as described in "physiological recording and analysis") were obtained and subsequently analysed for the presence of sleep disorders by a registered polysomnographic sleep technologist. Additionally, in order to ensure normal sleep–wake patterns and rule out anxiety and depression, all healthy volunteers completed the sleep disorders questionnaire [38], and the beck depression [39] and anxiety inventories [40].

Polysomnographic recording and analysis

Embla Titanium (Natus, Pleasanton, CA, USA) 34 channel electroencephalographic (EEG) systems were used to perform ambulatory polysomnographic recordings. For the patients, the length of recordings varied from ~ 22–26 h in duration, whereas the healthy volunteers underwent recordings of night sleep only. EEG data were recorded at sites Fz, C3, C4, Cz, and Pz according to the international 10–20 system. The data were referenced to Fpz with a ground at AFz. The sampling rate was 256 Hz. Online, a high pass filter of 0.1 Hz and a low pass filter of 220 Hz were applied. EOG data were also collected using electrodes placed on the outer canthi of the eyes. The EEG and EOG data were re-referenced offline to the contralateral mastoid derivations (M1 and M2). A submental EMG channel was also recorded as a bipolar derivation. Extra care was taken to ensure that the electrodes stayed in place during the recording (e.g., using EC2 paste). Due to problems with electrode adherence and other difficulties during initial attempts to acquire data, recordings from six patients did not contain data of sufficient quality and were discarded.

For the healthy volunteers, additional PSG measurements were collected. These measurements included: respiration (via thorax and abdomen respiratory belts); electrocardiographic activity (via electrodes placed on the surface of the skin below each clavicle); leg muscle activity (via electrodes placed on the surface of the skin on the anterior tibialis muscle of each leg); and blood oxygen saturation (via a finger probe placed on the index finger of the left hand).

All recordings were manually scored in 30-s epochs by a single, registered polysomnographic technologist (RPSGT)

with over 20 years of research and clinical experience (including extensive experience with the EEG of patients with head injuries) using the established criteria developed by Avantaggiato et al. [33] which categorizes sleep according to the presence or absence of the canonical features of sleep according to standard clinical criteria [38] using RemLogic software (Natus, San Carlos, CA, USA). The recordings were then reviewed by a senior researcher (SF) with extensive expertise in sleep physiology to confirm that staging had been correctly assigned. Epochs with disagreement were rescored. The technologist was blinded to the diagnosis of the patient during the scoring procedure. For some of the patients, atypical sleep patterns were noted. To quantify these abnormalities, standard sleep features of rapid eye movements (REMs), spindles, *k*-complexes, and slow waves were visually identified in accordance with standard Rechtschaffen and Kales and AASM criteria and recorded as present, absent, or atypical. More specifically, to be recorded as "present" and in addition to a low EMG muscle tone (indicating sleep), REMs were characterized as conjugate, irregular, sharply peaked eye movements with an initial deflection usually lasting < 500 s. Sleep spindles were characterized as brief (typically > 0.5–3 s) discrete phasic bursts of sigma (~ 11–16 Hz) activity, with a waxing and waning amplitude envelope. A sigma (11–16 Hz) filtered channel was employed to aid in the visual identification of sleep spindles (and to distinguish from alpha bursts or muscle artefacts). *k*-complexes were characterized by a well-delineated negative sharp wave immediately followed by a positive component standing out from the background EEG, with total duration of ≥ 0.5 s. Finally, slow waves were characterized as 0.5–2 Hz activity with an amplitude of ≥ 75 µV. If none of the above feature characteristics were present in the recording, the feature was scored as "absent". A feature was scored as "atypical" if some, but not all, of the feature characteristics were present, e.g., sleep spindles were scored as atypical if brief (> 0.5–3 s) and discrete phasic bursts of sigma (~ 11–16 Hz) activity were identified in the absence of the waxing and waning amplitude envelope. Sections of recordings contaminated by movement artifact that obscured the EEG traces were marked as movement and not used for visually identifying sleep features. Sleep specific slow waves and pathological, monotonous EEG activity were distinguished by EMG muscle tone, e.g., high (and variable) muscle tone when awake and low (and less variable) muscle tone when asleep. Finally, each patient's sleep pattern was categorised according to the presence or absence of normal sleep stages, following recent work involving adolescent patients with similar brain injuries [33]. Four sleep patterns were identified in the patient sample using this approach, as depicted in Fig. 1. These sleep patterns were: Biphasic, Non-REM quadriphasic, REM quadriphasic, and fully structured sleep.

As shown in Fig. 1, wakefulness was scored based on: EEG with mixed alpha and beta activity; EOG with eye blinks or REMs alongside high muscle tone; and/or EMG indicating high muscle tone and/or movement artefacts. Patients with a Biphasic sleep pattern additionally exhibited only one non-REM sleep stage; in one case, non-REM stage 3 (predominantly delta activity), and in the other two cases, non-REM stage 1 (predominantly low-voltage theta activity with some alpha activity). Patients with Non-REM quadriphasic sleep patterns additionally exhibited non-REM stage 1 sleep (predominantly low-voltage theta activity with some alpha activity) and non-REM stage 2 sleep (predominantly theta activity alongside *k*-complexes, sleep spindles, and minimal delta activity). Patients with REM quadriphasic sleep patterns exhibited no non-REM stage 3 sleep, but exhibited REM sleep (low-voltage, mixed frequency activity alongside saw tooth waves and REMs on EOG channels). Finally, patients with fully structured sleep (henceforth, full sleep) exhibited all three non-REM stages and REM sleep.

The EEG data were prepared for time–frequency analyses using Matlab (Mathworks, Inc., Natick, MA, USA) and the open-source Matlab toolbox, EEGLAB [39]. In the first step, any EEG channels that were disconnected before the end of the sleep period were discarded to ensure data equivalency across time. Unfortunately, two patients had continuous data available from only one uncompromised channel (C3). The spectral analyses were thus restricted to a single channel for all participants. For patients with a compromised channel C3, channels C4 (patients 1, 9 and 13) or Cz (patient 12) were used instead. In the second step, the EEG data were filtered offline from 0.5 to 40 Hz. The EOG data were filtered offline from 0.3 to 10 Hz, and the EMG data were filtered offline from 10 to 50 Hz. EEGLAB's built-in Hamming windowed finite infinite response filter (function 'pop_eegfiltnew') was used for all offline filtering. During the sleep scoring procedure, epochs (i.e., 30 s intervals) that were contaminated by artefacts for 50% or more of the interval were not scored and excluded from all analyses. Additional artefact rejection was completed prior to the time–frequency analyses. Using EEGLAB's automated artefact rejection procedure (function 'pop_eegthresh'), epochs containing EEG data with voltage exceeding ± 475 µV and/or EOG data exceeding ± 300 µV were discarded. The duration of data available for the computation of the time–frequency analyses is presented in Table 2.

The time–frequency analyses of the EEG data from each sleep stage and wakefulness were conducted using Matlab (Mathworks, Inc., Natick, MA, USA) and the open-source Matlab toolboxes, EEGLAB [39] and FieldTrip [40]. The EEG data were analysed in 1 Hz steps from 1 to 30 Hz. Spectral power was estimated for each frequency of interest using Fieldtrip's Fast Fourier Transform (method 'mtmfft' of the frequency analysis protocol,
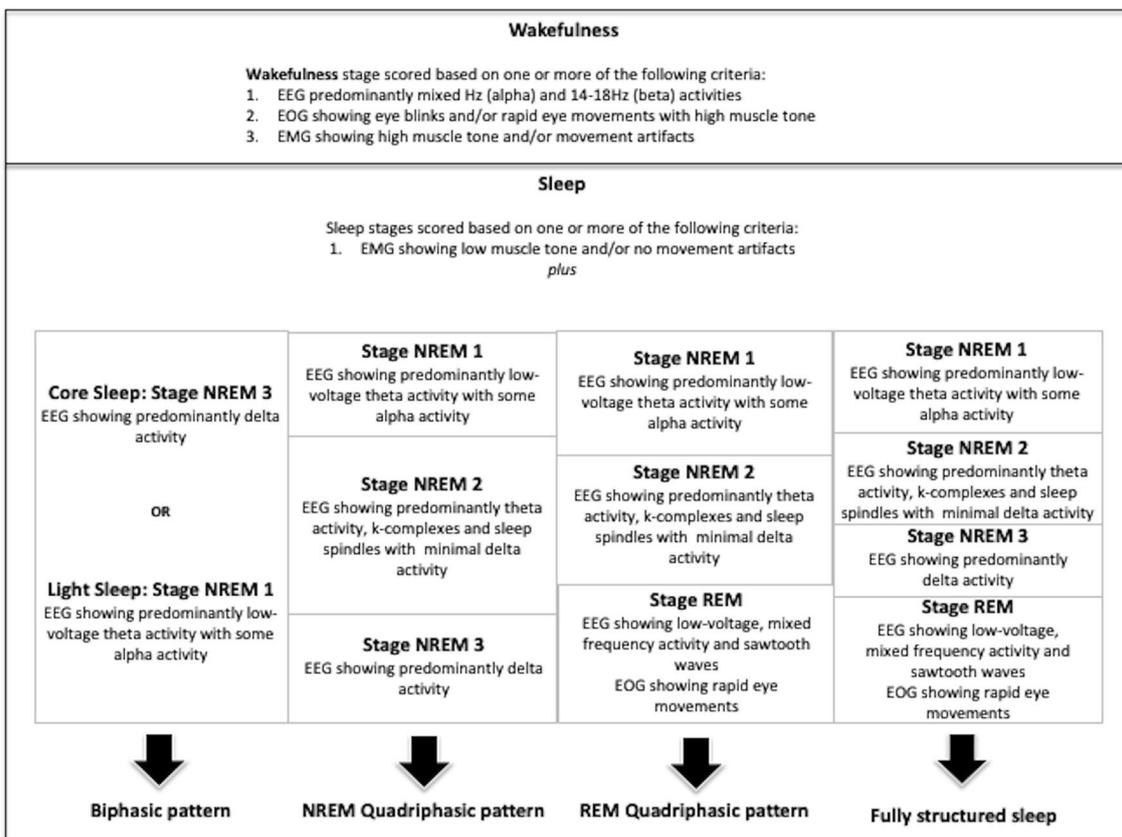
Fig. 1 Overview of the sleep patterns and scoring criteria for the patient data

'ft_freqanalysis'; see also www.fieldtriptoolbox.org/tutorial/timefrequencyanalysis#time-frequency_analysis_i). The estimates were computed using a Hanning taper. For each patient and healthy volunteer, relative spectral power for every sleep stage was calculated using the wakefulness period for the same participant.

Results

An overview of each patient's sleep and wake EEG data is presented in Table 3.

Standard sleep features

Overall, the patients diagnosed as being in a minimally conscious state exhibited more preserved sleep architecture compared to the patients diagnosed as being in a vegetative state (unresponsive wakefulness syndrome). Indeed, four of five patients diagnosed as being in a minimally conscious state exhibited full sleep, and all five patients exhibited

k-complexes and slow wave sleep. Only one patient did not demonstrate REM sleep (i.e., the patient demonstrated a Non-REM quadriphasic sleep pattern), and three patients did not demonstrate sleep spindles.

Among the patients diagnosed as being in a vegetative state (unresponsive wakefulness syndrome), two patients (P08 and P13) did not demonstrate any sleep signs and were classified with Biphasic sleep (i.e., alternating periods of non-REM stage 1 sleep and wakefulness). Of the remaining six patients, three patients exhibited full sleep, two patients exhibited REM quadriphasic sleep, and one patient exhibited Non-REM quadriphasic sleep. Five of six patients diagnosed as being in a vegetative state (unresponsive wakefulness syndrome) demonstrated REM sleep, k-complexes, and slow wave sleep, and four of these patients also demonstrated sleep spindles.

The patient diagnosed with Locked-in syndrome demonstrated a Biphasic sleep pattern consisting of wakefulness and non-REM stage 3 sleep; during these sleep periods, k-complexes and slow waves were identified without sleep spindles or REMs. The sleep data from each patient are presented as hypnograms in Fig. 2.

Table 2 Median duration and range (in minutes) of the wakefulness and sleep periods remaining following the removal of artefacts

Group	Wakefulness	Non-REM stage 1	Non-REM stage 2	Non-REM stage 3	REM
Patients	250 (29–825)	27 (0–168)	68 (0–191)	12 (0–88)	16 (0–85)
Volunteers	21 (4–113)	12 (5–31)	214 (105–293)	109 (16–194)	83 (52–125)

Spectral analyses

As there was variance in the number of epochs available for each sleep stage and wakefulness between individual patients and also between the healthy volunteers and patients (see Table 2), the findings of the spectral analyses are presented as spectra. The power spectra for the patients are presented in Figs. 3 and 4, alongside averaged spectra from the corresponding group of health volunteers (separated by age). The number of epochs (n) that contributed to the single-subject averaged spectra for each patient is provided above each plot. Asterisks mark frequency values at which the patient data deviated more than ± 1.96 standard deviations from the age-matched volunteer group data.

Discussion

The return of sleep–wake cycles and circadian rhythmicity is an important clinical feature after brain injury in that it may mark a person's transition from coma to another state of consciousness. For example, some patients undergoing intensive care following acute brain injury recovered circadian rhythmicity in parallel with behavioural markers of awareness [41]. With respect to patients diagnosed as being in a vegetative state (Unresponsive Wakefulness Syndrome) or a minimally conscious state, there is now increasingly converging evidence that the vast majority of these patients have some form of a sleep–wake cycle [18, 23, 42]. However, these sleep–wake cycles are often

Table 3 Summary of the patients' sleep scoring results and spectral profile as compared to the healthy volunteers

Patient ID	Diagnosis/sleep pattern/age	Rapid eye movements	Sleep spindles	*k*-complexes	Slow waves	Other sleep features
P01	VS (UWS)/REM Quad/65	Present	Absent	Present	Absent	Frequent arousals
P02	EMCS/NREM Quad/27	Absent	Present	Present	Atypical	Muscle tension reduced relative to wake Rapid eye movements outside of REM sleep
P03	MCS/full/40	Present	Absent	Present	Present	Daytime naps Muscle tension reduced relative to wake
P04	VS (UWS)/NREM Quad/46	Absent	Present	Present	Present	Frequent arousals Many eye movements
P05	LIS/biphasic[a]/55	Absent	Absent	Present	Present	Awake most of the night
P06	VS (UWS)/full/27	Present	Present	Present	Present	Muscle tension increased relative to wake
P07	EMCS/full/23	Present	Absent	Present	Present	None
P08	VS (UWS)/Biphasic/26	Absent	Absent	Absent	Absent	None
P09	VS (UWS)/REM Quad/21	Present	Present	Present	Absent	None
P10	VS (UWS)/full/14	Few	Present	Present	Present	Snoring
P11	MCS/full/31	Present	Present	Present	Present	None
P12	MCS/full/29	Present	Absent	Present	Present	None
P13	VS (UWS)/biphasic/28	Absent	Absent	Absent	Absent	Frequent movement and eye movements throughout recording
P14	VS (UWS)/full/25	Present	Absent	Present	Present	None

[a]Very little sleep

EMCS Emergence from a minimally conscious state, *NREM Quad* non-rapid eye movement quadriphasic, *VS (UWS)* vegetative state (unresponsive wakefulness syndrome)

abnormal, with certain features such as sleep spindles and REM sleep absent or severely reduced in frequency relative to the sleep of healthy people. In keeping with the majority of literature in this field, the current investigation did not identify any patients without a sleep–wake cycle. Moreover, this work adds to the existing literature about the sleep of patients with chronic disorders of consciousness through the quantification of the spectral profile of each patient's sleeping and waking EEG, with reference to a healthy sample of age-matched adults and the assistance of a previously tested sleep scoring criteria for this population [33].

Biphasic sleep patterns

A noteworthy finding in this investigation is that two patients diagnosed as being in a vegetative state

(unresponsive wakefulness syndrome) demonstrated a biphasic sleep–wake pattern. Both patients (P08 and P13) were younger men who had sustained traumatic brain injuries. Both patients exhibited one phase of wake electrophysiological activity and only one unique phase of sleep-like electrophysiological activity that most closely resembled non-REM stage 1 sleep. Neither patient demonstrated any standard sleep features. A similar biphasic sleep pattern was identified in 19 of 49 patients diagnosed as being in a vegetative state (unresponsive wakefulness syndrome) in a recent large-scale investigation [23]. The biphasic pattern in that investigation was described as one sleep-like phase characterized by severely attenuated EEG tracings and no classic sleep features, with alternating periods of wakefulness. Our patients' biphasic sleep pattern is most likely in keeping with this larger cohort.
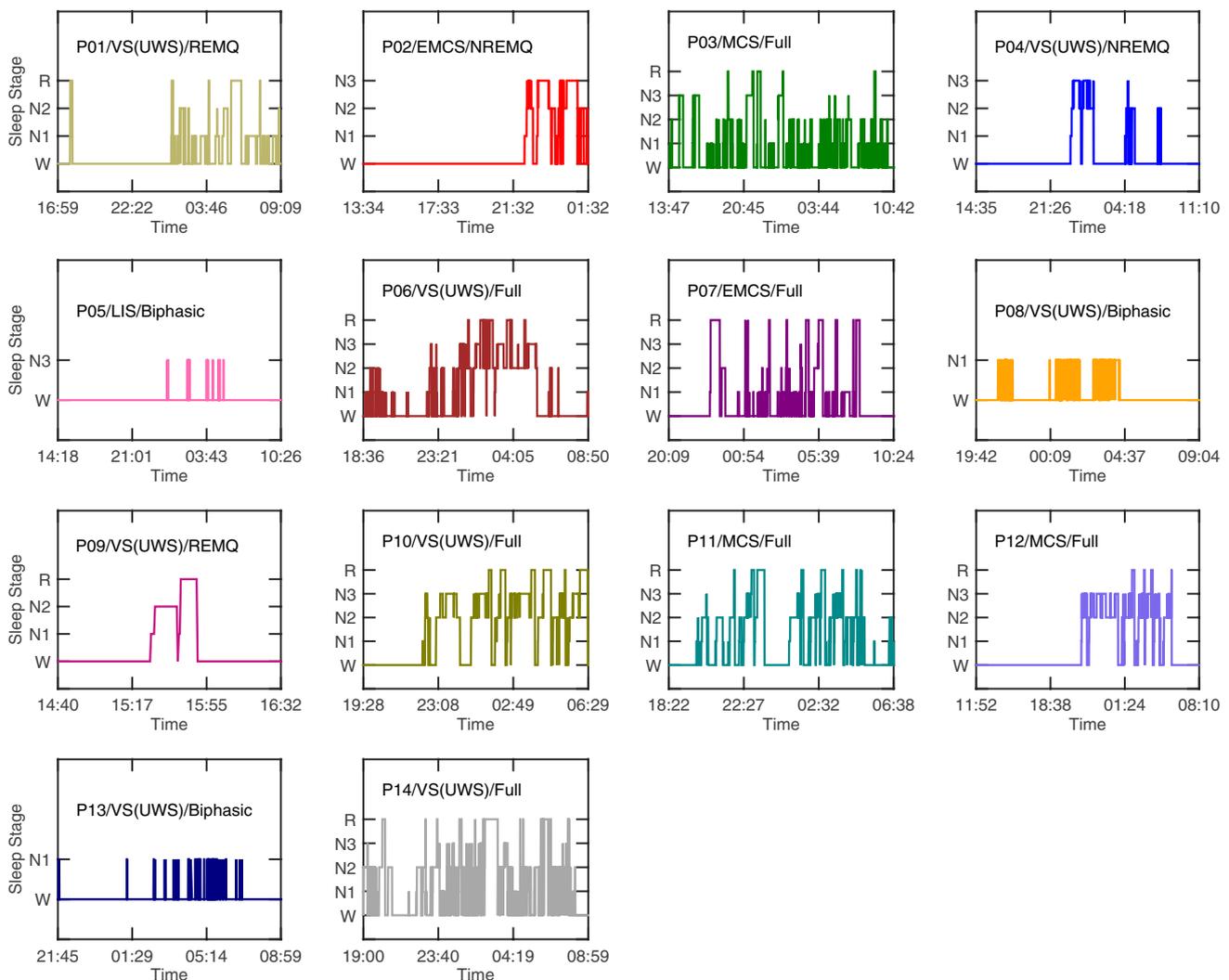

Fig. 2 Hypnograms for each patient. Please refer to Table 1 for demographic information. *EMCS* emergence from a minimally conscious state, *LIS* locked-in syndrome, *MCS* minimally conscious state, *N1-3* non-REM stages 1–3 sleep, *NREMQ* non-REM quadriphasic, *R* rapid eye movement sleep, *REMQ* REM quadriphasic, *W* wake, *VS* (*UWS*) vegetative state (unresponsive wakefulness syndrome)
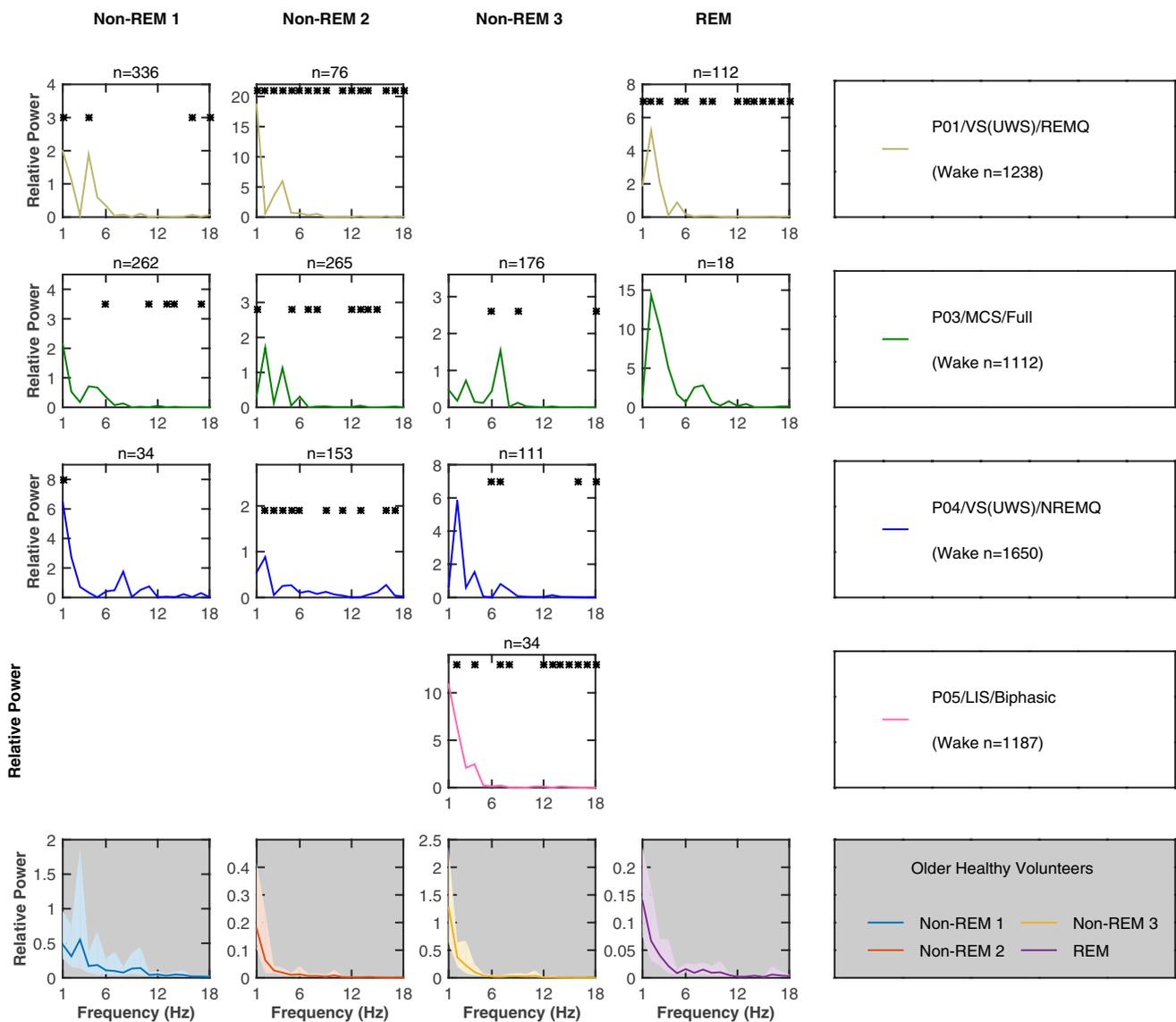
Fig. 3 Continuous relative power spectra by sleep stage for the older patients and healthy volunteers. The number of 30-s epochs (*n*) that contributed to the spectral analyses is provided above each plot for the sleep stages and indicated as inset text with the figure legends for wakefulness. The spectral averages for the healthy volunteers are depicted with shading that denotes 95% confidence intervals. Asterisks mark frequency values at which the patient data deviated more than ± 1.96 standard deviations from the age-matched volunteer group data

A third patient in our investigation demonstrated a biphasic sleep pattern. This patient was an older male with Locked-in syndrome following a brainstem stroke (P05). His pattern of sleep consisted of wake periods with alternating bouts of non-REM stage 3 sleep and featured very little sleep overall. While there is a paucity of data concerning sleep in patients with Locked-in syndrome, reduced total sleep time ranging from 1.25 to 6 h was previously reported in a sample of 21 patients [43]. Another case report of two patients with Locked-in syndrome also described limited sleep with short bursts of non-REM sleep, and this was partially attributed to injury extending into the pontine tegmentum [44].

Indeed, the pontine tegmentum has been described as the "switch" that mediates the transition between the non-REM and REM sleep phases [45]. Our patient's brainstem injury thus differentiates his biphasic sleep pattern from the other two patients in our sample and reflects direct compromise of the brainstem.

Slow wave sleep

Slow wave sleep has recently been highlighted as a potentially important correlate of behavioural responsiveness in patients with disorders of consciousness. In the previously discussed
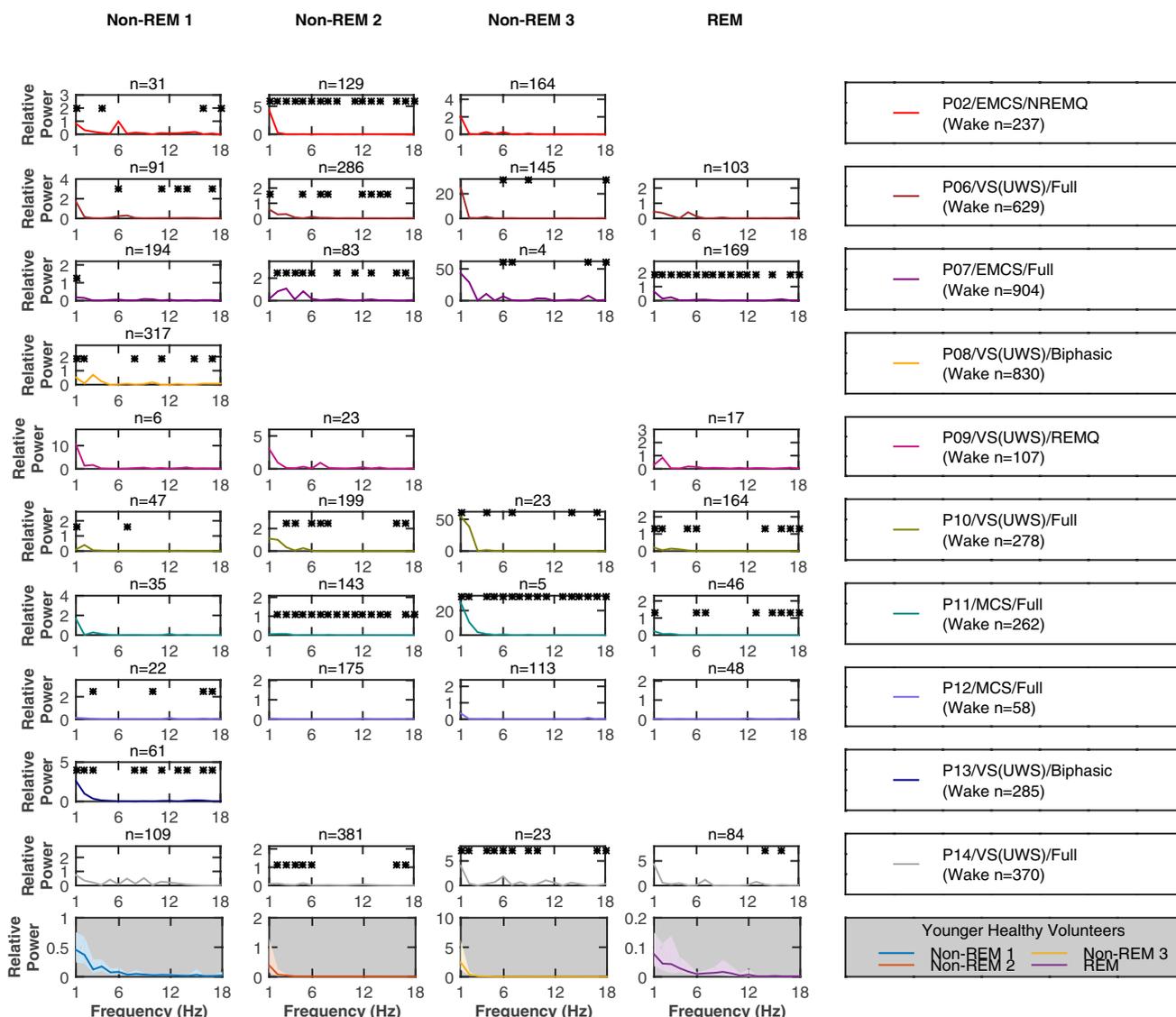
Fig. 4 Continuous relative power spectra by sleep stage for the younger patients and healthy volunteers. The number of 30-s epochs (*n*) that contributed to the spectral analyses is provided above each plot for the sleep stages and indicated as inset text with the figure legends for wakefulness. The spectral averages for the healthy volun-teers are depicted with shading that denotes 95% confidence intervals. Asterisks mark frequency values at which the patient data deviated more than ± 1.96 standard deviations from the age-matched volunteer group data

large-scale investigation of Rossi Sebastiano et al. slow wave sleep was positively correlated with behavioural responsive-ness measured by the coma recovery scale [23]. Similar find-ings have been demonstrated in previous investigations of patients with severe brain injuries [20, 21, 32]. Furthermore, slow wave sleep has been linked to learning and memory and is thought to have an important role in synaptic homeostasis [46, 47]. In light of these relationships, slow wave sleep has been likened to a marker of more complex neural circuitry that may underlie the association between slow wave sleep and greater responsiveness in patients with disorders of con-sciousness [23, 48]. In the current investigation, four patients

diagnosed as being in a vegetative state (unresponsive wake-fulness syndrome) did not demonstrate slow wave sleep; two of these patients demonstrated a non-REM quadriphasic sleep pattern (P01 and P09), and the other two patients demon-strated biphasic sleep patterns (P08 and P13). Although slow wave sleep was evident in all patients diagnosed as being in a minimally conscious state, our sample is unfortunately too small to draw meaningful inferences about the relationship between the behavioural scores of our patients and the pres-ence and absence of any sleep features. Nevertheless, these scores are included in Table 1 for use in meta-analyses or similar efforts in the future.

One possibility that has not yet been included in the recent discussions of slow wave sleep among patients with disorders of consciousness pertains to certain medical factors that are also associated with reductions in slow wave sleep. For example, medications such as benzodiazepines and opioids are sometimes associated with alterations in sleep architecture of uncertain clinical significance, including reductions in slow wave sleep [49]. Similarly, epilepsy and other seizure disorders are associated with reduced slow wave sleep [50, 51]. Seizure disorders are common in patients with acquired brain injuries, and some of the medications that treat these disorders are themselves associated with reduced slow wave sleep [49]. Complete medication lists were unfortunately not available as part of the current investigation and were also not discussed in the recent large-scale investigation of Rossi Sebastiano et al., but this information would be useful in future work to specifically address this potential confound.

REM sleep

From a neuroanatomical perspective, the brainstem is necessary and sufficient for REM sleep [52, 53]. When REM sleep is present despite the severe brain injuries associated with disorders of consciousness, these brainstem REM generators are presumably intact. There were five patients in this study who did not demonstrate REM sleep; two patients demonstrated a Non-REM quadriphasic sleep pattern (P01 and P09), and the remaining three patients demonstrated biphasic sleep (P05, P08, and P13). In previous studies of patients with disorders of consciousness, REM sleep has also been variably detected; for example, 23 of 55 patients diagnosed as being in a vegetative state (unresponsive wakefulness syndrome) and 21 of 36 patients diagnosed as being in a minimally conscious state demonstrated REM sleep in a recent large-scale investigation [23]. The presence of REM sleep among patients with disorders of consciousness has been estimated as ranging from 15 to 20% in more recent reports, although it was higher in some early investigations [42]. A further consideration is that it is difficult to ascertain the clinical significance of REM sleep because there is some controversy concerning the function of REM sleep [54]. For instance, selective REM sleep deprivation has been linked to mood, anxiety, cognitive deficits, and memory impairment in healthy sleepers [55], but there are also several case reports of individuals with brainstem lesions and no cognitive impairments despite very limited or absent REM sleep [56, 57]. Accordingly, it is difficult to assign clinical significance to the absence of REM sleep in patients with disorders of consciousness beyond the presumption of compromise to the brainstem.

Sleep spindles

Sleep spindles are generated by the thalamus and thalamocortical networks [58]. In patients with disorders of consciousness, the thalamus and most thalamocortical networks are compromised, and reduced responsiveness is associated with more extensive thalamic injury [59, 60]. Based on single-unit neural recordings, patients diagnosed as being in a vegetative state (unresponsive wakefulness syndrome) demonstrated a reduction of about 50% in active thalamic neurons versus those diagnosed as being in a minimally conscious state [61]. These results suggest that there may be a diagnostic role for sleep spindles in that patients diagnosed as being in a vegetative state (unresponsive wakefulness syndrome) are less likely to generate sleep spindles normally than patients diagnosed as being in a minimally conscious state. At least one previous report has specifically identified sleep spindles as an EEG feature that facilitated the discrimination of these two diagnostic categories [32]. In this investigation, two of five of patients diagnosed as being in a minimally conscious state and four of eight patients diagnosed as being in a vegetative state (unresponsive wakefulness syndrome) demonstrated sleep spindles. Sleep spindles were also more common in patients diagnosed as being in a minimally conscious state (8 of 36) versus a vegetative state (unresponsive wakefulness syndrome; 5 of 55) in a recent large-scale investigation [23]. It is important to note that there is some variability in the definitions of sleep spindles across sleep studies involving patients with disorders of consciousness; for example, the frequency of sleep spindles has been variably defined from 9 to 12 Hz, 10 to 16 Hz, 11 to 16 Hz, and 12 to 15 Hz in different reports [62]. Altogether, the presence of sleep spindles tends to confer a less severe brain injury, but there is not yet sufficient evidence to use sleep spindles to confirm the diagnosis of a vegetative (unresponsive wakefulness syndrome) versus minimally conscious state. Reduced or abnormal spindle production has been linked to deficits in intellectual disability [63, 64], and is associated with cognitive abilities [65–69] and the strengthening of newly acquired declarative and procedural memory (for a review, see [65, 70]). Thus, atypical spindles may be associated with reduced or impaired cognitive function disorders of consciousness.

Sleep scoring for patients with disorders of consciousness

An important consideration is that the patient sleep data presented in this investigation were scored using a technique based upon the standards of the American Academy of Sleep Medicine and modified for patients with disorders of consciousness, initially developed by Cologan et al. [71] and further refined by Avantaggiato et al. [33]. In their work, Avantaggiato et al. present sleep data from children and adolescents with disorders of consciousness. Their sleep scoring and classification criteria were developed using the modern guidelines for adult sleep of the American Academy of Sleep

Medicine [38], further refined using the classic guidelines for adult sleep from Rechtschaffen and Kales [72], and subsequently adjusted for their patients using previous investigations of sleep among both adult and pediatric patients with disorders of consciousness [29, 71]. Four clinicians from two hospitals contributed to sleep scoring and the classification of the patient sleep patterns over three rounds of independent, double-blinded scoring [33]. The authors of the current work selected the approach of Avantaggiato et al. because it was a transparently documented adaptation and logical extension of the standard criteria from the American Academy of Sleep Medicine, informed by previous studies of patients with disorders of consciousness and classic sleep guidelines intended for use in adult populations [29, 33, 38, 71, 72]. Therefore, this approach stands to have clinical utility and makes possible some direct comparisons to standard PSG scoring. Nevertheless, there are several published scoring systems for sleep among patients with disorders of consciousness, and any of these could have been selected instead. Indeed, one challenge of the study of sleep among patients with disorders of consciousness is that there is no consensus concerning the optimal technique to classify these data [73], and this lack of standardization can impair comparisons across investigations, including the current work.

The optimal manner in which sleep data are scored and categorized among patients with disorders of consciousness has yet to be determined. For instance, there is some debate as to whether it is appropriate to use expert scoring for sleep data from patients with disorders of consciousness at all, given that their EEG data are abnormal and do not necessarily demonstrate the features upon which human sleep is classically defined [18, 62, 73, 74]. Expert scoring approaches have been criticized for being potentially subjective and difficult to replicate, partly due to a lack of transparency in reporting modified criteria [18, 31, 62, 75]. Additionally, data-driven approaches to study sleep in these patients, though meritorious, have other limitations and are similarly afflicted by a lack of standardization in the literature as the expert scoring approaches [62, 73, 74]. To address these issues, calls have been made for consensus about scoring techniques and large-scale, multi-centred investigations, potentially facilitated by participation in the "Disorders of Consciousness Special Interest Group" of the International Brain Injury Association [48, 62, 75]. These advancements are necessary to develop evidence of sufficient quality to inform clinical decision-making and ultimately facilitate practice changes that benefit the patients who participate in these investigations. Nevertheless, there is also a role for smaller-scale investigations that employ different techniques to study sleep and other processes in this population to explore the merits of a given approach. These smaller investigations are more pragmatic in terms of resources and time, and the presentation of different techniques can spur further discussion and methodological refinement. For instance, the current work presents one previously described method for scoring sleep in

this population, rooted in standard and clinically relevant scoring criteria, alongside spectral analyses inclusive of age-matched healthy volunteers. These techniques highlight some of the challenges of applying classic sleep stage definitions in this population and provide a method to evaluate expert scoring.

Limitations

This investigation has some methodological limitations that are worthy of discussion. For instance, it has been recommended that sleep recordings from patients with disorders of consciousness be inclusive of more than night-time hours owing to daytime naps, the disruptive sleeping environment of clinical facilities, and the potential pathological prolongation of circadian rhythms in clinical populations [18, 62]. Indeed, a few commentaries have been published regarding the optimal duration of recordings and the pragmatics of obtaining very long recordings from patients with disorders of consciousness [42, 48, 62, 76]. The current investigators attempted to obtain 24-h recordings for all patients in line with these recommendations, but this was challenging. For example, several recordings were prematurely terminated due to care needs, caregiver availability, and other issues. The initial attempts at data collection for this investigation yielded some recordings without any useable data and prompted many adjustments to the acquisition protocol (for example, the addition of EC2 adhesive paste). Even after these adjustments were made, large portions of data were unfortunately lost for various reasons including patient movement and sweating. Caregivers were instructed to keep the artificial lighting off throughout dedicated sleeping hours and notify the researchers of any disruptions for care activities during this time, but this information was not consistently provided to the research team, partly due to changes in providers over the course of the recording (e.g., 12-h shifts with 4-h "floating" cross-coverage). Many of the aforementioned challenges in the current work could be addressed by incorporating infrared video recordings and continuous measurement of ambient lighting. Video recording would also support the sleep scoring procedure with the additional information about movement including nystagmus, interruption of sleep by care activities, and other possible sources of artefacts and variance in the data. Lastly, future investigations would also benefit from the inclusion of other physiological signals, such as electrocardiography, to further characterize circadian variability.

Summary and conclusions

All members of this small sample of patients with chronic disorders of consciousness demonstrated a sleep–wake cycle in some form or another, with notable heterogeneity between

individuals. In three patients, these cycles were limited to alternating periods of wakefulness and sleep-like electrophysiological activity that most closely resembled non-REM stage 1 sleep in two cases and non-REM stage sleep in the remaining case. Two patients demonstrated a sleep–wake cycle that included all sleep phases aside from non-REM stage 3, and another two patients demonstrated a sleep–wake cycle that included all sleep phases aside from REM. The remaining seven patients demonstrated all typical sleep phases, but three patients did not generate sleep spindles. Altogether, these findings are consistent with previous sleep studies of patients with disorders of consciousness and reinforce the understanding that these patients do sleep, albeit with abnormal electrophysiological markers that reflect their brain injuries and other inherent limitations of their recording and sleeping environment. The diagnostic and prognostic implications of this and similar investigations are limited until sufficiently large cohorts of data are available to determine the optimal manner in which such data are to be acquired, analysed and interpreted. Nevertheless, the study of sleep in patients with disorders of consciousness has practical value in that it provides additional information about each patient's probable subjective experience, such as whether and how much time the patient is able to rest during dedicated sleeping hours and remain alert during waking hours. Importantly, our study employed 24-h recordings, and given the marked disruption in terms of sleep characteristics, quality, duration and timing, highlights the importance of studying sleep not only during the night, but also throughout the day in this patient population. Our results further support the notion that sleep microarchitecture can help delineate the nature and consequences of severe acquired brain injury and provide complimentary insight into the primary and secondary symptoms of the disorders of consciousness.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval Both the patient and control studies were approved by the appropriate local ethics committee at Western University (London, Canada) and have therefore been performed in accordance with the ethical standards laid down in the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans 2 [77]. For the control studies, all participants gave their informed consent prior to their inclusion in the study. For the behaviourally non-responsive patients, each patient's designated substitute decision-maker gave their informed consent prior to the patient's inclusion in the study.

References

1. Bernat JL (2006) Chronic disorders of consciousness. Lancet 367:1181–1192. https://doi.org/10.1016/S0140-6736(06)68508-5
2. Laureys S, Celesia GG, Cohadon F et al (2010) Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med 8:68. https://doi.org/10.1186/1741-7015-8-68
3. Giacino JT, Ashwal S, Childs NL et al (2002) The minimally conscious state: definition and diagnostic criteria. Neurology 58:349–353. https://doi.org/10.1212/WNL.58.3.349
4. Moruzzi G, Magoun HW (1949) Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol 1:455–473
5. Plum F, Posner JB (1972) The diagnosis of stupor and coma. Contemp Neurol Ser 10:1–286
6. Tononi G (2012) Integrated information theory of consciousness: an updated account. Arch Ital Biol 150:293–329. https://doi.org/10.4449/aib.v149i5.1388
7. Hobson JA (2009) REM sleep and dreaming: towards a theory of protoconsciousness. Nat Rev Neurosci 10:803–813. https://doi.org/10.1038/nrn2716
8. Brown RE, Basheer R, McKenna JT et al (2012) Control of sleep and wakefulness. Physiol Rev 92:1087–1187. https://doi.org/10.1152/physrev.00032.2011
9. Parvizi J, Damasio AR (2003) Neuroanatomical correlates of brainstem coma. Brain 126:1524–1536. https://doi.org/10.1093/brain/awg166
10. Koch C, Massimini M, Boly M, Tononi G (2016) Neural correlates of consciousness: progress and problems. Nat Rev Neurosci 17:307–321. https://doi.org/10.1038/nrn.2016.22
11. Siclari F, Larocque JJ, Postle BR, Tononi G (2013) Assessing sleep consciousness within subjects using a serial awakening paradigm. Front Psychol 4:542. https://doi.org/10.3389/fpsyg.2013.00542
12. Hobson JA, Pace-Schott EF (2002) The cognitive neuroscience of sleep: neuronal systems, consciousness and learning. Nat Rev Neurosci 3:679–693. https://doi.org/10.1038/nrn915
13. Chaput J-P (2014) Sleep patterns, diet quality and energy balance. Physiol Behav 134:86–91. https://doi.org/10.1016/j.physbeh.2013.09.006
14. Sofi F, Cesari F, Casini A et al (2012) Insomnia and risk of cardiovascular disease: a meta-analysis. Eur J Prev Cardiol 21:57–64. https://doi.org/10.1177/2047487312460020
15. Tsuno N, Besset A, Ritchie K (2005) Sleep and depression. J Clin Psychiatry 66:1254–1269. https://doi.org/10.4088/JCP.v66n1008
16. De Biase S, Gigli GL, Lorenzut S et al (2014) The importance of polysomnography in the evaluation of prolonged disorders of consciousness: sleep recordings more adequately correlate than stimulus-related evoked potentials with patients' clinical status. Sleep Med 15:393–400. https://doi.org/10.1016/j.sleep.2013.09.026
17. Landsness E, Bruno M-A, Noirhomme Q et al (2011) Electrophysiological correlates of behavioural changes in vigilance in vegetative state and minimally conscious state. Brain 134:2222–2232. https://doi.org/10.1093/brain/awr152
18. Wislowska M, Del Giudice R, Lechinger J et al (2017) Night and day variations of sleep in patients with disorders of consciousness. Sci Rep 7:1–11. https://doi.org/10.1038/s41598-017-00323-4

19. Rossi Sebastiano D, Panzica F, Visani E et al (2015) Significance of multiple neurophysiological measures in patients with chronic disorders of consciousness. Clin Neurophysiol 126:558–564. https://doi.org/10.1016/j.clinph.2014.07.004

20. Mouthon A-L, van Hedel HJA, Meyer-Heim A et al (2016) High-density electroencephalographic recordings during sleep in children with disorders of consciousness. NeuroImage Clin 11:468–475. https://doi.org/10.1016/j.nicl.2016.03.012

21. Lanteri P, Corica A, Bianconi C et al (2010) Sleep homeostasis in the vegetative and minimally conscious states. J Psychophysiol 24:120–124. https://doi.org/10.1027/0269-8803/a000022

22. Matsumoto M, Sugama J, Nemoto T et al (2015) The nature of sleep in 10 bedridden elderly patients with disorders of consciousness in a Japanese hospital. Biol Res Nurs 17:13–20. https://doi.org/10.1177/1099800414523118

23. Rossi Sebastiano D, Visani E, Panzica F et al (2018) Sleep patterns associated with the severity of impairment in a large cohort of patients with chronic disorders of consciousness. Clin Neurophysiol 129:687–693. https://doi.org/10.1016/j.clinph.2017.12.012

24. Matsumoto M, Sugama J, Okuwa M et al (2013) Non-invasive monitoring of core body temperature rhythms over 72 h in 10 bedridden elderly patients with disorders of consciousness in a Japanese hospital: a pilot study. Arch Gerontol Geriatr 57:428–432. https://doi.org/10.1016/j.archger.2013.05.009

25. Blume C, Lechinger J, Santhi N et al (2017) Significance of circadian rhythms in severely brain-injured patients. Neurology 88:1933–1941. https://doi.org/10.1212/WNL.0000000000003942

26. Cruse D, Thibaut A, Demertzi A et al (2013) Actigraphy assessments of circadian sleep–wake cycles in the vegetative and minimally conscious states. BMC Med 11:18. https://doi.org/10.1186/1741-7015-11-18

27. Bekinschtein TA, Golombek DA, Simonetta SH et al (2009) Circadian rhythms in the vegetative state. Brain Inj 23:915–919. https://doi.org/10.1080/02699050903283197

28. Cologan V, Schabus M, Ledoux D et al (2010) Sleep in disorders of consciousness. Sleep Med Rev 14:97–105. https://doi.org/10.1016/j.smrv.2009.04.003

29. Chéliout-Heraut F, Rubinsztajn R, Ioos C, Estournet B (2001) Prognostic value of evoked potentials and sleep recordings in the prolonged comatose state of children. Preliminary data. Neurophysiol Clin 31:283–292. https://doi.org/10.1016/S0987-7053(01)00270-2

30. Arnaldi D, Terzaghi M, Cremascoli R et al (2016) The prognostic value of sleep patterns in disorders of consciousness in the sub-acute phase. Clin Neurophysiol 127:1445–1451. https://doi.org/10.1016/j.clinph.2015.10.042

31. Wielek T, Lechinger J, Wislowska M et al (2018) Sleep in patients with disorders of consciousness characterized by means of machine learning. PLoS ONE 13:1–14. https://doi.org/10.1371/journal.pone.0190458

32. Malinowska CC, Bruno M-A et al (2013) Electroencephalographic profiles for differentiation of disorders of consciousness. Biomed Eng Online 12:109. https://doi.org/10.1186/1475-925X-12-109

33. Avantaggiato P, Molteni E, Formica F et al (2015) Polysomnographic sleep patterns in children and adolescents in unresponsive wakefulness syndrome. J Head Trauma Rehabil 30:334–346. https://doi.org/10.1097/HTR.0000000000000122

34. Cornelissen L, Kim SE, Purdon PL et al (2015) Age-dependent electroencephalogram (EEG) patterns during sevoflurane general anesthesia in infants. Elife 4:e06513. https://doi.org/10.7554/eLife.06513

35. Akeju O, Pavone KJ, Thum JA et al (2015) Age-dependency of sevoflurane-induced electroencephalogram dynamics in children. Br J Anaesth 115:i66–i76. https://doi.org/10.1093/bja/aev114

36. Purdon PL, Pavone KJ, Akeju O et al (2015) The ageing brain: age-dependent changes in the electroencephalogram during propofol and sevofluranegeneral anaesthesia. Br J Anaesth 115:i46–i57. https://doi.org/10.1093/bja/aev213

37. Kalmar K, Giacino JT (2005) The JFK coma recovery scale—revised. Neuropsychol Rehabil 15:454–460. https://doi.org/10.1080/09602010443000425

38. Iber C, Ancoli-Israel S, Chesson AL, Quan SF (2007) The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL

39. Delorme A, Makeig S (2004) EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 134:9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

40. Oostenveld R, Fries P, Maris E, Schoffelen J-M (2011) FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011:156869. https://doi.org/10.1155/2011/156869

41. Duclos C, Dumont M, Arbour C et al (2017) Parallel recovery of consciousness and sleep in acute traumatic brain injury. Neurology 88:268–275. https://doi.org/10.1212/WNL.0000000000003508

42. Pavlov YG, Gais S, Müller F et al (2017) Night sleep in patients with vegetative state. J Sleep Res 26:629–640. https://doi.org/10.1111/jsr.12524

43. Patterson JR, Grabois M (1986) Locked-in syndrome: a review of 139 cases. Stroke 17:758–764. https://doi.org/10.1161/01.str.17.4.758

44. Cummings JL, Greenberg R (1977) Sleep patterns in the 'locked-in' syndrome. Electroencephalogr Clin Neurophysiol 43:270–271. https://doi.org/10.1016/0013-4694(77)90134-1

45. Lu J, Sherman D, Devor M, Saper CB (2006) A putative flip-flop switch for control of REM sleep. Nature 441:589–594. https://doi.org/10.1038/nature04767

46. Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10:49–62. https://doi.org/10.1016/j.smrv.2005.05.002

47. Diekelmann S, Born J (2010) The memory function of sleep. Nat Rev Neurosci 11:114–126. https://doi.org/10.1038/nrn2762

48. Rossi Sebastiano D, Franceschetti S (2018) A response to: "Sleep and circadian rhythms in severely brain-injured patients—a comment". Clin Neurophysiol 129:1788. https://doi.org/10.1016/j.clinph.2018.04.744

49. Roehrs T, Roth T (2010) Drug-related sleep stage changes: functional significance and clinical relevance. Sleep Med Clin 5:559–570. https://doi.org/10.1016/j.jsmc.2010.08.002

50. Bazil CW, Castro LHM, Walczak TS (2000) Reduction of rapid eye movement sleep by diurnal and nocturnal seizures in temporal lobe epilepsy. Arch Neurol 57:363–368. https://doi.org/10.1001/archneur.57.3.363

51. Miller LA, Ricci M, van Schalkwijk FJ et al (2016) Determining the relationship between sleep architecture, seizure variables and memory in patients with focal epilepsy. Behav Neurosci 130:316–324

52. Jouvet M (1962) Recherches sur les structures nerveuses et les meˊcanismes responsables des diffeˊrentes phases du sommeil physiologique. Arch Ital Biol 100:125–206

53. Weber F, Chung S, Beier KT et al (2015) Control of REM sleep by ventral medulla GABAergic neurons. Nature 526:435–438. https://doi.org/10.1038/nature14979

54. Born J, Gais S (2000) REM sleep deprivation: the wrong paradigm leading to wrong conclusions. Behav Brain Sci 23:912–913. https://doi.org/10.1017/S0140525X00264029

55. Krause AJ, Ben SE, Mander BA et al (2017) The sleep-deprived human brain. Nat Rev Neurosci 18:404–418. https://doi.org/10.1038/nrn.2017.55

56. Magidov E, Hayat H, Sharon O et al (2018) Near-total absence of REM sleep co-occurring with normal cognition: an

update of the 1984 paper. Sleep Med 52:134–137. https://doi.org/10.1016/j.sleep.2018.09.003

57. Vertes RP, Eastman KE (2000) The case against memory consolidation in REM sleep. Behav Brain Sci 23:867–876. https://doi.org/10.1017/S0140525X00004003

58. De Gennaro L, Ferrara M, Bertini M (2001) The boundary between wakefulness and sleep: quantitative electroencephalographic changes during the sleep onset period. Neuroscience 107:1–11. https://doi.org/10.1016/S0306-4522(01)00309-8

59. Fernández-Espejo D, Bekinschtein TA, Monti MM et al (2011) Diffusion weighted imaging distinguishes the vegetative state from the minimally conscious state. Neuroimage 54:103–112. https://doi.org/10.1016/j.neuroimage.2010.08.035

60. Lutkenhoff ES, Chiang J, Tshibanda L et al (2015) Thalamic and extrathalamic mechanisms of consciousness after severe brain injury. Ann Neurol 78:68–76. https://doi.org/10.1002/ana.24423

61. Magrassi L, Zippo AG, Azzalin A et al (2018) Single unit activities recorded in the thalamus and the overlying parietal cortex of subjects affected by disorders of consciousness. PLoS ONE 13:1–17. https://doi.org/10.1371/journal.pone.0205967

62. Schabus M, Wislowska M, Angerer M, Blume C (2018) Sleep and circadian rhythms in severely brain-injured patients—a comment. Clin Neurophysiol 129:1788. https://doi.org/10.1016/j.clinph.2018.04.744

63. Bixler EO, Rhodes JM (1968) Spindle activity during sleep in cultural-familial mild retardates. Psychophysiology 5:212

64. Gibbs EL, Gibbs FA (1962) Extreme spindles: correlation of electroencephalographic sleep pattern with mental retardation. Science 138:1106–1107. https://doi.org/10.1126/science.138.3545.1106

65. Fogel SM, Smith CT (2011) The function of the sleep spindle: a physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. Neurosci Biobehav Rev 35:1154–1165

66. Fang Z, Sergeeva V, Ray LB et al (2017) Sleep spindles and intellectual ability: epiphenomenon or directly related? J Cogn Neurosci 29:167–182

67. Fang Z, Ray LB, Owen AM, Fogel SM (2019) Brain activation time-locked to sleep spindles associated with human cognitive abilities. Front Neurosci 13:46

68. Fang Z, Ray LB, Houldin E et al (2020) Sleep spindle-dependent functional connectivity correlates with cognitive abilities. J Cogn Neurosci 32:446–466

69. Bódizs R, Kis T, Lázár AS et al (2005) Prediction of general mental ability based on neural oscillation measures of sleep. J Sleep Res 14:285–292

70. Ulrich D (2016) Sleep spindles as facilitators of memory formation and learning. Neural Plast 2016:1796715

71. Cologan V, Drouot X, Parapatics S et al (2013) Sleep in the unresponsive wakefulness syndrome and minimally conscious state. J Neurotrauma 30:339–346. https://doi.org/10.1089/neu.2012.2654

72. Rechtschaffen A, Kales A (1968) A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects. Washingt. Public Heal. Serv

73. Kotchoubey B, Pavlov YG (2018) Approaches to sleep in severely brain damaged patients: opposite or complementary? Reply to "sleep and circadian rhythms in severely brain-injured patients—a comment". Clin Neurophysiol 129:1785–1787. https://doi.org/10.1016/j.clinph.2018.03.049

74. Kotchoubey B, Pavlov YG (2018) Machine learning versus human expertise: the case of sleep stage classification in disorders of consciousness. Response to Wislowska et al. Clin Neurophysiol 129:2682–2683. https://doi.org/10.1016/j.clinph.2018.09.020

75. Wislowska M, Blume C, Angerer M et al (2018) Approaches to sleep in severely brain damaged patients—further comments and replies to Kotchoubey & Pavlov. Clin Neurophysiol 129:2680–2681. https://doi.org/10.1016/j.clinph.2018.08.029

76. Kotchoubey B, Pavlov YG (2018) Sleep patterns open the window into disorders of consciousness. Clin Neurophysiol 129:668–669. https://doi.org/10.1016/j.clinph.2018.01.006

77. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council (2018) Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans