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Retrospective analysis of sleep patterns in patients with chronic disorders of consciousness

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ABSTRACT

Analysis of sleep patterns in patients with chronic disorders of consciousness attracts attention from the perspective of the diagnosis and prognosis of the disease as well as the treatment. Yet, the very existence of normal sleep in patients in a vegetative or minimally conscious state is still a matter of debate. This paper presents a retrospective analysis of overnight polysomnographic records of 40 patients with chronic disorders of consciousness aimed at the possibility of establishing the connection between the degree of impaired consciousness and the presence and organization of polysomnographic graphical elements, associated with stages of sleep in normal individuals. Specialized software based on expert system artificial intelligence was developed to calculate indices and parameters that characterize sleep. It was shown that a remarkably low percentage of patients have a rhythmic change in sleep patterns, what indicates the prevalence of violations of the Sleep–Wake cycle in a vegetative state and minimally conscious state. Sleep spindles were not found in records, however, the absence can originate from the limitations of polysomnographic method applied to patients with severe brain damage. A positive correlation between the rhythmic change of sleep patterns, better outcome and CRS-R scores was confirmed.

1. Introduction

Rapid progress in intensive care efforts has increased the number of patients who survive severe acute brain damage [1]. Although the majority of these patients recover from subsequent coma within the first days after the insult, some permanently lose all brain function (brain death), while others evolve to a state of “unresponsive wakefulness” or vegetative state (VS). Those who recover from this state, typically progress through different stages, e.g. minimally conscious state (MCS) before fully or partially regaining consciousness [1,2]. Traditionally it is considered that chronic (persistent) disorder of consciousness (DOC) lasts more than three months for a non-traumatic lesion and more than 12 months in a traumatic lesion [3]. According to Ref. [4] the chances of regaining consciousness are significantly reduced after 1.5 years with traumatic genesis and after 6 months with a non-traumatic origin of the disease. However, no clear time frame has been identified for the recovery of consciousness which makes the quest for finding methods for predicting the recovery of consciousness an urgent and practically significant task.

Differential diagnosis between VS and MCS patients is also extremely challenging, leading to a high rate of misdiagnoses [5]. Among the possible neurophysiological markers of VS and MCS more attention is drawn to the analysis of sleep patterns which can provide substantial assistance in the solution of the two above-mentioned tasks [6,7]. In 2020, the European Academy of Neurology issued guidelines for the diagnosis of coma and other disorders of consciousness [8]. The guidelines suggest searching for sleep patterns (especially slow-wave and REM) as one of the complex multimodal diagnostic methods for the disorders of consciousness. The manual also mentions that EEG analysis using machine learning methods and artificial intelligence (AI) can be an additional clarifying factor which increases the accuracy of diagnostics.

Moreover, the neurophysiology of sleep, which has been thoroughly studied in healthy people, suggests that the presence of

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sleep correlates with normal cognitive and emotional processes in wakefulness [9], contributing to memory consolidation [6–10], hormonal regulation [11], and the functioning of the immune system [12]. Thus, it can be stated that restoring and maintaining circadian rhythms can help regain consciousness and improve the overall somatic condition of patients.

Yet, the very existence of normal sleep in patients in a vegetative or minimally conscious state is still a matter of debate [13]. Polysomnography (PSG) as a method of sleep study is recognized worldwide and in some cases is crucial for diagnosis and confirming of the success of therapy [14], appeared to have good correlation with CRS-R score [15]. However, PSG, being the most affordable method for assessing cortical activity, does not demonstrates specificity in determining and predicting consciousness [16–20].

Sleep studies in patients in VS via PSG methods have been conducted since the 1960s, but the conclusions in many cases are based on a small number of observations and are heterogeneous and contradictory. Before 2010, a relatively small number of papers were published on this topic [13,21–29], dealing with the identification of various sleep stages in VS, especially the REM sleep stage [26,27]. In some cases, slow-wave sleep was also observed [21,22] but some researchers have described the change in sleep phases as disorganized and unpredictable, which do not correspond to the circadian cycles of a healthy person [29]. *M. Isono* et al. recorded the primary presence of stages I and II of slow-wave sleep [24] whereas in Ref. [28] it is noted that sleep spindles, which are one of the main signs of stage II of slow-wave sleep, are absent in more than half of cases.

Since 2010–2013, the volume of publications related to PSG sleep pattern in the VS, the number of patients participating in research and the number of phenomena studied has increased significantly, however, the results of the study remain largely contradictory. *Landsness* et al. [30] deny that there are any signs of sleep in the observed patients, whereas *Bedini* et al. [31] point out the sleep cycle and the presence of specific traits in all subjects. *Arnaldi* et al. [32] showed no signs of slow-wave sleep, while REM sleep was observed in 15% of cases. On the contrary, in Ref. [29,31] slow-wave sleep predominates in the frequency of occurrence over REM sleep. In the study of *Rossi Sebastiano* et al. nighttime PSG revealed that attenuation of the signal amplitude was the only sign of sleep in patients who were diagnosed with VS [33].

The conflicting information about the presence of sleep cycles and various neurophysiological phenomena in PSG suggests a possible variation in the parameters of these phenomena, their variability in the population, and probably different approaches in determining the stages of sleep.

Taking into account the significance of PSG sleep studies for diagnosis, prognosis, and therapy, the aim of this research is to investigate the possibility of establishing the connection between the degree of impaired consciousness and the presence and organization of polysomnographic graphical elements, within the framework of a unified approach, which involves using AI as a second opinion.

2. Materials and methods

2.1. Participants

Forty adult patients participated in the study. The group was made up of in-patients, admitted to Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology throughout a period of 3 years. Inclusion criteria involved persistent or permanent DOC due to severe acquired brain damage of different etiology, such as traumatic brain injury (TBI), anoxic brain injury (ABI), vascular lesions (VL), and inflammatory diseases (ID). Time since injury substituted less than a year, but not less than one month at the study enrollment. Exclusion criteria comprised age over 70 years old, disability associated with the central nervous system that preceded the insult, epilepsy, myoclonus, hemodynamic instability, the need of mechanical ventilation, which can interfere with sleep [34]. None of the patients received tranquilizers, barbiturates, antipsychotics, or antidepressants.

No more than two days before the enrollment in the study two trained and certified neurologists (M.K., D.Y.) evaluated all patients and determined the level of consciousness according to the CRS-R scale according to Administration and Scoring Guidelines [35], assessing auditory, visual, verbal and motor functions, as well as the level of communication and arousal. Given the fluctuations of the clinical responses in DOC patients, a re-assessment was carried out one week after the beginning of the study.

CT or MRI studies were performed to rule out brain stem lesions and confirm the diagnosis of VS or MCS. Medical reports on the studies can be found in the attached file in Supplementary Data (link).

No less than 3 months after the discharge from the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology catamnesis data were acquired for each patient to access the outcome of the disease and evaluate prognostic significance of sleep patterns.

Table 1 summarizes the demographic and clinical characteristics of the patients.

2.2. Data acquisition

PSG recordings of all patients were obtained overnight, from the afternoon or evening of the previous day to the morning of the following day. The mean duration of recordings was 14.7 h (SD = 3.8 h). It should be noted that medical manipulations and measurements, trachea-bronchial tree sanitation, etc. were carried out at about 4 am, which disrupted the patients' sleep and introduced a large number of artifacts.

Data were acquired with SOMNOscreen™ plus PSG system. For EEG acquisition six Ag/AgCl electrodes were placed on the patients' head, corresponding to the standard 10/20 system [53] in F3, F4, C3, C4, O1, and O2 positions. Additional reference was provided with earlobe electrodes, placed in A1 and A2 positions. Two electrooculogram (EOG) channels were added in cross-montage, two bipolar EMG channels were used to record deltoid activity, and in some cases one bipolar electrocardiographic (ECG) derivation was supplemented.

During the recording, EEG impedances were kept under 5 kOhm. In a small number of recordings, some channels are missing due to the character of head trauma and data acquisition bugs. All the recordings are available in Supplementary Data (link).

2.3. Data processing

For the analysis of sleep patterns, specialized software in *Python Programming Language* was developed with the use of *NumPy, scipy, matplotlib, mne,* and *yasa* [36] libraries. Software provides bandpass filtering in the 0.5–35 Hz range for EEG and EOG signals and 5–200 Hz range for EMG signal. Artefact removal is performed by using independent component analysis with automatic search of components, corresponding to contaminating channel (i.e. EMG or EOG).

All PSG tracks are divided into 30-s epochs for further staging. For each epoch characteristic graphical elements such as sleep spindles, slow waves, etc., are detected; the prominence of alpha,

Table 1
Demographic and clinical characteristics of the patients included in the study.

Case	Age/Sex	Primary disease	Duration of the disease at study enroll.[a]	CRS-R score first assessment/CRS-R score re-assessment							State of consciousness	Change of Stages	Rhythmic Change of Stages	Sleep patterns	Outcome of the disease
				Auditory Function Scale	Visual Function Scale	Motor Function Scale	Oromotor/ Verbal Function Scale	Communication Scale	Arousal Scale	Total score					
1	37/f	ABI	4	1/1	1/2	1/1	0/0	0/0	2/2	5/6	VS	1	0	0	PDOC
2	28/f	TBI	3	3/3	3/4	4/3	2/2/	1/1	3/3	16/16	MCS+	1	1	1	Consc
3	42/f	ABI	2	1/1	1/1	1/1	0/0	0/0	2/2	5/5	VS	1	0	0	PDOC
4	48/f	ABI	4	1/2	1/1	0/1	0/0	0/0	2/1	4/5	VS	1	0	0	PDOC
5	35/m	TBI	3	3/3	3/3	3/4	1/1	1/1	3/3	14/15	MCS+	1	1	1	Consc
6	65/f	VL	3	1/0	1/1	2/1	1/1	0/1	2/2	7/6	VS	0	0	0	Consc
7	62/m	TBI	3	0/1	1/1	1/1	1/1	0/0	2/1	5/5	VS	0	0	0	PDOC
8	51/m	ABI	3	0/1	0/1	1/1	0/0	0/0	2/2	3/5	VS	0	0	0	PDOC
9	45/m	ABI	5	1/2	1/1	1/1	0/0	0/0	2/2	5/6	VS	1	0	0	PDOC
10	18/m	TBI	4	1/1	1/1	1/2	1/1	0/1	2/1	6/6	VS	1	0	0	PDOC
11	22/m	TBI	5	0/1	0/0	0/0	0/0	0/0	2/2	2/3	VS	0	0	0	D
12	22/f	TBI	22	2/2	0/1	1/1	0/1	0/0	2/0	5/7	VS	1	0	0	PDOC
13	39/f	TBI	4	1/1	2/1	1/1	1/1	0/1	2/1	7/7	VS	1	0	0	Consc
14	68/m	VL	3	1/0	1/1	1/1	1/1	0/0	2/2	6/5	VS	0	0	0	PDOC
15	41/m	TBI	2	2/3	4/3	3/3	2/2	1/1	3/3	15/16	MCS+	1	1	1	Consc
16	20/f	TBI	4	0/1	1/2	2/1	1/1	0/0	2/1	6/6	VS	1	0	0	Consc
17	53/f	TBI	6	2/1	1/1	1/1	1/1	0/0	2/2	7/6	VS	1	0	0	PDOC
18	42/f	ABI	4	2/2	1/2	2/2	0/0	0/0	2/1	7/7	VS	1	0	0	PDOC
19	61/m	ABI	5	2/1	0/1	1/0	1/1	0/0	2/2	6/5	VS	0	0	0	PDOC
20	58/m	ABI	3	0/0	1/0	0/1	0/1	0/0	2/1	3/4	VS	0	0	0	PDOC
21	41/m	TBI	4	1/1	1/1	1/1	2/1	0/0	2/1	7/7	VS	0	0	0	Consc
22	23/m	TBI	4	2/1	1/1	1/1	1/1	0/0	2/2	7/6	VS	0	0	0	Consc
23	70/f	VL	2	1/2	1/1	1/1	1/1	0/1	2/2	6/7	VS	0	0	0	PDOC
24	64/m	VL	4	2/1	2/2	2/3	1/1	0/1	2/2	9/9	MCS-	1	0	0	D
25	45/f	TBI	3	2/2	2/2	3/2	1/1	0/0	2/2	10/9	MCS-	1	0	0	Consc
26	44/m	TBI	2	1/1	2/2	4/3	1/1	0/0	2/2	9/10	MCS-	0	0	0	Consc
27	30/m	TBI	3	3/3	3/3	3/4	2/2	1/1	2/2	15/16	MCS+	1	1	1	Consc
28	43/f	TBI	3	2/2	2/2	2/2	1/1	0/0	2/2	9/9	MCS-	0	0	0	Consc
29	70/f	ABI	3	0/1	1/1	1/1	0/0	0/0	2/2	4/5	VS	1	0	0	D
30	58/m	ID	9	1/0	0/1	1/1	0/0	0/0	2/1	4/4	VS	1	0	0	D
31	45/m	TBI	3	1/2	2/2	0/1	1/1	0/0	2/2	6/8	VS	0	0	0	PDOC
32	63/m	VL	2	0/0	0/1	1/1	1/1	0/0	1/1	3/4	VS	0	0	0	D
33	36/m	ABI	6	0/0	1/0	0/0	1/1	0/0	2/2	4/3	VS	0	0	0	PDOC
34	26/m	TBI	3	1/1	1/1	1/1	1/1	0	2/1	6/5	VS	0	0	0	Consc
35	30/f	ABI	6	1/1	1/1	1/1	2/1	0/0	2/1	7/6	VS	1	0	0	PDOC
36	40/m	ABI	4	1/1	1/1	1/1	1/1	0/0	2/2	6/6	VS	0	0	0	PDOC
37	38/f	VL	2	3/3	4/4	4/4	3/3	1/1	2/2	17/17	MCS+	1	1	1	Consc
38	32/f	ABI	5	3/2	0/1	3/3	2/1	0/0	2/2	10/9	MCS-	1	0	0	PDOC
39	40/m	TBI	3	2/1	1/1	1/1	1/1	0/0	2/2	7/6	VS	0	0	0	PDOC
40	32/m	TBI	7	2/1	2/0	1/1	1/1	0/0	2/1	8/4	VS	1	0	0	PDOC

Abbreviations: m – male, f – female; TBI - traumatic brain injury; ABI – anoxic brain injury; VL - vascular lesion; ID - inflammatory disease; D – death, Consc – conscious, PDOC – permanent DOC.
[a] In month.

beta, theta, and delta rhythms, instantaneous and average values of the signal amplitudes are calculated. According to computation results, each epoch is automatically scored in compliance with R&K criteria [37], which are represented as the body of knowledge ("if–then" rules) for the expert system. The main advantage of AI software based on expert system is a complete transparency of the process of classification and the adaptability of "if-then" rules for patients with DOC.

According to the results of AI scoring, it is possible to automatically construct a hypnogram for each patient. Herewith, all unscored epochs, dubious results and graphical elements of interest for each PSG track were manually checked and corrected, if needed, by trained neurophysiologists (A.S., J.N.). Ultimately, segments with unclear and debatable scores were not included in the study results.

Extensive explanation of principles of graphical elements detections is available in Supplementary Data (link).

2.4. Statistics

All data, presented in Table 1, except for the age of patients at the time of injury, proved to be nonnormally distributed after the Kolmogorov–Smirnov test. Hence, nonparametric tests for inferential statistics were used. Spearman's rank correlation coefficients were calculated between different quantitative variables.

Significance at *P* values were set below 0.05. The values of the correlation coefficient were interpreted in accordance with the Chaddock scale to assess the direction and strength of the correlation. The Mann–Whitney *U* test was used for testing differences in clinical scores between patients with and without patterns of sleep.

To present and compare quantitative data the standard deviation (SD), minimum and maximum values were calculated. Nominal data were described with absolute values and percentages.

All statistical analyses were carried out using "Statistica" Data Analysis Software System, version 10 (StatSoft Inc.).

2.5. Ethics statement

This study was carried out in compliance with the Declaration of Helsinki and was approved by the Ethical Committee of Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology. Patients' relatives provided written informed consent for the participation in the study.

3. Results

3.1. Demographic data and clinical scales

In this section, clinical and demographic characteristics of 40 patients with chronic DOC are reported. Mean age at the time of injury constituted 43.17 years (SD = 14.75years) for the group in question.

With respect to the level of consciousness, 30 patients (75%) were diagnosed with VS, 5 patients (12,5%) – with MCS+ and 5 patients (12,5%) – with MCS- (see Fig. 1, a).

With respect to the etiology, 20 patients (51.3%) suffered from TBI, 13 (33.3%) presented with ABI, 6 patients (12.8%) had vascular lesions and 1 patient in the group had multiple IDs (suffered meningitis and two encephalitis) (see Fig. 1, b).

At first assessment at the study enrollment, median value for the CRS-R points constituted 6.0 (range, 2–17) with the most frequent values of 6 and 7 (20% of patients each). At second assessment, median value for the CRS-R points also constituted 6.0 (range, 3–17) with the most frequent value of 6 (25% of patients).

For ABI, the correlation between age and CRS-R score is moderately negative ($r = -0.57$ at $p < 0.05$). For TBI, the correlation is positive, weak ($r = 0.25$, $p < 0.05$). For VL, the correlation is negative, strong ($r = -0.88$, $p < 0.05$). According to the acquired data, for ABI and VL patients with the rise of age CRS-R score is decreasing. TBI patients tend to increase CRS-R score with age, but the relationship has low level of correlation.

Mean duration of the disease at the study enrollment was 4.25 (SD = 3.24, range = 2–11). Among the participants, 17 patients (42.5%) were female, 23 patients – male.

3.2. Sleep patterns in chronic DOC patients

The character of change in sleep stages found among the group can be in the first approximation divided into three types:

1. *No change in sleep stages*: No change of stages can be found on the basis of a PSG recordings. Usually, the electroencephalogram (EEG) of patients with missing change in sleep stages is characterized by dominant, diffuse delta (1–4 Hz) and/or theta (4–6 Hz) activity, sometimes together with high amplitude activity in the beta band (14–30 Hz) due to muscle tension. In the first case, the sleep is described primarily by Stages III and IV, in case of myogenic artefacts present epochs can be classified as Stage I or Wake. In both cases, EEG is aperiodic; no peaks can be detected at frequencies higher than 6 Hz. Hypnogram exhibit

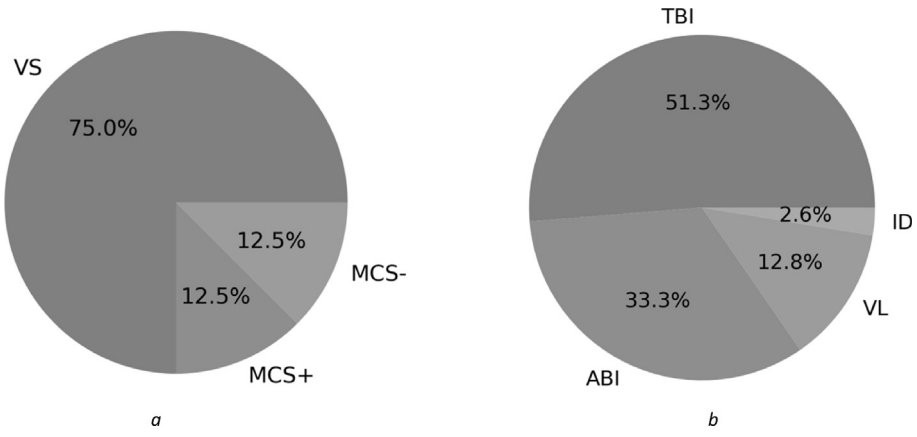


Fig. 1. Patient's characteristics according to the level of consciousness (a) and the etiology of the disease (b).

minor changes at the level of measurement and calculation error (Fig. 2).

2. *Disorganized change in sleep stages:* The change of sleep stages is unpredictable, does not follow normal SleepeWake cycle and result in a hypnogram in chaotic change between Stages III or IV, which correspond to slow-wave brain activity, and Wake or Stage I, mostly due to the rise of myogenic artefacts(Fig. 3, a).

3. *Rhythmic change in sleep stages:* This pattern can be registered as a cyclic alternation of polygraphic pictures, which is the only one type of stage change considered in current research as an evidence of presence of SleepeWake cycle in PSG, though disrupted and distorted [38].

In Table I, results of sleep patterns calculations are reported. Among the group, 17 patients (42.5%) demonstrated at least some changes of sleep stages, however, these changes could not be considered as rhythmic; 18 patients (45%) showed no change in sleep stages at all; 5 patients (12.5%) had rhythmic changes of sleep pattern, i.e. patterns of sleep (Fig. 4, a).

Stage Wake and Stage I (Fig. 4, b) were present in significant amount of PSG records. Stage II appears to be missing in chronic DOC patients. It is deduced from the lack of sleep spindles, which are absent in all patients in standard frequency range (11–16 Hz). Individual graphic elements of sleep spindles marked by the software were manually checked and then rejected due to their non-neurogenic origin, e.g. influence of myogenic activity in the EEG, fluctuations in the sub-electrode potential, etc. However, the absence of Stage II cannot be assuredly stated due to the following considerations (see Discussion Section).

Stages III and IV of NREM sleep, i.e. slow-wave activity, prevailed in the group of patients. In 10 patients the total duration of stages III and IV was more than 90%. In such patients, there is generalized, almost constant slow-wave activity.

REM sleep patterns were not detected though the rapid eye movements were noted in abundance in the PSG tracks. It is explained by the fact that found REMs did not match the muscular atony and speedup of EEG activity and, therefore, did not satisfy the criteria for REM sleep.

3.3. Correlations between sleep patterns and the clinical data

The consciousness level in all patients with a rhythmic change in sleep stages is MCS+, collecting the points from 14 to 17 on the CRS-R scale. Statistical analysis of the correlations between the PSG patterns and CRS-R points revealed a direct moderate relationship with $r = 0.58$ at $p < 0.05$. Mann–Whitney *U* test for the group with CRS- R scores and sleep patterns show statistically significant differences at $p < 0.01$.

With respect to the etiology, all patients with sleep patterns had TBI. No patients with ABI or VL demonstrated rhythmic change in sleep stages.

Correlation between sleep patterns and outcomes is positive, moderate ($r = 0.47$ at $p < 0.05$). In this case, the outcomes were taken as follows: *D* - 1, *PDOC* - 2, *Consc* - 3. This implies a relationship between the presence of sleep patterns and a positive

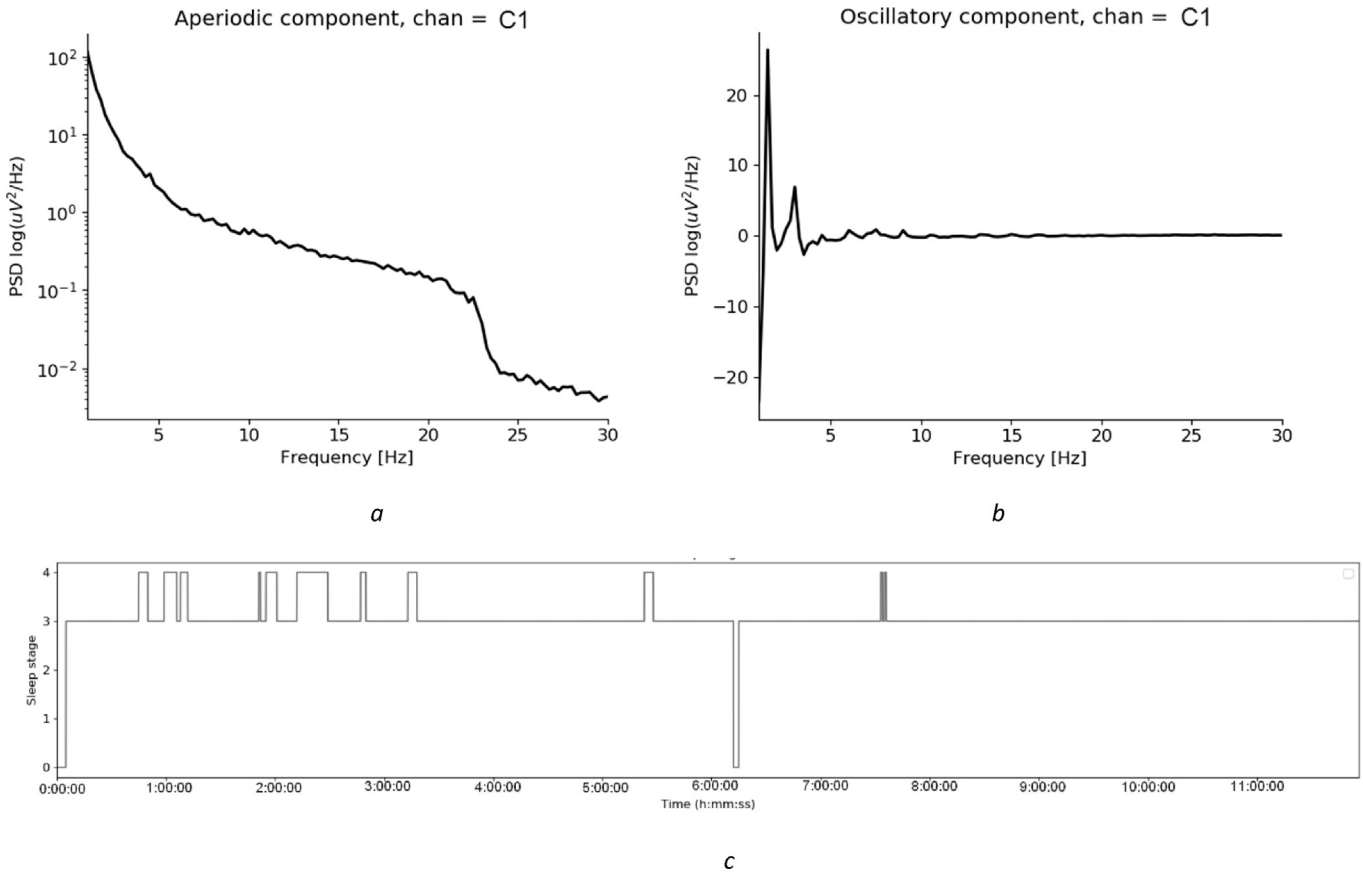


Fig. 2. Missing change in sleep stages: a – aperiodic component of EEG of patient № 4 in channel C1; b – oscillatory component of EEG of patient № 4 in channel C1; c - 12-h piece of hypnogram (from 23.59 of the previous day to 12.00 in the next morning) of patient № 4 with missing change of sleep stages (Stages III and IV).

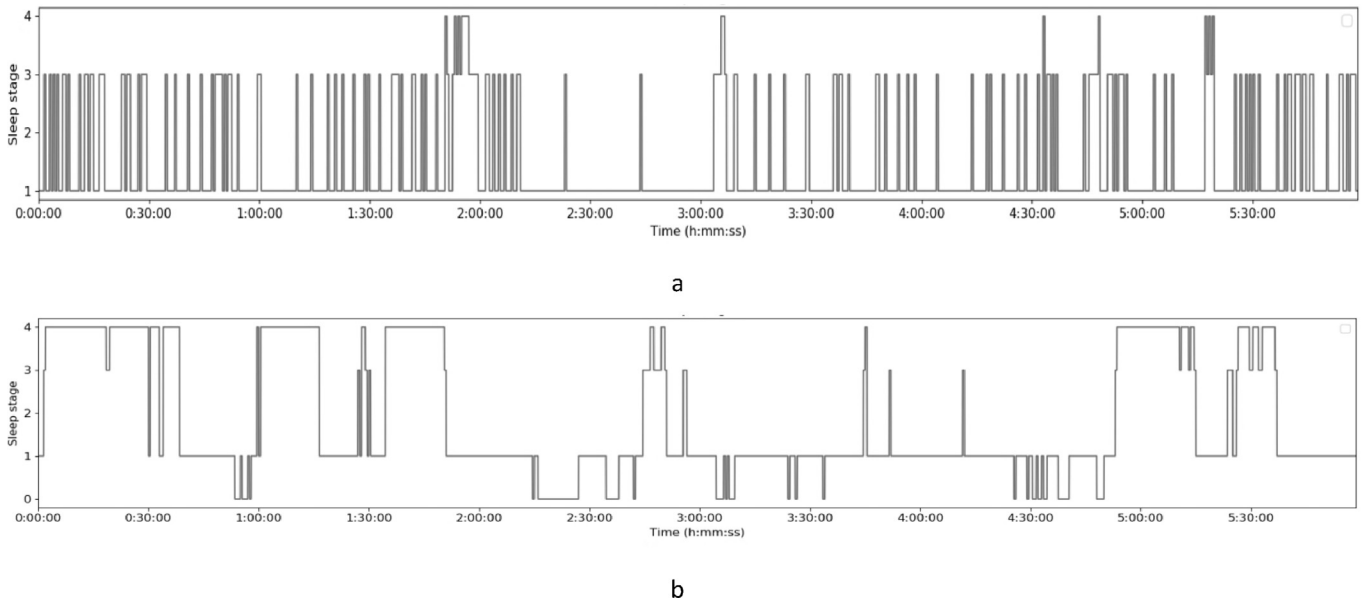
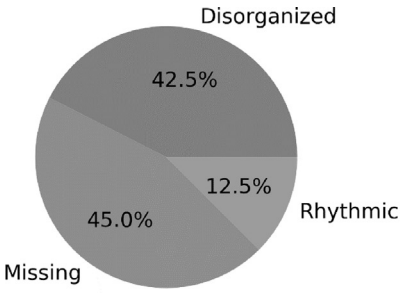


Fig. 3. 6-hours pieces of hypnogram (from 23.59 of the previous day to 06.00 in the next morning) of patient № 18 with disorganized change of sleep stages (a) and patient № 5 with rhythmic change in sleep stages (b).



a

Sleep stage	Number of patients
Wake	31 (77.5 %)
Stage I	38 (95 %)
Stage II	-
Stages III and IV	38 (95 %)
REM sleep	-

b

Fig. 4. Presence and change of sleep stages in the group of patients: a-the character of the change in sleep stages; b – the presence of different sleep stages.

outcome. Correlation between sleep patterns and outcomes is also positive, moderate with $r = 0.48$ at $p < 0.05$.

4. Discussion

The aim of this study was to investigate the capability of sleep study via PSG method to predict the outcome of the acquired severe brain injury in persistent phase and to help in differential diagnosis between VS and MCS. Results of the conducted study of 40 PSG tracks showed that a positive correlation between the presence of sleep patterns, higher CRS-R scores and favourable outcome does exist and is statistically confirmed. Justification and in some cases necessity to use sleep pattern study for clarification of diagnosis of DOC can also be inferred.

However, a number of serious restrictions of the PSG method and limitations of the study must be taken into account.

1. PSG method is not adequately informative in cases of significant damage to the cerebral cortex like a loss of most of the cortical neurons, a drastic decrease in the number of interneuron connections in the cerebral cortex, diffuse axonal damage with subsequent degeneration of cortical neurons, reduction in the activity of the caudal group of nuclei of the basal forebrain (BF). Diffuse lesions of the cerebral cortex lead to a quantitative decrease in the main functional units of the nervous system and their connections, which is electrophysiologically converted into a slowdown in cortical rhythm and their inability to translate high–frequency activity of subcortical structures. Thus, sleep spindles, which are scalp reflections of the synchronized post-synaptic excitatory potentials of cortical neurons, while the sigma rhythm itself is generated by the thalamus, can be distorted or even absent in EEG recordings. *Silverman* et al. [38], earlier noted that the presence of spindles in the EEG indicates a relatively preserved cerebral cortex and a favorable prognosis.

In our study of difficult patients with serious lesions to cerebral cortex the aforementioned considerations resulted in complete absence of sleep spindles visible on the EEG. It must be mentioned, that in the current study the detection of K-complexes was not performed. Thus, the lack of sleep spindles only is not sufficient to exclude the presence of Stage II. Hence, Stage II was impossible to distinguish from Stage I, as well as to conclude about the presence or absence of this stage. The diagram of the thalamocortical chain responsible for the generation and distribution of sleep spindles is presented in Fig. 5.

Similar considerations can be applicable to REM sleep. Since rapid eye movements (REMs) are produced jointly by brainstem, midbrain (superior colliculi) and cortical regions (frontal and

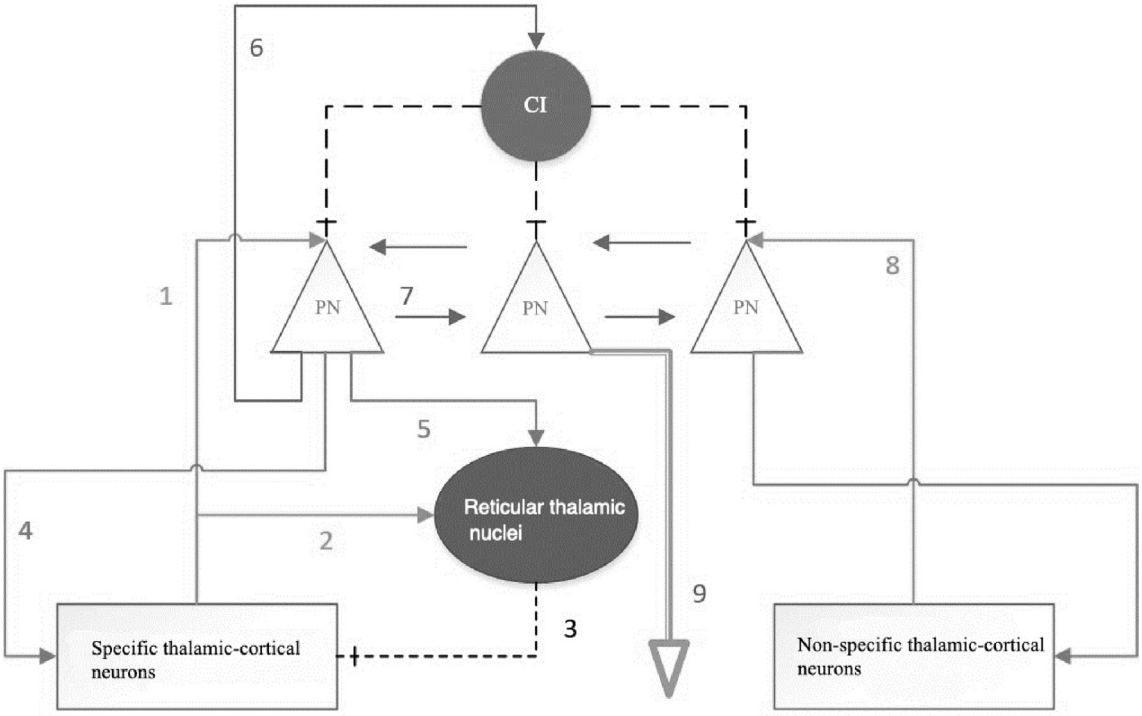


Fig. 5. Diagram of the thalamocortical chain responsible for the generation and distribution of sleep spindles. Specific thalamic-cortical neurons excite pyramidal neurons (PN) of the 6th cortical layer belonging to the same thalamic-cortical bundle (line 1) and neurons of the reticular thalamic nuclei (line 2). Reticular nuclei (line 3) inhibit specific thalamic-cortical neurons. Pyramid neurons form feedbacks to the thalamus (lines 4, 5) and make a branched neural network with other pyramid neurons and cortical interneurons (CI lines 6, 7). Non-specific thalamic-cortical neurons form similar bonds with neurons of the same bundle and also excite neurons of the higher cortical layers (line 8). Neurons of intermediate layers (the triangle in the middle of the diagram) generate an output signal and excite neurons of other bundles (arrow 9).

parietal eye fields), the scarcity of interneuron connections in cerebral cortex and hence the weakening of downward cortical influence can eliminate REMs in sleep [39]. The data obtained in current research do not give grounds to conclude that there is or there is no REM sleep due to significant damage to the cerebral cortex in patients with chronic DOC.

2. Due to aforementioned reasons, PSG analysis conducted in consistence with traditional methodic and approaches can be considerably hindered. Moreover, *Cologan* et al. [28] noted that many patients in VS have impaired background EEG activity, which is difficult to attribute to a particular stage of sleep. This can significantly complicate the PSG analysis of sleep patterns, and in many cases do not allow it to be carried out efficiently. Thus, the methods for analysis of sleep in DOC patients will most likely require serious improvement and reconsideration. Attempts to introduce criteria to distinguish between different sleep patterns have been made for pediatric DOC patients [34], however the research in this field for adult DOC patients is still urgently required. Especially it is demanded for AI analysis of sleep patterns. The capacity to translate these criteria into machine learning language can significantly increase the feasibility of the method.
3. Another problem arise when recording PSG tracks in intensive care units (ICU). Receiving signals, which are of acceptable quality in ISUs is a notably demanding task, because common artifacts caused by perspiration, skull and skin deformities, thermal dysregulation, physiological processes of breathing, eye movements, as well as additional artifacts of a technical nature caused by the resuscitation equipment, medical manipulations, etc., can entail completely unpredictable results of the study. Complicated filtering methods such as independent component analysis, Wiener and Kalman filtering, wavelet analysis may be required to filter out only the myogenic artifacts often appearing in patients with VS. The time of PSG recording is also limited by medical manipulations. The lack of medical personnel and the inability to control electrode placement overnight can impose a problem of the loss of quality of recordings by morning. The formation of pressure sores on the patient's head limits the frequency of the method application and requires the development and availability of more expensive equipment to avoid this problem.

In the current study recording durations was limited to less than the duration of a circadian cycle (24 h) due to the reasons listed above. Thus, some sleep stages may have been missed by the recordings.

4. A remarkably low percentage of patients with a rhythmic change in sleep patterns (12.5%) can indicate not only the bad prognosis and low level on consciousness, but also the prevalence of violations of the Sleep—Wake cycle, which is typical in patients in VS and MCS. External factors such as the lack of sunlight, artificial lighting, noise stimulus, and being in a new, physiologically unusual environment can cause these disorders. Authors believe, that restoring and maintaining circadian rhythms can not only help patients regain consciousness and improve the overall somatic condition, but also to improve the accuracy of the PSG method of sleep study.

Authors can speculate on several ways to avoid or mitigate these limitations. First, a good way to go would be to introduce indirect methods of sleep analysis including recordings of heart rate, blood pressure, actigraphy, eye-tracking, cardiopulmonary

monitoring, laboratory works on hormones involved on Sleep–Wake cycle regulation, assessment of external signs of sleep from video recordings, such as eye movements, blinking, etc. These methods can augment PSG study and substitute additional in-research PSG applications, though additional research of them in groups of DOC patients are needed [40,41], [42]. In a study carried out by *Pattoneri* et al. [40] in 10 patients who were in a persistent VS, it was observed that their heart rate and arterial pressure did not show significant changes during the night. Similar results were found in [41], but in this case, 16 patients registered a decrease in body temperature, levels of melatonin, and cortisol during sleep. Although the number of questions may at first exceed the number of answers, the authors consider these methods to be a necessary step towards accurate sleep analysis.

Second, new criteria for PSG sleep analysis for DOC patients are still required. The validation of them is preferable to be conducted simultaneously with the study of behavioral, physiological, and normative signs of sleep. It worth noting, that these methods can occur to be different for different groups of DOC patients. In our study, traditional methods worked best for patients underwent TBI or VL and appeared to give the less informative results in patients with severe ABI.

Third, the number of patients and recorded data from each patient must be and actually tend to rise nowadays. AI products, which usually increase the accuracy with the growth of the amount of data, can make signal analysis less time-consuming. The data mining ability of AI could be in handy for the search of correlations between different signals and for clusterization of patients according to the signals.

5. Conclusion

In accordance with previous works, current study confirms the clinical validity of the presence of sleep patterns for diagnosis and prognosis of the chronic DOC. The differential diagnostics between persistent VS and MCS is confirmed to be possible via PSG sleep analysis. We state that rhythmic change in sleep stages can be considered as a marker of higher level of consciousness and a predictor of better outcome. However, our study rises an issue of incomplete informability of PSG method and brings up the question of finding new ways to analyze sleep patterns in chronic DOC patients, either as standalone methods or in combination with PSG.

AI methods of sleep analysis proved to be a promising tool and can be recommended for future sleep studies, especially in the light of significant growth of the amount of data.

Authors contribution

Nekrasova Julia: Conceptualization, Methodology, Software, Investigation. Writing - Original Draft

Kanarskii Kanarskii: Conceptualization, Methodology, Investigation

Yankevich Dmitrii: Writing- Review and Editing, Project administration

Andrey Shpichko: Investigation, Data curation

Borisov Ilya: Methodology, Investigation

Pradhan Pranil: Investigation

Maria Miroshnichenko: Investigation

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleepx.2020.100024.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleepx.2020.100024.

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