Sleep patterns associated with the severity of impairment in a large cohort of patients with chronic disorders of consciousness

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HIGHLIGHTS

- PSG is a reliable means of studying chronic DOC patients.
- UWS/VS patients with even severe impairment show residual sleep patterns.
- The presence of slow-wave sleep is correlated with high CRS-R scores.

ABSTRACT

Objective: We assessed sleep patterns in 85 patients with chronic disorders of consciousness (DOC) in order to reveal any relationship with the degree of the impairment.
Methods: Nocturnal polysomnography (PSG) was scored in patients classified as being in an unresponsive wakefulness syndrome/vegetative state (UWS/VS; n = 49) or a minimally conscious state (MCS; n = 36) in accordance with the rules of the American Academy of Sleep Medicine. The PSG data in the two diagnostic groups were compared, and the PSG parameters associated with the degree of impairment were analysed.
Results: In 19/49 UWS/VS patients, signal attenuation was the only EEG pattern detectable in sleep. Non-REM 2 (NREM2) and slow-wave sleep (SWS) (but not REM) stages were more frequent in the MCS patients. The presence of SWS was the most appropriate factor for classifying patients as UWS/VS or MCS, and the duration of SWS was the main factor that significantly correlated with revised Coma Recovery Scale scores.
Conclusion: The presence of NREM sleep (namely SWS) reflects better preservation of the circuitry and structures needed to sustain this stage of sleep in DOC patients.
Significance: PSG is a simple and effective technique, and sleep patterns may reflect the degree of impairment in chronic DOC patients.

1. Introduction

Brain injury due to severe anoxic, hemorrhagic or traumatic events often lead to chronic disorders of consciousness (DOCs), which have recently received increasing attention because of growing medical and ethical concerns relating to patient management. A considerable proportion of survivors of severe brain damage enter an unresponsive wakefulness syndrome/vegetative state (UWS/VS) or minimally conscious state (MCS) (Laureys et al., 2010) and a number of studies have assessed more or less extensive series of DOC patients using imaging procedures or neurophysiological evaluations designed to provide information supporting the clinical assessment of different degrees of DOCs or to identify prognostic markers (see reviews by Bender et al., 2015; Kondziella et al., 2015).

One significant advantage of sleep evaluation arises from the fact that long polysomnographic (PSG) recordings are easy to make at a patient's bedside as they do not need complex technical support. Each study and each technique has its advantages and

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limitations, but evidence collected over the last 50 years (Bergamasco et al., 1968; Evans and Bartlett, 1995; Valente et al., 2002; Landsness et al., 2011; Malinowska et al., 2013; Cologan et al., 2010, 2013; De Biase et al., 2014; Arnaldi et al., 2016; Pavlov et al. 2017) indicates that electro-encephalography (EEG) and PSG recordings can contribute to predicting outcomes in patients observed shortly after the time of their brain injury and help in the differential diagnosis of MCS and UWS/VS. As a whole, studies of DOC patients have found that sleep patterns in MCS patients are better preserved than those UWS/VS patients, although significant differences can be found. One of the most important and cited studies by Landsness et al. (2011) did not find any markers of sleep in UWS/VS patients, thus supporting the idea that they only show behavioural signs of sleep, whereas a recent study by Pavlov et al. (2017) found that UWS/VS patients may retain circadian changes and show sleep patterns such as rapid eye movement (REM) and slow wave sleep (SWS) even in some patients with very severe clinical impairment or long-lasting illness.

Our previous neurophysiological study of chronic DOC patients found that a simple sleep score was one of the most effective parameters even in the case of extremely severe conditions, and that it was suitable for classifying the severity of brain damage and subsequent DOC (Rossi Sebastiano et al., 2015). However, this study had the limitations that sleep was only roughly classified using a semi-quantitative scale (Synek, 1988), in order to compare it with the other neurophysiological measures, and was not scored as suggested by the guidelines of the American Academy of Sleep Medicine (AASM).

The present study describes the specific and sometimes particular PSG patterns observed during whole-night recordings of 85 patients with chronic DOCs (classified on the basis of the AASM guidelines, Iber et al., 2007), and was carried out in order to assess their value in supporting clinical evaluations: the PSG data of the patients with UWS/VS or MCS group were compared, and the PSG parameters associated with the degree of the clinical impairment were analysed.

2. Methods

2.1. Patients

The study involved 85 patients consecutively admitted to Carlo Besta Neurological Institute, who were evaluated by the staff of the Coma Research Centre between January 2012 and February 2014. The DOC patients were scored using the Italian version of the revised Coma Recovery Scale (CRS-R) (Lombardi et al., 2007), and were as being in a UWS/VS (54 patients aged 49.4 ± 14.4 years, 17 women; time since the acute brain insult 35.9 ± 41.2 months) or MCS (31 patients aged 49.5 ± 14.1 years; 16 women; time since the acute brain insult 48.2 ± 43.9 months) using the Aspen criteria (Seel et al., 2010). At the time of observation, there was no between-group difference in the patients' age or the time since the brain-damaging event. Thirty-six patients had experienced anoxic damage, and 49 a traumatic or hemorrhagic brain insult.

The study was approved by the Ethics Committee of the Carlo Besta Neurological Institute in Milan, and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients' legally authorized representatives.

2.2. Polysomnography

All of the consecutively enrolled DOC patients underwent a PSG recording, which started at 2.00 p.m. on the second day after admission and lasted until 9.00 a.m. on the following day.

The recordings involved 19 EEG channels with the electrode array being placed in accordance with the international 10–20 system; two electro-oculogram channels (EOG); one electromyography channel recorded from the mylohyoid muscle (EMG); bipolar precordial electrocardiography (ECG); and impedance-based thoracic pneumography (PNG). The recordings were made using Ag/AgCl surface electrodes (impedance <5 kΩ), and the signals were acquired using a computerised Micromed Brain Quick System (Micromed SpA, Mogliano Veneto, Treviso, Italy) at a sampling rate of 256 Hz.

2.3. Sleep scoring

The PSG traces between 8.00 pm and 8.00 am were scored in 30-second epochs by two expert clinical neurophysiologists (DRS and SF) who were blinded to the patient's clinical assessments. The two raters first agreed on the rules for sleep scoring and then independently staged each recording; the traces were subsequently revised, if there was disagreement between the staging of epochs and the recognition of arousals. Uncertain epochs were not considered in the statistical analyses.

Total sleep time (TST), the duration of the REM, non-REM 2 (NREM2) and SWS stages of sleep, and of the number of phase transitions and arousals per hour (without any partition into A1, A2 or A3) were quantified. When the EEG signal was asymmetric or showed epileptic activity, we evaluated it on the hemisphere preserving the better organisation. The recordings that were interrupted early during the night, or showed artefacts preventing signal evaluation were excluded from the subsequent analyses.

We evaluated the recordings taking into account the characteristics of the EEG signals, together with the information provided by the polygraphic recordings (EMG, EOG, PNG and ECG). The PSG recordings were scored following the AASM rules as much as possible (Iber et al., 2007), with some adjustments, given to the particular nature of the sleep patterns in DOC patients.

We considered "wakefulness" as being reflected by all of the epochs showing EEG-polygraphic characteristics that did not suggest sleep, but indicated some degree of activity (usually eye-blinking and steady or variable tonic EMG activity). NREM1 sleep was excluded from the quantitative analyses, because the standard description of this stage is insufficiently clear in DOC patients (Cologan et al., 2013).

We rarely found the classical spindles and K-complexes characterising physiological NREM2 sleep. Hence we also considered repeated diffuse transients associated with fragments of alpha-theta activity as markers of NREM2, as well as similar epochs with "atypical" slow (10–12 Hz) spindles of long duration.

The epochs characterised by dominant low-voltage slow waves (<75 μV) (Cologan et al., 2013), and those characterised by "standard" high-amplitude slow waves were both considered as indicating SWS.

"Attenuation" was defined as a predominance of epochs of very low EEG signal amplitude (<20 μV), without any other physiological feature of sleep, in the absence of EMG activity eye blinking; "attenuation" was distinguished from REM stage mainly by the lack of saw-tooth eye movements.

2.4. Statistical analysis

The individual measures of each MCS and UWS/VS patient were compared using t, Mann-Whiney U (U-Mann) or chi-squared tests, depending on the characteristics of the variables. Logistic analysis was used on the whole patient population to identify the variables of primary interest associated with MCS and UWS/VS. The cut-off value for the predicted probability was set to 0.5.

Spearman's correlation was used to evaluate the relationships between the individual sleep stages and CRS scores. Subsequently a multiple linear regression was applied to identify the variable of primary interest and reduce spurious correlations.

The data were analysed using SPSS software, version 14 (SPSS Inc., Chicago, IL, USA) and a significance level of 5%. Bonferroni's correction was applied when appropriate.

3. Results

Tables 1 and 2 summarise the PSG data of the MCS and UWS/VS groups. The agreement between raters was high, 4,8% of uncertain epochs and arousals were removed from the subsequent analyses. TST ranged from 21 to 515 minutes (mean 184.7 ± 110.6 minutes), and was significantly longer in the MCS patients. Even in the case of long-lasting sleep, its course seemed to be fragmentary and was interrupted by repeated arousals and phase transitions, with no statistically significant difference between the two groups.

NREM2 sleep and SWS were significantly more frequent in the MCS patients (Table 1), who also experienced a significantly longer average total duration of NREM sleep and a significantly longer duration of each NREM stage. Clear spindles were rare but more frequent in the MCS patients (n = 8, 25.8% vs n = 5, 9.1%; χ^2 = 4.1; p = .041); the spindles were often long lasting (>5 sec.) and recurred as "alpha" sequences (slow spindles) at frequencies of 9–11 Hz (Fig. 1A). NREM2 sleep in the VS and MCS patients accounted for respectively 23.0 ± 26.9% and 42.7 ± 20.8% of total sleep duration, and SWS for respectively 6.4 ± 14.3% and 22.2 ± 1 4.2% (Fig. 1B). PSG changes fitting REM sleep occurred in both groups without any statistically significant difference between them, had a similar duration, and accounted for respectively 8.8 ± 12.9% and 10.2 ± 12.9% of total sleep duration. Nineteen VS/

UWS patients, but none of the MCS patients, showed signal attenuation as the only sleep pattern, and this was more frequent in the VS patients with post-anoxic damage (41.7%) than in those with other etiologies (8.2%; χ^2 = 6.2; p = .013). REM sleep occurred in only three of the VS/UWS patients, in whom most of the sleep time characterised by a poor and attenuated signal (Fig. 1C and D). Fig. 2 shows example hypnograms of four patients, including one (A) whose sleep showed only "attenuation" and the repeated recurrence of REM stages during the night.

There were relatively few patients with post-anoxic damage in the MCS group, but most of the differences in SWS and NREM2 sleep between the UWS/VS and MCS patients persisted even when the patients were grouped on the basis of the post-anoxic or traumatic/vascular etiology of the brain damage (see Table 2).

Using logistic regression analysis to compare all of the parameters that individually showed a significantly different distribution in the two groups (NREM2, SWS and "attenuation"), a model including only the presence or the absence of SWS was significant (p < .001). This model allowed to correctly classify 78.8% of the cases (90.4% of the MCS and 72.2% of the VS patients).

Evaluation of the associations between discrete CRS scores and the different sleep measures revealed significant relationships with the duration of TST, NREM2, SWS and REM (ρ = 0.399, p = 0.001; ρ = 0.581, p < 0.001, ρ = 0.661, p < 0.001 and ρ = 0.337, p = 0.002) (Fig. 3). The multiple linear regression was significant (F(4, 80) = 9.743, p < 0.001) and showed that the overall duration of NREM2 and SWS sleep were the main factors significantly correlated with CRS scores (p = 0,043 and p < .008). Correlations between CRS score, sleep data and etiology are shown in Supplementary Table S1.

4. Discussion

The aim of this study was to assess sleep patterns in patients with chronic DOC in order to identify the parameters that are potentially capable of supporting clinical scores. The sleep of all of the studied DOC patients was quite short, fragmented by a number of phase transitions, and interrupted by repeated arousals. Nevertheless, we found that most chronic UWS/VS or MCS patients undergoing protracted PSG recordings including one night show modulated PGS changes indicating the occurrence of sleep, with the MCS patients having a more complex and preserved sleep pattern than the UWS/VS patients.

The "poorest" sleep pattern consisted of an extremely attenuated EEG signal without any physiological features of sleep, which was observed in 19 UWS/VS patients: i.e. the only "stage" of sleep in about one-third of the UWS/VS patients. About half of these patients showed extremely attenuated EEG activity throughout the recording, and the absence of blinking, reduced EMG tone, decreased heart rate variability, and more regular breathing were the only PSG "markers" of sleep. This finding supports the persistence of a basic sleep-wake cycle even in the presence of extremely severe impairment of the structures involved in generating physiological sleep activities. It may also represent an archaic condition preserving the integration of behavioural/vegetative changes even in the absence of a higher level of integration leading to more physiological and modulated sleep patterns (Murillo-Rodríguez et al., 2009; Fort et al., 2009). Interestingly, data from a very recent study of sleep characteristics in 15 UWS/VS patients has confirmed that "the majority of vegetative state patients retain some important circadian changes" regardless of the severity of the disease and/or the duration of the UWS/VS (Pavlov et al., 2017).

The occurrence of REM sleep in UWS/VS patients has been previously reported. Oksenberg et al. (2001) detected REM sleep in all eleven of their UWS/VS patients using 24-hour EEG, whereas De Biase et al. (2014) detected it in four of their 27 MCS patients

Table 1
PSG data of UWS/VS and MCS groups.

Duration In minutes (mean ± SD)	UWS/VS (n° 55)	MCS (n° 36)	Significance (T test)
TST	154.8 ± 88.9	229.7 ± 123.2	= 0.001
Attenuation	44.9 ± 10.5	0	–
NREM2	35.7 ± 44.5	93.2 ± 69.6	< 0.001
SWS	14.0 ± 30.6	55.8 ± 43.9	< 0.001
REM	16.3 ± 30.5	21.3 ± 32.3	ns
Number of events per hour of sleep (mean ± SD)	UWS/VS (n° 55)	MCS (n° 36)	Significance (U-Mann test)
Phase transitions	31.5 ± 17.6	33.3 ± 14.7	ns
Arousals	11.6 ± 8.3	10.5 ± 6.6	ns

Table 2
Number and percentage of patients (per etiology) reaching sleep stages.

Total (n° 91)	UWS/VS (n° 55)	MCS (n° 36)	Significance (χ^2)
NREM2	29 (52.7%)	35 (97.2%)	<0.001
SWS	16 (29.1%)	31 (86.1%)	<0.001
REM	23 (41.8%)	21 (58.3%)	ns
Post-anoxic etiology (n° 38)	UWS/VS (n° 29)	MCS (n° 9)	Significance (χ^2)
NREM2	12 (41.4%)	9 (100.0%)	p = 0.002
SWS	5 (17.2%)	8 (88.9%)	p < 0.001
REM	12 (41.4%)	5 (55.6%)	ns
Traumatic/vascular etiology (n° 53)	UWS/VS (n° 26)	MCS (n° 27)	Significance (χ^2)
NREM2	17 (65.4%)	26 (96.3%)	p < 0.001
SWS	11 (42.3%)	23 (85.2%)	p = 0.001
REM	11 (42.3%)	16 (59.3%)	Ns
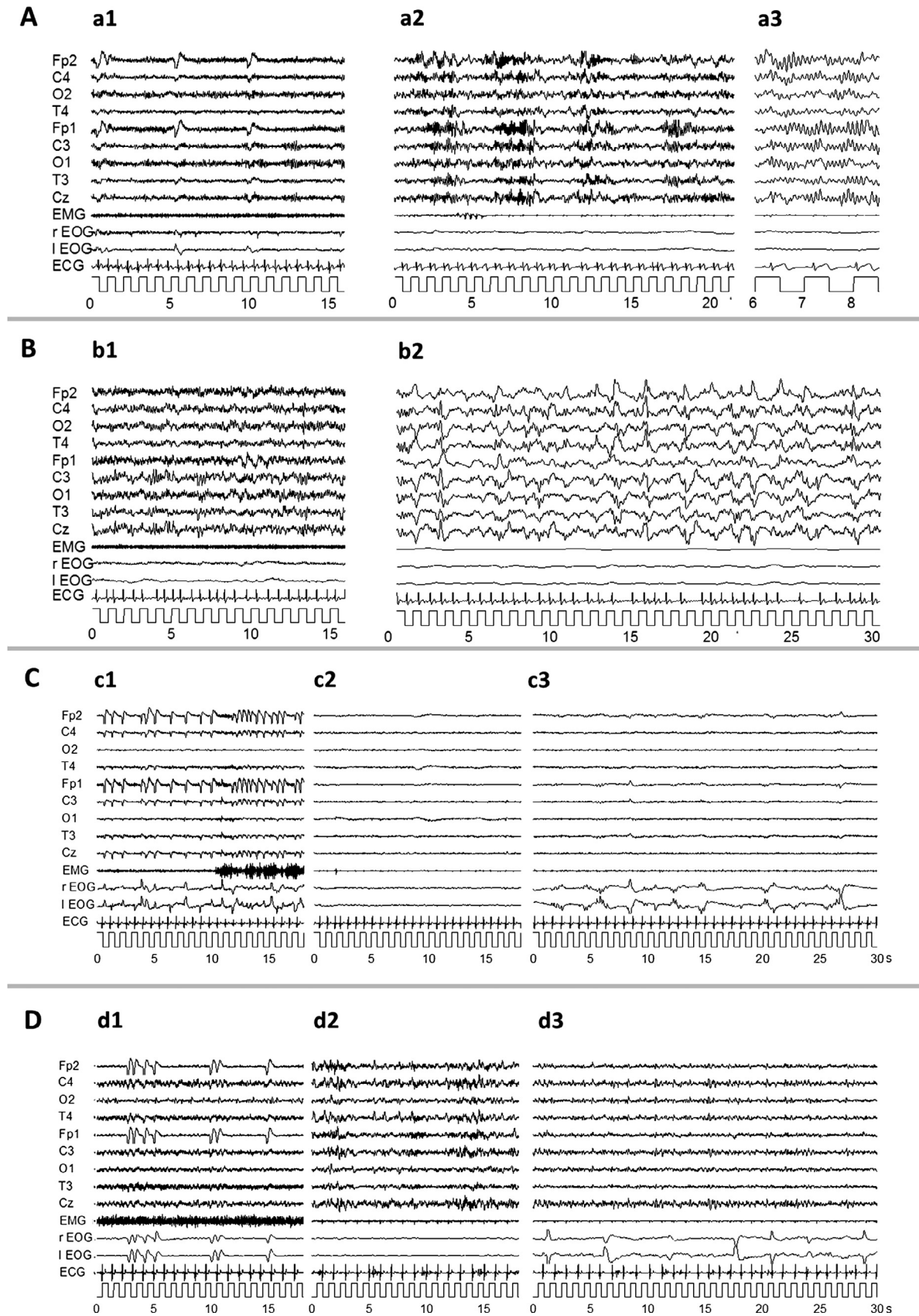
Fig. 1. Samples of PSG recording from four patients. A: a 44 years old man with traumatic brain injury (CRS = 7) showed a NREM2 sleep including frequent «slow» long-lasting spindles (a2, magnification in a3); B a 50 years old woman with post-hemorrhagic brain damage (CRS = 19) showed a SWS pattern (b2); C a 50 years old man (CRS = 6) showed EEG attenuation (c2), and fast eye movement fitting REM (c3); D: a 38 years old man (CRS = 12) showed both NREM2 (d2) and REM (d3) patterns. PSG of an awake epoch is shown for each patient in a1, b1, c1, d1, respectively. Calibration 50 μV.
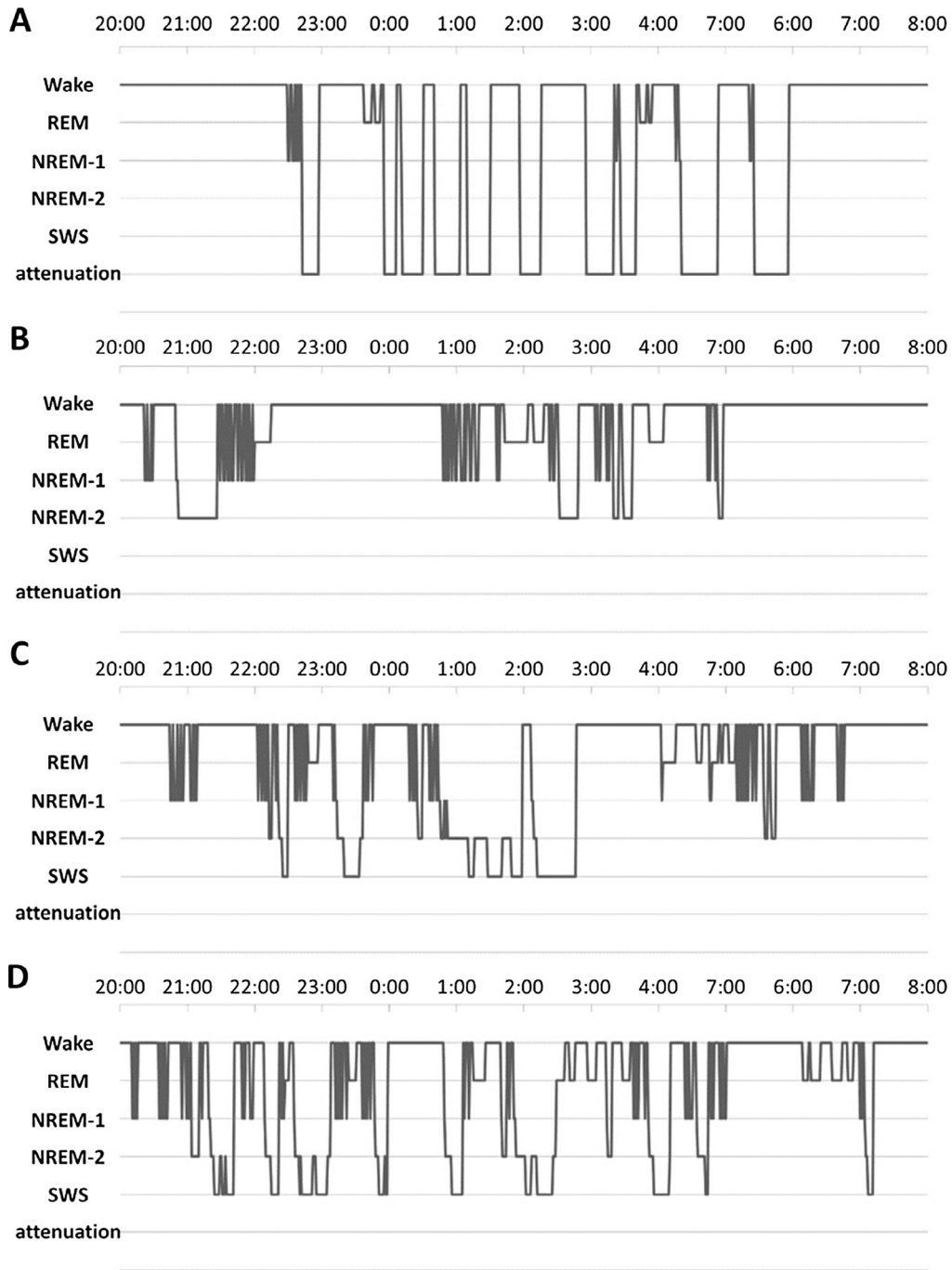
Fig. 2. Hypnograms of four patients. A: 50 years old man (CRS = 6, diagnosis of UWS/VS), corresponding to patient C of Fig. 1; B 60 years old man (CRS = 7, diagnosis of UWS/VS); **C** 42 years old woman (CRS = 9, diagnosis of MCS); D 38 years old man (CRS = 12), corresponding to the patient D of Fig. 1.

but in none of their five UWS/VS patients. We identified a polygraphic pattern fitting REM sleep without any significant difference between UWS/VS and MCS patients. This difference may have been due to chronicity and perhaps circuitry reorganisation in chronic UWS/VS patients, but was more probably due to the fact the we identified REM sleep on the basis of PSG criteria in patients with poor EEG signals, thus making it possible to recognise it even in the three UWS/VS patients with almost isoelectric EEG signals. The persistence of this pattern (which obviously cannot be compared with the physiological pattern) suggests a preserved brainstem mechanism for REM sleep (Luppi et al., 2012) even in the presence of extremely disruptive brain damage, similar to that

occurring as the earliest component of cycling EEG in very immature subjects (Scher et al., 2005).

More complex sleep patterns were a transition towards EEG activity that included transients and figures compatible with NREM2 sleep, and a prominent slow wave pattern compatible with SWS. Typical sleep spindles and K-complexes (the classical markers of NREM2 sleep) were rare and only observed in the UWS/VS patients. Spindles are attributed to thalamic and corticothalamic networks (De Gennaro and Ferrara, 2003); hence the presence of typical or atypical sleep spindles may indicate some degree of preservation of these pathways. Abnormal spindling has been reported in patients with severe DOC due to brain damage or meta-
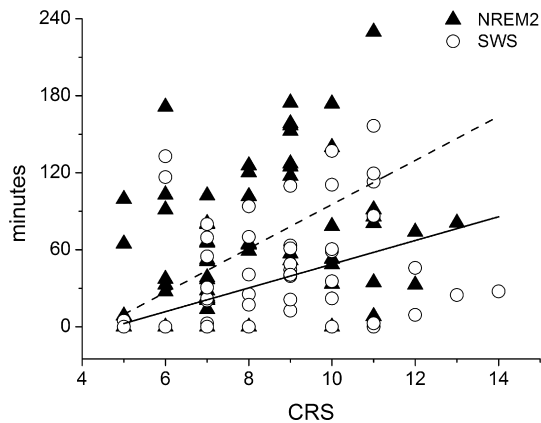
Fig. 3. Relationship between CRS scores and total duration of NREM2 and Slow Wave Sleep triangles represent NREM2 and open circles SWS.

bolic disorders (Austin et al., 1988), whereas spindling is better preserved in less severely impaired patients (Arbour et al., 2015).

We identified NREM2 sleep in the presence of diffuse transients suggesting "rudimental" K-complexes, or in the presence of long spindles appearing as long trains in the alpha range (10–12 Hz) during sleep, but we never observed a pattern fitting alpha or spindle coma. The observed long and slow spindles recall the pattern observed in elderly subjects, who showed a slow decline in spindle frequency: this decline is possibly due to disrupted sleep physiology matching an age-related decline in hippocampal-dependent learning (Mander et al., 2014). A decrease in fast (13–15 Hz) spindles but preserved slow (11–13 Hz) spindles has also been found in patients with Alzheimer's disease (Gorgoni et al., 2016; Novelli et al., 2016) and in early infancy, thus suggesting that fast and slow spindling may involve different circuitries and that they are differently sensitive to brain damage or immaturity.

It is known that cortical slow wave oscillations (<1 Hz), thalamo-cortical spindles and hippocampal sharp wave-ripples (Fogel and Smith, 2011; Logothetis et al., 2012) support memory consolidation function which depends by the hierarchical nesting of these rhythms during NREM sleep (Diekelmann and Born, 2010; Dudai et al., 2015). It can therefore be assumed that DOC patients showing a longer pattern of NREM sleep may preserve some degree of the function of memory consolidation.

Many of the measures we used were differently distributed in the patients who were clinically defined as being in a UWS/VS or MCS. TST and the time spent in the different stages of sleep were longer in the MCS patients, thus indicating that better-preserved cortico-subcortical interactions are needed to organise a sleep structure that is similar to the physiological structure. Although the appearance and duration of SWS and NREM2 sleep were significantly different in our UWS/VS and MCS patients, further statistical evaluations indicated that the presence (but not the total duration) of SWS was the only useful parameter clearly distinguishing them. This suggests that even short epochs of SWS indicate some preservation of complex cortico-subcortical integration, thus allowing this sleep stage to appear in patients with anoxic or traumatic/hemorrhagic brain damage.

CRS scores of the severity of the disorder (rather than just the categorisation of a UWS/VS or MCS) seemed to correlate with additional sleep characteristics, including the total duration of SWS and NREM2 sleep. This is probably due to the reductive nature of categorisation and further suggests that a simple sleep classification of all DOC patients can make a significant contribution to their assessment; however, multiple linear regression analysis showed that NREM2 sleep and SWS were the main factors that positively correlating with CRS scores.

We carried out the study also in order to assess whether sleep patterns correlate with residual levels of consciousness. If so, this would provide quite easily reachable information about the condition of DOC patients that would help clinicians in the management of further rehabilitative efforts. Many of our patients were on the border between VS and MCS and, in such cases, residual sleep organisation may offer further evidence to corroborate or contradict clinical diagnostic hypotheses. Our data suggest that SWS is the strongest marker of better-preserved circuitry organisation in patients with chronic DOC. Experimental data indicate that the slow EEG oscillations characterising SWS are due to fluctuations in the membrane potentials of cortical neurons and specific changes in the firing properties of thalamic neurons (Steriade, 1997), and thus require complex machinery including the specific activities and organisation of cortical and sub-cortical structures. Moreover, SWS certainly plays an important function in cognitive processes, as it is a physiological marker of both brain development (Ringli and Huber, 2011) and pathological aging (Mander et al., 2014; Pace-Schott and Spencer, 2015). There is evidence indicating a direct relationship between slow waves and synaptic density (see Tononi, 2009, for a review), thus supporting the view that SWS can act as an effective indicator of preserved integrative structures and circuitry in patients with DOC.

5. Conclusion

In conclusion, our findings support the hypothesis that PSG recordings and staging can contribute to the assessment of patients with chronic DOCs and, despite the sleep fragmentation and repeated artefacts due to frequent arousals, that the visual evaluation of PSG traces is a simple and reliable method of assessment. We also believe that our findings can contribute to improving our understanding of the functional conditions underlying sleep patterns in patients with highly destructive brain damage as they show that even patients with severe UWS/VS can show a residual sleep pattern, and that the presence and, albeit to a lesser extent, the duration of non-REM sleep (i.e. SWS) is one of the main factors correlating with MCS and high CRS scores. Our findings support a relevant role of sleep evaluation as a parameter useful to decide further rehabilitative work-up in chronic DOC patients, given that clinical evaluation does not always detect spare capacity. In particular, the significance of the presence of preserved SWS seems to be so consistent to advise PSG evaluation and accurate staging in acute as in chronic DOC patients.

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and we affirm that our report is consistent with those guidelines.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinph.2017.12.012.

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