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SCIENTIFIC INVESTIGATIONS

Sleep/Wake Modulation of Polysomnographic Patterns has Prognostic Value in Pediatric Unresponsive Wakefulness Syndrome

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Study Objective: Sleep patterns of pediatric patients in unresponsive wakefulness syndrome (UWS) have been poorly investigated, and the prognostic potential of polysomnography (PSG) in these subjects is still uncertain. The goal of the study was to identify quantitative PSG indices to be applied as possible prognostic markers in pediatric UWS.

Methods: We performed PSG in 27 children and adolescents with UWS due to acquired brain damage in the subacute phase. Patients underwent neurological examination and clinical assessment with standardized scales. Outcome was assessed after 36 mo. PSG tracks were scored for sleep stages and digitally filtered. The spectral difference between sleep and wake was computed, as the percent difference at specific spectral frequencies. We computed (1) the ratio between percent power in the delta and alpha frequency bands, (2) the ratio between alpha and theta frequency bands, and (3) the power ratio index, during wake and sleep, as proposed in previous literature. The predictive role of several clinical and PSG measures was tested by logistic regression.

Results: Correlation was found between the differential measures of electroencephalographic activity during sleep and wake in several frequency bands and the clinical scales (Glasgow Outcome Score, Level of Cognitive Functioning Assessment Scale, and Disability Rating Scale) at follow-up; the Sleep Patterns for Pediatric Unresponsive Wakefulness Syndrome (SPPUWS) scores correlated with the differential measures, and allowed outcome prediction with 96.3% of accuracy.

Conclusions: The differential measure of electroencephalographic activity during sleep and wake in the beta band and, more incisively, SPPUWS can help in determining the capability to recover from pediatric UWS well before the confirmation provided by suitable clinical scales.

Keywords: brain injury prognosis, electroencephalographic frequency analysis, pediatric brain injury, polysomnography, unresponsive wakefulness syndrome

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INTRODUCTION

Severe disorders of consciousness (DOC) comprise a spectrum of syndromes with severely altered consciousness. The lower boundary is coma, which is characterized by complete failure of the arousal system. The transition from coma to unresponsive wakefulness syndrome (UWS), also termed vegetative state (VS), is accompanied by the reemergence of arousal patterns (so-called sleep-wake cycles). Although patients do have periods of eye opening, they are by definition unaware of themselves and/or the environment, and they show no purposeful interaction with the environment.[1] In minimally conscious state (MCS), a startle of minimal but definite behavioral evidence of self or environmental awareness is found. The upper boundary of severe DOC is the acute confusional state, which marks the restoration of functional communication and/or objects handling (see **Tables S1a** and **S1b** in the supplemental material for nosology and symptoms).

Because arousal levels fluctuate and patients suffer from perceptual, attentional, and motor deficits, the detection of signs of awareness and the prediction of patients' recovery are extremely challenging in this population. This fact becomes even more important in the case of pediatric patients, in which the acquired brain injury (ABI) disrupts the normal development process and negatively interacts with the learning curves, in both the cognitive and motor domains.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Despite the difficulties in applying the classic criteria for sleep staging, previous studies observed behavioral, but no electrophysiological, sleep-wake patterns in adult patients in a vegetative state, while they found near-to-normal patterns of sleep in adults in a minimally conscious state; unfortunately, such evidences have never been validated in pediatric cohorts, as only two pediatric case studies can be traced back in literature. The goal of the current study is to provide a quantitative depiction of sleep-wake alternation in pediatric patients with unresponsive wakefulness syndrome.

Study Impact: The report extends to the pediatric age previous findings about a possible predictive role of polysomnography in the determination of clinical outcome in adults in a UWS. Our work confirms that pediatric patients exiting from coma and lingering in a UWS experience power increase in the delta frequency band during sleep, and decreased alpha, sigma, and beta activities; we also demonstrate the consistent gain in outcome prediction due to the employment of the Sleep Patterns for Pediatric Unresponsive Wakefulness Syndrome scale.

For years the clinical assessment of the level of consciousness has relied on the administration of clinical scales, such as the Coma Recovery Scale-Revised (CRS-R).[2] However, as scales inherently rely on the patients' ability to demonstrate their awareness to the examiner, they retain an unacceptably high rate of misdiagnoses.[3]

For circumventing the limitation of behavioral methods, during the past decade researchers have focused on neurophysiological approaches, which allow the detection of brain-based evidence of consciousness.

Previous studies on patients with DOC have mainly focused on the spectral characteristics of electroencephalography (EEG) at rest. It was shown that adults with UWS have increased delta and theta power, decreased alpha power, and decreased connectivity in the theta and alpha bands at rest, compared to patients in an MCS[4–7]; additionally, patients in MCS show notably increased power in the delta band, compared to patients with severe DOC.[8] Hence, slow wave activity seems to be increasingly present in the lowest states of consciousness,[4–9] and it appears to characterize the poorest outcomes in late stages of recovery from coma, whereas increase in EEG frequencies and reinstitution of the alpha and beta activities reflect good prognosis and are associated with favorable outcome. On the other hand, a recent study on children with DOC showed global reduction in the slow wave activity buildup during sleep; this reduction was most pronounced over parietal brain areas, where slow wave activity buildup was lowest in patients showing poor outcome.[10]

Given the capability of EEG during wake to detect the existence of a continuum in the severity of consciousness disorders, efforts have been made to identify predictive indexes, which may allow for a refined diagnosis and serve as electroencephalographic predictors of outcome.

Lechinger et al.[4] proposed the alpha/theta ratio and the resting spectral peak as outcome measures, as they were found to correlate with the behavioral CRS-R scores. Other studies proposed several mathematical and complexity indices[11–15] for an accurate discrimination between consciousness levels.

However, the emergence from coma to UWS is marked by the reinstatement of arousal patterns, triggered by the suprachiasmatic nucleus of the hypothalamus (SCN).[16] Thus, the capability to modulate wake and sleep alternation could still be preliminary to the reorganization of any neuroelectrical pattern during wake.

Following severe brain injury, the determination of sleep and the distinction of different sleep phases by polysomnography (PSG) and according to the standard criteria is challenging,[17] because sleep-wake cycling is often highly altered,[18–20] and graphoelements are seldom similar to those seen in healthy individuals in terms of frequency, length, and intensity, due to damage to specific brain areas and disruptions in neuronal pathways. In addition, difficulties in the identification of wakefulness and sleep in DOC are due to lack of knowledge about whether the oscillations recorded by EEG still reflect the same cellular mechanisms as in normal physiological sleep.[21]

Despite the difficulties in applying the classic criteria for sleep staging, Landsness et al.[22] observed behavioral, but no electrophysiological, sleep-wake patterns in patients in a VS, while they found near-to-normal patterns of sleep in patients in a MCS. Valente et al.[23] were able to classify EEG patterns of sleep in patients with DOC into five categories based on signal complexity, and they related these to the eventual outcome; results suggest that more complex sleep patterns relate to more preserved brain functioning and to better prognosis.

In a previous pediatric study published by our group, we proposed a prognostic scale rating global sleep reorganization, named Sleep Patterns for Pediatric Unresponsive Wakefulness Syndrome (SPPUWS).[24] We identified six PSG patterns, corresponding to increasing neuroelectrical complexity; we observed that, in the subacute stage, the uprising of reorganized sleep pattern of broadening complexity (i.e., higher levels of the scale) are predictive of increasingly favorable outcome, as assessed by several clinical and rehabilitation scales. Taking this into consideration, our hypothesis is that the quantification of the brain capability to modulate wake and sleep stages can be a predictive index of outcome, superior to the characterization of the sole EEG activity during wake. This hypothesis could have even more relevance in children, because their brain is still maturing.

The current study aims at providing a quantitative depiction of sleep in pediatric patients suffering from a brain injury. We searched for measures able to easily capture the capability of the brain to modulate the electroencephalographic activity across the two main physiologic states, wake and sleep. We tested the prognostic role of such indicators of the restructuring of pediatric sleep after comatose state, also with respect to SPPUWS.

METHODS

Participants

Thirty-five brain-injured pediatric patients with UWS were screened for participation in the study. The group was made up of inpatients admitted to the rehabilitation center of the Scientific Institute IRCCS Eugenio Medea for intensive neurorehabilitation treatment (physical, dysphagia, and sensory stimulation therapies) throughout a period of 4 y. Inclusion criteria were: (1) severe ABI; (2) age 18 y or younger; and (3) time since injury of 1 y or less at the enrollment. Exclusion criteria were: (1) congenital neurological pathology and (2) need of mechanical ventilation (due to the interfering effect of ventilation on sleep).[25,26]

At the enrollment, a multidisciplinary team evaluated all the patients and concluded that they fulfilled the criteria for UWS diagnosis according to the Royal College of Physicians[27] and to Giacino et al.[28] Seven patients were excluded before T_0 evaluations, due to recurrent epileptic seizures/activity that would have dominated the EEG and would have impeded the correct sleep staging; one patient was excluded after T_0, due to recurrent movement artifacts detected on the PSG track, which overwhelmed the neurophysiological evidences. A final group of 27 patients was selected for the current study. **Table 1** reports the demographic and clinical characteristics of the patients. A complete list of the sedative drugs and dosages administered at the time of the study is provided for each patient in **Table S2** in the supplemental material.

Table 1—Demographic and clinical data.

Number	Age/Gender	State of Consciousness (T_0/T_1)	SPPUWS	GCS (at insult)	GOS (T_1)	LOCFAS (T_0/T_1)	DRS (T_0/T_1)	C/NCS (T_1)	MRI Classification
1	11/m	UWS/exit-MCS	6	4	4	2/8	24/7	1	II
2	14/m	UWS/UWS	2	7	2	2/2	24/22	3	I
3	16/m	UWS/exit-MCS	5	4	4	2/6	23/9	1	II
4	5/m	UWS/exit-MCS	5	3	4	2/5	24/9	1	I
5	2/m	UWS/UWS	4	3	1	2/2	24/30	4	n.a.
6	14/m	UWS/UWS	3	3	1	2/2	28/24	2	III
7	13/m	UWS/MCS	3	6	3	2/2	24/23	2	n.a.
8	4/m	UWS/MCS	3	4	3	2/2	24/20	2	IV
9	5/m	UWS/MCS	6	6	3	2/3	23/20	1	II
10	14/m	UWS/UWS	2	6	2	2/2	24/22	2	IV
11	5/m	UWS/MCS	5	6	3	2/3	24/19	1	I
12	12/f	UWS/exit-MCS	6	5	4	2/7	22/8	2	I
13	13/f	UWS/exit-MCS	6	3	4	2/5	23/9	1	I
14	13/m	UWS/MCS	4	3	3	2/3	24/19	1	II
15	15/f	UWS/exit-MCS	5	5	3	2/6	23/7	1	I
16	5/f	UWS/MCS	6	4	3	2/3	24/21	2	IV
17	4/m	UWS/exit-MCS	5	4	4	2/6	22/8	1	IV
18	4/m	UWS/MCS	5	6	3	2/3	27/17	1	IV
19	9/m	UWS/MCS	5	4	3	2/3	25/18	4	II
20	3/m	UWS/MCS	5	3	3	2/3	25/20	1	I
21	18/m	UWS/MCS	3	4	3	3/3	25/20	2	II
22	6/f	UWS/exit-MCS	5	3	3	1/5	26/6	1	IV
23	14/m	UWS/exit-MCS	6	3	3	3/5	26/7	2	IV
24	4/f	UWS/UWS	3	3	2	2/2	24/22	2	I
25	2/m	UWS/UWS	4	3	2	2/2	23/22	2	I
26	2/m	UWS/MCS	5	3	3	2/3	23/20	1	I
27	1/m	UWS/UWS	1	5	2	2/2	26/24	3	I

From left to right: patient's number, age at injury (y) and sex (m, male; f, female), State of Consciousness at time of electroencephalography (EEG) (T_0) and at follow-up (T_1; UWS, unresponsive wakefulness syndrome and vegetative state; MCS, minimally conscious state; exit-MCS, recovery of consciousness), Sleep Group according to the SPPUWS,[24] Glasgow Coma Scale (GCS) score at insult, Glasgow Outcome Score (GOS) at follow-up, Level of Cognitive Functioning Assessment Scale (LOCFAS) at time of EEG and at follow-up, Disability Rating Scale(DRS) at time of EEG and at follow-up, Coma/Near Coma Scale (C/NCS) at follow-up, and MRI classification according to the scale by Firsching et al.[40] Of note, high scores on the GCS, LOCFAS and GOS reflect a less impaired clinical picture; by contrast, the higher the DRS and C/NCS scores, the more marked the difficulties. T_0, time at study; T_1, time at follow-up; n.a., not available.

This study was carried out in compliance with the Declaration of Helsinki and was approved by the Ethics Committee of the Scientific Institute IRCCS Eugenio Medea, located in Bosisio Parini (LC – Italy). Patients' relatives (or legal guardians) provided written informed consent for the participation in the study.

Clinical Evaluations and Measures

On admission, the medical history was collected, including Glasgow Coma Scale (GCS) score at insult[29] (see **Table 1**). At the time of study (T_0), the Disability Rating Scale (DRS),[30,31] which focuses on the functional abilities, and the Level of Cognitive Functioning Assessment Scale (LOCFAS),[32] which is specifically used for the punctual evaluation of the cognitive functions, were administered. For the final group of 27 patients, a clinical follow-up (T_1) was also performed after 36 mo from the first evaluation (T_0); the follow-up included the patients' evaluation by the standardized Glasgow Outcome Score (GOS),[33,34] which provides the general degree of recovery, the DRS, the LOCFAS and the Coma/Near Coma Scale (C/NCS),[35] which estimates the level of responsiveness damage, depending on the responses to the stimulation of the different sensory channels. C/NCS was applied in compliance with the American Congress of Rehabilitation Medicine Disorders of Consciousness Task Force guidelines.[36] The staff who administered the clinical scales were blinded to the research study rationale.

EEG Processing

After admission to the rehabilitation center, all 27 patients were recorded overnight, uninterruptedly from the afternoon to the morning of the following day, by PSG. See "Polysomnographic recordings" in the supplemental material for a description of PSG settings and recording method. During the

recording, patients' caregivers were instructed to accurately report any event in a standard form, also called the sleep diary. After visual selection and exclusion of the artifactual periods from PSG tracks, including intervals affected by muscular electrical activity, two trained and certified neuropsychiatrists independently ascertained the presence of spindles and rapid eye movement (REM) periods. PSG tracks were then partitioned in 30-sec epochs, and staged using the SPPUWS (see **Table S3** in the supplemental material for a synthetic description).[24]

One independent sleep expert conducted a separate study for the PSG frequency content. Analysis was performed blindly with respect to the clinical scales, SPPUWS scores, and neuroimaging information. Digital band-pass filtering was set in the range between 0.1 Hz and 48 Hz, and it was applied to the raw EEG and electrooculography channels. The expert selected five EEG intervals lasting 30 sec for wake and five for a non-wake stage, for each subject, according to what was reported in the sleep diary and on the basis of the work by Cologan.[37] Selection of wake and non-wake intervals to be processed by frequency analysis was based on the following rules: (1) absence of artifacts throughout the interval; (2) whenever possible, the five intervals of a specific stage type were selected from different repetitions of that stage over the night; and (3) if the previous rule could not be satisfied, the five intervals of a specific stage type were selected from the highest number possible of repetitions, and as far as possible within the same repetition of that stage.

For each patient, EEG power spectral analysis was then performed on the selected time intervals, using Embla software. Six monopolar derivations were chosen for the analysis: F3, F4, C3, C4, O1, and O2. The analysis was performed as follows:

1. For each patient, one nonwake sleep stage was selected.
2. One power spectrum was calculated for any of the five EEG segments previously selected for that stage, and for every electrode. This made up a total of 30 EEG spectra.
3. Spectra were subsequently averaged, so as to obtain a mean spectrum.
4. Then, for the mean spectrum, the relative EEG bandpower was calculated, defined as the areas under the spectral curve within the respective frequency borders, divided by the area under the whole curve from 0.5 to 30 Hz. Relative EEG bandpower was computed in the conventional delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–14 Hz), and beta (14–30 Hz) frequency bands. Relative EEG bandpowers were then converted to percentage values, for intuitive interpretation. Specifically, the power percentage in the delta band was termed $\delta_{S\%}$, and analogous notation was applied to the other frequency bandpower ($\theta_{S\%}$ for the theta band, $\alpha_{S\%}$ for the alpha band, etc.)
5. The procedure (from 1 to 4 of this list) was repeated for the wake stage. The percentage in the delta band was termed $\delta_{W\%}$ ($\theta_{W\%}$, $\alpha_{W\%}$, etc.) in this case.

The spectral difference between sleep and wake was then computed, by calculating the percent difference for each of the aforementioned spectral frequency bands. In the case of the delta band, such difference was termed $\delta_{S\%-W\%}$. Differential values in the other frequency bands were termed accordingly.

For making our results comparable with the previous literature available, we computed the ratio between percent power in the delta and alpha frequency bands during wake $(\delta/\alpha)_W$ and during sleep $(\delta/\alpha)_S$, as proposed in the study by Leon-Carrion et al.,[38] and we calculated the ratio between percent power in the alpha and theta frequency bands during wake $(\alpha/\theta)_W$ and during sleep $(\alpha/\theta)_S$. The differential values between sleep and wake were then calculated for both measures, thus obtaining $(\delta/\alpha)_{S-W}$ and $(\alpha/\theta)_{S-W}$.

Last, we computed the power ratio index during wake $(PRI)_W$ and during sleep $(PRI)_S$, according to the following formula:

$$(PRI)_i = \frac{\delta_i + \theta_i}{\alpha_i + \sigma_i + \beta_i}$$

being i the sleep state (wake W or sleep S), and being $\delta,\ldots\beta$ the power in the respective frequency bands. See also Leon-Carrion et al.[38] and Nagata et al.[39] for the method implementation. $(PRI)_{S-W}$ was also computed.

Descriptive Statistics, Comparisons, and Correlations

Demographic and clinical characteristics were reported by descriptive statistics. Due to the small size of the dataset, we applied nonparametric tests for inferential statistics on the PSG data. The Mann-Whitney U test was used for testing differences between patients who had undergone brain trauma and patients who had brain damage due to cause other than traumatic at the time of the study (T_0), and for testing differences in EEG power and indexes between sleep and wake periods. Comparisons with ordinal variables (e.g., with magnetic resonance imaging [MRI] grades) were made using the chi-square test. Pearson correlation coefficients were calculated for the numerical variables; Spearman rank correlation coefficients were obtained to determine the relationship between quantitative variables and ordinal measures. In both cases, coefficients were adjusted for the age at injury. We initially set significance at p values below 0.05, then we applied Bonferroni correction for multiple correlations. The relationship between the differential EEG activity in single frequency bands and the SPPUWS was further tested by regression analysis, with SPPUWS, age at injury, and sex as regressors. All statistical analysis was carried out using the NCSS statistical package (Kaysville, UT, USA).

Predictive Models

Logistic regression analysis was performed to check whether the prediction of the level of consciousness at outcome could benefit from the quantification of PSG frequency content at T_0. Level of consciousness at T_1 (i.e., outcome) was encoded as a three-states categorical variable (0 = UWS; 1 = MCS; 2 = exit-MCS). At this purpose, three multinomial logistic regression models were tested. MODEL_1 tested the prediction of the "Level of consciousness at T_1" as dependent variable, by entering "age at event" as numeric independent variable, together with "sex," "LOCFAS at T_0" and "DRS at T_0" as categorical/

ordinal independent variables; MODEL_1 provided the predictive power intrinsic to the clinical scales at T_0. MODEL_2 included as numeric independent variable the percent difference between sleep and wake stages for each of the spectral frequency bands, additionally to those described for MODEL_1; MODEL_2 quantifies the modification of the prediction due to the inclusion of the differential measure in each PSG frequency band. MODEL 3 included as ordinal independent variable the "SPPUWS" scores, additionally to those described for MODEL_1; SPPUWS scale is a synthetic measure of PSG variability and complexity, across frequency bands. All statistical analyses were carried out using the NCSS statistical package.

MRI Scan and Grades

Within 1 w after the PSG recording, patients underwent a brain MRI. Brain MRI acquisition was performed by using a 3.0 T imaging scanner (Philips Medical Systems, Best, the Netherlands). Patients received light sedation. A three-dimensional (3D) T_1-weighted fast-field echo sequence (repetition time/echo time = 25/4.6 msec; flip angle = 30°; 200 contiguous axial sections; voxel size = 0.9 × 0.9 × 0.8 mm; matrix size = 256 × 256; field of view = 230 mm^2) was acquired. Radiological evidences are reported in **Table S2** for single patients.

In order to determine the severity of the anatomical and radiological lesions, a four-grade scoring system was applied, as proposed by Firsching et al.[40] and later recalled by Mannion et al.[41] (see also **Table S4** in the supplemental material). The patients' lesions were assessed and scored by two independent neuroradiologists, who were blind to the patients' clinical conditions. Scoring results are reported in **Table 1**. Two patients could not undergo brain MRI, as they had dental implants interacting with the magnetic field.

RESULTS

Demographic Data and Clinical Scales

In this section we report the clinical characteristics of 27 children and adolescents with UWS. With respect to the etiology, 15 children (56%) presented with an acquired brain lesion due to a brain trauma, whereas 12 patients (44%) had a nontraumatic etiology (brain tumor, encephalitis, hypoxic damage). In the study group, seven patients (26%) exhibited epilepsy, and at the time of the study four patients (15%) were receiving pharmacological treatment including drugs with potential sedative effects in dosages exceeding the recommended ranges (see **Table S2**).

The study cohort had 8.44 ± 5.33 y at injury on average (range, 2–18, 21 males). At follow-up (T_1), 9 patients (33% of total sample) recovered consciousness (exit-MCS), 11 patients (41%) were in a MCS, and 7 patients (26%) had a UWS. Median value for the SPPUWS was 5. Median value for the GCS score at insult was 4 (range, 3–7). At the time of the study, median value for LOCFAS score was 2, and median value for DRS score was 24. At the follow-up, median value for the GOS score was 3, for LOCFAS score was 3, for DRS score was 20, and for the C/NCS score was 2. The MRI-based evaluation of the brain damage classified 11 patients (41%) at grade I, 6 patients (22%) at grade II, 1 patient only (less than 4%) at grade III, and 7 patients (26%) at grade IV of the severity scale.

Additionally, two groups of patients were formed, according to the etiology of their lesions: traumatic and nontraumatic. A statistical comparison was made between the two groups on the main clinical variables to verify their homogeneity. No significant differences were found, with the exception of the age at insult variable (t = 4.75, $p < 0.001$). Indeed, patients with traumatic brain injury were significantly older at the time of insult than patients with brain lesions due to other etiologies (mean age: 11.67 ± 4.32 y versus 4.42 ± 3.40 y); nonetheless, the two groups were comparable on the other clinical features. Consequently, further comparisons and correlations were adjusted for the age at insult variable.

Table 2—Mean percent (%) power in each electroencephalographic frequency band.

	Frequency Range (Hz)	Wake (%)	Sleep (%)
Delta	0.5–4	49.92 (8.96)	62.73 (8.16)
Theta	4–8	19.63 (3.98)	17.44 (3.48)
Alpha	8–12	13.00 (3.46)	9.22 (2.54)
Sigma	12–14	9.53 (3.14)	6.27 (1.98)
Beta	14–30	6.43 (2.10)	3.70 (1.35)

Columns, from left to right, report the frequency ranges, and the results for the wake and sleep states respectively. Results of mean percent power are reported as mean ± standard deviation, and refer to the whole cohort. In all the frequency bands, mean percent power during wake and sleep states differed with $p < 0.001$ at the statistical t-test.

Frequency Analysis Results

The PSG tracks were initially studied for possible differences in bandpower percentages during the sleep and wake periods. As expected, all five frequency bands proved to be significantly different between the two states (**Table 2**). The percent power in the delta band was higher during sleep with respect to wake ($\delta_{S\%} > \delta_{W\%}$, $Z = 4.44$, $p < 0.001$) in all the patients except one. Conversely, theta percent power was lower during sleep with respect to wake in 19 patients (70%), with clear opposite trend observed for 4 patients, and approximately stable percentage in the other cases (overall, $\theta_{S\%} < \theta_{W\%}$, $Z = 3.71$, $p < 0.001$). Alpha, sigma, and beta percent power were lower during sleep with respect to wake, for all patients with no exceptions ($\alpha_{S\%} < \alpha_{W\%}$, $Z = 4.35$; $\sigma_{S\%} < \sigma_{W\%}$, $Z = 4.54$; $\beta_{S\%} < \beta_{W\%}$, $Z = 4.54$; $p < 0.001$); gamma percent power revealed analogous trend (30–48 Hz; $\gamma_{S\%} < \gamma_{W\%}$, $Z = 4.23$, $p < 0.001$), but four patients showed marginal power (< 1%) in both sleep and wake states (results not shown).

Correlation between EEG Indexes from Literature and the Clinical and MRI Scales

We correlated the differential value between sleep and wake states of δ/α,[38] α/θ,[4] and PRI ratios,[39] with all the available clinical and MRI scores. Our aim was to probe whether any of the global electroencephalographic indexes from the literature, measured at T_0, would anticipate the outcome, as later

Table 3—Correlations between the patients' clinical assessment, and the differential value between sleep and wake states in any of the traditional electroencephalography frequency bands.

	δ_{S-W}	θ_{S-W}	α_{S-W}	σ_{S-W}	β_{S-W}
GCS	−0.407 (0.039)*	+0.301 (0.135)	+0.425 (0.030)*	+0.290 (0.151)	+0.354 (0.076)
LOCFAS (T_0)	+0.146 (0.476)	−0.213 (0.297)	−0.100 (0.628)	−0.087 (0.671)	−0.095 (0.644)
DRS (T_0)	−0.342 (0.088)	+0.035 (0.865)	+0.247 (0.223)	+0.382 (0.054)	+0.214 (0.293)
GOS	+0.406 (0.040)*	+0.002 (0.991)	−0.343 (0.087)	−0.407 (0.039)*	−0.541 (0.004)*
LOCFAS (T_1)	+0.491 (0.011)*	−0.133 (0.518)	−0.417 (0.034)*	−0.483 (0.012)*	−0.561 (0.003)*
DRS (T_1)	−0.508 (0.008)*	+0.170 (0.405)	+0.480 (0.013)*	+0.413 (0.036)*	+0.573 (0.002)
C/NCS	−0.326 (0.104)	−0.047 (0.820)	+0.238 (0.241)	+0.336 (0.093)	+0.276 (0.173)
MRI scale	−0.293 (0.165)	+0.449 (0.028)*	+0.085 (0.693)	+0.162 (0.449)	+0.051 (0.814)
REM	+0.567 (0.003)*	−0.095 (0.645)	−0.467 (0.016)*	−0.597 (0.001)*	−0.558 (0.003)*
Spindles	+0.437 (0.026)*	+0.011 (0.959)	−0.413 (0.036)*	−0.255 (0.208)	−0.490 (0.011)*
Consciousness	+0.492 (0.011)*	−0.027 (0.897)	−0.472 (0.015)*	−0.444 (0.023)*	−0.627 (< 0.001)**

Rows list the scores obtained by the clinical scales administration, at the time of study (T_0) and at outcome (T_1), and by the evaluation through the radiological scale. Additionally, the presence/absence of rapid eye movement sleep and spindles, and the evaluation of the state of consciousness at outcome are considered. Columns, from left to right, indicate the difference in delta, theta, alpha, sigma, and beta frequency bands between sleep and wake states. Values are reported as Spearman r for the clinical and magnetic resonance imaging ordinal scales and as r-pbis for the categorical (dichotomous) classifications. All correlations are adjusted for the age at injury. *p < 0.05. **p < 0.0009 after Bonferroni correction. C/CNS, Coma/Near Coma Scale; DRS, Disability Rating Scale; GCS, Glasgow Coma Scale score; GOS, Glasgow Outcome Score; LOCFAS, Level of Cognitive Functioning Assessment Scale; MRI, magnetic resonance imaging; REM, rapid eye movement.

provided by the clinical scores recorded at T_1. All the results are reported in **Table S5** in the supplemental material. The indexes $(\delta/\alpha)_{S-W}$ and $(PRI)_{S-W}$ showed inverse correlation with GCS, acquired at the time of injury (noncorrected p = 0.05). None of the indexes correlated with the LOCFAS, nor with DRS scores recorded at the time of the study (T_0). At outcome (T_1), $(\delta/\alpha)_{S-W}$ showed direct correlation with LOCFAS and inverse correlation with DRS; $(PRI)_{S-W}$ showed direct correlation with GOS and LOCFAS, and inverse correlation with DRS. $(\alpha/\theta)_{S-W}$ provided no significant correlation with the clinical scores at T_0, nor with those recorded at T_1. Additionally, both $(\delta/\alpha)_{S-W}$ and $(PRI)_{S-W}$ showed direct correlation with the presence of REM periods in the PSG. Last, all three indexes we considered, $(\delta/\alpha)_{S-W}$, $(\alpha/\theta)_{S-W,}$ and $(PRI)_{S-W,}$ showed direct correlation with the state of consciousness at T_1. MRI grades provided no significant correlations with the EEG indexes from literature. After Bonferroni adjustment for multiple correlations, however, none of the reported correlations survived.

Correlation between the Differential EEG Activity and the Clinical and MRI Scales

We correlated the differential value between sleep and wake states in any of the traditional EEG frequency bands with all the available clinical and MRI scores. Our aim was to probe whether modulatory activity in any of the electroencephalographic frequency bands measured at T_0 would anticipate the outcome, as later provided by the clinical scores recorded at T_1. All the results are reported in **Table 3**.

The differential measure $\delta_{S\%-W\%}$ showed significant direct correlation with GOS (see also **Figure 1**) and LOCFAS scales at T_1, whereas it showed inverse correlation with GCS at insult and with DRS at T_1 (see also **Figure 2**). Direct correlation was also found with the presence of REM and spindles, and with the level of consciousness at outcome. $\alpha_{S\%-W\%}$ showed significant direct correlation with GCS at insult and with DRS at T_1, while it showed inverse correlation with LOCFAS at T_1, with the presence of REM and spindles in PSG tracks, and with the level of consciousness at T_1.

$\sigma_{S\%-W\%}$ had direct correlation with DRS at T_1, and inverse correlation with GOS and LOCFAS at T_1; inverse correlation was also found with the presence of REM and with the level of consciousness at T_1. $\beta_{S\%-W\%}$ showed inverse correlation with GOS and LOCFAS at T_1, with the presence of REM and spindles, and with the level of consciousness at T_1. Last, $\theta_{S\%-W\%}$ provided significant direct correlation with the MRI grades. After Bonferroni adjustment, only the correlation between $\beta_{S\%-W\%}$ and the level of consciousness at T_1 survived.

Correlation between the Differential EEG Activity and the SPPUWS

For each of the five frequency bands, the bandpower percentages during the wake periods were tested for possible correlations with the SPPUWS. No significant correlation was observed for any of the bands. Then, the bandpower percentages during the sleep periods were tested for correlations with the same SPPUWS; significant correlations were found for the $\delta_{S\%}$ ($\rho = 0.404$, p = 0.041), $\alpha_{S\%}$ ($\rho = -0.403$, p = 0.041), and $\beta_{S\%}$ ($\rho = -0.482$, p = 0.013).

However, when the differential value between sleep and wake states was tested against the SPPUWS, high correlations were found in four frequency bands: $\delta_{S\%-W\%}$, $\alpha_{S\%-W\%}$, $\sigma_{S\%-W\%}$, and $\beta_{S\%-W\%}$. Similar results were obtained by applying two different statistical approaches: the age-corrected Spearman correlation, and the regression analysis with SPPUWS, age, and sex as regressors (**Table 4**). Results from the age-corrected Spearman correlation survived after Bonferroni adjustment.

Figure 1—Differential values between sleep and wake states in the delta frequency band are higher, at higher values of GOS.

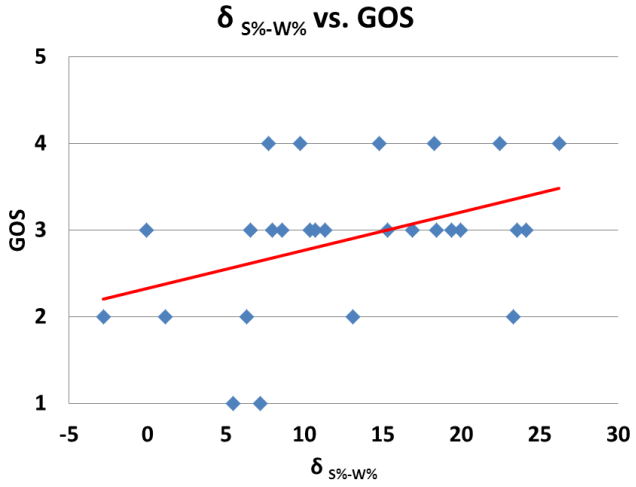
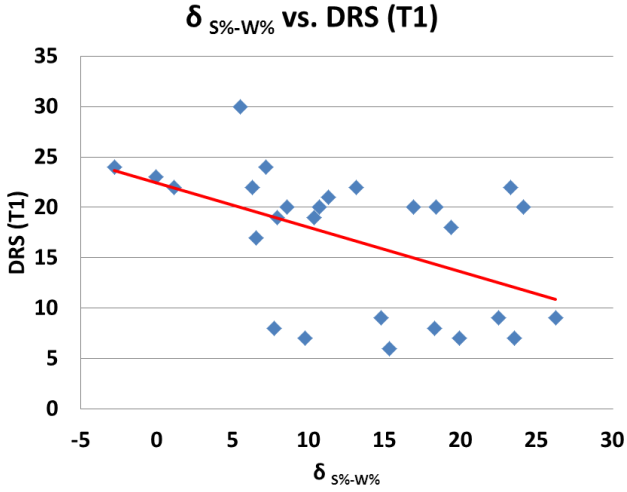


Figure 2—Differential values between sleep and wake states in the delta frequency band are higher, at lower values of DRS.



While DRS scores show discontinuity between 10 and 15, differential values in the delta frequency show a continuum.

Predictive Role of the Clinical Scales and of the PSG

The predictive performance of the three logistic regression models is reported in **Table 5**. MODEL_1 predicted the "Level of Consciousness at T_1" on the basis of multinomial logistic regression method and by including demographic predictors (age at event and sex), and the clinical scales (LOCFAS and DRS at T_0). Despite the model did not reach overall significance ($p = 0.122$), it could correctly classify 74.1% of the subjects. Of the 27 patients, 4 patients in a UWS, 1 in MCS and 2 who exited MCS were misclassified. MODEL_2 predicted the "Level of Consciousness at T_1" by alternatively including $\delta_{S\%-W\%}$, $\theta_{S\%-W\%}$, $\alpha_{S\%-W\%}$, $\sigma_{S\%-W\%}$ and $\beta_{S\%-W\%}$ in addition to the regressors of MODEL_1. In all cases but one ($\sigma_{S\%-W\%}$), data fitting improved, and the overall model reached significance for $\delta_{S\%-W\%}$ and $\beta_{S\%-W\%}$. However, classification worsened by including the differential power in the δ band (70.4%), whereas it improved when considering the β band (81.5%), and specifically for the classification of the UWS status (85.7%). MODEL_3 included the SPPUWS scores, which condense the information of EEG variability and complexity across frequency bands; both data fitting ($p = 0.003$) and classification (96.3%) improved.

Table 4—Tests between the differential value between sleep and wake states in each frequency band and the Sleep Patterns for Pediatric Unresponsive Wakefulness Syndrome.

	Spearman Correlation		Regression Analysis	
	rho	p	F	p
$\delta_{S\%-W\%}$	0.64	0.0004**	6.68	0.0049*
$\theta_{S\%-W\%}$	−0.05	0.7959	0.79	0.4657
$\alpha_{S\%-W\%}$	−0.57	0.0025*	4.88	0.0166*
$\sigma_{S\%-W\%}$	−0.59	0.0014*	2.91	0.0739
$\beta_{S\%-W\%}$	−0.59	0.0013*	8.20	0.0019*

From left to right, the differential indices, the results from the age-corrected Spearman correlation (ρ and p values) and the results from the regression analysis (Fisher modulus and p values) are listed. Regression analysis was performed with Sleep Patterns for Pediatric Unresponsive Wakefulness Syndrome, age and sex as regressors. *p < 0.05. **p < 0.003 after Bonferroni correction.

DISCUSSION

PSG tracks from 27 children and adolescents with UWS were recorded as soon as possible after exit from coma. The analysis of PSG spectrum during both wake and sleep periods put into evidence increased delta during sleep, and decreased alpha, sigma, and beta activities. In previous works focusing on the diagnostic and classificatory role of EEG, Lechinger et al.[4] found higher delta and theta activities and strongly decreased activity in the alpha band for patients in a VS, with respect to controls and MCS; Leon-Carrion et al.[8] observed that patients in MCS show notably increased power in the delta band, compared to patients with severe DOC (i.e. the upper boundary of MCS); and literature investigating the EEG during coma has analogously focused on the prognostic role of neuroelectrical activity in the delta and theta frequency bands,[42,43] further buttressing the statement that the slower the EEG activity, the poorer the outcome.

We observed inverse correlation between the two indices $(\delta/\alpha)_{S-W}$ and $(PRI)_{S-W}$ and GCS, together with the absence of correlation between the same two indices and the neuropsychological scales at T_0; this fact is in line with the preemptive role of GCS in characterizing the acute condition, and it confirms the inability of neuropsychological and neuroradiological scales alone to draw clear prediction from the acute stage.[38,44] Our findings in children further extend those by Leon-Carrion et al.,[38] who observed high delta/alpha ratio associated with poor outcome in adults with ABI who had undergone 6 mo

Table 5—Logistic regression models.

	Model	Deviants			Percent of Correctly Classified			
	p	Names	χ^2	p	Total	VS	MCS	Exit-MCS
Model 1								
Age, Sex, LOCFAS at T_0, DRS at T_0	0.122	–	–	–	74.1	42.9	90.9	77.8
Model 2								
Age, Sex, LOCFAS at T_0, DRS at T_0, ($\delta_{S\%-W\%}$)	0.016*	Age	32.58	0.002	70.4	28.6	72.7	100.0
		Delta	30.92	0.004				
Age, Sex, LOCFAS at T_0, DRS at T_0, ($\theta_{S\%-W\%}$)	0.087	–	–	–	74.1	42.9	90.9	77.8
Age, Sex, LOCFAS at T_0, DRS at T_0, ($\alpha_{S\%-W\%}$)	0.099	Age	6.57	0.037	74.1	42.9	81.8	88.9
Age, Sex, LOCFAS at T_0, DRS at T_0, ($\sigma_{S\%-W\%}$)	0.135	–	–	–	74.1	42.9	90.9	77.8
Age, Sex, LOCFAS at T_0, DRS at T_0, ($\beta_{S\%-W\%}$)	0.032*	Beta	8.27	0.016	81.5	85.7	81.8	77.8
Model 3								
Age, Sex, LOCFAS at T_0, DRS at T_0, SPPUWS	0.003*	Age	11.82	0.003	96.3	100.0	90.9	100.0
		SPPUWS	28.10	0.002				

Model 1 fits the scores obtained from the clinical scales at T_0. Model 2 additionally includes one electroencephalography frequency band. Model 3 includes scores from the neurophysiological classification, made according to the Sleep Patterns for Pediatric Unresponsive Wakefulness Syndrome scale. "Age" and "Sex" data are included in all models. *p < 0.05. C/CNS, Coma/Near Coma Scale; DRS, Disability Rating Scale; GCS, Glasgow Coma Scale score; GOS, Glasgow Outcome Score; LOCFAS, Level of Cognitive Functioning Assessment Scale; MCS, minimally conscious state; SPPUWS, Sleep Patterns for Pediatric Unresponsive Wakefulness Syndrome; VS, vegetative state.

of comprehensive, intensive and multidisciplinary neurorehabilitation. Indeed, correlations between $(\delta/\alpha)_{S-W}$ and LOCFAS and DRS at outcome, and correlation between $(PRI)_{S-W}$ and GOS, LOCFAS, and DRS all support the conclusion that the wider the power modulation in PSG between sleep and wake, the greater the capability to recover to higher awareness level.

Although the modulatory activity between sleep and wake in the δ and θ bands finds some reflection in the GCS results, apparently no relationship can be traced between the frequency measures and the clinical assessment at T_0; conversely, multiple correlations were found between the differential PSG measures and the neurophysisological and neuroimaging scales at T_1; further, $(\delta/\alpha)_{S-W}$, $(\alpha/\theta)_{S-W}$, $(PRI)_{S-W}$, $\delta_{S\%-W\%}$, $\alpha_{S\%-W\%}$, $\sigma_{S\%-W\%}$, and $\beta_{S\%-W\%}$ all showed direct correlation with the state of consciousness at outcome. These results once more vouch for the prognostic value of PSG with respect to the final level of consciousness.[45–47]

Additionally, correlations of both the spectral indices and the differential PSG measures with the presence of REM and, less starkly, with spindles are supported by the notions that the reappearance of REM periods is a sign of good prognosis in adults and children,[20,24] that REM restructuring comes along with the (regained) capability to modulate the neuroelectrical activity across the diverse PSG stages, and that absence of spindles is a sign of bed outcome.[47,48] Further, when the differential value between sleep and wake states was tested against the SPPUWS, high correlations were found between SPPUWS scores and the differential value in four frequency bands: delta, alpha, sigma, and beta.

The employment of a prediction model showed that clinical assessment at T_0 intrinsically possesses some predictive capability, which is nevertheless insufficient to neatly forecast the patients' level of consciousness at outcome. The inclusion in the model of PSG information restricted to a specific frequency band can improve data fitting, but it does not guarantee better prediction of the level of consciousness at outcome, especially when the lowest frequency bands are considered. Rather, the introduction of the SPPUWS index of global neuroelectrical modulation (i.e., complexity), despite qualitative and frequency-aspecific, seems to be ameliorative to both data fitting and outcome prediction. These findings are globally in line with the work by Beridze et al.,[49] in which multinomial logistic regression revealed the significance of clinical scales and EEG pattern for predicting functional outcome of coma.

In conclusion, the restructuring of wake and sleep cycles after pediatric coma due to injury should be regarded as a progressive phenomenon, which mainly consists of the reacquisition of the ability to regulate the neuroelectrical activity in the specific frequency bands, in the restoration of those PSG stages classified by the standard criteria,[17] and in the regained capability to successfully shift across them. This also entails a boost in complexity, which emerges at different scales: with the increase of spectral variation, with plurality of generated sleep patterns, with larger number of observed sleep stages overnight, with the reappearance of specific graphoelements, and with the increase of mathematical complexity of the PSG signal. The employment of appropriate indices of global neuroelectrical complexity, such as SPPUWS, in the clinical routine could help moving towards better prediction of outcome.

From the clinical perspective, our data purport the primary role of two prognostic elements: the global complexity of PSG patterns, summarized by SPPUWS scores in this work, and the specific residual modulation activity in the beta band across

sleep and wake stages, indicated here as $\beta_{S\%-W\%}$. In our sample, we could confirm that SPPUWS scores, if employed conjointly with clinical data, correctly predicted the outcome for all patients who remained in VS and for all those who later shifted to levels of consciousness higher than MCS. MCS itself remains the most challenging prognostic condition, causing failures in prediction through SPPUWS; in this case, the specific presence of wide modulatory activity in the beta band across sleep and wake stages seems to hint to more favorable outcome.

Secondary to the main clinical finding, an additional remark arose. Although we captured some correlation between $\delta_{S\%-W\%}$ and DRS at T_1, none of the patients received a DRS score between 10 and 15; conversely, $\delta_{S\%-W\%}$ values for the same subjects distributed more homogeneously over a range (**Figure 1**, x axis). We interpret this result as the evidence that EEG restructuring proceeds throughout a continuum during the exit from coma, which is not properly captured by behavioral approaches of assessment, such as the DRS instrument.

Limitations

Although this work attempted to face and overcome some limitations of the previous studies, still a few of them remain unsolved:

1. Due to lack of validation in pediatric populations, the CRS-R could not be employed, despite it being a gold standard in investigations of adult cohorts.[50] A number of alternative scales, validated for children, were applied instead (see **Table 1**).
2. At the time of PSG recording some of the children were undergoing light sedative therapy (see **Table S2**), which could not be interrupted due to ethical reasons. Sedative drugs, and especially benzodiazepines, can consistently alter the EEG tracks by increasing the rapid activity during wake and by boosting the increase of spindle density,[51] and the decrease of the slow wave activity during sleep. These effects could have potentially influenced the modulus of $\delta_{S\%-W\%}$ and $\beta_{S\%-W\%}$ for some patients. However, patients who received the highest dosages of sedative drugs do not coincide with those who showed the worst clinical scores in T_0 and the worst state of consciousness at follow-up, nor with those who had extreme values of $\delta_{S\%-W\%}$ and $\beta_{S\%-W\%}$. Consequently, no link can be established between the sedative therapy and these measures.
3. Additionally, some patients had pharmacologically treated epilepsy at the time of PSG recording. Epilepsy can sensibly distort the macrostructure of sleep and the EEG frequency content, and can relevantly mask sleep microstructure.[52] The reader should note, however, that patients with severe epileptic encephalopathy were excluded from the analyses.

CONCLUSIONS

The report extends to the pediatric age previous findings about a possible predictive role of PSG in the determination of clinical outcome in adults with UWS. Our work confirms that pediatric patients exiting from coma with lingering UWS experience power increase in the delta frequency band during sleep, and decreased alpha, sigma, and beta activities. However, the residual capability to modulate neuroelectrical activity between sleep and wake stages seems to conceal a key clue of the later chance to recover. From this evidence, we initially introduce a differential index of sleep-wake complexity in the specific frequency bands; however, its early prognostic role is only demonstrated for the beta frequency band.

Based on a previous study by our group,[24] we then test the descriptive and prognostic values of the SPPUWS. We highlight the relationship existing between the SPPUWS classification and the differential value between sleep and wake states in the frequency bands, and we demonstrate the consistent gain in outcome prediction due to SPPUWS.

To the authors' knowledge, no published work discusses these issues for a pediatric population with UWS, and for the specific differential index we described. After further confirmation on independent samples, SPPUWS could be introduced in clinics as a marker of future outcome, in addition to the already-in-use behavioral scales.

ABBREVIATIONS

ABI, acquired brain injury
C/NCS, Coma/Near Coma Scale
CRS-R, Coma Recovery Scale-Revised
DOC, disorders of consciousness
DRS, Disability Rating Scale
EEG, electroencephalography
GCS, Glasgow Coma Scale
GOS, Glasgow Outcome Scale
LOCFAS, Level of Cognitive Functioning Assessment Scale
MCS, minimally conscious state
MRI, magnetic resonance imaging
PSG, polysomnography
REM, rapid eye movement
SCN, suprachiasmatic nucleus of the hypothalamus
SPPUWS, Sleep Patterns for Pediatric Unresponsive Wakefulness Syndrome
UWS, unresponsive wakefulness syndrome
VS, vegetative state

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