Sleep Organisation in Depression and Schizophrenia: Index of Endogenous Periodicity of Sleep as a State Marker

Andrej Ilankovic1, Aleksandar Damjanovic2, Vera Ilankovic3, Srdjan Milovanovic2, Dusan Petrovic4, Nikola Ilankovic1*

1Center of Clinical Neurophysiology & Sleep research, University Psychiatric Clinic, Belgrade, Serbia; 2University Psychiatric Clinic, Belgrade, Serbia; 3Faculty of Special Education and Rehabilitation, University of Belgrade, Serbia; 4University Psychiatric Clinic, Kragujevac, Serbia


Abstract

Background: Sleep disorders are frequent symptoms described in psychiatric patients with major depression or schizophrenia. These patients also exhibit changes in the sleep architecture measured by polysomnography (PSG) during sleep. The aim of the present study was to identify potential biomarkers that would facilitate the diagnosis based on polysomnography (PSG) measurements.

Subjects and Methods: 30 patients with schizophrenia, 30 patients with major depression and 30 healthy control subjects were investigated in the present study. The mean age in the group with schizophrenia was 36.73 (SD 6.43), in the group of patients with depression 40.77 (SD 7.66), in the healthy controls group 34.40 (SD 5.70). The gender distribution was as follows: 18 male, 12 female in the group with schizophrenia; in the group of patients with depression 11 male, 19 female; in the control group 16 male and 14 female. All subjects underwent polysomnography (PSG) for a minimum time of 8 hours according to the criteria of Rechtschaffen & Kales (1968). The following polysomnographic (PSG) parameters were analyzed: sleep latency (SL), total sleep time (TST), waking time after sleep onset (WTASO), number of awakenings (NAW), slow wave sleep (SWS), rapid eye movement sleep (REM), rapid eye movement sleep latency (REML), first REM period (REM 1), and first NREM period (NREM 1). We tested the potential of multiple sleep variables to predict diagnosis in different groups by using linear discriminate analysis (LDA).

Results: There were significant differences in polysomnography (PSG) variables between healthy control subjects and psychiatric patients (total sleep time, sleep latency, number of awakenings, time of awakening after sleep onset, REM 1 latency, REM 1 and index of endogenous periodicity). Importantly, LDA was able to predict the correct diagnosis in 88% of all cases.

Conclusions: The presented analysis showed commonalities and differences in polysomnography (PSG) changes in patients with major depressive disorder and in patients with schizophrenia. Our results underline the potential of polysomnography (PSG) measurements to facilitate diagnostic processes.

Introduction

Schizophrenia and the major depressive disorder (MDD) are both among the most frequent psychiatric disorders and make up a substantial share in the global burden of disease [1, 2]. A reliable diagnosis is crucial in providing efficient treatment strategies for patients. However, until today diagnostic procedures have largely relied on clinical evaluation and reliable biomarkers have not yet been identified. It has been suggested that there is a substantial overlap in the clinical symptomatology in patients with MDD and patients with schizophrenia. Specifically, sleep disturbances represent a common symptom that can be found in all stages of MDD and schizophrenia [3, 4]. In some cases this can lead to low reliability of established diagnostic procedures. Therefore, EEG measurements could provide an important tool to detect biomarkers [5] in order to investigate the sleep architecture before the treatment and over the course of the disease.

Polysomnography or sleep EEG provides numerous variables to objectify sleep characteristics by means of EEG recordings while subjects are asleep. Among those, the most frequently used variables are: the amount of slow-wave sleep, sleep latency, total sleep time, total awake time, REM sleep latency and the percentage of REM sleep. It has been suggested [6]...
that the index of endogenous perturbation of sleep (IEP) might be an important parameter to characterize sleep architecture in psychiatric patients. The IEP represents the ratio between REM1/NREM1 (IEP = REM1/NREM1). It has been reported that the IEP is a significant marker in patients with major depression [6].

Numerous abnormalities have been reported in schizophrenia, as measured by polysomnography (PSG) and particularly during rapid-eye-movement (REM) phases. Significant changes in sleep latency, total sleep time and sleep efficiency index have been reported in patients with schizophrenia as compared to healthy controls in a recent meta-analysis of sleep variables [7]. Additionally, some studies have reported changes in the total awake time [8-10], slow-wave sleep [11] and rapid-eye-movement latency (REML) [8, 12]. Moreover, the REM percentage of total sleep time [7, 13] seems to be abnormal in those patients, but not all studies confirmed these findings [12-19]. It has also been reported that the severity of clinical symptoms is related to EEG disturbances during sleep [13, 20, 21].

Similarly to patients with schizophrenia, subjects with depression show abnormal sleep architecture – especially during REM sleep periods [5]. A recent meta-analysis of abnormal EEG patterns in patients with MDD suggests that abnormal REM density and NREM sleep might represent potential biomarkers that persist beyond remission [22]. These abnormalities have been related to the severity of clinical symptoms [22]. Finally, it has also been suggested that abnormal sleep architecture might represent a vulnerability factor for affective disorders [23-25].

In the present study sleep disturbances in patients with schizophrenia, depression as well as in healthy controls were investigated with polysomnographic measurements. The aim was to identify reliable biomarkers associated with MDD and schizophrenia. The sleep variables were entered into a multivariate classification model to allow prediction of diagnostic categories. In this way the usability of polysomnographic measurements in clinical diagnostic procedures was investigated.

Our hypotheses were that: 1) the structure and architecture of nocturnal sleep as measured with polysomnography (PSG) in schizophrenic and depressive patients and in healthy control subjects show significant group differences with regard to some parameters (variables) of the polysomnogram; and 2) the variables of nocturnal sleep in polysomnogram have a good potential to help the differential diagnostic process in schizophrenia and major depressive disorders.

Subjects and Methods

We tested 30 patients with MDD (age, gender), 30 patients with schizophrenia (age, gender) and 30 healthy controls (age, gender). All patients were diagnosed by an experienced clinical psychiatrist and fulfilled ICD-10 criteria (World Health Organization, n.d.) [27] for either major depression (F32.2) or schizophrenia (F20). The mean duration of the illness in the group with schizophrenia was 12.60 years (SD 6.53) and in the group with depression 12.93 years (SD 6.13). All patients were in-patients. The exclusion criteria for all subjects were the following: presence of neurological or medical illness, current or recent alcohol abuse or drug addiction (except for nicotine), presence of any psychiatric disorder in the group of healthy control subjects and any comorbid psychiatric disorder in patients. All subjects provided written informed consent to participate in the study. The study was approved by the Ethics Committee of the University of Belgrade.

All subjects underwent a 16-channel EEG recording for 24 hours using the Oxford Medilog 9000 ambulatory EEG system plus 2 EOG (electrooculogram) and 1 EMG (submental electromyography) channels. The analysis was restricted to an 8-hour-period from 10 p.m. until 6 a.m. For the subsequent statistical analysis the following sleep parameters were extracted: total sleep time, sleep latency, number of awakenings, time of awakening after sleep onset, slow wave sleep, REM latency, REM 1, Non-REM 1, index of endogenous periodicity (Table 1).

Table 1: Sleep variables.

<table>
<thead>
<tr>
<th>Sleep variable</th>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep latency</td>
<td>SL</td>
<td>From the moment the lights are turned off to consecutive 10 minutes of stage 2, 3 or 4 (minutes)</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>TST</td>
<td>Minutes of sleep during the recording of sleep</td>
</tr>
<tr>
<td>Waking Time after Sleep Onset</td>
<td>WTASO</td>
<td>Minutes of sleep during the recording of sleep</td>
</tr>
<tr>
<td>Number ofAwakenings</td>
<td>NAWs</td>
<td>Number of awakenings through the night</td>
</tr>
<tr>
<td>Slow-wave-sleep</td>
<td>SWS</td>
<td>Duration of SWS time in TST (minutes)</td>
</tr>
<tr>
<td>Rapid-eye-movement sleep</td>
<td>REM</td>
<td>Duration of REM time in TST (minutes)</td>
</tr>
<tr>
<td>Rapid-eye-movement sleep latency</td>
<td>REML</td>
<td>Minutes from sleep onset to the first REM sleep</td>
</tr>
<tr>
<td>First REM period</td>
<td>REM 1</td>
<td>First REM period (minutes)</td>
</tr>
<tr>
<td>First NREM period</td>
<td>NREM 1</td>
<td>First NREM period (minutes)</td>
</tr>
<tr>
<td>Index of Endogenous Periodicity</td>
<td>IEP</td>
<td>Ratio between REM 1 and NREM 1</td>
</tr>
</tbody>
</table>

Clinical Scales

For the assessment of clinical symptoms during the study and for the sample definition two psychiatric instruments were used: Positive and Negative Schizophrenia Scale (PANSS) for the differentiation of positive and negative subtypes of schizophrenia and the Hamilton Depression Scale (HAM-D) for the measurement of depressive symptoms.

Statistical Analysis

All statistical analyses were conducted using the R statistical language of computing [26] (Team et al. 2010). Initially, an analysis-of-variance (ANOVA) was conducted with the sleep variables as dependent
variables to identify differences between the diagnostic groups (healthy, schizophrenia, MDD). In case of significant main effects, post-hoc tests were conducted to specify group differences. In order to investigate the relationship between sleep polysomnographic parameters and clinical symptomatology a linear regression analysis was conducted with the sleep parameters as dependent variable. In the group of schizophrenic patients, PANSS positive and PANSS negative scores were used as predictor variables whereas HAMD scores were used as predictor variables in the MDD group. The relationship between age and parameters of polysomnogram was investigated using a linear regression with age as a predictor for parameters of polysomnogram, separately for every diagnostic group (schizophrenia, MDD, healthy controls).

**Results**

ANOVA indicated significant main effects of the factor group (schizophrenia, MDD, healthy controls) for the total sleep time, sleep latency, number of awakenings, the time of awakening after sleep onset, REM 1 latency, REM 1 and index of endogenous periodicity. In order to investigate those results in a more detailed way a post-hoc analysis was conducted (Table 2).

<table>
<thead>
<tr>
<th>Sleep Variables</th>
<th>Sleep Time</th>
<th>Sleep LAT</th>
<th>Number of awakenings</th>
<th>Slow Wave Sleep</th>
<th>REM 1 Latency</th>
<th>REM</th>
<th>REM 1</th>
<th>Index of endogenous Periodicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-value</td>
<td>51.884</td>
<td>0.0276</td>
<td>0.0001</td>
<td>0.1834</td>
<td>0.0252</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This analysis indicated significant differences between schizophrenic patients and healthy controls for the following sleep variables: total sleep time, sleep latency, number of awakenings, time of awakening after sleep onset, REM 1 latency, REM 1, index of endogenous periodicity. The group of subjects with MDD differed from the healthy control group regarding the following sleep variables: sleep latency, number of awakenings, the time of awakening after sleep onset, slow wave sleep, REM 1 latency, Non-REM 1 and index of endogenous periodicity. Non-schizophrenic patients differed from MDD patients with respect to the total sleep time, slow wave sleep, REM 1 latency, REM 1, Non-REM 1 and index of endogenous periodicity.

**Table 4: Regression analysis with PANSS positive and negative scores predicting different sleep variables in schizophrenic subjects.**

<table>
<thead>
<tr>
<th>Sleep variables</th>
<th>PANSS Positive</th>
<th>PANSS Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-value</td>
<td>0.017</td>
<td>0.003</td>
</tr>
<tr>
<td>P-value</td>
<td>0.960</td>
<td>0.945</td>
</tr>
</tbody>
</table>

In subjects with major depression, especially REM 1 latency and REM 1 showed a significant relationship to clinical symptomatology measured by HAMD scores (see Table 5). Interestingly, none of the sleep variables showed a significant relationship with clinical symptomatology in subjects with schizophrenia, measured by PANSS positive or PANSS negative score. This might suggest that sleep EEG abnormalities found in those patients represent general trait markers or a vulnerability factor that is not related to the current state of the disease (see Table 4).

**Table 5: Regression analysis with HAM-D scores predicting different sleep variables in depressed subjects.**

<table>
<thead>
<tr>
<th>Sleep variables</th>
<th>b</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sleep Time</td>
<td>0.036</td>
<td>0.719</td>
<td>0.472</td>
</tr>
<tr>
<td>Sleep LAT</td>
<td>0.042</td>
<td>0.710</td>
<td>0.477</td>
</tr>
<tr>
<td>Number of awakenings</td>
<td>-0.044</td>
<td>0.735</td>
<td>0.463</td>
</tr>
<tr>
<td>Slow Wave Sleep</td>
<td>0.042</td>
<td>0.720</td>
<td>0.468</td>
</tr>
<tr>
<td>REM 1 Latency</td>
<td>-0.044</td>
<td>0.735</td>
<td>0.463</td>
</tr>
<tr>
<td>REM</td>
<td>0.042</td>
<td>0.720</td>
<td>0.468</td>
</tr>
<tr>
<td>REM 1</td>
<td>-0.044</td>
<td>0.735</td>
<td>0.463</td>
</tr>
<tr>
<td>Index of endogenous Periodicity</td>
<td>0.042</td>
<td>0.720</td>
<td>0.468</td>
</tr>
</tbody>
</table>

The linear discriminate analysis (LDA) was conducted to investigate the usability of sleep EEG parameters as a tool to assist in differential diagnosis. With the use of sleep EEG parameters the overall diagnostic accuracy predicted by LDA was 88.78% (see Table 6).

**Table 6: Confusion matrix showing the prediction from linear discriminant analysis (LDA).**

<table>
<thead>
<tr>
<th>True diagnosis</th>
<th>LDA diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>26</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
</tr>
<tr>
<td>Healthy control</td>
<td>1</td>
</tr>
</tbody>
</table>

Sensitivity for patients with schizophrenia was 92.31%, for patients with MDD 92.86% and for healthy controls 80.56 %. The specificity for patients with schizophrenia was 90.62%, for MDD 92.86% and for healthy controls 98.15%. This suggests that sleep EEG parameters might be sufficiently reliable to serve in day-to-day clinical practice.
are characteristic features of schizophrenic patients regardless of either their medication status (drug-naive or previously treated) or the phase of the clinical course (acute or chronic). Regarding the sleep architecture, the majority of studies indicate that stage 4 NREM sleep and REM latency are reduced in schizophrenia, whereas REM sleep duration tends to remain unchanged [9].

Disturbed sleep can be found in 30-80% of schizophrenic patients, depending on the degree of psychotic symptomatology. Measured by polysomnography, reduced sleep efficiency and total sleep time, as well as increased sleep latency, are found in most patients with schizophrenia and appear to be an important part of the pathophysiology of this disorder. Some studies also reported alterations of stage 2 sleep, slow-wave sleep and REM sleep variables, i.e. reduced REM latency and REM density [9]. A number of sleep parameters, such as the amount of slow wave sleep and the REM latency are significantly correlated to clinical variables, including severity of illness, positive symptoms, negative symptoms, outcome, neurocognitive impairment and brain structure. There are no consistent effects of first-generation antipsychotics on measures of sleep continuity and sleep structure, including the percentage of sleep stages or sleep and REM latency in healthy controls. In contrast to first-generation antipsychotics, the atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone, ziprasidone and paliperidone) demonstrate a relatively consistent effect on measures of sleep continuity, with an increase in either total sleep time or sleep efficiency, and individually varying effects on other sleep parameters. On the other hand, withdrawal of such treatment is followed by a change in the sleep structure mainly in the opposite direction, indicating a deterioration of the quality of sleep. Specific sleep disorders, such as RLS (Restless Legs Syndrome), sleep-related breathing disorders, night-eating syndrome, somnambulism and rhythm disorders have been described as possible adverse effects of antipsychotics and should be considered in the differential diagnosis of disturbed or turbulent sleep in this population [10].

Delta wave deficits during sleep have also been observed in patients with schizophrenia. Decreased slow-wave sleep is reported to be associated with negative symptoms. Laterality of frontal cortex delta wave counts during all-night sleep was investigated by a computer analysis. Total delta wave counts were lower in patients with schizophrenia than in control subjects. Control subjects showed significantly higher delta wave counts in the right frontal cortex than in the left. This asymmetry was not observed in patients with schizophrenia. These findings suggest that reduced right frontal delta wave dominance is involved in the pathophysiology of schizophrenia [11].

The investigation of sleep in depression was
performed in a group of 60 samples divided into three subgroups: a) healthy, b) exogen (reactive, non-psychotic) and c) endogen (psychotic) depressives. 130 parameters (variables) of hypnograms were exposed to exact statistical testing. With 130 parameters (variables) of polysomnogram (PSG) discriminative models were formed (Discriminative Profile of Sleep - DPS). The dominant discriminative factor in reactive non-psychotic depression was the increased number of nocturnal awakenings (NAW) - hypnogramic enoxigenic depression. The transition in endogenic psychotic depression was characterized by the following: shortening of REM-latency, reduction of delta-sleep and increase in the Index of Endogenic Periodicity/Perturbation (IEP = REM 1/ NREM 1)- hypnodisrrhythmic endogenic depression [6]. These models contribute not only to the problem of correct differential diagnosis, but also to the accurate choice of therapy depending on the course (evolution, de-evolution) of the illness and to the appraisal of therapeutic sensitivity-insensitivity and affectivity of pharmacotherapy.

Riemann et al., 2001 [37] has demonstrated in his original clinical study that in depression, besides disturbances of sleep continuity, polysomnograms are characterized by a reduction of slow wave sleep, a shortening of REM latency, prolongation of the first REM period and increased REM density. These results correspond mostly to the results of our research and support our thesis about the neurophysiologic and clinical importance of alterations of the REM/NREM ratio by psychiatric disorders.

As a conclusion, the presented results confirm previous reports of substantial abnormalities in the sleep architecture as measured by EEG in patients with depression and schizophrenia. Depression and schizophrenia show different patterns of changes in sleep variables. Most importantly, the discriminate analysis provided a correct diagnosis in 88% suggesting a potential role of sleep EEG measurements (polysomnography) for the clinical diagnostic routine and for more targeted pharmacotherapy. Some parameters (variables) of polysomnograms show significant differences when measuring sleep in patients with schizophrenia and sleep in patients with depression. The Index of Endogenous Periodicity (IEP = REM 1/ NREM 1) could be a state marker for affective versus schizophrenia spectrum disorders. This index makes the sleep test very economical – the nocturnal sleep registration can be shortened to 1.5 hour (the first REM/NREM cycles).

Acknowledgement

The authors would like to thank Nemanja Nestorovic and Veselinka Kijanovic for their technical contribution in sleep registration (PSG).

References

in schizophrenia. Arch Gen Psychiatry. 1991; 48: 348–56.


