J Biol Phys (2008) 34:393–404
DOI 10.1007/s10867-008-9096-x

ORIGINAL PAPER

Comparison of Different Methods for the Evaluation of Treatment Effects from the Sleep EEG of Patients with Major Depression

V. Carolina Figueroa Helland · Svetlana Postnova · Udo Schwarz · Jürgen Kurths · Bernd Kundermann · Ulrich Hemmeter · Hans A. Braun

Received: 18 February 2008 / Accepted: 17 June 2008 /
Published online: 31 July 2008

Abstract In healthy subjects, sleep has a typical structure of three to five cyclic transitions between different sleep states. In major depression, this regular pattern is often destroyed but can be reestablished during successful treatment. The differences between healthy and abnormal sleep are generally assessed in a time-consuming process, which consists of determining the nightly variations of the sleep states (the hypnogram) based on visual inspection of the electroencephalogram (EEG), electrooculogram, and electromyogram. In this study, three different methods of sleep EEG analysis (spectrum, outlier, and recurrence analysis) have been examined with regard to their ability to extract information about treatment effects in patients with major depression. Our data suggest that improved sleep patterns during treatment with antidepressant medication can be identified with an appropriate analysis of the EEG. By comparing different methods, we have found that many treatment effects identified by spectrum analysis can be reproduced by the much simpler technique of outlier analysis. Finally, the cyclic structure of sleep and its modification by antidepressant treatment is best illustrated by a non-linear approach, the so-called recurrence method.

V. C. Figueroa Helland (✉) · U. Schwarz · J. Kurths
Interdisciplinary Center for Dynamics of Complex Systems, University of Potsdam, Potsdam, Germany
e-mail: carolina_fi79@yahoo.com

S. Postnova · H. A. Braun
Institute of Physiology, University of Marburg, Marburg, Germany

B. Kundermann · U. Hemmeter
Clinic of Psychiatry and Psychotherapy, University of Marburg, Marburg, Germany

U. Hemmeter
Center of Education and Research (COEUR), Psychiatric Services of the County of St. Gallen, St. Gallen, Switzerland

J. Kurths
Potsdam Institute for Climate Impact Research, Potsdam, Germany

Keywords Sleep EEG · Depression · Sleep structure · Recurrence · Power spectrum · Hypnogram

1 Introduction

Sleep disturbance is a prominent symptom of various mental diseases, such as major depressive disorder (MDD). Major depression is characterized by depressed mood, loss of interest and pleasure, and suicidal ideation. Diagnosis of depression and the estimation of its intensity and of treatment effects is essentially based on standardized interviews and questionnaires, e.g., the Structural Clinical Interview (SCID) and the Hamilton Depression Rating Scale [1, 2].

With the mostly accepted assumption is that the strength of depression and the severity of sleep disturbance are strongly associated, additional measures of depressive disorders can be provided by the analysis of the characteristically disturbed sleep patterns. Of course, sleep disturbances have a strong subjective component, but they can be quantified by polysomnography. This is a nightly recording of the electroencephalogram (EEG) together with the electrooculogram (EOG) and the electromyogram (EMG) which give information about brain activity, eye movements, and muscle tone, respectively.

These recordings are used to classify sleep into different stages according to criteria as suggested by Rechtschaffen and Kales [3]. There are two light sleep stages (S1 and S2) and two deep sleep stages (S3 and S4). Additionally, a particular sleep state of rapid eye movements (REM) is considered as well as the wake state (W) [4, 5]. When these states are determined for successive 20- or 30-s time intervals and then plotted over the course of the night in a hypnogram, a typical pattern appears which shows cyclic transitions through the different sleep states. In more or less regular intervals of about 90–120 min, a healthy person repeatedly goes from light sleep through deep sleep to REM sleep and back. In three to five successive cycles, towards the morning, the amount of REM sleep increases, while non-REM sleep is shortened and less deep.

In depressive patients, this regular pattern is characteristically destroyed [6, 7]. The hypnograms show irregular transitions between the different sleep states with many interruptions by awakenings. Depressive patients have significantly reduced deep sleep stages and lengthened REM sleep. This especially holds true for the first REM phase which also appears with a shortened latency. The treatment effects on sleep disturbance are generally measured by a “normalization” of these parameters.

All these parameters may provide significant measures of treatment effects—on the average. For individual patients the effects can be very different and even different drugs of comparable efficacy can influence different sleep parameters in different ways [8, 9]. Hence, the exactness which such numerical values of specific measures imply may be misleading. Moreover, one should not forget that the hypnograms still have a subjective component. The classification of the sleep states is done by visual inspection of the EEG, EOG, and EMG in a time-consuming process.

Our actual approach aims to examine whether other methods of sleep analysis are available or can be developed which can provide an easier and more objective measure of the efficacy of medical treatment in depressed patients. To achieve this goal, we have focused on the sleep EEG. We have neglected the other measures from the EOG and EMG to keep the requirements on the recordings and on the analytical procedures as simple as possible. This can be justified considering that the different sleep states are essentially characterized by the frequency and amplitude of the EEG. Deep sleep is clearly indicated

by slow EEG waves of high amplitudes, described as delta and theta activity, which covers a frequency range below 8 Hz. The transition to light sleep and REM phases, apart from the occurrence of specific waves (sleep spindles, etc.), can be recognized by increasing EEG frequencies of lower amplitudes. The EEG during REM sleep is similar to waking states, showing beta waves with frequencies above 12 Hz.

We propose here three different methodological approaches. The first is based on the spectrum analysis of the EEG, calculating the power of selected frequency bands [10, 11]. This is a more conventional approach which repeatedly has been used in combination with the hypnograms. Secondly, we have implemented a very simple approach, called the "outlier analysis". The method consists only of counting the EEG values above a certain threshold. Last but not least, we have introduced a non-linear analysis of the EEG dynamics [12] which is called the "recurrence method".

2 Data and Methods

2.1 Polysomnographic Measurements

Five female patients suffering from an acute major depressive disorder have been diagnosed according to the Structural Clinical Interview (SCID) [1]. The severity of depression and treatment response were determined by the Hamilton Depression Rating Scale [2]. After baseline assessment without medication, all patients have been treated with a continuous antidepressant monotherapy of 30 mg mirtazapine throughout the study.

The polysomnographic recordings were preceded by an adaptation night. They were obtained at baseline (unmedicated) and after several weeks of medication (1 to 10 weeks after the beginning of the treatment). All polysomnograms were recorded between 11 p.m. and 7 a.m. by means of standard procedures: horizontal electrooculogram (EOG), submental electromyogram (EMG), electrocardiogram (ECG), and electroencephalogram (EEG). The EEG data which are analyzed here were obtained with electrode pairs F3–A1 for three of the patients and C3–A2 for two patients. The EEG data were sampled at 100 Hz. The records were scored by two experienced raters independently in time steps of 30 s to determine the sleep stages according to standardized criteria [3] following the definitions in the standard program described by Lauer et al. [13].

2.2 Computational Techniques

Three different methods have been applied to examine their ability to extract information about the effects of medical treatment by analysis of the sleep EEG: (1) spectrum analysis, as a more conventionally used tool, (2) outlier analysis, a simpler approach based on statistical properties of the EEG data, and (3) recurrence analysis, a more refined non-linear approach suitable for dealing with the non-stationarity of the data. Furthermore, the data were analyzed within a sliding window of 50 s width with 80% overlap, i.e., a shift of 10 s.

2.2.1 Spectrum Analysis

We use the spectrum analysis of the sleep EEG to calculate the power of two frequency bands. The first one covers the delta range (0.5–4 Hz) which represents slow oscillations

in deep sleep states. The second one comprises the high-frequency oscillations of the beta band (12–30 Hz) which appear in REM sleep and during waking episodes.

We use the FIR filter class [14] to decompose the original signal according to these two bands and than calculate the power P_δ and P_β for the delta and beta frequency bands, respectively. To assess the relationship between the power of the slow and fast oscillations we use their quotient [15]:

$$Q_{\delta,\beta} = \frac{P_\delta}{P_\beta}. \tag{1}$$

2.2.2 Outlier Analysis

The term "outlier" conventionally denotes data points which are outside the expected range of a signal and therefore are regarded as artifacts. The simplest way to cut these measurements off is to set a threshold and eliminate all values which are lying above. Here we have used this simple method first to remove artifacts and then to mark the occurrence of slow-wave activity in the sleep EEG.

We standardize the EEG and then eliminate the largest artifacts by discarding EEG values whose absolute value is greater than 4. Then we recalculate the mean and standard deviation. For the identification of slow-wave EEG activity, we use a threshold value of $2\sigma_x$ above the mean.

The background for such an approach is the well-known relation between frequency and amplitude of the EEG waves: the slow delta waves have a much higher amplitude than the high frequency beta waves [16]. Hence, with an appropriate setting of the threshold value, the slow oscillations with their high amplitudes should produce a high number of outliers while the high-frequent beta activity with low amplitudes should not cross the threshold value.

We evaluate the number of outliers with a sliding window (see Fig. 1) according to:

$$n_{W(t)} = Card\left\{x_t \,|t \in W(t)\,, x_t > \bar{x} + 2\sigma_x\right\},$$

$$W(t) = [tf_sT + 1,\, f_sT(t+1)]\,,$$

where $n_{W(t)}$ is the number of values x of the time series within the time window $W(t)$ that starts at time t, such that x is larger than a fixed threshold of two standard deviations ($2\sigma_x$) above the EEG mean.

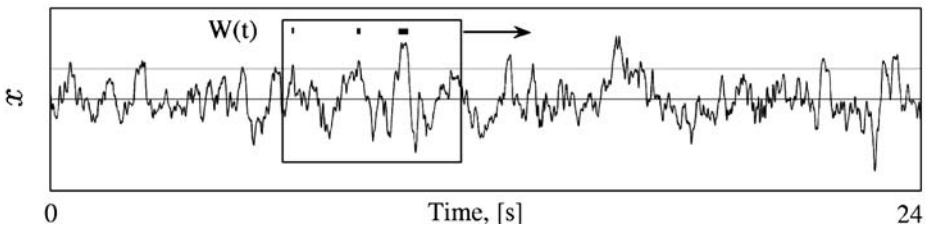

Fig. 1 Example of a sleep EEG recording to illustrate the outlier analysis with a moving window $W(t)$ as indicated by the *box* and the *arrow*. The *lower horizontal line* shows the mean of the EEG and the *upper line* the threshold value at $(\bar{x} + 2\sigma_x)$. The *marks in the window box* indicate the occurrence of outliers

The window begins at time t indicated in seconds and has length T= 50 s (corresponding to 5,000 data points). Above, f_s is the sampling frequency (100 Hz).

2.2.3 Recurrence Quantification Analysis

Recurrence plots (RP) have been introduced for the investigation of dynamical systems [17, 18]. They are especially suitable for studying non-stationary behavior. Recurrence plots, as their name implies, are a visual tool useful for illustration of recurrent behavior and state transitions of the system, which is hypothesized to underlie the observed time series.

The behavior of the dynamical system may be conceptualized as a trajectory of points in a phase space of dimension m, each representing a variable of the dynamical system. This trajectory, according to the time delay embedding method [19], may be reconstructed from a time series $\{x_t\}$ as $\overrightarrow{X_t} = \left\{x_t, x_{t+\tau}, x_{t+2\tau}, \ldots x_{t+(m-1)\tau}\right\}$.

The embedded vector constructed by the time delay method has m components (Fig. 2a). Here m is the dimension of the phase space. The time interval τ is used for generating the components of the embedded vector from the time series. This time interval accounts for

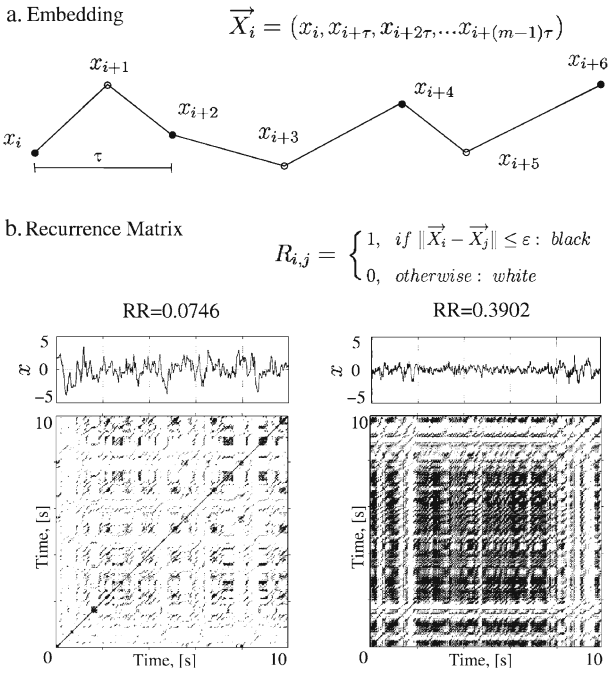

Fig. 2 Recurrence analysis of sleep EEG. **a** Time delay embedding. For each recording of the EEG x_i, a vector $\overrightarrow{X_i}$ is constructed. This vector is depicted here with elements represented as *solid circles* with a time delay τ (in the figure represented equal to two). This embedding procedure gives a trajectory in phase space (in the figure, 4-dimensional). **b** Construction of recurrence plot and evaluation of recurrence rate. For each vector $\overrightarrow{X_i}$, the vectors $\overrightarrow{X_j}$ within a distance ε of $\overrightarrow{X_i}$ are represented as *black points* in the recurrence plot, corresponding to a value of 1 in the recurrence matrix $R_{i,j}$. The recurrence rate (RR) is the fraction of *black points* on the matrix $R_{i,j}$. Observe that the recurrence plot of a time series with high variability (*left*) gives low values of RR, while one with low variability (*right*) gives high values of RR

dependence between components of the vector $\overrightarrow{X_t}$ and should be chosen to maximize their independence [20].

Upon obtaining the set of vectors, namely, the trajectory $\left\{\overrightarrow{X_t}\right\}$ for each time t in the time series $\{x_t\}$, the recurrence plot is defined as the matrix

$$R_{i,j} = \Theta\left(\varepsilon - d\left(\overrightarrow{X_i}, \overrightarrow{X_j}\right)\right). \tag{2}$$

Here $\overrightarrow{X_i}$ and $\overrightarrow{X_j}$ are vectors in m-dimensional space with $i, j = 1, 2, \ldots, N$, where N is the number of vectors in the trajectory. The expression $d\left(\overrightarrow{X_i}, \overrightarrow{X_j}\right)$ denotes the Euclidean distance between the vectors $\overrightarrow{X_i}$ and $\overrightarrow{X_j}$. The value ε within the brackets specifies the size of the neighborhood around each point $\overrightarrow{X_i}$. $\Theta(\cdot)$ is the Heaviside function, which takes the value of 1 when the argument is greater than or equal to 0, and 0 otherwise. This means, points $\overrightarrow{X_j}$ that are within a distance ε from $\overrightarrow{X_i}$ give a black point in the recurrence plot (corresponding to a value of 1 in the matrix $R_{i,j}$, see Fig. 2b).

The recurrence matrix $R_{i,j}$ may be inspected visually for patterns. However, the amount of visual data in the RP as well as the necessity for their objective quantification has brought about the introduction of recurrence quantification analysis. In this paper, we use the recurrence rate (RR) [17, 18]. We also calculated the recurrence time [18] which, however, is not further considered in this paper because the results are comparable to the more simple measure RR.

The RR is the fraction of recurrence points in the recurrence plot:

$$RR = \frac{1}{N^2} \sum_{i,j=1}^{N} R_{i,j}. \tag{3}$$

Time series with high variability, as is the case with slow-wave sleep in the EEG, yield low values of RR, while those with low variability give high values of RR (see Fig. 2).

We calculated the recurrence rate RR on the low pass filtered EEG along a moving window of 50 s with 80% overlap. We use the discrete wavelet transform (DWT) as a low pass filtering technique to observe the behavior of the signal up to frequencies of 6 Hz. Given the length of the EEG and the high computational demand of the recurrence method, we base our choice of the DWT on its utility as a data compression tool. The DWT offers a means to efficiently down-sample long data series and simultaneously capture transient behavior at different time scales [21].

3 Results

We examine whether appropriate analytical methods are available or can be developed for the purpose of extracting treatment effects on depressed patients from the raw, unprocessed EEG. Thereby, we do not search for singular events of the sleep pattern, e.g., REM latency, but focus on two more general aspects of sleep disturbances in depressed subjects. These are (1) reduced slow-wave sleep and (2) disturbances of the cyclic sleep structure [9, 22]. Successful treatment is expected to enhance deep sleep and to regularize the sleep structure.

Three of the five patients could be classified as “responders” according to the Hamilton scale, which means that these patients achieved a significantly improved mood after drug

treatment. One patient did not respond on the drug treatment. The Hamilton rating of the other patient did not decrease sufficiently to be considered a "responder" according to the general criterion (50% reduction) but the decreased value from 21 to 14 at least indicates a positive drug effect.

We have analyzed the EEGs of these five patients with different approaches as described in Section 2: (1) spectrum analysis, (2) outlier analysis, and (3) recurrence method. Examples of EEG analysis from two patients, each before and after treatment, are shown in Fig. 3 in comparison with the hypnograms. Patient 1 (left) is from the group of responders. Patient 2 (right) is the abovementioned person whose Hamilton rating was only reduced by 30%. This selection was made to illustrate the power of the different methods when the Hamilton rating indicates significant mood improvement in comparison to more subtle medication effects.

In the recordings from patient 1, the cyclic structure of the sleep pattern is easy to recognize, even before treatment, by the periodic alternations of the delta/beta ratio (Fig. 3, left upper traces). However, the cyclic structure becomes clearly more pronounced after treatment, especially because the delta/beta ratio reaches much higher values. Therefore, it may be expected that the patient, after treatment, has an increased delta power during deep sleep states. This, however, is not necessarily the case [13, 23]. The increasing values of the delta/beta ratio are essentially caused by reduced beta activity. Reduced beta activity, in turn, does not mainly reflect less pronounced REM phases but comes from less frequent awakenings.

Also, the outlier analysis of the sleep EEG of patient 1 (Fig. 3, second traces on the left) strongly suggests a significant reduction of the awakenings by drug treatment. The large but short peaks in the outlier values which, before treatment, can be seen throughout the night are obviously indicating not short phases of slow-wave sleep, but rather the frequent awakenings of this patient. After treatment, such short and strong deflections are drastically

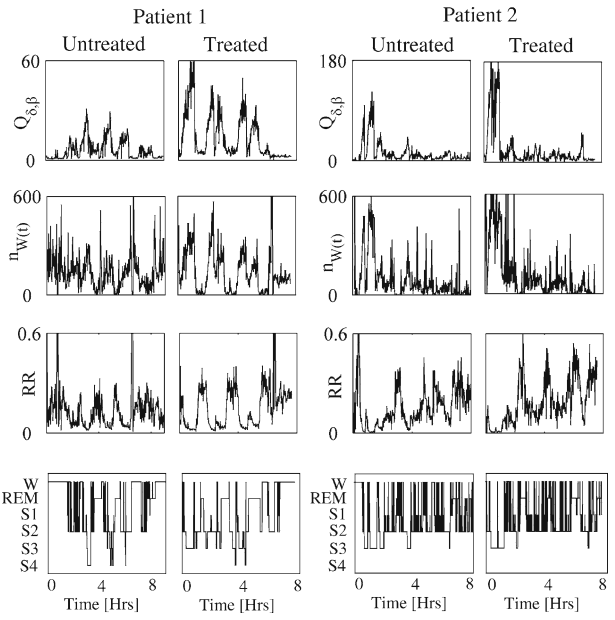

Fig. 3 Comparison of different methods of sleep EEG analysis of two patients with major depression before and after treatment with mirtazapine. *Upper traces*: spectrum analysis (delta/beta ratio, $Q_{\delta/\beta}$); *second traces from top*: outlier analysis (number of outliers, $n_{W(t)}$); *third traces* from top: recurrence rate (RR); *lowest traces*: hypnograms, illustrating the transitions between different sleep states from wake (W) to REM sleep, two states of light sleep (S1 and S2), and two deep sleep states (S3 and S4)

reduced. The patient has a much more regular sleep. The outlier values are more gradually increasing in parallel with the delta/beta ratio, which suggests that both measures now rather reflect the occurrence of slow-wave sleep (delta activity) than disturbances.

The improved sleep structure by drug treatment can also be seen in the plots of the recurrence rate (RR) of patient 1 (Fig. 3, left diagrams, third traces from top). This measure again depends on whether the EEG is dominated by high-frequent beta or low-frequent delta waves. In contrast to the other curves, RR decreases with high delta activity and increases with high beta activity. The reason is that the strong deflections in the EEG curves during delta activity change the recurrence vector much more than the much smaller fluctuations during beta activity, especially when they are additionally attenuated by the low pass filtering (see Section 2). As a consequence, the RR also appears less sensitive to disturbances through electrode movements during awakenings.

For patient 1, the effects of mirtazapine treatment are immediately obvious with all three methods. Each of them shows a more clearly structured sleep pattern with an increasing amount of slow-wave sleep. This can also be seen with the simplest method, the outlier analysis, where the differences are even clearer because the outlier values do not only show the regularization of the sleep patterns but also the disappearance of irregular awakenings. This result is concordant with the effects of mirtazapine, which is known to reduce the number of awakenings and their duration [9, 24].

The situation is different for patient 2 (Fig. 3, right diagrams) who does not have a sufficient reduction of the Hamilton rating to be classified as a responder. In this case, the delta/beta ratio (upper traces) cannot detect significant changes before and after treatment. In the outlier curves (second traces from top), the most obvious difference is that the outlier values are considerably higher after the treatment all over the night. There is a most pronounced peak in the first part of the night. These high outlier values at the beginning of the night, indeed, may reflect an improved deep sleep during the first sleep cycle which is considered one of the first signs of sleep regularization [24].

Such a medication effect is also indicated by the recurrence rate. The RR values go close to zero for almost 1 h, suggesting a long-lasting state of deep slow-wave sleep. Moreover, the recurrence method, better than the other approaches, elucidates a clear treatment effect on the sleep structure. During treatment, a comparably regular sleep pattern develops with regular cyclic alterations between low and high RR values.

Furthermore, in both RR curves, before and after treatment, it can clearly be seen that the minimum values keep further away from the zero line in successive cycles. This bias reflects a well-known healthy time course of less deep sleep phases towards the end of the night. This specific feature of the sleep structure can also be observed, but only after treatment, in the sleep diagrams of patient 1. In the curves of the delta/beta ratio and the outliers, such effects appear as continuously decreasing amplitudes of the deep sleep peaks.

Altogether, among the three different methods have been applied here, it seems that the recurrence analysis has a certain advantage, as it can detect a sleep structure and its changes even when these cannot be seen with the other approaches. The specific value of this new approach can be particularly well seen in comparison with the conventionally used hypnograms (Fig. 3, lowest traces).

The hypnograms of both patients, before and after treatment, look rather unstructured. Indeed, for patient 1, some treatment effects may be assumed due to a higher probability of S2 and S3 states and less frequent wake states. However, the establishment of a cyclic sleep pattern by the medication, which becomes immediately evident in the RR diagrams, can hardly be recognized in the corresponding hypnograms.

To extract some treatment effects from the hypnograms of patient 2 (Fig. 3, lowest diagrams on the left) should be a particular challenge also for experts. Indeed, there is a comparably high probability of sleep state 3 (S3) at the beginning of the night, indicating a first deep sleep phase. However, this appears in both hypnograms, before and after treatment. Further in the night, both hypnograms seem to switch rather irregularly between different states, mostly between the light sleep states S2 and S1, the REM and the wake state (W). In the hypnograms, practically nothing can be seen of the cyclic sleep structure which is clearly manifested especially in the RR values, even in the untreated patient.

Nevertheless, with a closer look, it can be recognized that the hypnograms and the RR plots show significant coincidences in many details. In both cases, untreated and treated, at the beginning of the night, the RR values decrease toward zero when, in the hypnogram, the S3 state occurs. The slight deflections to higher values appear exactly whenever the S3 state in the hypnogram is interrupted. Even the short transition to the S3 state in the hypnogram on the right (treated) towards the end of the night is reflected in the RR plot by a strong downward deflection. An attentive observer can detect even more coincidences in specific details. Nevertheless, this will not help to extract the 90-min sleep cycles from the hypnograms while they can immediately be seen in the RR plots, including their enhancement by the medication.

4 Discussion

We have used different methodological approaches to analyze the sleep EEG of five patients with major depression before and during treatment with the antidepressant drug mirtazapine. This study was made in search for more simple and reliable methods of sleep EEG analysis for the evaluation of treatment efficacy. In contrast to the conventionally used hypnograms, these methods are not primarily designed to quantify specific sleep parameters like REM latency or the amount of REM and deep sleep, but to elucidate sleep improvements from more general characteristics whereby the most prominent changes have been seen in the cyclic structure of sleep, i.e., a periodic alteration between non-REM and REM phases. This temporal pattern is more or less destroyed in depressed patients, but can be reestablished by successful treatment. In comparison of the different methods, we have found that such effects are most clearly elucidated by a non-linear approach, the recurrence analysis.

Indeed, it is not a problem, for any of the methods, to demonstrate an improved sleep structure when the drug exerts clearly positive effects on mood. Such an example is illustrated with recordings from patient 1 who unambiguously can be classified as a “responder” with a more than 50% reduction of the Hamilton score. The different methods thereby may reflect different aspects of sleep improvement. For example, an increasing delta/beta ratio can indicate both a reduction of beta activity and enhanced delta activity. In any case, it suggests that the patient is more often in a more pronounced slow-wave sleep and has fewer disturbances by awakenings. When the patient is mainly cured of frequent awakenings, this may best be recognized with the simplest method, the outlier analysis. The outliers react sensitively to any kind of disturbances with strong deflections and these should disappear during successful treatment.

The advantage of the more complicated, non-linear recurrence method mainly becomes evident in situations of less clear treatment effects as illustrated with the example of patient 2. For this patient, compared to baseline, the Hamilton ratings were reduced by only 30%. Most psychiatrists would not classify such a patient as a responder, though some would.

Such threshold values are arbitrarily set. In any case, also this patient somehow "responds" to the treatment and this can be recognized by the analysis of the EEG. In the delta/beta ratio and the outlier curves, however, the treatment effects are mainly indicated by enhanced values during the first sleep cycle. Only the recurrence method can clearly elucidate the cyclic sleep pattern, even before the treatment, and can demonstrate its regularization due to the treatment. Additionally, both RR curves show the typical bias towards less deep sleep states in the course of the night.

Following up on these encouraging results, our future studies will be focused on improving the power of the recurrence method and also of the other approaches, especially the outlier analysis. In case of the spectrum analysis, we do not expect to easily achieve further significant improvements, because much effort in this respect already has been made in many previous studies [25, 26]. Other studies have shown that the delta/beta ratio provides the most information about the alterations of the sleep structure [27].

The recurrence method has clear advantages, presumably because such non-linear approaches are better adjusted to the non-linear dynamics of the sleep-controlling systems. The use of more complex measures, however, often comes at the cost of an intuitive understanding. Therefore, further efforts shall be made to examine which of the specific characteristics in the EEG allows the recurrence method to extract information about improved sleep patterns better than the other approaches. As an example, from previous non-linear approaches on EEG sleep recordings, it is known that the correlation dimension successfully distinguishes slow-wave episodes of sleep from other stages [28]. The correlation dimension is high for REM sleep and low for slow-wave sleep. These results can be immediately related to our study by considering that the correlation dimension is a logarithmic expression of the recurrence rate. The elucidation of the underlying features could provide new insight also into the EEG dynamics.

For the other approaches, the relations between the EEG and the analytical results are better understood. In case of the spectrum analysis, the relevant parameter is the frequency of the EEG, or more precisely its power. In case of the outlier analysis, even simpler, it is the EEG amplitude. It is more remarkable that the outlier analysis, which looks on only one parameter, the amplitude, detects the alterations of the sleep EEG at least as well as the spectrum analysis.

We can think about further improvement of the outlier analysis, e.g., with a dynamical threshold which adapts to gradually changing EEG power, or with more refined filtering procedures as are also part of the recurrence analysis. However, we have to be careful not to destroy relevant information. For example, the irregular occurrence of outliers before treatment is a major indicator of disturbances and their disappearance in the course of the treatment is an important measure of improved sleep. In any case, the use of statistical learning algorithms can be very helpful to optimize the analytical tools.

It is one of the major and most surprising outcomes of this study that the cyclic structure of the sleep pattern and its enhancement by drug treatment can immediately be recognized especially well in the RR curves, even when it cannot be seen in the conventionally used hypnograms. The reason may be that the hypnograms are built up on a few discrete steps, while the recurrence rate rather resembles an analog curve which better reflects the typically gradual transitions of physiological parameters.

However, the transformation of the sleep pattern into discrete values can have specific advantages. The hypnograms allow calculation of numerical values of sleep parameters which are considered important markers of depression, like the duration of deep sleep or REM states or the REM latency. Such numerical values can also be used for further

statistical analysis while our approaches, so far, mainly provide graphical information and have to compare individual sleep EEGs. This is not necessarily a disadvantage for the clinical routine, where the decisions about treatment effects have to be made for each individual patient in any case. It is questionable whether mean values and standard deviations of large groups of patients can really give more information than the comparison of individual data.

Quantifiable measures, however, will be desired as soon as clinical decisions begin to be made on the basis of a new approach, irrespective of whether these values will also be used for statistical analysis or not. It will be necessary to prove the reliability of newly established approaches on the basis of these measures, especially in comparison with the disease-relevant sleep parameters of the hypnograms as well as with the ratings and evaluations of psychiatrists. Hence, it will be one of the next tasks to search for numerically quantifiable measures of sleep improvements from the methods which have been introduced here.

To underline the significance of our results, it also will be necessary to extend the data basis. Only with larger data sets, it will be possible to develop statistical learning algorithms on the basis of the actual results and to evaluate their efficacy. Moreover, it could be examined whether one or another measure, or a combination of them, exhibits specific, eventually bimodal distributions which justify a crisp distinction between responders and non-responders. It will be of particular interest to see how these values are related to the alterations of the Hamilton ratings, especially to the 50% reduction which is used in practice as a threshold value to separate responders from non-responders. Further extension of the data pool shall be made to compare the effects of different antidepressant drugs which are known to affect different sleep parameters [9, 24]. With the availability of even broader data pools, it will be interesting to examine whether the new methods also allow detection of systematic differences in sleep disorders of different origin.

Acknowledgements This work was supported by the European Union through the Network of Excellence BioSim, contract no. LSHB-CT-2004-005137.

References

1. Spitzer, R.L., Williams, J.B., Gibbon, M., First, M.B.: The structured clinical interview for DSM-III-R (SCID) I: History, rationale, and description. Arch. Gen. Psychiatry **49**(8), 624–629 (1992)
2. Hamilton, M.: Development of a rating scale for primary depressive illness. Br. J. Soc. Clin. Psychol. **6**(4), 278–296 (1967)
3. Rechtschaffen, A., Kales, A. (eds.): A manual of standardized terminology, techniques and scoring system for sleep stages in human subjects. U. S. Government Printing Office (1968)
4. Silber, M.H., Ancoli-Israel, S., Bonnet, M.H.: The visual scoring of sleep in adults. J. Clin. Sleep Med. **3**(2), 121–131 (2007)
5. Iber, C., Ancoli-Israel, S., Chesson, A., Jr., Quan, S.: The AASM manual for the scoring of sleep and associated events. American Academy of Sleep Medicine (2007)
6. Benca, R.M., Obermeyer, W.H., Thisted, R.A., Gillin, C.H.: Sleep and psychiatric disorders. Arch. Gen. Psychiatry **49**(8), 651–668 (1992)
7. Riemann, D., Schnitzler, M., Hohagen, F., Berger, M.: Depression und Schlaf—der gegenwärtige Forschungsstand. Fortschr. Neurol. Psychiatr. **62**(12), 458–478 (1994)
8. Murck, H., Nickel, T., Künzel, H., Antonijevic, I.A., Schill, J., Zobel, A., Steiger, A., Sonntag, A., Holsboer, F.: State markers of depression in sleep EEG: dependency on drug and gender in patients treated with tianeptine or paroxetine. Neuropsychopharmacology **28**(2), 348–358 (2003). doi:10.1038/sj.npp.1300029
9. Mayers, A.G., Baldwin, D.S.: Antidepressants and their effect on sleep: a systematic review. Hum. Psychopharm. Clin. Exp. **20**(8), 533–559 (2005). doi:10.1002/hup.726

10. Press, W.H., Teukolsky, S.A., Vetterling, W.T., Flannery, B.P.: Numerical Recipes: The Art of Scientific Computing, 3rd edn, pp. 600–719. Cambridge University Press, New York (2007)
11. Priestley, M.B.: Spectral Analysis and Time Series. Academic Press, London (1981)
12. Stam, C.J.: Nonlinear dynamical analysis of EEG and MEG: review of an emerging field. Clin. Neurophysiol. **116**(10), 2266–2301 (2005). doi:10.1016/j.clinph.2005.06.011
13. Lauer, C.J., Riemann, D., Wiegand, M., Berger, M.: From early to late adulthood changes in EEG sleep of depressed patients and healthy volunteers. Biol. Psychiatry **29**(10), 979–993 (1991). doi:10.1016/0006-3223(91)90355-P
14. Digital Signal Processing Committee: Programs for Digital Signal Processing. IEEE Press, New York (1979)
15. Röschke, J., Kögel, P., Grözinger, M.: Lorazepam and the sleep EEG's microstructure: a novel approach to quantitative pharmaco-EEG investigations. Ger. J. Psychiatr. **3**(3), 13–18 (2000)
16. Kilkenny, T., Grenard, S.: In: Sleep staging and respiratory scoring of polysomnograms. RT for decision makers in respiratory care, August/September (2000) http://www.rtmagazine.com/issues/articles/2000-08_03.asp. Cited 14 Feb (2008)
17. Webber, C.L., Jr., Zbilut, J.P.: Dynamical assessment of physiological systems and states using recurrence plot strategies. J. Appl. Physiol. **76**(2), 965–973 (1994)
18. Marwan, N., Romano, M., Thiel, M., Kurths, J.: Recurrence plots for the analysis of complex systems. Phys. Rep. **438**(5–6), 237–329 (2007). doi:10.1016/j.physrep.2006.11.001
19. Packard, N.H., Crutchfield, J.P., Farmer, J.D., Shaw, R.S.: Geometry from a time series. Phys. Rev. Lett. **45**(9), 712–716 (1980). doi:10.1103/PhysRevLett.45.712
20. Kantz, H., Schreiber, T.: Nonlinear Time Series Analysis. Cambridge University Press, Cambridge (1997)
21. Jensen, A., la Cour-Harbo, A.: Ripples in Mathematics: The Discrete Wavelet Transform. Springer, Berlin (2001)
22. Winokur, A., Sateia, M.J., Hayes, J.B., Dazet, W.B., MacDonald, M.M., Gary, K.A.: Acute effects of mirtazapine on sleep continuity and sleep architecture in depressed patients: a pilot study. Biol. Psychiatry **48**(1), 75–78 (2000). doi:10.1016/S0006-3223(00)00882-9
23. Armitage, R., Hoffmann, R., Fitch, T., Trivedi, M., Rush, A.J.: Temporal characteristics of delta activity during NREM sleep in depressed outpatients and healthy adults: group and sex effects. Sleep **23**(5), 607–617 (2000)
24. Schittecatte, M., Dumont, F., Machowski, R., Cornil, C., Lavergene, F., Wilmotte, J.: Effects of mirtazapine on sleep polygraphic variables in major depression. Neuropsychobiology **46**(4), 197–201 (2002). doi:10.1159/000067812
25. Borbely, A.A., Tobler, I., Loepfe, M., Kupfer, D.J., Ulrich, R.F., Grochocinski, V., Doman, J., Matthews, G.: All-night spectral analysis of the sleep EEG in untreated depressives and normal controls. Psychiatry Res. **12**(1), 27–33 (1984). doi:10.1016/0165-1781(84)90135-5
26. Buysse, D.J., Hall, M., Begley, A., Cherry, C.R., Houck, P.R., Land, S., Ombao, H., Kupfer, D.J., Frank, E.: Sleep and treatment response in depression: new findings using power spectral analysis. Psychiatry Res. **103**(1), 51–57 (2001). doi:10.1016/S0165-1781(01)00270-0
27. Röschke, J., Kögel, P., Schlösser, R., Wagner, P., Mann, K., Rossbach, W., Benkert, O.: Analysis of sleep EEG microstructure in subchronic paroxetine treatment of healthy subjects. Psychopharmacology (Berl.) **132**(1), 44–49 (1997). doi:10.1007/s002130050318
28. Achermann, P., Hartmann, R., Gunzinger, A., Guggenbuhl, W., Borbely, A.A.: Correlation dimension of the human sleep electroencephalogram: cyclic changes in the course of the night. Eur. J. Neurosci. **6**(3), 497–500 (1994). doi:10.1111/j.1460-9568.1994.tb00292.x