Dex/CRH-test response and sleep in depressed patients and healthy controls with and without vulnerability for affective disorders

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Abstract

Sleep electroencephalographic (EEG) abnormalities and increased hypothalamo–pituitary–adrenal (HPA) axis activity are the most prominent neurobiological findings in depression and were suggested as potential biomarker for depression. In particular, increased rapid eye movement sleep (REM) density, deficit in slow wave sleep and excessive stress hormone response are associated with an unfavorable long-term outcome of depression. Recent studies indicate that the sleep and endocrine parameters are related to each other. This study investigated the association of sleep structure including a quantitative EEG analysis with the results of the combined dexamethasone (Dex)/corticotropin-releasing hormone (CRH)-test in 14 patients with a severe major depression, 21 healthy probands with a positive family history of depression (HRPs) and 12 healthy control subjects without personal and family history for psychiatric disorders. As expected patients with depression showed an overactivity of the HPA axis, disturbed sleep continuity and prolonged latency until slow wave sleep in the first sleep cycle. Differences in microarchitecture of sleep were less prominent and restricted to a higher NonREM sigma power in the HRP group. Dexamethasone suppressed cortisol levels were positively associated with higher NonREM sigma power after merging the three groups. We also observed an inverse association between the ACTH response to the Dex/CRH-test and rapid eye movement sleep (REM) density in HRPs, with suggestive evidence also in patients, but not in controls. This contra-intuitive finding might be a result of the subject selection (unaffected HRPs, severely depressed patients) and the complementarity of the two markers. HRPs and patients with high disease vulnerability, indicated by an elevated REM density, seem to have a lower threshold until an actual disease process affecting the HPA axis translates into depression, and vice versa. To summarize, our findings provide further evidence that the HPA axis is involved in the sleep regulation in depression. These associations, however, are not unidimensional, but dependent on the kind of sleep parameters as well as on the selection of the subjects.

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1. Introduction

Disturbed sleep electroencephalographic (EEG) patterns are one of the most prominent neurobiological findings in depression and were suggested as potential biomarker for depression. In detail, slow wave sleep deficit in the first sleep cycle, decreased sleep continuity, short latency to rapid eye movement (REM) sleep and increase in its phasic components, i.e., the density of the REMs, have been repeatedly described (Reynolds and Kupfer, 1987; Lauer et al., 1992; Steiger et al., 1989; Wichniak et al., 2000). Interestingly, phasic and tonic REM sleep parameters differ in their neurophysiological regulation and have been characterized as distinct functional substrates within REM sleep (Holsboer-Trachsler et al., 1993; Quattrochi and Hobson, 1999; Wehrle et al., 2007). There is good evidence that phasic REM sleep parameters play a significant role in memory consolidation (Fogel et al., 2007) in particular with respect
to avoidance task learning (Datta, 2000; Mavanji and Datta, 2003). The increase in REM density was demonstrated not only as one of the most significant and stable abnormalities of sleep in patients with depression but also in individuals who are at a high familial risk to develop the disease (high-risk probands, HRP; "Munich Vulnerability Study on Affective Disorders"). Therefore, this parameter has been suggested as vulnerability marker for affective disorders (Modell et al., 2002, 2005). In view of the ontogeny of REM sleep a deficit in postnatal REM sleep inhibition was proposed to account for the life-long REM sleep abnormalities in humans predisposed to the disease (Vogel et al., 2000). On the other hand, there is compelling evidence that the excessive increase in hypothalamo–pituitary–adrenal (HPA) axis activity is one of the most relevant endocrine abnormalities in depression resulting from an impaired corticosteroid receptor function as the key mechanism in the pathogenesis of the disease (Holsboer, 2000; DeKloet et al., 2005). The function of the HPA axis can be most sensitively assessed by the combined dexamethasone (Dex)/corticotropin-releasing hormone (CRH) test (Heuser et al., 1994). Recent studies on the course and treatment response suggest this test as a potential biomarker in depression (Ising et al., 2005a). HRPs for affective disorders demonstrated moderately abnormal hormone response in the Dex/CRH-test lying inbetween the levels of healthy controls and patients with depression (Holsboer et al., 1995; Modell et al., 1998), which, however, was not predictive for the development of an affective disorders in HRPs (Ising et al., 2005b).

Numerous studies revealed that both sleep and endocrine alterations are associated with an unfavorable long-term outcome of depression (Kupfer et al., 1993; Thase et al., 1998; Buysse et al., 1997; Clark et al., 2000; Zobel et al., 1999, 2001). In addition, a recent study by Hatzinger et al. (2004) found that sleep variables unfavorable for long-term outcome were related to excessive stress hormone response. It has been suggested that underlying mechanisms may affect both sleep regulation and long-term course of depression.

The aim of this study was to examine the association between the microstructure of sleep and stress hormone regulation. For this purpose, we analyzed the associations between spectral sleep EEG parameters and the neuroendocrine response to the Dex/CRH-test in patients suffering from Major Depression, in a subgroup of HRPs from the "Munich Vulnerability Study on Affective Disorders", and in healthy control subjects without personal or familial history for psychiatric disorders.

2. Methods

2.1. Study samples

Twenty-one non-obese inpatients suffering from severe major depression (ICD10 F32.2, F33.2) who participated in a previous study investigating acute cortisol administra-

tion on sleep and growth hormone secretion were recruited (Schmid et al., 2008). Patients underwent a careful clinical evaluation to exclude concomitant severe somatic, neurological or endocrinological diseases or substance abuse. They were free of any psychotropic medication in including benzodiazepine hypnotics for a wash out period of at least 5 days prior to the endocrinological testing and at least 7 days prior to the sleep EEG recordings. There was a total number of n = 6 drop-out cases (n = 1 diagnosed as rapid cycling, n = 2 withdrew consent, n = 3 refused to participate until the end of the protocol, n = 1 refused to participate in blood sampling). Due to technical reasons the sleep recordings of n = 1 patient in the baseline night could not be analyzed. Therefore, the data of n = 14 patients (8 men, 6 women; age M = 47.2, SD = 11.6; Hamilton Depression Rating Scale (HDRS), M = 19.1, SD = 6.4, ranging from 18 to 38) were examined with respect to sleep profile and HPA system function.

Additionally, 21 healthy subjects (high-risk probands, HRPs) with at least one first-degree relative suffering from an affective disorder participated, who were a subgroup of participants in the “Munich Vulnerability Study on Affective Disorders”. During two study periods of the “Munich Vulnerability Study on Affective Disorders” 740 psychiatric inpatients with a diagnosis of major depression, bipolar disorder, or “bipolar II” disorder (bipolar disorder not otherwise specified) were screened. We looked for patients who had at least one first-degree relative with an affective disorder or schizophrenia and at least one first-degree relative with no current of lifetime diagnosis of a psychiatric disorder, the latter verified by the Structured Clinical Interview for DSM-III-R (SCID I, German Version, Wittchen et al., 1990). This relative was then identified as HRP. The inclusion criteria mentioned above were fulfilled by 136 patients, and 50 patients of this group agreed to participate in the study (index patients). These patients led to 101 HRPs. Out of this group, quantitative analysis of sleep EEG was established in n = 21 HRPs (12 men, 9 women; age M = 27.1, SD = 6.1). These 21 HRPs belonged to 12 families. Thus, our study group consisted of several siblings since one family provided four HRPs, one family three HRPs, 4 families two HRPs, and 6 families one HRPs. None of the index patients or the HRPs participating in the “Munich Vulnerability Study on Affective Disorders” was related to the patients with depression examined in the present study.

The sleep–endocrine data of the HRPs and patients with depression were compared to the data of 12 healthy control subject without personal (SCID I) or family history (semi-structured clinical interview) of psychiatric disorders (CPs; 3 men, 9 women; age M = 28.0, SD = 5.9) recruited in the “Munich Vulnerability Study on Affective Disorders”.

2.2. Experimental Protocol

Before entering the study, patients, HRPs and CPs underwent extensive physical, psychiatric, and laboratory
examinations including haematology, virology, clinical chemistry, endocrinology, electroencephalography (EEG), and electrocardiography (ECG). We excluded patients with accompanying severe somatic, neurological or endocrinological diseases or substance abuse and subjects with medical treatment for at least 3 months prior to the study, personal (HRPs, CPs) or family history (CPs) of psychiatric disorders. In addition, shift workers and patients or subjects having travelled across time zones within the previous 6 weeks were excluded. All subjects (HRPs, CPs) slept two consecutive nights in our sleep laboratories, the first night serving for adaptation to the laboratory setting and exclusion of sleep disorders (periodic leg movements, sleep apnea, parasomnia). The data analysis of the present study was based on the EEG recording during the second night. After this second night, patients participated in a placebo controlled experimental study examining the effects of exogenous cortisol on night sleep, which will be reported elsewhere.

At least 72 h before entering the sleep recordings the patients, HRP and CPs underwent the combined Dex/CRH-test to determine the status of HPA axis function as described elsewhere (Heuser et al., 1994; Zobel et al., 2001). In short, a single oral dose of dexamethasone 1.5 mg was given at 11 p.m. at the evening before the test. At 08:30 h next morning cortisol levels were determined. At 11.5 mg was given at 11 p.m. at the evening before the test. In short, a single oral dose of dexamethasone 1.5 mg was given at 11 p.m. at the evening before the test. At 08:30 h next morning cortisol levels were determined. At 11 p.m. the patients received CRH stimulation with 100 μg CRH (Clinalfa, La¨ufelfing, Switzerland) and blood samples were collected from 3 p.m. to 4.15 p.m. to assess the circulating levels of cortisol and corticotropin.

All investigations were performed at the Max Planck Institute of Psychiatry in Munich. The experimental protocol was approved by the Ethics Committee for Human Experiments of the Bayerische Landesärztekammer (Munich, Germany). Written informed consent was obtained after the procedures had been fully explained. The details on the procedure of study in patients with depression and the “Munich Vulnerability Study on Affective Disorders” are described elsewhere (Holsboer et al., 1995; Modell et al., 2002).

2.3. Sleep Recordings

The polysomnographic recordings (11 p.m.–7 a.m.) included two EEGs (C3-A2/C4-A1, time constant 0.3 s, notch filter at 50 Hz, low pass at 70 Hz), a vertical and horizontal electrooculogram (EOG), electromyogram (EMG) and ECG. The filtered EOG, EEG, EMG, and ECG signals were transmitted to a polygraph (Schwartzter, ED 24), digitalized via an eight-bit analog-to-digital converter (sampling rate 100 Hz), and stored on disk. Sleep stages were visually scored according to standard guidelines (Rechtschaffen and Kales, 1968) by experienced raters who were not aware of whether the subjects belonged to the HRP group, the healthy controls or the patient group. The sleep parameters including sleep architecture and sleep continuity were computed as described elsewhere (Friess et al., 1994). Quantitative EEG analysis was done on C3-A2/ C4-A1 EEG derivations using a fast Fourier transformation to compute sleep state-specific EEG power spectra. State-specific power of 50 frequency bins at 0.39 Hz intervals were cumulated across the delta (0.4–4.3 Hz), theta (4.7–7.8 Hz), low alpha (8.2–10.1 Hz), alpha (10.5–11.7 Hz), low sigma (12.1–13.7 Hz), high sigma (14.1–16.0 Hz) and beta range (16.4–19.1 Hz) as described previously (Friess et al., 2004).

2.4. Hormone measurements

The plasma concentrations of cortisol, ACTH and GH were determined by commercially available radioimmunoassay kits (corticotropin and GH: Nichols Institute Diagnostics, San Juan Capistrano, CA; cortisol: ICN Biomedicals, Inc. Carson, CA). All blood samples were analyzed in duplicate in the same assay with a maximum intra- and interassay coefficients of variation below 8%, respectively. The detection limits for ACTH and cortisol were 4.0 pg/ml and 1.0 ng/ml, respectively.

2.5. Data analysis

The statistical analysis of the quantitative EEG data focused on measures indicating the degree of EEG synchronization during NonREM sleep, i.e. the spectral power in the delta frequencies (0.8–4.3 Hz) and the sigma (12.1–16.0 Hz), low sigma (FB 12.1–13.7 Hz) and high sigma (FB 14.1–16.0 Hz) frequency range (Achermann and Borbély, 1998; Friess et al., 2004). Neuroendocrine response to the combined Dex/CRH-test was evaluated by calculating the area under the response curves (AUC) separately for ACTH and cortisol. Additionally, baseline corrected responses (net AUC, AUC minus baseline equivalent) were computed. Due to technical reasons ACTH measurements were available only in 11 patients, but in all HRP and CPs. Multivariate analyses of covariance (MANCOVA) controlling for age and gender were applied to detect group differences. Post-hoc Bonferroni–Holm tests were conducted for pair-wise group comparisons in case of significant univariate effects correcting for three simultaneous comparisons. Associations between sleep and HPA system regulation for the combined group of patients, HRP, and controls were evaluated by partial correlations controlling for age and gender. Group-wise association analyses were conducted non-parametrically with Spearman rank correlations. Means and standard deviations are reported. The level of significance was set to $P = 0.05$ (two-tailed). Global test $P$ values $< 0.10$ are reported as trends.

3. Results

3.1. Group differences

Gender distribution was not significantly different ($P = 0.159$), but the three groups differed in age ($P < 0.001$)
with MDEs older than HRPs ($P < 0.001$) and CPs ($P < 0.001$), respectively. All analyses were conducted after controlling for the effects of age and gender.

Group effects were found for dexamethasone suppressed ACTH and cortisol concentrations (baseline) and for the total cortisol response (AUC) to the combined Dex/CRH-test. Post-hoc test revealed significantly higher cortisol baseline concentrations in MDEs compared to CPs and HRPs ($F_{2,41} = 7.60, P < 0.01$), and higher cortisol AUC in MDEs compared to CPs ($F_{2,41} = 3.73, P < 0.05$, see Fig. 1).

Polysomnographic sleep analysis showed group differences for the number of awakenings and for the latency until slow wave sleep with MDEs showing the highest number of awakenings and highest slow wave sleep latency compared to HRPs and CPs (see Table 1).

No significant group differences were found for the total night spectrum analysis. We observed a trend suggesting marginal group differences for the NonREM low $(F_{2,42} = 3.10, P = 0.055)$ and high sigma band $(F_{2,42} = 3.05, P = 0.058)$. Post-hoc test did not reveal significant pair-wise group differences (see Fig. 2).

Significant group differences were observed for the second $2 \text{ h}$ epoch (1 a.m.–3 a.m.) in sigma, low sigma, and high sigma bands with HRPs showing the highest power values (see Table 2).

### 3.2. Sleep/HPA system associations

We observed for the combined groups of MDEs, HRPs, and CPs ($n = 47$) a negative association between REM density and elevated ACTH response to the Dex/CRH-test (net AUC $r = -0.33, P < 0.05$). This inverted association could be replicated in HRPs alone ($r = -0.54, P = 0.011$), in trend for MDEs alone ($r = -0.56, P = 0.071$), but not in controls ($r = 0.29, P = 0.366$). Fig. 3 gives a scatterplot of the individual values of REM density and net AUC of ACTH in both groups.

![Fig. 1. Dex/CRH-test response in healthy controls without personal or family history of psychiatric disorders (CP, $n = 12$), high-risk probands (HRP, $n = 21$), and patients suffering from major depressive episode (MDE, $n = 14$).](image)

Table 1

| Sleep EEG parameters in healthy controls (CP) without personal or family history of psychiatric disorders, high-risk probands (HRP), and patients suffering from major depressive episode (MDE) |
|---------------------------------|----------------|----------------|----------------|
| CP                | HRP            | MDE            |                |
|                   | $M$            | $SD$           | $M$            | $SD$           | $F_{2,42}$ | $p$   |
| Sleep period time (min)      | 462.21 ±16.06  | 459.71 ±18.98  | 431.39 ±45.21  | 0.32          | 0.730     |
| Sleep onset latency (min)     | 14.50 ±8.68    | 15.21 ±16.04   | 36.68 ±35.69   | 1.75          | 0.185     |
| Number of awakenings          | 11.58 ±5.14a   | 12.67 ±8.67a   | 30.57 ±16.70a  | 7.38          | 0.002     |
| REM latency (min)             | 75.71 ±19.02   | 70.67 ±32.24   | 91.11 ±41.76   | 1.33          | 0.275     |
| SWS latency (min)             | 13.33 ±4.62b   | 18.70 ±12.74b  | 66.12 ±40.95b  | 4.38          | 0.019     |
| SWS (min)                     | 72.04 ±23.21   | 70.38 ±31.29   | 45.77 ±33.33   | 1.16          | 0.324     |
| REM density                   | 1.76 ±0.58     | 2.30 ±0.89     | 2.93 ±1.04     | 2.23          | 0.120     |
| REM density 1st sleep cycle   | 0.89 ±0.73     | 1.50 ±1.05     | 2.26 ±1.49     | 1.71          | 0.193     |
| REM density 2nd sleep cycle   | 1.68 ±1.16     | 2.12 ±1.00     | 2.94 ±1.22     | 0.94          | 0.400     |

Note: Analysis of covariance controlling for age and gender.

SWS: slow wave sleep.

Post-hoc Bonferroni–Holm tests revealed significantly higher values in MDE compared to CP ($p < .01$) and HRP ($p < .01$).

Post-hoc Bonferroni–Holm tests revealed significantly higher values in MDE compared to CP ($p < .05$) and HRP ($p < .05$).
In the combined sample (n = 47), NonREM high sigma power was correlated with elevated dexamethasone suppressed baseline cortisol concentrations (r = 0.30, P < 0.05), which could not be replicated in the separate groups analyses (see Fig. 4).

When the sleep period is divided in 2 h epochs, significant associations between high sigma power and elevated dexamethasone suppressed baseline cortisol concentrations were observed for the third (3 a.m.–5 a.m.: r = 0.32, P < 0.05) and fourth (5 a.m.–7 a.m.: r = 0.33, P < 0.05) epochs. These effects were not found in the replication analyses separately for MDEs, HRPs, and CPs.

4. Discussion

This study investigated whether sleep macro- and micro-architecture and function of the HPA axis are correlated in individuals with normal and abnormal levels of HPA dysfunction. The study groups consisted of patients with an acute and severe depressive episode who were not treated with medication (MDE), healthy subjects at a high familial risk to develop an affective disorder (HRP) and healthy controls. The activity of HPA axis function was assessed by the combined Dex/CRH-test. The influence of age and gender were controlled in the statistical analysis.
As expected, the patients with major depression showed an excessive hormone response in the Dex/CRH-test. There is good evidence that the dysfunctional stress hormone regulation is due to an impaired corticosteroid receptor function as the key mechanism in the pathogenesis of depression (Holsboer, 2000; DeKloet et al., 2005). In addition, patients showed some but not all of the sleep abnormalities characteristic for depression (Reynolds and Kupfer, 1987; Lauer et al., 1992; Steiger et al., 1989; Wichniak et al., 2000). We observed a disturbed continuity (increased awakenings) and prolonged latency to the occurrence of slow wave sleep in the first sleep cycle. The overall amount of slow wave sleep and REM density did not differ significantly between the groups. However, REM density was highest and slow wave sleep lowest in the patient group which is in line with previous literature. As to sleep microarchitecture we observed a trend to an overall difference in the sigma wave band during NonREM sleep. A separate analysis of the second 2-h-period of the night sleep showed the highest sigma power values in the group of HRP and to a lesser extend in patients with depression when compared to the control group. One reason for the lack of statistical differences between MDD, HRP, and controls might be the small sample size. In addition, there were substantial differences in age between patients and HRP and controls. Even so we statistically corrected for these differences, we cannot exclude that the age difference might have confounded the outcome of the group comparisons.

With respect to the association between the microstructure of sleep and the results of the Dex/CRH-test we observed for the combined study groups: (1) an inverse association of the ACTH response (net AUC) to the Dex/CRH-test and REM density, and (2) a positive association of suppressed baseline cortisol levels and EEG frequencies in the higher spindle frequency range (14–16 Hz). The negative association of REM density and CRH stimulated ACTH levels could be replicated when the analysis was restricted to HRP, in trend for depressed patients, but not for controls.

These results appear somewhat contradictory to previous findings, suggesting that elevated REM density and elevated hormonal responses to the Dex/CRH-test are both potential markers for affective disorder (Lauer et al., 1995; Holsboer et al., 1995; Modell et al., 1998, 2002,
In addition, several studies showed that a persisting increase in REM density (Buysse et al., 1997, 2001; Clark et al., 2000) as well as a persistently altered stress hormone regulation (Ising et al., 2005b, 2007) are both predictive for a less favorable outcome in depression. Moreover, Hatzinger et al. (2004) reported that elevated REM density: (1) predicted an unfavorable long-term outcome and (2) was related to excessive stress hormone response in the DEX/CRH-test in patients during acute depression medicated with the tricyclic antidepressant trimipramine. The authors suggested a trait-like association pattern between distinct sleep variables and dysfunctional stress hormone regulation that could reflect a common underlying process of the disease. However, our results do not support this conclusion but suggest an opposite association of altered REM density and increased activity of the HPA axis. We would like to propose that the negative association of REM density and HPA axis regulation is a result of the selection of subjects (unaffected HRPs, severely depressed patients) and the complementarity of the two markers. Regarding REM density, there is considerable evidence that this is a stable vulnerability marker indicative for the genetic risk to develop an affective disorder (Modell et al., 2002, 2005). Altered regulation of the HPA axis could also be observed in high-risk subjects (Holsboer et al., 1995; Modell et al., 1998) but did not predict the onset of an affective disorder (Ising et al., 2005b). However, during the acute process of the disease impaired HPA axis regulation can be observed in the majority of depressed patients, while effective antidepressant treatment gradually normalizes this alteration (Ising et al., 2005b, 2007). These findings suggest that the Dex/CRH-test is rather a biomarker reflecting the actual disease process. To interpret our finding of a negative association between REM density and the ACTH response to the Dex/CRH-test in HRPs and depressed patients, we need to take into account that these markers were evaluated in unaffected HRPs without history of depression as well as in severely depressed patients. Considering this, one could speculate that subjects carrying a high genetic vulnerability, indicated by an elevated REM density, have a lower threshold until a latent disease process affecting HPA axis regulation translates into depression, and vice versa. Accordingly, HRPs with high REM density, who were unaffected at the time of the investigation, were more likely to present with a less pronounced response to the Dex/CRH-test than HRPs with low REM density; the same may apply to the group of depressed patients selected for severe depression, where a high genetic vulnerability indicated by increased REM density might also be accompanied by a lower threshold until impaired HPA axis regulation translated into severe depression. It needs to be mentioned, that ACTH levels could have been determined only in a reduced sample of n = 11 patients limiting the interpretation of this finding. However, the correlation coefficient, which can interpreted as a sample-independent effect size measure suggest a similar association effect in HRPs and patients.

No association was found in controls with a negative personal and family history for psychiatric disorders, which again might be explained by the subject selection resulting in a low likelihood for a genetic vulnerability or for an actual disease process, making it unlikely to find associations between disease-related markers.

The discrepancy between our results and the findings by Hatzinger et al. (2004) mentioned above may result from methodological differences. The major difference between both studies is that in our study HRPs as well as the depressed patients were unmedicated. Therefore, it may be speculated that an association between the given sleep and endocrine parameters is treatment dependent. There is considerable evidence that an efficacious antidepressant medication in particular with trimipramine attenuates an altered dysregulation of the HPA axis (Frieböes et al., 2003; Ising et al., 2005b), which occurs before a clinical response becomes apparent (Ising et al., 2007). REM sleep, on contrary, is enhanced under treatment with the antidepressant trimipramine (Sonntag et al., 1996), which has been applied in the study by Hatzinger et al. (2004). These opposing effects on REM sleep and stress hormone regulation might explain the positive association in patients treated with trimipramine.

The elevated sigma power in the group of HRPs and to a lesser extent also in the patients with depression is difficult to interpret. An early report in patients with depression showed a reduced spindle density (DeMaertelaer et al., 1987) which could not be replicated in the present study. EEG activity in the sigma frequency range represent sleep spindles of two different frequency types, the low and high frequency spindles. The amount of sleep spindles and slow delta waves reflect the process of EEG synchronization during NonREM sleep (Dijk, 1995). It has been suggested that the linear increase in low sigma frequencies (11–13 Hz) throughout the night serve to maintain sleep when highly synchronized delta waves are already at a low level (Dijk and Czeisler, 1995). In addition, it is known that a significant proportion of the general population lack the typical age-dependent decline of low sigma sleep spindles after puberty and exhibit a high power values in these frequencies also during adulthood. The physiological relevance of this phenomenon is unclear (Gibbs and Gibbs, 1950; Shinomiya et al., 1999). In contrast, high sigma spindles (14–16 Hz) appear to occur “age-resistant” (Landolt et al., 1996) and show opposite dynamics within night sleep since they peak in the initial hours together with delta waves (Aeschbach et al., 1997; Wei et al., 1999; Tagaya et al., 2000). It cannot be excluded that the increased amount of lower sigma frequencies in the group of HRPs is an artifact and due to the proportion of subjects carrying this variant of within the norm. On the other hand, the observed result may indicate subtle signs of a disturbed EEG synchronization in these subjects.

With regard to hormone response and sleep EEG composition we observed a significant positive association between dexamethasone suppressed cortisol levels in the
Dex/CRH-test and high sigma power for the combined groups of subjects and patients. However, a separate groups-wise association analysis failed to replicate this finding. Fig. 4 demonstrates that an equal number of HRPs and patients with depression and also one healthy subject exhibited high values in both parameters with respect to the mean of the control group. Excessive increase in HPA activity is one of the most relevant endocrine abnormalities in depression and suggested to impair the generation of slow wave sleep or sleep intensity, respectively (for review see Steiger, 2003). Therefore, a negative association between signs of HPA hyperactivity and in particular the amount of slow waves would have been expected. However, sleep of both the HRPs and the patient group was not characterized by a slow wave sleep deficit though the patients suffered from an acute and severe depression. This might explain the lack of the expected inverse relation between delta power and HPA hyperactivity. The observed positive association of suppressed cortisol levels and high sigma power was pronounced in the second half of night sleep where the increase in cortisol release reflects the predominating influence of the HPA axis on sleep regulation. Our results indicate that HPA hyperactivity may disturb the sleep-associated process of EEG synchronization already on a subthreshold level where the generation of slow waves is not yet affected. It has to be mentioned, however, that the EEG recordings of the present study was restricted to central derivations. Thus, the occurrence of high sigma frequencies may have been overestimated in comparison to low sigma power with maximal values in frontal derivations.

Previous findings, partly replicated in the present study, suggest suitability of the combined Dex/CRH and of sleep parameters as possible biomarkers in depression; our presented findings provide further evidence that the HPA axis is involved in the sleep regulation in depression. These associations, however, are not unidimensional, but dependent on the kind of sleep parameters as well as on the selection of the subjects.

Role of Funding Source

There was no external funding of the study.

Conflict of Interest

All authors declare that they have no conflict of interests.

Contributors

Sieglinde Modell recruited and screened the high-risk probands for affective disorders and the healthy subjects. Dagmar Schmid recruited the patients with depression. Elisabeth Friess wrote the manuscript and designed the present study. Christoph Lauer and Florian Holsboer initiated the “Munich Vulnerability Study on Affective Disorders” and contributed substantially to the design of study on the acute effects of cortisol in patients with depression. Hans Brunner prepared the sleep EEG data for statistical analysis that was done by Marcus Ising who also contributed substantially to the manuscript. All authors contributed to and have approved the final manuscript.

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References

Aeschbach D, Dijk DJ, Borbély AA. Dynamics of EEG spindle frequency activity during extended sleep in humans: relationship to slow-wave activity and time of day. Brain Research 1997;748:131–6.


