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ORIGINAL PAPER

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Sleep in obsessive compulsive disorder

Polysomnographic studies under baseline conditions and after experimentally induced serotonin deficiency

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Abstract Several lines of evidence suggest that brain serotonergic systems may be disturbed in obsessive compulsive disorder (OCD). The serotonergic system strongly affects sleep and characteristic abnormalities of sleep are documented in depression. This study, therefore, aimed to investigate sleep structure of OCD patients in order to evaluate whether similar changes as in depression are present. Up to now, this issue has been addressed only in few studies with small numbers of patients. Sleep patterns of 62 unmedicated patients with primary OCD and 62 age- and sex-matched healthy controls were investigated by polysomnography. Additionally, the impact of tryptophan depletion on sleep was studied in a subgroup of 12 OCD patients and 12 controls. The OCD patients exhibited moderate, but significant disturbances of sleep continuity measures but no abnormalities of slow wave sleep or REM sleep, except a significant elevation of 1st REM density. Tryptophan depletion induced a worsening of sleep continuity, but no changes of REM sleep or slow wave sleep. Assuming that changes of sleep architecture indicate underlying neurobiological abnormalities, this study indicates that neurobiological disturbances are different in primary OCD as compared with primary depression.

Key words obsessive-compulsive disorder · polysomnography · sleep · tryptophan depletion test · serotonin · treatment

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Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurrent obsessive thoughts, images, or impulses that evoke anxiety and compulsive behaviors (e.g., handwashing) or mental acts (e.g., ritualistic praying) aimed at decreasing discomfort. The lifetime prevalence is comparatively high at 2–3% of the population [1, 2]. Both pharmacotherapy with serotonin reuptake inhibitors and cognitive behavioural treatment with exposure have been shown to reduce symptoms in short-term studies and in long-term follow up investigations [2–5]. There is a large body of evidence that neurobiological factors play an important role in the pathophysiology of OCD. Currently, a disturbance of fronto-striato-thalamocortical circuits is discussed as the main abnormality [6], a hypothesis which is also supported by neuropsychological findings [see 7 for overview, 8]. But a disturbance of serotonergic neurotransmission is discussed as well. The latter hypothesis is mainly based on the selective therapeutic efficacy of serotonin (5-HT) reuptake inhibitors [9, 10]. Furthermore, several studies demonstrated an exacerbation of obsessive-compulsive (OC) symptoms after the 5-HT agonist metachlorophenylpiperazine (m-CPP) in patients with OCD [11–13]. The observation that additional treat-

ment with the 5-HT antagonist metergolin worsens symptoms in OCD patients being improved with clomipramine further supports the role of the serotonergic system for OCD [14]. Recently, Kang et al. [15] found that treatment with serotonin reuptake inhibitors normalized glucose metabolic rates in basal ganglia, which correlated with improvements of specific neuropsychological functions, that are known to be disturbed in OCD [7, 8]. Further support for a serotonin deficit comes from a recent study with single photon emission tomography (SPECT) demonstrating reduced serotonin transporter availability [16].

On the other hand, other findings do not support the hypothesis that the serotonergic system is alterated in OCD. For example, cerebrospinal fluid levels of 5-hydroxy-indol acetic acid (5-HIAA), a metabolite of 5-HT, have not been found to be reliably different in OCD patients compared with controls [17, see 18 for overview]. Furthermore, tryptophan depletion, which lowers central nervous system 5-HT transmission, did not induce an exacerbation of OC symptoms in two studies [19, 20], whereas about 50–60% of recovered, formerly depressed patients treated with serotonin reuptake inhibitors exhibit a reoccurrence of depressive symptoms after tryptophan depletion [see 21 for overview].

It is, therefore, questionable, whether OCD patients exhibit alterations of the serotonergic system that contribute to the pathophysiology of the disorder.

One paradigm to investigate central nervous 5-HT activity is sleep, since the cyclic alternating pattern of rapid eye movement (REM) sleep and non-REM sleep is strongly influenced by the 5-HT system [22]. The significance of 5-HT for sleep in humans was also underlined by studies investigating the impact of tryptophan depletion on sleep. For example, Bhatti et al. [23] demonstrated a shortening of REM latency following tryptophan depletion in depressive patients and in healthy subjects. Other groups found slight but significant alterations of non-REM sleep such as a decrease of non-REM stage 2 and an increase of wake periods in healthy human subjects [24, 25]. Similar changes were also observed in insomniac patients [26]. These findings fit well with the role of 5-HT in sleep and especially with its role for the cyclically alternating pattern of Non-REM sleep and REM sleep. In this model a further decrease of serotonergic activity would result in REM sleep disinhibition.

Changes of the sleep structure have been extensively studied in depressive disorders [see 27, 28, for reviews]. It has been consistently demonstrated that depressive patients exhibit disturbances of both REM sleep and non-REM sleep. These abnormalities have been interpreted in terms of an imbalance between cholinergic and aminergic, i.e. noradrenergic and serotonergic activity [28]. In this view a relatively decreased 5-HT neurotransmission should be one contributing factor explaining the sleep abnormalities in depression.

Comparatively few studies up to now dealt with sleep in OCD. Whereas Insel et al. [29] demonstrated similar changes of sleep in OCD as compared with depressive patients, later studies by Walsleben et al. [30] and an own study in 22 patients [31], which was the largest at that time, did not replicate the earlier findings of Insel et al. [29]. Neither a recent study by Robinson et al. [32] was in accord with the initial findings of Insel et al. [29]. However, the conflicting results might have been caused by the comparatively small samples in the previous studies and many factors might have contributed to heterogeneity of the study samples. Therefore, no definite conclusion can be drawn from the previous studies.

It was therefore the aim of this investigation to study a large group of unmedicated patients with OCD to clarify whether this clinical condition is associated with abnormalities of sleep structure. The hypothesis was that untreated patients with OCD exhibit alterations of REM sleep, such as an increased REM density. It was a further aim to investigate whether an anti-5-HT challenge test might be able to reveal potential abnormalities of sleep structure not detectable under baseline conditions. We hypothesized that tryptophan depletion might significantly reduce REM sleep latency in OCD patients, i.e. unmask REM sleep alterations in the OCD patients.

Patients and methods

The study protocols were approved by the Ethical Committee of the Albert-Ludwig-University of Freiburg. Written informed consent was obtained from all subjects prior to study entry. The study has been carried out in accordance with the declaration of Helsinki. 62 patients with a primary OCD, who were free of any psychotropic medication, were recruited for this study. All of them were inpatients and admitted to our hospital for cognitive behavior treatment. Data of a subgroup of 22 of the patients had been published earlier [31]. Investigations were carried out during the first two weeks before the beginning of specific measures such as exposure treatment.

Diagnoses were established by means of a structured clinical interview, the SCID [33, German translation by 34]. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [35, 36, German translation by 37] rating had to exceed 16 points. Patients with OC symptoms occurring in association with an affective illness or schizophrenia were excluded from the study. In addition to the OCD, which in all cases was the principle diagnosis leading to admission to the hospital, many patients, however, suffered from mild or moderate depressive symptoms. In these cases depression occurred in the course of the underlying OCD and did not precede the OC symptoms according to the clinical judgement. Depressive mood was evaluated by means of the 21-item Hamilton Depression Rating Scale.

Sixty-two age- and sex-matched healthy subjects with no personal history of a psychiatric disorder and no first-degree relative having a psychiatric disorder served as controls. For demographic data of the patients and subjects see Table 1.

Exclusion criteria were intake of any psychotropic drugs including hypnotics during and at least 1 week prior to the study. In the case of pretreatment with fluoxetine, irreversible monoa-

Table 1 Demographic data of patients and subjects

	OCD patients	Healthy subjects
Whole group		
N	62	62
Mean age ($x \pm$ SD)	35.6 ± 11.2 years	35.8 ± 11.0 years
Female/male	29/33	29/33
Y-BOCS-score ($x \pm$ SD)	27.3 ± 6.5	–
HDRS-21 score ($x \pm$ SD)	15.6 ± 8	–
Number of drug-naive patients*	29	–
Subgroup participating additionally to tryptophan depletion test		
N	12	12
Mean age ($x \pm$ SD)	31 ± 11 years	34 ± 9 years
Male/female	6/6	6/6
Y-BOCS ($x \pm$ SD)	23.8 ± 7.2	0
HDRS ($x \pm$ SD)	11.2 ± 5.8	0.1
Number of drug-naive patients*	5	

* Never treated with psychotropic drugs

mino-oxidase inhibitors, depot neuroleptics or long acting benzodiazepines, a wash-out period of at least 4 weeks was required. Apart from 11 patients, the wash-out period was even longer than 14 days and 29 of the patients reported that they had never taken psychotropic drugs in their life ("drug naive" patients). Further exclusion criteria were substance abuse, significant medical or neurological disorders, pregnancy, post partum depression, lactating, history of sleep apnea syndrome or restless legs syndrome or a circadian rhythm disorder. Before inclusion in the study, all patients and subjects were screened by a careful physical and neurological examination, an electroencephalogram, an electrocardiogram, routine blood tests and a urine test for intake of benzodiazepines or illicit drugs. All OCD patients were additionally investigated by either a computer tomography or a magnetic resonance imaging of the brain. In the case of significant abnormal findings or a positive urine screening test, patients or healthy subjects were excluded from the study. For at least 1 week prior to the study, all patients and subjects had to keep a regular sleep-wake schedule corresponding to the polysomnographic registration time for at least 1 week prior to the study.

After the end of the polysomnographic investigations, all patients were treated with cognitive behavior therapy and a subgroup of the patients also with 5-HT reuptake inhibitors. Pharmacological treatment was not standardized. Some patients received more than one psychotropic medication (additional hypnotics or sedative antidepressants for insomnia or neuroleptics for augmentation of the effect of the 5-HT-reuptake inhibitors). In 43 of 62 patients a Y-BOCS follow-up rating was repeated about 3 months after beginning of treatment.

Procedures

The study was carried out in the sleep laboratory of the Department of Psychiatry and Psychotherapy of the University in Freiburg. All had 2 consecutive polysomnographies, the first for adaptation to the sleep laboratory conditions and the second one to obtain baseline sleep parameters.

Sleep recordings were made by 14-channels Nihon-Kohden EEG polysomnographs from "lights-out" (23.00 h) to "lights-on" (7.00 h) at a paper speed of 10 mm/s. All recordings included EEG (C3–A2; C4–A1), EOG (horizontal and vertical) and EMG (submental) and were scored visually by experienced raters according to Rechtschaffen and Kales [38] criteria. During the adaptation night 1, all subjects were screened for apneas and periodic leg movements by monitoring abdominal and thoracic effort, nasal airflow, oxymetry, and bilateral tibialis anterior EMG. More than 5 apneas or hypopneas per hour or more than 5 periodic leg movements per hour with arousal were exclusion criteria. For further details of polysomnography in our sleep laboratory see Voderholzer et al. [25].

Sleep recordings were evaluated for parameters of sleep continuity and architecture, and REM sleep. Sleep continuity variables included: (1) sleep efficiency: ratio of total sleep time (TST) to time in bed (TIB) × 100%: (2) sleep onset latency: time from lights out until sleep onset (defined as first epoch of stage 2); (3) number of awakenings: at least one epoch of stage wake during sleep period time (SPT = time from sleep onset till the final awakening during the record).

Sleep architecture variables included: amounts of stages wake, 1, 2, 3, 4, and REM expressed as percentage of SPT. REM sleep variables were: (1) REM latency: time from sleep onset till the first epoch of REM sleep; (2) REM latency corrected was calculated by subtracting wake time between sleep onset and the first REM period from REM latency; (3) duration of the first REM period in min; (4) total number of rapid eye movements during the whole night; (5) eye movement density of the first REM period in %; (6) total REM density, i.e., eye movement density of all REM periods taken together in % (REM density is defined as the ratio of 3 s mini-epochs per REM period including at least one rapid eye movement to the total number of 3-s mini-epochs per REM sleep × 100%).

Tryptophan depletion test

To study the impact of tryptophan depletion on sleep, a subgroup of 16 consecutively admitted patients with OCD was recruited. The same inclusion criteria were also chosen for the tryptophan depletion test, that is, only patients off psychotropic drugs (washout period at least 7 days) were recruited. Four patients dropped out: 2 patients because of OCD-related difficulties with filling out the self-rating scales, one woman because of intake of metoclopramide because of severe nausea after the amino acid drink, and one patient because of withdrawal of consent. The demographic data of the remaining 12 patients are shown in Table 1. The first night served for adaptation to the sleep laboratory conditions, the second night to obtain baseline sleep parameters. For the tryptophan depletion test, patients stayed two further nights in the sleep laboratory. From the morning after the second night, they received standardized nutrition consisting of a low protein diet with about 160 mg tryptophan per day, 18.6 g of protein and 2.500 kcal for the male patients and 2.000 kcal for the female patients on day 3 and on day 4 until midday. Meals had to be taken in the research ward. This diet was similar to the diet used by Delgado et al. [39]. The polysomnographic effects of tryptophan depletion were measured in night 4. On day 4 after lunch, subjects were not allowed to take any food or drink except water. At 18.00 h, i.e. 5 h prior to the beginning of sleep recording, they received a tryptophan-free amino acid drink. The amino acid mixture was the same as used by Young et al. [40] and other authors [39, 41]. Because of the unpleasant taste, methionine, cysteine, and arginine were given in capsules. After the intake of the amino acid drink, subjects did not receive any further food except water until 10.00 h on the following morning.

Blood samples for determination of tryptophan were obtained at 17.00 h and at 22.00 h on days 2 and 4 and at 8.00 h on days 3 and 5. Total serum tryptophan was determined by the perchloric acetic acid (PCA) precipitation method (coefficient of variation 8.2%).

To evaluate behavioral and emotional effects of tryptophan depletion, a set of psychometric ratings and self-rating scales was completed on days 2 and 4 at 17.00 h and 22.00 h and on days 3 and 5 at 7.00 h. Several subjective rating scales were used to determine how the subjects felt at the moment: AMS (adjective mood scale, a scale with 28 items predominantly focusing on affective states, von Zerssen [42], B-L (Beschwerdeliste, a list with somatic complaints, von Zerssen [42], and analogue scales being divided in six grades for the items mood, anxiety and tension. In addition, the 6-item version of the HDRS [43] was repeated at the same time points. As the Y-BOCS has not been demonstrated to be sensitive for short-term changes in the severity of OC symptoms, analogue scales with 6 grades for the severity of obsessions and compulsions, and the ability to resist them were performed at the different time points.

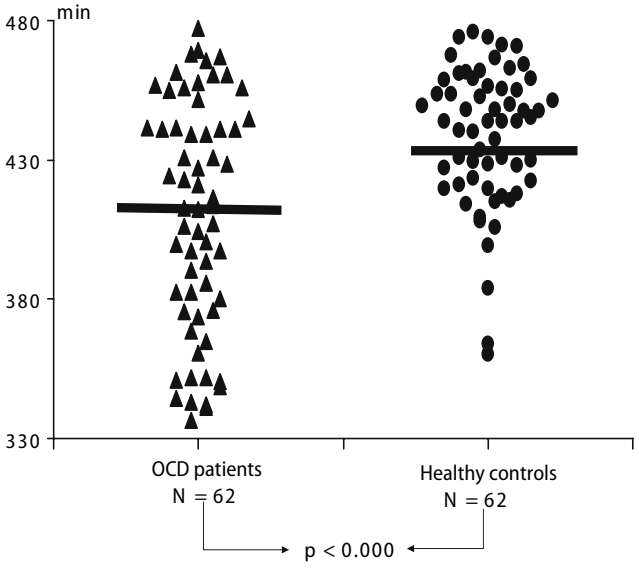

Fig. 1 Total sleep time in unmedicated OCD patients and age- and sex-matched healthy controls. Results for the baseline night

Statistical analysis

For statistical evaluation of sleep parameters the data of the first adaptation night were excluded from the analysis. For descriptive purposes means and standard deviations (SD) were calculated for all sleep parameters of the second night. The groups of patients and healthy subjects were compared by 2-tailed Student's *t*-test for independent samples.

In order to evaluate the impact of age, severity of OC and depressive symptoms, and of pretreatment, two-sided Pearson correlation coefficients were calculated between the Y-BOCS and HDRS and the sleep parameters. Since REM latency is not normally distributed, non-parametric Spearman coefficients of correlation (two-sided) were calculated between Y-BOCS and HDRS ratings and REM latency.

To evaluate the polysomnographic effects of tryptophan depletion, only night 4 (after the amino acid drink) and night 2 (baseline) were statistically analyzed by 2×2 ANOVA (factors night and group). The data of night 3 were not analyzed, since statistical analysis of the data in healthy subjects in comparison with a placebo condition did not demonstrate significant effects on sleep after of a low protein diet alone taken for one day [25]. The main reason for monitoring the third night in the sleep laboratory was to maintain the adaptation of the patients to the sleep laboratory conditions, i.e. to avoid reoccurrence of adaptation effects in night 4, which could have confounded the effects of tryptophan depletion.

Since REM latency did not follow a normal distribution, non-parametric comparisons with the Mann-Whitney *U*-test were performed for this parameter. *p*-values were corrected according to the Bonferroni method. For all statistical calculations, $p < 0.05$ was considered to be significant.

Results

Polysomnography under baseline conditions

OCD patients had a significantly lower sleep duration (Fig. 1) and sleep efficiency, and significantly more wake% during the sleep period time compared with the healthy controls (Table 2). Regarding sleep architecture, the percentage of slow wave sleep, of REM sleep and of non-REM stage 1 and 2 did not differ between the groups. REM latency (Fig. 2) and corrected REM latency were similar in the OCD patients and the healthy subjects, whereas REM density of the first REM period was significantly elevated.

Impact of symptom severity

The severity of OC-symptoms showed a weak but non-significant correlation with sleep continuity measures ($r = -0.157$, $p = 0.22$ for sleep duration, $r = 0.206$, $p = 0.11$ for wake%) and a weak positive, but significant correlation with REM density and the REM density of the first REM period (0.274, $p = 0.03$, $r = 0.287$, $p = 0.02$, respectively). There were no significant correlations between severity of OC-symptoms and other sleep parameters. The HDRS-21 correlated positively with the Y-BOCS ($r = 0.289$, $p = 0.026$). There was a weak negative yet significant correlation between the HDRS-21 and sleep duration ($r = -0.318$, $p = 0.014$) and a weak positive correlation between the HDRS-21 and wake% ($r = 0.271$, $p = 0.038$). There were no significant correlations between HDRS-21 and other sleep parameters, such as, for example, REM latency ($r = 0.146$, $p = 0.257$). The Hamilton Depression Rating Scale (HDRS-21) correlated positively with the Y-BOCS ($r = 0.289$, $p = 0.026$) and were negatively correlated with sleep duration ($r = -0.318$, $p = 0.014$). There was a weak positive, but non-significant correlation between the HDRS and REM density, as well as the REM density of the first REM period ($r = 0.141$, $p = 0.288$, $r = 0.229$, $p = 0.081$, respectively).

Impact of age and pretreatment on sleep

As expected, there was a significant negative correlation between age and sleep continuity measures (sleep duration $r = -0.457$, $p = 0.000$, sleep efficiency $r = -0.387$, $p = 0.002$) and a significant positive correlation between age and wake% ($r = 0.336$, $p = 0.010$). No significant correlations between pretreatment and measures of sleep were found, except for a slightly higher REM density in those patients who had been treated with antidepressants in the past compared to those who had never been on psychotropic drugs before (31.6 ± 8.06 versus 23.7 ± 8.74, $t = -3.43$, $p = 0.01$).

Predictive value of polysomnography for therapeutic response

To evaluate the impact of the polysomnographic findings on treatment outcome, correlations were calculated between the sleep parameters and the difference between the Y-BOCS scores at follow-up

Table 2 Polysomnographic parameters of OCD patients and a control group of age- and sex-matched healthy subjects ($x \pm$ SD)

	OCD patients ($N = 62$)	Healthy subjects ($N = 62$)	*t*-test / Mann-Whitney *U* t = / Z =	*p*-value
Sleep period time (SPT, min)	447 ± 27.8	455 ± 22.3	−1.86	0.07
Total sleep time (TST, min)	410 ± 41.1	437 ± 28.7	−4.15	**0.000*** **
Sleep efficiency (%)	86.9 ± 8.63	91.6 ± 5.22	−3.68	**0.000*** **
Sleep onset latency (min)	18.2 ± 16.5	15.9 ± 10.2	0.90	0.37
Waking periods (N)	15.7 ± 10.1	13.6 ± 11.1	1.13	0.26
Wake% SPT	8.10 ± 8.00	4.10 ± 4.00	3.53	**0.001***
Stage 1% SPT	6.13 ± 3.61	6.48 ± 4.38	−0.48	0.63
Stage 2% SPT	53.1 ± 9.15	56.6 ± 6.72	−2.41	0.02
Slow wave sleep% SPT	8.80 ± 8.22	9.10 ± 7.85	−0.19	0.85
REM sleep% SPT	23.3 ± 5.91	23.0 ± 4.81	0.30	0.77
REM latency (min)**	69.6 ± 37.9	72.3 ± 33.6	−0.82	0.41
REM latency corrected (min)**	61.2 ± 27.9	66.2 ± 30.0	−0.84	0.40
Duration of 1st REM period	20.8 ± 16.8	16.8 ± 11.9	1.53	0.13
Rapid eye movements (*N*)	578 ± 257	498 ± 203	1.91	0.06
REM density (%)	27.4 ± 9.54	23.9 ± 8.30	2.23	0.03
1st REM density	23.0 ± 12.7	16.1 ± 10.1	3.35	**0.001***

** Mann-Whitney *U*-Test
*** = <0.001 bonferroni-corrected; * = <0.05 bonferroni-corrected

after 3 months and baseline in 43 patients who were rated at both time points. The mean change of the Y-BOCS-scores after 3 months of treatment was −13.6 ± 8.7 points and varied between +1 and 34 points. No significant correlations were found for most sleep parameters, apart from REM latency, which showed a positive and significant correlation with the reduction of the Y-BOCS scores ($r = 0.317$, $p = 0.038$, two-sided Spearman correlation). This indicated a trend towards a better treatment outcome in patients with longer REM latencies. However, it must be pointed out that pharmacological treatment was not standardised.

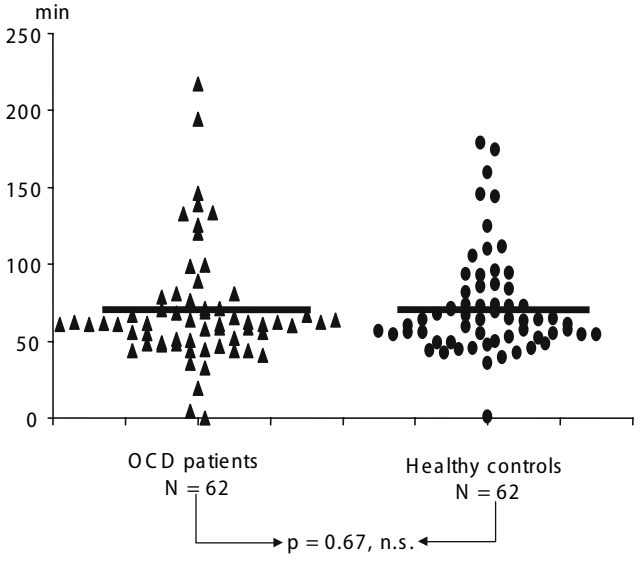

Fig. 2 REM latency in drug-free OCD patients and healthy controls. Results of the second night (baseline night) in the sleep laboratory, respectively. 3 of 62 OCD patients and one healthy control exhibited very short REM latencies below 20 min

Impact of tryptophan depletion

The impact of tryptophan depletion on sleep was studied in the last of 4 consecutive nights in a subgroup ($n = 12$) of the whole study population ($n = 62$). Four hours after ingestion of the amino acid drink, i.e. at 22.00 h shortly before start of polysomnography, tryptophan levels were on average reduced to 20% of baseline values in the OCD group and to 15% of baseline values in the healthy controls. Apart from mild and transient nausea, no relevant side-effects occurred.

Results of polysomnography are given in Table 3. The 2 × 2 ANOVA including the data of a healthy control group ($n = 12$) revealed significant night effects for sleep efficiency (Fig. 3) and total sleep time, wake% and sleep stage 2 as well as for the number of eye movements and REM density. A significant interaction effect was not found.

Confirmatory contrasts showed that in OCD patients there was a significant increase of wake% and a significant reduction of stage 2 sleep% compared with baseline, whereas controls showed a significant reduction of stage 2 sleep% and an increase of the number of eye movements. Healthy subjects showed slightly but significantly more stage 1 sleep compared with the OCD patients. This difference was, however, not confirmed when comparing the group of 62 OCD patients with 62 age- and sex-matched healthy controls.

Psychometric ratings 4 h after intake of the amino acid drink and on the morning after did not demonstrate significant changes in depression or OC-symptoms compared to baseline values.

Table 3 Impact of tryptophan depletion on sleep in OCD patients and controls

	OCD patients (n = 12)		Healthy controls (n = 12)		2 × 2 ANOVA					
	Baseline night	Tryptophan Depletion	Baseline night	Tryptophan depletion	Group effect F-value	Group effect df = 1 p-value	Night effect F-value	Night effect df = 1 p-value	Interaction F-value	Interaction df = 1 p-value
SPT (min)	445.4 ± 23.4	445.9 ± 35.5	452.3 ± 16.8	456.7 ± 13.8	1.384	0.252	0.154	0.698	0.093	0.763
TST (min)	417.1 ± 33.8	390.1 ± 48.7	429.2 ± 21.2	421.5 ± 34.2	3.224	0.086	**4.429**	**0.047**	1.368	0.255
SE (%)	87.8 ± 7.1	82.2 ± 9.6	89.7 ± 4.7	88.4 ± 7.1	2.617	0.120	**4.454**	**0.046**	1.718	0.203
SOL (min)	21.0 ± 21.4	18.3 ± 31.4	17.5 ± 10.9	16.7 ± 12.6	0.147	0.705	0.110	0.743	0.038	0.848
Waking p. (N)	14.0 ± 5.3	16.7 ± 10.3	14.6 ± 9.3	18.2 ± 10.1	0.108	0.746	2.373	0.138	0.041	0.841
wake% SPT	6.4 ± 4.7	12.7 ± 7.5	5.1 ± 4.4	7.8 ± 6.3	2.477	0.130	**10.341**	**0.004**	1.596	0.220
Stage 1% SPT	5.3 ± 1.5	6.0 ± 3.2	8.2 ± 3.6	8.1 ± 3.6	**4.392**	**0.048**	0.497	0.488	0.821	0.375
Stage 2% SPT	55.5 ± 5.8	46.5 ± 10.6	58.1 ± 6.7	53.0 ± 7.2	2.402	0.135	**27.594**	**0.000**	2.106	0.161
SWS % SPT	8.4 ± 7.8	9.4 ± 7.5	6.3 ± 7.0	7.1 ± 5.5	0.634	0.434	1.241	0.277	0.019	0.891
REM %	23.9 ± 6.9	25.0 ± 5.6	21.7 ± 4.2	23.4 ± 4.3	1.166	0.292	1.217	0.282	0.038	0.847
REM lat.10 (min)	64.1 ± 21.8	61.0 ± 36.9	67.3 ± 22.8	80.0 ± 19.8	1.590	0.221	0.625	0.438	1.672	0.209
REM lat. 10 corr. (min)	60.6 ± 17.4	46.4 ± 38.0	65.8 ± 22.2	66.5 ± 19.0	2.629	0.119	0.976	0.334	1.177	0.290
Duration of 1st REM period	12.8 ± 8.7	14.4 ± 11.0	17.4 ± 12.1	13.0 ± 7.0	0.321	0.577	0.232	0.635	1.136	0.298
Eye mov. (N)	575.7 ± 272.7	641.5 ± 283	469.6 ± 189.7	626.7 ± 245.3	1.852	0.510	**7.417**	**0.030**	0.288	0.352
REM density %	27.1 ± 9.5	28.3 ± 8.4	24.6 ± 10.0	29.1 ± 10.1	0.053	0.820	**4.991**	**0.036**	1.537	0.228
1st REM density	19.8 ± 12.7	22.6 ± 15.4	17.7 ± 9.9	22.0 ± 9.5	0.095	0.761	2.684	0.116	0.132	0.720

SPT = sleep period time; TST = total sleep time; SE = Sleep efficiency; SOL = sleep onset latency; waking p = number of waking periods; REM lat. 10 = REM latency 10-Min-criteria; REM lat. 10 corr. = corrected REM latency 10-Min-criteria (REM latency minus intermittent wakefulness), 1st REM-p. = duration of 1st REM period; eye mov. = Total number of rapid eye movements during REM sleep, 1st REM densitiy = REM density of 1st REM period

* <0.05 bonferroni-corrected

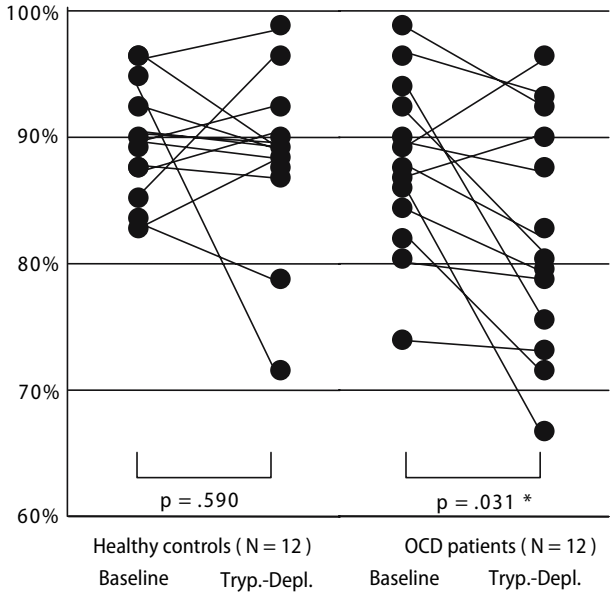

Fig. 3 Impact of tryptophan depletion on sleep efficiency in OCD patients (right column) and a healthy control group (left column). Results from the second (baseline) and the fourth (tryptophn depletion night) of four consecutive nights in the sleep laboratory

Discussion

This study demonstrated that patients with OCD do not show the characteristic abnormalities of sleep structure such as reduced REM latency or diminished slow wave sleep, that have been repeatedly and consistently described in depressive disorders [27, 28]. Our study is clearly the largest study of sleep in OCD so far and the patients differed from healthy controls only with regard to some sleep continuity measures and an increased 1st REM density, which remains the only similarity with regard to the known features of sleep in depression.

All patients were unmedicated at the time of investigation and at least 7 days prior to the first polysomnography. A substantial part of the patients was drug naive with regard to psychotropic medication. We did not find an impact of pretreatment on sleep measures except for a correlation with REM density, which was higher in those who had been treated with antidepressants in the past compared to those who had never been on medication before. This could not be attributed to differences of severity of OC or depressive symptoms. This finding might be explained by either long lasting alterations of central nervous neurotransmitter receptor sensitivity after exposure to antidepressant drugs or by an impact of the psychiatric history, that is, for example, those with a higher REM density, a biological marker for depression, might also be more likely to have been treated with antidepressant drugs. However, we would like to emphasize that no impact of pretreatment was found on other sleep parameters such as sleep continuity, the amount of REM sleep or REM latency.

Focussing on the serotonergic hypothesis of OCD, the effects of tryptophan depletion on sleep were investigated. After this challenge test a worsening of sleep continuity was observed without changes of REM or slow wave sleep. A disturbed sleep continuity following tryptophan depletion is not explained by unspecific stress of the procedure itself (for example unpleasant taste and nausea), since the "placebo" procedure with a drink containing additional tryptophan has been shown to have no influence on sleep [25].

Our results only partly confirmed several earlier studies with smaller sample sizes [29–32] which had also reported unspecific disturbances of sleep continuity in OCD patients. This might be explained by a psychophysiological hyperarousal as a consequence of negative feelings, tension and anxiety associated with the obsessions and compulsions. This view is supported by the weak, but positive correlation between the severity of obsessions and compulsions and sleep continuity measures. Unspecific disturbances of sleep maintenance have also been demonstrated in a part of the studies in patients with anxiety disorders [44, 45], whereas other authors could not demonstrate significant changes in comparatively small groups of patients with panic disorder [46] or patients with social phobia [47].

Our study clearly demonstrated that patients with OCD do not show changes of the tonic aspects of REM sleep, such as REM latency and the percentage of REM sleep. It has to be pointed out that in our study the total number of included patients was higher than the total number of patients in all four earlier studies taken together [29–32], which indicates that the negative findings in 3 of the earlier studies regarding REM sleep abnormalities were not referable to a small sample size. The study did not replicate the early findings of Insel et al. [29] who reported a shortening of REM latency in their sample of OCD patients similarly as in patients with depression. It has to be emphasized that nearly all our patients had a severe OCD, in almost all cases lasting for many years and that depression ratings showed a mean HDRS of 15.6, a typical finding in patients with severe OCD which is frequently associated with secondary depressive symptoms. Patients with a history of a primary depressive disorder unrelated to the OCD were not included. Since REM sleep abnormalities are a consistent finding in primary depressive disorders [27, 28, for overview], our results indicate, that OCD may be neurobiologically different from depression, even when patients become depressed in association to severe OC symptoms [48].

It has to be mentioned that REM sleep abnormalities are not a specific phenomenon of depressive disorders, since later studies have demonstrated them also in patients with schizophrenia [49] or alcoholics

[50]. In the view of the frequency of REM sleep abnormalities in different psychiatric disorders, it is moreover an obvious finding that in OCD, in which neurobiological factors play an important role, no tonic REM sleep abnormalities are found.

The methodology of tryptophan depletion was performed according to Delgado et al. [39] except the time of administration of the amino acid drink which was administered at 18.00 h in contrast to most other studies in which the drink was given in the morning hours. We chose this time of the day in order to induce a maximum decrease of tryptophan levels immediately before beginning of polysomnography. The results of the tryptophan depletion test did not indicate a specific reaction of OCD patients to the drink, since a statistical analysis including a healthy control group did not demonstrate any significant interaction effect. However, because of sample sizes of $n = 12$ in the OCD patients and healthy controls, respectively, the statistical power of the effects may have not been large enough to detect specific reactions. In both groups, tryptophan depletion induced a worsening of sleep continuity measures which was confirmed by significant night effects for total sleep time, sleep efficiency, wake% and stage 2 sleep%. When contrasting the polysomnographic findings following the amino acid drink in comparison with baseline in each group separately, the effect of the drink was less pronounced in the healthy controls with only minimal reductions of sleep duration and sleep efficiency and a stronger effect in the OCD patients ($p = 0.049, 0.032$, respectively), which, however, was not significant after Bonferroni correction. Nonetheless, this might indicate a trend that sleep of OCD patients is more sensitive to serotonin deficiency. However, a study in larger samples would be necessary to confirm it. Despite the fact, that sleep changes did not occur after a sham depletion session [25], it cannot be ruled out that OCD patients might have a higher sensitivity to be disturbed by an experimental procedure. Another finding is the lack of any significant influences of tryptophan depletion on REM sleep measures. As far as we know, there are no other studies on the tryptophan depletion test and sleep in OCD patients. The absence of REM sleep changes after tryptophan depletion is not in line with a study by Bhatti et al. [23] and Moore et al. [24] who reported significant reductions of REM latency in healthy controls and in depressive patients with this test. However, recent studies in healthy men [51] and in patients with primary insomnia [26] did also not show a significant impact of tryptophan depletion on REM sleep. One study even found a significant prolongation of REM latency after rapid tryptophan depletion in the mid-morning (Arnulf et al. 2002).

On the other hand, this study demonstrated that an experimentally induced serotonin deficiency has a clear impact on sleep continuity, especially on Non-REM sleep. This would be in line with the serotonergic hypothesis of sleep [52], which, however, was not supported by a variety of later studies (see [53] for overview). In animals severe insomnia occurred after destruction of the serotonergic raphe nuclei [54] or after experimental serotonin depletion by administration of *p*-chlorophenylalanine (PCPA), which inhibits the tryptophan hydroxylase [55]. Our findings are also in agreement with the model of sleep regulation proposed by Hobson and McCarley [22], describing a cycling alternating pattern of monoaminergic activity during Non-REM sleep and cholinergic activity during REM sleep. In this view, a weakening of the serotonergic tone would weaken Non-REM sleep generation and therefore explain the decrease of Non-REM sleep stage 2 in our study.

Tryptophan depletion did not induce a provocation of OC symptoms in our study, at least not in repeated self-ratings in the evening after the test and on the next morning. It is difficult to measure changes of OC symptoms within a short time interval and under experimental conditions differing from the daily stimulus conditions of the patients. Regarding psychometric measurements, the lack of effect on OC symptoms agrees with earlier studies using the tryptophan depletion test in OCD patients [19, 20].

Do our results support the serotonergic hypothesis of OCD? This question cannot be answered from our studies, since the baseline measurements do not allow pathophysiological conclusions. The results of the challenge tests regarding specific reactions of OCD patients were negative, at least on the statistical level. However, the similarity between the changes of sleep in a large group of OCD patients (reduced sleep efficiency, reduced total sleep time, increase of wake percent) are strikingly similar to the changes of sleep, which can be provoked by experimentally induced 5-HT deficiency in healthy humans.

Therefore, the two major conclusions from these studies remain that, confirming earlier studies in much smaller samples, OCD patients do not seem to exhibit characteristic changes of sleep structure as described in a large number of studies in depression and, second, that depletion of the CNS from serotonin predominantly impairs non-REM sleep.

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