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Clinical Science

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

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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 processes 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.

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

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 (HAMD) 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 indentify 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 2: ANOVA results with main effects of diagnosis (healthy, schizophrenia, depression) for different sleep parameters.

Sleep Variables	F-value	p-value
Total Sleep Time	78.455	0.0063
Sleep Latency	217.759	<0.0001
Number of Awakenings	334.386	<0.0001
Waking Time after Sleep Onset	768.521	<0.0001
Slow wave Sleep	18.292	0.1797
REM 1 Latency	58.972	0.0172
REM	33.024	0.0726
REM 1	189.857	<0.0001
Non-REM 1	17.977	0.1834
Index of endogenous Periodicity	51.884	0.0252

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

Table 3: Post-hoc t-test investigating sleep variable differences between diagnostic groups.

	Schizophrenia vs Controls			Depression vs Controls			Schizophrenia vs Depression		
Sleep Variables	t	df	p	t	df	p	t	df	p
Total Sleep Time	-3,148	57,23	0,003	1,727	55,91	0,090	-4,503	57,64	<0,001
Sleep Latency	4,150	37,16	<0,001	7,370	57,92	<0,001	0,387	37,73	0,701
Number of Awakenings	5,851	55,78	<0,001	6,725	57,80	<0,001	0,000	54,48	1,000
Waking Time after Sleep Onset	10,059	36,26	<0,001	9,793	38,34	<0,001	1,058	57,03	0,294
Slow wave Sleep	1,732	55,14	0,089	-8,204	55,06	<0,001	8,902	48,75	<0,001
REM 1 Latency	-2,861	54,35	0,006	2,222	51,60	0,031	-4,423	57,39	<0,001
REM	-1,772	57,79	0,082	0,727	57,45	0,470	-2,553	56,61	0,013
REM 1	-4,511	53,36	<0,001	0,554	57,12	0,582	-4,776	56,22	<0,001
Non-REM 1	1,718	55,19	0,092	-8,204	55,06	<0,001	8,898	48,81	<0,001
Index of endogenous Periodicity	-4,385	54,52	<0,001	6,903	42,58	<0,001	-9,485	49,59	<0,001

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. Schizophrenic patients differed from MDD patients with respect to the total sleep time, slow wave sleep, REM 1 latency, REM, 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.

	PANSS Positive			PANSS Negative		
Sleep variables	B	t	p	b	t	p
Total Sleep Time	0,178	0,272	0,787	0,814	0,949	0,351
Sleep Latency	0,200	0,454	0,653	-0,318	-0,542	0,592
Number of Awakenings	-0,348	-0,547	0,589	-0,143	-0,167	0,868
Waking Time after Sleep Onset	-0,591	-0,862	0,396	-0,837	-0,918	0,366
Slow wave Sleep	-0,671	-0,992	0,330	-0,279	-0,305	0,763
REM 1 Latency	-0,220	-0,346	0,732	0,746	0,889	0,382
REM	0,877	1,612	0,118	-0,153	-0,203	0,841
REM 1	-0,035	-0,059	0,953	-0,328	-0,418	0,679
Non-REM 1	-0,652	-0,962	0,344	-0,280	-0,305	0,762
Index of endogenous Periodicity	1,213	0,467	0,644	-1,651	-0,477	0,637

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.

Sleep variables	b	t	p
Total Sleep Time	0,397	0,714	0,481
Sleep Latency	1,221	1,196	0,242
Number of Awakenings	-0,217	-0,283	0,779
Waking Time after Sleep Onset	0,385	0,526	0,603
Slow wave Sleep	1,342	1,360	0,185
REM 1 Latency	1,032	2,069	0,048
REM	-0,232	-0,376	0,710
REM 1	2,166	4,217	<0.001
Non-REM 1	1,340	1,360	0,185
Index of endogenous Periodicity	1,049	0,676	0,505

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).

	Diagnose as detected by LDA		
True diagnose	schizophrenia	depression	healthy control
schizophrenia	25	1	4
depression	2	26	2
healthy control	0	1	29

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.

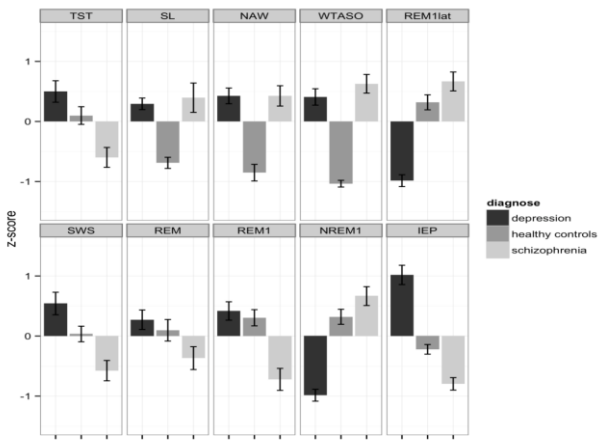

Figure 1: Barplot indicating mean z-scores of different sleep variables for schizophrenic subjects, depressed subjects and healthy controls. Error-bars indicate 95%-confidence intervals. TST (total sleep time), SL (sleep latency), NAW (number of awakenings), WTASO (waking time after sleep onset), REM1lat (REM 1 latency), SWS (slow wave sleep), NREM 1 (Non-REM 1), IEP (index of endogenous periodicity).

Discussion

In the present study we provide evidence for sleep disturbances in patients with MDD and schizophrenia as measured by EEG during sleep. Several parameters showed significant alterations in the patients' groups as compared to healthy controls. Among all sleep parameters the changes in the IEP index differed to the largest extent between the two psychiatric populations showing an increase in MDD patients and a decrease in patients with schizophrenia. Thus IEP might have the strongest discriminative potential to separate patients with schizophrenia and patients with MDD. Most interestingly, owing to the linear discriminate analysis, the correct diagnose could be detected (schizophrenia, depression or healthy) in 88%. Thus parameters derived from sleep EEG measurements provide biomarkers that might support the diagnostic process.

However, it needs to be noted that there are some limitations to the presented analysis. Firstly, the presented results are derived from a sample of moderate size. Even though there is substantial support for the reported findings by previous studies [7, 9-13, 28], further investigations with larger samples are needed to confirm our observations. Also, there are some potential covariates that might have deluded the presented effects. Importantly, multiple studies report that antidepressants [29-32] or antipsychotic medication [33] have some effect on sleep variables measured by EEG. Also other environmental factors such as the smoking status [34], alcohol abuse [35] or cannabis abuse [36] might represent potential confounding factors for EEG measurements.

Sleep-onset and sleep-maintenance insomnia 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) exogenic (reactive, non-psychotic) and c) endogenic (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) - hypnofragmentic exogenic 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).

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References

1. Miret M, Ayuso-Mateos JL, Sanchez-Moreno J, Vieta E: Depressive disorders and suicide: Epidemiology, risk factors, and burden. Neurosci Biobehav Rev. 2013.
2. Rössler W, Salize HJ, Van Os J, Riecher-Rössler A: Size of burden of schizophrenia and psychotic disorders. Eur Neuropsychopharmacol. 2005; 15: 399–409.
3. Benca RM, Obermeyer WH, Thisted RA, Gillin JC: Sleep and psychiatric disorders. A meta-analysis. Arch Gen Psychiatry. 1992; 49: 651–68.
4. Tsuno N, Besset A, Ritchie K: Sleep and depression. J Clin Psychiatry. 2005; 66: 1254–69.
5. Steiger A, Kimura M: Wake and sleep EEG provide biomarkers in depression. J Psychiatr Res. 2010; 44: 242–52.
6. Ilankovic N, Marinkovic D, Bugarski D, Ignjatovic M: Models of exogenous and endogenous sleep perturbation as diagnostic and therapeutic predictors in depression. Methods Find Exp Clin Pharmacol. 1986; 8: 513–17.
7. Chouinard S, Poulin J, Stip E, Godbout R: Sleep in untreated patients with schizophrenia: a meta-analysis. Schizophr Bull. 2004; 30: 957–67.
8. Benson KL, Faull KF, Zarcone VP Jr: Evidence for the role of serotonin in the regulation of slow wave sleep in schizophrenia. Sleep. 1991; 14: 133–39.
9. Benson KL, Sullivan EV, Lim KO, Lauriello J, Zarcone VP Jr, Pfefferbaum A: Slow wave sleep and computed tomographic measures of brain morphology in schizophrenia. Psychiatry Res. 1996; 60: 125–34.
10. Keshavan MS, Reynolds III CF, Miewald JM, Montrose DM, Sweeney JA, Vasko Jr RC, Kupfer DJ: Delta sleep deficits in schizophrenia: evidence from automated analyses of sleep data. Arch Gen Psychiatry. 1998; 55: 443.
11. Sarkar S, Katshu MZUH, Nizamie SH, Praharaj SK: Slow wave sleep deficits as a trait marker in patients with schizophrenia. Schizophr Res. 2010; 124: 127–33.
12. Ganguli R, Reynolds CF, Kupfer DJ: Electroencephalographic sleep in young, never-medicated schizophrenics. A comparison with delusional and nondelusional depressives and with healthy controls. Arch Gen Psychiatry. 1987; 44: 36–44.
13. Poulin J, Daoust AM, Forest G, Stip E, Godbout R: Sleep architecture and its clinical correlates in first episode and neuroleptic-naive patients with schizophrenia. Schizophr Res. 2003; 62: 147–53.
14. Gaillard JM, Iorio G, Campajola P, Kemali D: Temporal organization of sleep in schizophrenics and patients with obsessive-compulsive disorder. Advances in biological psychiatry. 1984; 15: 76-83.
15. Jus K, Bouchard M, Jus AK, Villeneuve A, Lachance R: Sleep EEG studies in untreated, long-term schizophrenic patients. Arch Gen Psychiatry. 1973; 29: 386–90.
16. Kempenaers C, Kerkhofs M, Linkowski P, Mendlewicz J: Sleep EEG variables in young schizophrenic and depressive patients. Biol Psychiatry. 1988; 24: 833–38.
17. Nishino S, Mignot E, Benson KL, Zarcone VP Jr:. Cerebrospinal fluid prostaglandins and corticotropin releasing factor in schizophrenics and controls: relationship to sleep architecture. Psychiatry Res. 1998; 78: 141–50.
18. Riemann D, Kammerer J, Löw H, Schmidt MH: Sleep in adolescents with primary major depression and schizophrenia: a pilot study. J Child Psychol Psychiatry. 1995; 36: 313–26.
19. Van Cauter E, Linkowski P, Kerkhofs M, Hubain P, L'Hermite-Balériaux M, Leclercq R, Brasseur M, Copinschi G,

Mendlewicz J: Circadian and sleep-related endocrine rhythms in schizophrenia. Arch Gen Psychiatry. 1991; 48: 348–56.

20. Tandon R, Lewis C, Taylor SF, Shipley JE, DeQuardo JR, Jibson M, Goldman M: Relationship between DST nonsuppression and shortened REM latency in schizophrenia. Biol Psychiatry. 1996; 40: 660–63.

21. Yang C, Winkelman JW: Clinical significance of sleep EEG abnormalities in chronic schizophrenia. Schizophr Res. 2006; 82: 251–60.

22. Pillai V, Kalmbach DA, Ciesla JA: A meta-analysis of electroencephalographic sleep in depression: evidence for genetic biomarkers. Biol Psychiatry. 2011; 70: 912–919.

23. Friess E, Modell S, Brunner H, Tagaya H, Lauer CJ, Holsboer F, Ising M: The Munich vulnerability study on affective disorders: microstructure of sleep in high-risk subjects. Eur Arch Psychiatry Clin Neurosci. 2008; 258: 285–91.

24. Modell S, Ising M, Holsboer F, Lauer CJ: The Munich Vulnerability Study on Affective Disorders: stability of polysomnographic findings over time. Biol Psychiatry. 2002; 52: 430–37.

25. Modell S, Ising M, Holsboer F, Lauer CJ: The Munich vulnerability study on affective disorders: premorbid polysomnographic profile of affected high-risk probands. Biol Psychiatry. 2005; 58, 694–699.

26. Team R et al: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna: Austria, 2010.

27. World Health Organisation. ICD-10 Classifications of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic Guidelines. W H O. http://www.who.int/classifications/icd/en/

28. Kupfer DJ, Reynolds III CF: Sleep and psychiatric disorders: a meta-analysis. Arch Gen Psychiatry. 1992; 49: 669.

29. Haro R., Drucker-Colín R: Effects of long-term administration of nicotine and fluoxetine on sleep in depressed patients. Arch Med Res. 2004; 35: 499–506.

30. Jobert M, Jähnig P, Schulz H: Effect of two antidepressant drugs on REM sleep and EMG activity during sleep. Neuropsychobiology. 1999; 39: 101–109.

31. Riemann D, Velthaus S, Laubenthal S, Müller WE, Berger M: REM-suppressing effects of amitriptyline and amitriptyline-N-oxide after acute medication in healthy volunteers: results of two uncontrolled pilot trials. Pharmacopsychiatry. 1990; 23: 253–58.

32. Landsness EC, Goldstein MR, Peterson MJ, Tononi G, Benca RM: Antidepressant Effects of Selective Slow Wave Sleep Deprivation in Major Depression: A High-Density EEG Investigation. J Psychiatr Res. 2011; 45: 1019–26.

33. Cohrs S: Sleep disturbances in patients with schizophrenia: impact and effect of antipsychotics. CNS Drugs. 2008; 22: 939–62.

34. Zhang L, Samet J, Caffo B, Bankman I, Punjabi NM: Power spectral analysis of EEG activity during sleep in cigarette smokers. Chest. 2008; 133: 427–32.

35. Tarokh L, Van Reen E, Acebo C, LeBourgeois M, Seifer R, Fallone G, Carskadon MA: Adolescence and parental history of alcoholism: insights from the sleep EEG. Alcohol Clin Exp Res. 2012; 36: 1530–41.

36. Nicholson AN, Turner C, Stone BM, Robson PJ: Effect of Delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. J Clin Psychopharmacol. 2004; 24: 305–13.

37. Riemann D, Berger M, Voderholzer U: Sleep and depression--results from psychobiological studies: an overview. Biol Psychol. 2001;57(1-3):67-103.