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POLYSOMNOGRAPHIC SLEEP PATTERNS IN DEPRESSIVE, SCHIZOPHRENIC AND HEALTHY SUBJECTS

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SUMMARY

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

Subjects and methods: *Thirty (30) patients with schizophrenia, 30 patients with major depression and 30 healthy control subjects were investigated in the present study. All subjects underwent PSG measurements for a minimum time of 8 hours according to the criteria of Rechtscahffen & Kales (1968). We tested the potential of multiple sleep variables to predict diagnosis in different groups by using linear discriminant analysis (LDA).*

Results: *There were significant differences in 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 PSG changes in patients with major depressive disorder and in patients with schizophrenia. Our results underline the potential of PSG measurements to facilitate diagnostic processes.*

Key words: *sleep - polysomnography - schizophrenia – depression - biological markers*

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INTRODUCTION

Schizophrenia and major depressive disorder (MDD) both reside among the most frequent psychiatric disorders and are associated with substantial global disease burden (Miret et al. 2013, Rössler et al. 2005). The reliable diagnosis is crucial to provide efficient treatment strategies for patients. However, until today diagnostic processes largely rely on clinical evaluation and reliable biomarkers have not yet been identified. It has been suggested that there is substantial overlap in 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 the disease in MDD and schizophrenia (Benca et al. 1992, Tsuno et al. 2005). In some cases this can lead to low reliability of established diagnostic procedures. Therefore, EEG measurements could provide an important tool to detect biomarkers (Steiger & Kimura 2010) in order to investigate sleep architecture before treatment and during the course of the disease.

Polysomnography 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, the sleep latency, total sleep time, total awake time, REM sleep latency and the percentage of REM sleep. It has been suggested (Ilankovic et al. 1986) 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 of in patients with major depression (Ilankovic et al. 1986).

Numerous abnormalities have been reported in schizophrenia, measured by polysomnography (PSG) and particularly during REM phases. The significant changes in sleep latency, total sleep time and sleep efficiency index have been reported in patients with schizophrenia compared to healthy controls in a recent meta-analysis of sleep variables (Chouinard et al. 2004). Additionally, some studies reported changes in total awake time (Benson et al. 1991, 1996, Keshavan et al. 1998), slow-wave sleep (Sarkar et al. 2010) and rapid-eye-movement latency (REML) (Benson et al. 1991, Ganguli et al. 1987). Moreover, REM percentage of total sleep time (Chouinard et al. 2004, Poulin et al. 2003) seem to be abnormal in those patients, but not all studies confirmed these findings (Gaillard et al. 1984, Ganguli et al. 1987, Jus et al. 1973, Kempenaers et al. 1988, Keshavan et al. 1998, Nishino et al. 1998, Poulin

et al. 2003, Riemann et al. 1995, Van Cauter et al. 1991). It has also been reported that severity of clinical symptoms is related to EEG disturbances during sleep (Poulin et al. 2003, Tandon et al. 1996, Yang & Winkelman 2006).

Similarly to patients with schizophrenia, subjects with depression show abnormal sleep architecture – especially during REM sleep periods (Steiger & Kimura 2010). 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 (Pillai et al. 2011). These abnormalities have been related to the severity of clinical symptoms (Pillai et al. 2011). Finally, it has also been suggested that abnormal sleep architecture might represent a vulnerability factor for affective disorders (Friess et al. 2008, Modell et al. 2002, 2005).

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 the identification of 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. More specifically, we expected the polysomnograms by shizofrenic, depressive, and health control subject to show significant differences in sleep structure and sleep architecture. In addition, it was expected that the variables of nocturnal sleep (polysomnogram) would facilitate the diagnostic process by being able to predict the diagnoses of schizophreania and major depression.

SUBJECTS AND METHODS

We tested 30 patients with MDD, 30 patients with schizophrenia and 30 healthy controls. The mean age in schizophrenia group was 36.73 (SD 6.43), in group with depression 40.77 (SD 7.66), and in healthy control 34.40 (SD 5.70). The gender distribution was: male 18, female 12 in schizophrenia group; in depression group male 11, female 19; in control group male 16, and female 14. All patients were diagnosed by an experienced clinical psychiatrist and fulfilled ICD-10 criteria (World Health Organisation, n.d.) for either major depression (F32.2) or schizophrenia (F20). The exclusion criteria for all the subjects were the following: presence of neurological 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 Ethics Committee of the University of Belgrade.

All subjects underwent 16-channel EEG recording for 24 hours using the Oxford Medilog 9000 ambulatory EEG system plus 2 chanel EOG (electrooculogram), 1 chanel EMG (electromiogram) and 1 chanel EKG (electrocardiogram). Analysis was restricted to an 8 hours period from 10 p.m. until 6 a.m. For 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.

Regarding the assessment of clinical symptoms, two psychiatric instruments were used: Positive and Negative Schizophrenia Scale (PANSS) for the differentiation of positive and negative subtype of schizophrenia, and Hamilton Depression Scale (HAMD) for the measurement of depressive symptoms.

Statistical Analysis

All statistical analysis was conducted using the R statistical language of computing (Team et al. 2010). Initially, analysis-of-variance (ANOVA) was conducted with the sleep variables as dependent variable to indentify differences between the diagnostic groups (healthy, schizophrenia, MDD). In case of significant main effects, post-hoc test were conducted to specify group differences. In order to investigate the relationship between sleep polysomnographic parameters and clinical symptomatology linear regression analysis was conducted with the sleep parameters as dependent variable.

Table 1. Sleep variables used in this study

Sleep variable	Acronym	Definition
Sleep latency	SL	From lights off to consecutive 10 minutes of stage 2, 3 or 4 (minutes)
Total sleep time	TST	Minutes of sleep during recording of sleep
Waking Time after Sleep Onset	WTASO or TAT	Waking Time after Sleep Onset (minutes)
Number of Awakening	NAW	Number of Awakening through 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 first epoch of 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

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) (Table 1).

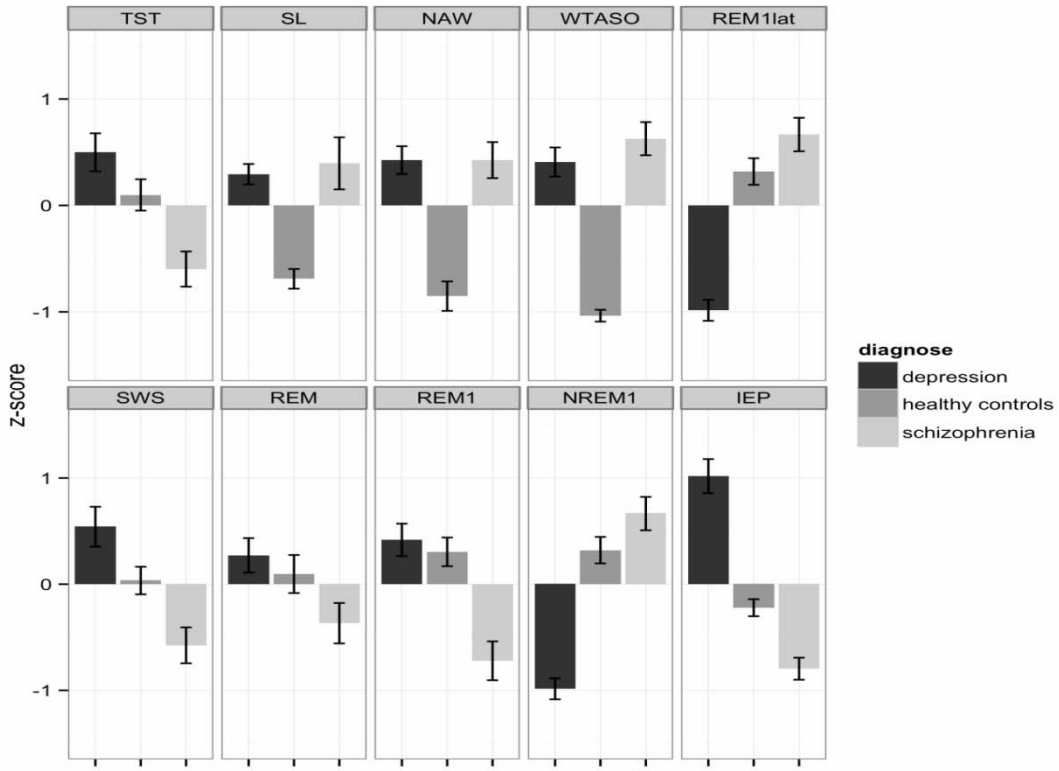
RESULTS

The ANOVA indicated significant main-effects of the factor group (schizophrenia, MDD, healthy controls) for the total sleep time, sleep latency, number of awakenings, 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 post-hoc analysis was conducted. This indicated significant differences between schizophrenic patients and healthy controls for the following sleep variables: the 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 the subjects with MDD differed from the healthy control group regarding the following sleep variables: sleep latency, number of awakenings, 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 2. Results of the ANOVA with the main effect 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 Periodicitiy	51.884	0.0252

In subjects with major depression, especially REM 1 latency and REM 1 showed significant relationship to clinical symptomatology measured by HAMD scores (see Table 6). Interestingly, none of the sleep variables showed a significant relationship with clinical symptomatology in subjects with schizophrenia, measured by



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

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

PANSS positive or PANSS negative score. This might suggest that sleep EEG abnormalities found in those patients represent a general trait markers or a vulnerability factor that is not related to the current state of the disease (see Table 5).

Linear discriminant analysis (LDA) was conducted to investigate the usability of sleep EEG parameters as a tool to assist differential diagnosis. Using sleep EEG parameters the overall diagnostic accuracy predicted by LDA was 88.78% (see Table 7). 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 have a sufficient reliability to serve in day-to-day clinical practice (Figure 1, Table 2-7).

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

Sleep Variables	Schizophrenia vs Controls			Depression vs Controls			Schizophrenia vs Depression		
	t	df	p	t	df	p	t	df	p
Total Sleep Time	-3.148	57.233	0.003	1.727	55.917	0.090	-4.503	57.640	<0.001
Sleep Latency	4.150	37.162	<0.001	7.370	57.926	<0.001	0.387	37.738	0.701
Number of Awakenings	5.851	55.787	<0.001	6.725	57.807	<0.001	0.000	54.484	1.000
Waking Time after Sleep Onset	10.059	36.266	<0.001	9.793	38.344	<0.001	1.058	57.030	0.294
Slow wave Sleep	1.732	55.148	0.089	-8.204	55.065	<0.001	8.902	48.756	<0.001
REM 1 Latency	-2.861	54.351	0.006	2.222	51.601	0.031	-4.423	57.399	<0.001
REM	-1.772	57.792	0.082	0.727	57.456	0.470	-2.553	56.615	0.013
REM 1	-4.511	53.361	<0.001	0.554	57.126	0.582	-4.776	56.226	<0.001
Non-REM 1	1.718	55.197	0.092	-8.204	55.065	<0.001	8.898	48.819	<0.001
Index of endogenous Periodicitiy	-4.385	54.520	<0.001	6.903	42.582	<0.001	-9.485	49.595	<0.001

Table 4. Regression analysis with age predicting different sleep variables separately in schizophrenic, depressed and healthy subjects

Sleep variables	Schizophrenia			Depression			Controls		
	b	t	p	b	t	p	b	t	p
Total Sleep Time	0.198	0.148	0.884	-3.558	-2.708	0.011	0.572	0.430	0.670
Sleep Latency	-0.961	-1.081	0.289	0.428	0.156	0.877	1.410	0.670	0.508
Number of Awakenings	1.233	0.956	0.347	1.253	0.623	0.538	1.427	1.022	0.316
Waking Time after Sleep Onset	0.773	0.546	0.590	-0.073	-0.038	0.970	1.835	0.521	0.606
Slow wave Sleep	-0.052	-0.037	0.971	1.627	0.611	0.546	2.088	1.368	0.182
REM 1 Latency	0.254	0.194	0.847	-3.223	-2.539	0.017	-1.294	-0.866	0.394
REM	-0.075	-0.064	0.949	-2.043	-1.295	0.206	0.277	0.253	0.802
REM 1	0.633	0.525	0.603	-0.467	-0.271	0.788	0.533	0.367	0.716
Non-REM 1	-0.046	-0.033	0.974	1.624	0.611	0.546	2.085	1.368	0.182
Index of endogenous Periodicitiy	2.789	0.524	0.604	-2.039	-0.498	0.622	-5.028	-0.829	0.414

Table 5. Regression analysis with PANSS positive and negative scores predicting different sleep variables in schizophrenic patients

Sleep variables	PANSS Positive			PANSS Negative		
	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 Periodicitiy	1.213	0.467	0.644	-1.651	-0.477	0.637

Table 6. 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 Periodicitiy	1.049	0.676	0.505

Table 7. Confusion matrix showing predictions based on the linear discriminant analysis (LDA)

	Diagnosis as detected by LDA		
True diagnosis	Schizophrenia	Depression	Healthy control
Schizophrenia	25	1	4
Depression	2	26	2
Healthy control	0	1	29

DISCUSSION

In the present study we provide evidence for sleep disturbances in patients with MDD and schizophrenia measured by EEG during sleep. Several parameters showed significant alterations in the patient 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 strongest discriminative potential to separate patients with schizophrenia and patients with MDD. Most interestingly, linear discriminant analysis was able to detect the correct diagnosis (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. First the presented results are derived from a sample of moderate size. Even though there is substantial support for the reported findings by previous studies (Benson et al. 1991, 1996, Chouinard et al. 2004, Ganguli et al. 1987, Keshavan et al. 1998, Kupfer & Reynolds 1992, Poulin et al. 2003, Sarkar et al. 2010), further investigations in 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 effect of antidepressants (Haro & Drucker-Colín 2004, Jobert et al. 1999, Landsness et al. 2011, Riemann et al. 1990) or antipsychotic medication (Cohrs 2008) on sleep variables measured by EEG. Also other environmental factors such as smoking status (Zhang et al. 2008), alcohol abuse alcohol (Tarokh et al. 2012) or cannabis (Nicholson et al. 2004) might represent potential confounds to EEG measurements.

Sleep-onset and maintenance insomnia is a characteristic feature 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 sleep architecture, the majority of studies indicate that stage 4 sleep and REM latency are reduced in schizophrenia, whereas REM sleep duration tends to remain unchanged (Benson et al. 1996).

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 (Benson et al. 1996). 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 sleep structure mainly in the opposite direction, indicating a deterioration of sleep quality. 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 (Keshavan et al. 1998).

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 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 (Sarkar et al. 2011)

With polysomnography and characteristic sleep patterns it is posssible to establish differences between psychiatric disorders. The specific alterations in sleep architecture are the basis for choosing adequate pharmacotherapy for the normalization of sleep parameters („Schloss-Schlüssel-Prinzips“) (Saletu & Saletu-Zyhlarz 2001, Saletu-Zyhlarz et al. 2013). Saletu et al (2013) point out that the past two decades have witnessed substantial progress in methodology and knowledge in sleep research all over the world. They emphasize a European project (SIESTA) focusing on the creation of an automatic sleep classification system and a normative database, including polysomnographic (PSG) and psychometric measures, in order to make it possible to diagnose sleep-disordered patients in correlation with mental illnesses and compared with age- and sex-matched healthy controls.

CONCLUSIONS

The presented results confirm previous reports of substantial abnormalities in 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 discriminant analysis provided correct diagnosis in 88% suggesting a potential role of sleep EEG measurements (polysomnography, PSG) for clinical diagnostic routine and for more targeted pharmacotherapy. The Index of Endogenous Periodicity (IEP) could be a state marker for affective versus schizophrenia spectrum disorders. The shortened variant of PSG (the first NREM/REM cycles in the night sleep), after further research, could be indicated in patients with depression and schizophrenia routinely, in a day-to-day work, to facilitate the differential diagnosis of these mental disorders.

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References

1. *Benca RM, Obermeyer WH, Thisted RA, Gillin JC: Sleep and psychiatric disorders. A meta-analysis. Arch Gen Psychiatry 1992; 49:651–68.*
2. *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.*
3. *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.*
4. *Chouinard S, Poulin J, Stip E, Godbout R: Sleep in untreated patients with schizophrenia: a meta-analysis. Schizophr Bull 2004; 30:957–67.*
5. *Cohrs S: Sleep disturbances in patients with schizophrenia: impact and effect of antipsychotics. CNS Drugs 2008; 22:939–62.*
6. *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.*
7. *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.*
8. *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.*
9. *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.*
10. *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.*
11. *Jobert M, Jähnig P, Schulz H: Effect of two antidepressant drugs on REM sleep and EMG activity during sleep. Neuropsychobiology 1999; 39:101–109.*
12. *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.*
13. *Kempenaers C, Kerkhofs M, Linkowski P, Mendlewicz J: Sleep EEG variables in young schizophrenic and depressive patients. Biol Psychiatry 1988; 24:833–38.*
14. *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.*

15. Kupfer DJ, Reynolds III CF: Sleep and psychiatric disorders: a meta-analysis. Arch Gen Psychiatry 1992; 49:669.
16. 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.
17. Miret M, Ayuso-Mateos JL, Sanchez-Moreno J, Vieta E: Depressive disorders and suicide: Epidemiology, risk factors, and burden. Neurosci Biobehav Rev 2013; 37: 2372-4.
18. 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.
19. 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.
20. 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.
21. 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.
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. 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.
24. 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.
25. 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.
26. Rössler W, Salize HJ, Van Os J, Riecher-Rössler A: Size of burden of schizophrenia and psychotic disorders. Eur Neuropsychopharmacol 2005; 15:399–409.
27. Saletu B, Saletu-Zyhlarz GM: Was Sie schon immer über Schlaf wissen wollten. Ueberreuter, Wien, 2001.
28. Saletu-Zyhlarz GM, Anderer A, Saletu B: Sleep disorders in psychiatry and their treatment (Schlafstoerungen in der Psychiatrie and therapeutische Massnahmen). Psychiatr Danub 2013; 25:447-452.
29. Saletu B, Anderer P, Saletu-Zyhlarz GM: Recent advances in sleep research (Neue Erkenntnise in der Schlafforschung). Psychiatr Danub 2013; 25:426-434
30. 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.
31. Steiger A, Kimura M: Wake and sleep EEG provide biomarkers in depression. J Psychiatr Res 2010; 44:242–52.
32. 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.
33. 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.
34. Team R et al: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, 2010.
35. Tsuno N, Besset A, Ritchie K: Sleep and depression. J Clin Psychiatry 2005; 66:1254–69.
36. 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.
37. World Health Organisation: ICD-10 Classifications of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic Guidelines. http://www.who.int/classifications/icd/en/
38. Yang C, Winkelman JW: Clinical significance of sleep EEG abnormalities in chronic schizophrenia. Schizophr Res 2006; 82:251–60.
39. 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.

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