Characterization of the sleep EEG in acutely depressed men using detrended fluctuation analysis

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Abstract

Objective: The aim of the present paper is to study the fluctuations of the sleep EEG over various time scales during a specific pathological condition: major depressive episode. Focus is made on scaling behaviour, which is the signature of the absence of characteristic time scale, and the presence of long-range correlations associated to physiological constancy preservation, variability reduction and mostly adaptability.

Methods: Whole night sleep electroencephalogram signals were recorded in 24 men: 10 untreated patients with a major depressive episode (41.70 ± 8.11 years) and 14 healthy subjects (42.43 ± 5.67 years). Scaling in these time series was investigated with detrended fluctuation analysis (time range: 0.16–2.00 s). Scaling exponents ($\alpha$) were determined in stage 2, slow wave sleep (stages 3 and 4) and during REM sleep. Forty-five epochs of 20 s were chosen randomly in each of these stages.

Results: The median values of $\alpha$ were lower in patients during stage 2 and SWS.

Conclusions: Major depressive episodes are characterized by a modification in the correlation structure of the sleep EEG time series. The finding which shows decreasing rate of the temporal correlations being different within the two groups in stage 2 and SWS provides an electrophysiologic argument that the underlying neuronal dynamics are modified during acute depression.

Significance: The observed modifications in scaling behaviour in acutely depressed patients could be an explanation of the sleep fragmentation and instability found during major depressive episode.

Keywords: Sleep; EEG; Energy fluctuations; Scaling properties; Scaling exponents; Depression

1. Introduction

In recent years, time series analysis has become an important tool in investigating the behaviour of many natural phenomena. In the specific case of the study of the electrical activity of the brain recorded by electroencephalography (EEG), various methods have been used to extract different aspects of the neuronal dynamics from the scalp potentials. They range from the traditional linear analysis which involves frequency decomposition, topographic mapping, etc. (Niedermeyer, 2003), to time-frequency analysis that uses wavelet transform (Blanco et al., 1996), to non-linear analysis that is particularly suitable for learning about possible chaotic behaviour of the brain or for quantifying physiological conditions in non-linear-dynamics terms. For an extensive review of this field, see (Stam, 2005).

More precisely, scale-invariant properties in various biological systems have received much attention during the last decade (Bassingthwaighte et al., 1994). Concepts of scaling and detection of long-range correlations in spatial and temporal patterns of biological organization have led to the elucidation of organization principles in seemingly irregular biological data sequences. In fact, a broad variety of signals show complex behaviours which exhibit
long-range power-law correlations and/or non-stationary trends; including, DNA sequences (Peng et al., 1994), heartbeat rate dynamics (Peng et al., 1995), human electroencephalogram time series (Lee et al., 2002; Shen et al., 2003; Hwa and Ferree, 2004; Stam and de Bruin, 2004; Ferri et al., 2005), weather records (Kiraly and Janosi, 2005), and economic series (Vandewalle and Ausloos, 1997).

Scaling analysis quantifies the temporal fluctuations of a time series in terms of power laws. Its application to EEG is motivated first, by the observation that the brain is a highly complex system and second, by the difficulties satisfying the assumptions of either linear or chaos analysis.

Nowadays, major depressive disorder (MDD) is considered to be one of the most frequent and prominent causes of sleep disturbances. In fact, more than 90% of depressed patients complain about impairments in sleep quality (Mendelson et al., 1977). Typically, patients suffer from difficulties falling asleep, frequent nocturnal awakenings, and early morning awakening. Moreover, depression is associated with neurobiological factors, such as EEG sleep alterations and cognitive impairment. Systematic sleep EEG investigations in unmedicated depressed patients using formalized diagnostic criteria were initiated by the group of Kupfer (Kupfer and Foster, 1972; Kupfer, 1976). Besides sleep continuity disturbances, sleep in depression is also characterized by a reduction of slow wave sleep (SWS) and a shortening of the interval between sleep onset and the occurrence of the first REM period (i.e., REM latency). Further abnormal features include an increased amount of REM sleep, a prolongation of the first REM period and an increased number of eye movements during REM periods (i.e., REM density). For an extensive review of this field, see Kupfer (Kupfer, 1995) and Riemann (Riemann et al., 2001).

The aim of the present study is to explore dynamic properties of the human sleep EEG in terms of energy fluctuations in a specific pathological condition: major depressive episode. As it is the case in various diseases and some physiological conditions (Goldberger et al., 2002), we postulate that acute depression could modify the dynamic structure of the sleep EEG, reflecting a neuronal dysregulation, perhaps, in terms of more instability.

2. Subjects and methods

2.1. Subjects

Fourteen control subjects and 10 unmedicated inpatients with acute major depression according to DSM-IV-TR criteria were included in this study (American Psychiatric Association, 2000). Descriptive clinical features of acutely depressed patients and healthy control subjects are presented in Table 1. Healthy controls were recruited from the community by advertisements. On the basis of an extensive clinical interview, they were determined to be free of DSM-IV-TR axis I or evident axis II diagnoses and they had no family history of major psychiatric disorders. They reported a regular sleep–wake schedule and no current or past sleep disorders. Before signing an informed consent, each subject received a detailed description and demonstration of the procedure involved in the study, and was deemed capable. The study protocol was approved by the local Ethics Committee of the Erasme Academic Hospital-Free University of Brussels.

Patients were recruited from both the Sleep Laboratory and an inpatient psychiatry ward at the Erasme Academic Hospital where they were hospitalized for both major depressive disorder and sleep disturbances. Disturbances included difficulty falling asleep, difficulty staying asleep and early morning awakening. Self-reports of sleep were obtained by Pittsburgh Sleep Quality Index (PSQI). The PSQI (range 0–21, higher values indicating greater sleep disturbances) is a self-rated questionnaire which assesses sleep quality and disturbances during the previous 1 month time interval (Buysse et al., 1989). The 19 self-rated questions assess a wide variety of factors relating to sleep quality, including estimates of sleep duration and latency, and of the frequency and severity of specific sleep-related problems. A global PSQI score of ≥ 5 was found to correctly discriminate between “good” and “poor” sleepers (Buysse et al., 1989). Patients were evaluated initially for a major depressive disorder by a psychiatrist using DSM-IV-TR criteria. Depressive symptom severity was assessed with the 24-item Hamilton Rating Scale for Depression (HAM-D). They were included in the present study if they fulfilled the following five criteria: (1) they suffered from primary major depression (unipolar without psychotic features); (2) they were free of all prescription and non-prescription psychotropic medications; (3) they had a HAM-D score of 20 or greater (Hamilton, 1967); (4) they had a PSQI of five or greater; (5) they did not suffer from untreated or poorly controlled conditions that may have confounded the sleep EEG results (e.g., Cushing’s disease), or require treatment with agents that may do either (i.e., β-blockers or corticosteroids). Both controls and patients were medically screened by way of physical examination (performed by an internist), chest X-ray, electrocardiography, electroencephalography and laboratory tests, such as liver and kidney function tests, hematology profile, thyroid function tests, and urinalysis.

They did not show cardiovascular or endocrine abnormalities, or other systemic illness. Subjects or patients with a BMI greater than 29 were excluded.

We have also excluded from our samples, controls or patients showing primary sleep disorders such as apnea–hypopnea syndrome, periodic leg movement syndrome, and parasomnia.

2.2. EEG sleep methodology

EEG sleep studies were performed in the Sleep laboratory of the Erasme Academic Hospital. In the patient group, sleep studies were conducted after at least a 2 weeks, psychotropic medication-free evaluation period. Polysomno-
graphic recordings were obtained during three consecutive nights, of which, only the latter two were examined in this study, because of the well-recognized “first night effect” on sleep measures (Agnew et al., 1966). For the purposes of this analysis, one artifact-free night was chosen from the latter two nights. If both nights showed any artifact, then one was randomly selected. Artifacts were detected by visual observation using the software Endymion (Endymion 1993–2006, Sleep laboratory, Erasme Hospital), which was developed in our laboratory for data analysis.

Patients and controls were instructed not to drink alcohol or coffee during the same time frame, nor to use over-the-counter sleep aids. Subjects went to bed and got up at their usual times. During bedtime hours, controls and patients were supine with lights off. They awoke spontaneously in the morning, and daytime naps were strictly prohibited. Both controls and patients had a minimum of six consecutive hours of recorded time in bed.

Polysomnography was recorded with a 19-channel digital polygraph (Brainnet™, MEDATEC, Brussels, Belgium).

Two electrooculograms (EOG), three electroencephalograms (Fz-Ax, Cz-Ax, Oz-Ax, where Ax is the left mastoid reference), one submental electromyogram (EMG), and electrocardiographic activity (ECG) were recorded. Oxyhemoglobin saturation was measured using pulse-oximetry (Biox 3740™, OHMEDA, Louisville, CO), oro-nasal airflow was detected with thermistors (Infinity™, Sleepmate Technologies, Midlothian, VA), thoracic and abdominal respiratory movements were recorded with piezoelectric sensors (Resp-EZ™, Sleepmate Technologies, Midlothian, VA), and leg movements were detected with ankle piezoelectric movement strain gauges (Moving Images™, Sleepmate Technologies, Midlothian, VA).

To eliminate low frequency artifacts, drifts, and offsets, the following time constants were set in the Brainnet™ polygraph: 0.3 s (0.53 Hz) for the EEG and 1 s (0.16 Hz) for the EOG. Before sampling, the signals were filtered through a low-pass anti-aliasing analog filter, with a cut-off frequency of 35 Hz. All channels were sampled at 200 Hz.

Respiratory sound was recorded with a microphone (MKE™, Sennheiser, Wedemark, Germany) which was then fixed to the larynx. The sound was sampled at 2000 Hz and a rectified sound envelope was also sampled at 50 Hz. This technique allows for the visual display of sound intensity and for the EEG-synchronised audio replay through headphones. The Brainnet™ polygraph samples the signals on 12 bits and sends the resulting data to a Ethernet network, via the Netbios protocol. An acquisition program has been developed (Endymion 1993–2006, Sleep laboratory, Erasme Hospital) to read and store the data in the EDF file format (Kemp et al., 1992). For subsequent analyses, EEG was stored at 100 Hz, the EOG at 50 Hz, and the ECG at 200 Hz. Data analysis was obtained from Cz. To avoid aliasing, appropriate low-pass filters were applied before subsampling.

All subsequent analyses, such as stage determination and spectrum calculation, were carried out on the sampled data, avoiding synchronisation problems between the stages and the other calculations. Using the Endymion program, each 20-s epoch was visually scored according to standard criterion (Rechtschaffen and Kales, 1968).

### Table 1

Demographic and clinical characteristics of controls and acutely depressed patients

<table>
<thead>
<tr>
<th>Demographics and clinical variables means ± SD median (min–max range)</th>
<th>Normal controls (n = 14)</th>
<th>Acutely depressed patients (n = 10)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.43 ± 5.67</td>
<td>41.70 ± 8.11</td>
<td>0.797</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.27 ± 1.76</td>
<td>25.06 ± 3.75</td>
<td>0.977</td>
</tr>
<tr>
<td>Marital status, No (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-never married</td>
<td>0</td>
<td>1 (10)</td>
<td>NA</td>
</tr>
<tr>
<td>Married</td>
<td>6 (42.88)</td>
<td>5 (50)</td>
<td>NA</td>
</tr>
<tr>
<td>Other</td>
<td>8 (57.14)</td>
<td>4 (40)</td>
<td>NA</td>
</tr>
<tr>
<td>Employment status, No (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manager</td>
<td>4 (28.57)</td>
<td>3 (30)</td>
<td>NA</td>
</tr>
<tr>
<td>Employed</td>
<td>10 (71.43)</td>
<td>4 (40)</td>
<td>NA</td>
</tr>
<tr>
<td>Other</td>
<td>1 (7.14)</td>
<td>3 (30)</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of current episode, No (%) &gt;12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal controls</td>
<td>NA</td>
<td>10 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>Acutely depressed patients</td>
<td>NA</td>
<td>39.14 ± 3.45</td>
<td>NA</td>
</tr>
<tr>
<td>PPI at baseline*</td>
<td>1 (1–4)</td>
<td>14 (7–17)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are expressed as means ± standard deviations (SD) or indicated by (*) as median with minimum–maximum range. HRSD-24 items, the 24-items Hamilton Rating Scale for Depression. PSQI, the Pittsburgh Sleep Quality Index. NA means “Non Applicable”.

### 2.3. Detrended fluctuation analysis

A standard way to quantify dependency between different time points of a signal is to use the autocorrelation
function, which is a measure of the correlation between the original signal and its time-shifted version (Bendat and Piersol, 2000). In case of non-stationarities, such as different trends with unknown duration, the use of the conventional autocorrelation function is not suitable, as non-stationarities may cause spurious detection of correlations (Peng et al., 1992, 1995). For studies of the intrinsic dynamics of a system, it is desirable to discard trends exogenous to the system, which in EEG might be caused by slight postural changes, visceral inputs or sudden acoustic stimuli.

The specific method we propose to use in this report is the detrended fluctuation analysis (DFA), which is a technique for discovering and quantifying scale-independent properties in complex systems. It can be applied to detect long-range temporal correlations (LRTC) in noisy non-stationary signals, as is frequently the case in biological systems. The fundamental idea is to determine how the stationary signals, as is frequently the case in biological systems, it is desirable to discard trends exogenous to the system, which in EEG might be caused by slight postural changes, visceral inputs or sudden acoustic stimuli.

The scaling exponent $z$ provides a quantitative measure of the temporal correlations that exist in the time series. Scaling behaviour (or scale-free behaviour) means that no characteristic scales dominate the dynamics of the underlying process. When the signal is completely uncorrelated, the calculation of the scaling exponent yields $z = 0.5$. When applied to a signal with LRTC and power-law scaling, DFA will generate scaling exponents with either $0 < z < 0.5$ or $0.5 < z < 1$. When $0.5 < z < 1$, the data are correlated such that large fluctuations are likely to be followed by large fluctuations and small fluctuations are likely to be followed by small fluctuations. When $0 < z < 0.5$, the time series has LRTC, but the signal is “anti-correlated” such that large fluctuations are likely to be followed by small fluctuations and vice versa. As the scaling exponent increases from $z = 0.5$ toward $z = 1$, the temporal correlations in the time series are persistent (decay more slowly with time). When $z > 1$, however, the correlations no longer exhibit power-law behaviour versus time and decay more rapidly with increasing $z$. A special case of $z = 1$ corresponds to 1/*f* noise (Bak et al., 1987). When $z = 1.5$, it indicates Brownian noise: the integration of white noise. The $z$ exponent can also be viewed as an indicator that describes the “roughness” of the original time series: the larger the value of $z$, the smoother the time series. As well, a large scaling exponent reflects slow fluctuations and a small scaling exponent reflects more rapid fluctuations. In this context, 1/*f* noise ($z = 1$) can be interpreted as a “compromise” between the complete unpredictability of white noise (very rough “landscape”) and the very smooth “landscape” of Brownian noise ($z = 1.5$) (Peng et al., 1992; Buldyrev et al., 1994).

In the present study, we applied DFA to each contiguous 20-s epoch considered for scoring; $n$ ranged thus from 4 to 500 (i.e., 0.04–5 s). The scaling exponent was determined by least-squares linear fit in the Log($F(n)/\log(n)$) plot with approximately equidistant $n$ values in the range 16–200 (i.e., 0.16–2.00 s).

### 2.4. Statistical analysis

For each of the three sleep stages (stage 2, SWS [stages 3 and 4] and REM), we collected samples of 45 scaling exponents computed on 45 epochs randomly chosen from the epochs of the sleep stage of interest. Average scaling exponents were then obtained from these samples for stage 2, SWS and REM. The number of epochs, 45, was arbitrarily chosen to obtain a common quantum to carry out our
study despite the great disparity in the number of epochs during the different sleep stages.

Statistical analysis was carried out using the software Statistical Package for the Social Sciences, version 13.0 for Windows. For DFA and correlations analysis, the Kruskal–Wallis test and the Spearman’s rank correlation coefficient were performed because of the small size of the sample and the non-Gaussian distribution of most of the variables. For conventional sleep analysis, Student’s t-test or Mann–Whitney test was applied. Power spectrum analysis of the delta range was also performed on our sets of randomly chosen epochs in each sleep stage of interest (Table 2).

All analyses were performed with \( \alpha \) (type I error) set at 0.05.

3. Results

3.1. Classical sleep characteristics

The two groups do not differ significantly in age or in body mass index (BMI). The conventional sleep EEG parameters according to Rechtschaffen and Kales are summarized in Table 2.

The depressed patient group showed several of the well-known pathognomonic sleep changes, such as decreased sleep efficiency and decreased stage 2 percentage. We also observed increased sleep onset latency, stage 1 percentage, and awakenings throughout the night (in terms of number and percentage), increased REM sleep percentage, REM density, and number of sleep stage shifts. We also observed decreased percentage of SWS and REM latency. However, the latter eight parameters did not differ significantly between the two groups in our sample, but were significantly different in a large number of previous reports (Kupfer and Foster, 1972; Kupfer, 1976; Feinberg et al., 1982; Kerkhofs et al., 1991; Hubain et al., 1995; Fossion et al., 1998).

3.2. LRTC analyses in patients and controls

As cited above, DFA may detect hidden patterns in complex signals (Havlin et al., 1999). Examples of recorded signals for three epochs of various sleep stages of interest

| Table 2 | Conventional electroencephalographic sleep measures in controls compared with acutely depressed patients |
|---|---|---|---|
| EEG sleep variables | Healthy controls (n = 14) | Acutely depressed patients (n = 10) | p value |
| **Sleep continuity** | | | |
| Time in bed (min) | 489.78 ± 76.9 | 514.23 ± 79.58 | 0.457 |
| Total sleep time (TST) (min) | 431.81 ± 56.92 | 401.33 ± 87.76 | 0.312 |
| Sleep latency (min) | 19.14 ± 11.34 | 34.83 ± 30.06 | 0.086 |
| Sleep efficiency (%) | 85.69 (81.73–93.60) | 81.06 (55.64–91.87) | 0.008 |
| No.of awakenings | 41.07 ± 15.55 | 49.30 ± 20.51 | 0.275 |
| Awake (min) | 45.06 ± 25.91 | 55.84 ± 48.68 | 0.489 |
| Awake (% SPT) | 8.31 ± 4.20 | 14.36 ± 9.38 | 0.082 |
| Awake last 3 h (No.) | 17.36 ± 6.87 | 20.80 ± 7.87 | 0.267 |
| REM sleep (min) | 16.43 ± 12.65 | 28.77 ± 20.31 | 0.080 |
| No. of stage shifts | 232.49 ± 41.60 | 272.90 ± 58.54 | 0.060 |
| Mean duration of one continuous stage 2 episode (min) | 3.71 ± 1.24 | 3.28 ± 0.97 | 0.006 |
| Mean duration of one continuous REM sleep episode (min) | 4.73 (2.57–11.93) | 5.19 (2.76–10.44) | 0.682 |
| Mean duration of one continuous SWS episode (min) | 0.88 (0.40–3.55) | 0.62 (0.33–1.44) | 0.266 |
| **Sleep architecture** | | | |
| NREM sleep measures | | | |
| Stage 1 (% TST) | 6.84 ± 2.73 | 10.69 ± 6.72 | 0.115 |
| Stage 2 (% TST) | 64.21 (48.29–73.12) | 57.08 (42.23–71.18) | 0.056 |
| SWS (% TST) | 9.86 ± 5.55 | 7.53 ± 3.75 | 0.261 |
| REM sleep measures | | | |
| No. of REM periods | 5 (3–7) | 4 (3–6) | 0.255 |
| REM (min) | 86.45 ± 17.67 | 100.03 ± 31.55 | 0.240 |
| REM (TST %) | 21.07 ± 3.56 | 23.11 ± 6.66 | 0.339 |
| Latency (min) | 76.11 ± 26.31 | 57.83 ± 21.90 | 0.086 |
| Density (units/min) | 2.7 (1.61–13.69) | 3.4 (1.13–15) | 0.841 |
| **Spectral analysis (μV)²** | | | |
| Delta power in stage 2 | 147.16 ± 53.45 | 174.93 ± 52.07 | 0.218 |
| Delta power in SWS | 475.07 ± 144.78 | 501.34 ± 177.02 | 0.693 |
| Delta power in REM sleep | 33.13 ± 10.04 | 32.26 ± 7.20 | 0.818 |

Values are expressed as means ± standard deviations (SD) or indicated by (•) as median with minimum–maximum range.

TST, total sleep time.
REM, rapid eye movement.
NREM, non-rapid eye movement.
SWS, slow wave sleep.
for one of the depressed patients and one of the healthy controls are displayed in Fig. 1. It is clear that visual inspection alone could not discriminate the patient from the control. Fluctuations, $F$, showed a linear behaviour versus time scale of observation in a log–log plot for controls and patients in the investigated epochs of the sleep stages of interest. Such behaviour is illustrated, for example, for a depressed patient in Fig. 2. The power spectrum (range of 0.5–25 Hz) for the three selected epochs (20 s) of the same depressed patient is illustrated in Fig. 3.

Compared to arousal, where a previous study has reported different values of scaling exponent values in the range $(0.5 < \alpha < 1)$ (Linkenkaer-Hansen et al., 2005; Parish et al., 2004), all of our scaling exponents during sleep ranged between 0.72 and 1.17. This shows that energy fluctuations in both groups have persistent LRTC with $(0.5 < \alpha < 1)$ or without $(\alpha > 1)$ power-law form. As also described in previous reports (Shen et al., 2003; Lee et al., 2004), we observed that the scaling exponents for both groups increased from light sleep to SWS, but decreased during REM sleep; therefore, EEG energy patterns would approach the smoothness of Brownian noise during deep sleep.

In order to probe differences between network dynamics of the depressed and non-depressed brain, we compared the scaling exponents between the two groups. Medians and minimum–maximum ranges of scaling exponents of healthy controls and acutely depressed patients for the three sleep stages are presented in Table 3. The depressed group shows evidence of long-range temporal correlations in the three sleep stages (median values of $\alpha$ are in the range 0.5–1), but with scaling exponents that were significantly smaller than those in healthy controls during stage 2 and SWS. This deviation is not found during REM sleep. Fig. 4 shows the grand averages of the DFA in the two groups during the three sleep stages.

Fig. 1. Recorded signals for three epochs of various sleep stages of interest for one healthy control (A) and one depressed patient (B).

Fig. 2. Plot of $\log F(t)$ versus $\log t$ for three epochs in different sleep stages. Log–Log plot of the fluctuations $F$ versus the time scale of observation $t$ (expressed in second) for one depressed subject for three epochs in the different sleep stages of interest. Filled circles represent stage 2, open circles REM and triangles SWS. The range $[0.16, 2.00]$ s for scaling exponent determination is delimited and the corresponding power-law fits are illustrated.
In summary, we revealed a decrease of long-range temporal correlations during stage 2 and SWS in depressive patients in comparison with the healthy controls.

3.3. Analysis of the relation between scaling exponents’ behaviours and the Hamilton Score of Depression

A further extension of our project is to test whether the LRTC was related to the severity of depression in the pathological group. A strong linear correlation was observed between the DFA exponents and the HAM-D score during SWS. A trend was also detected during stage 2, but without statistical significance.

Thus, the more depressed the patient, the less autocorrelated are the signals during SWS. This correlation was not observed during REM sleep. Correlation values of the severity of depression and scaling exponents are illustrated in Fig. 5.

3.4. Study of the values of DFA exponents compared to the total number of sleep stage shifts during the sleep stages of interest

As one of the sleep characteristics in depression is sleep fragmentation, we also tested relationship between DFA exponents and the number of sleep stage shifts.

In fact, DFA provides a quantitative index of statistical dependencies in fluctuations on different time scales. That being stated, the study of sleep continuity (in terms increased/decreased fragmentation), through determining the total number of sleep stage shifts, could be a correct way to describe, in a “macroscopic view”, instability. Correlation values between DFA exponents and the total number of sleep stage shifts are illustrated in Fig. 6.

With the same method, the determination of mean durations for each of a continuous stage 2, SWS or REM sleep episode has also been performed. Results are presented in Table 2. First, we observe that, despite no statistical significance, trends actually exist during stage 2 and SWS as: scaling exponents decrease, total number of sleep stage shifts increase.
shifts increase. This trend is not observed during REM sleep. Secondly, the mean duration of one continuous stage 2 or one SWS episode is less important in the depressed group ($p > 0.05$). An inverse trend is observed during REM sleep.

4. Discussion

4.1. Altered LRTC in acutely depressed patients as "a fractal physiologic complexity view"

The present study explored the dynamic structure of the human sleep EEG in terms of energy fluctuations in patients suffering from a major depressive episode. Using DFA, the analysis of energy fluctuations in human sleep EEG networks shows persistent long-range correlations over time scales that were consistent across both control and patient groups. By LRTC, we mean slow power-law decay of autocorrelations. In spite of different studies’ designs, our results are in agreement with previous reports (Watters, 1998a,b, 2000; Linkenkaer-Hansen et al., 2001, 2005; Shen et al., 2003; Hwa and Ferree, 2004; Lee et al., 2004; Parish et al., 2004; Nikulin and Brismar, 2005), showing that a persistent process exhibiting temporal self-similarity must be accounted for by the dynamics of the EEG. It is well acknowledged that a defining feature of healthy functioning is adaptability, the capacity to respond to unpredictable stimuli, and stresses. Fractal physiology, exemplified by long-range correlations in human EEG, may be adaptive from at least two perspectives (Ivanov et al., 1999): (i) long-range correlations serve as (self-) organizing mechanisms for highly complex processes that generate fluctuations across a wide range of time scales; and (ii) the absence of a characteristic scale inhibits the emergence of highly periodic behaviours, which would greatly narrow functional responsiveness.

In our study, patients displayed abnormally small autocorrelations during stage 2 and SWS in comparison to healthy controls. These results are in keeping with the growing evidence that physiologic systems in a healthy state generate activity fluctuations on many time scales, and that disease states are associated with a breakdown

Fig. 5. Correlation values between scaling exponents and the Hamilton Depression Rating Scale in Stage 2 (a), SWS (b) and REM sleep (c).
of this rich temporal structure (Goldberger et al., 2002; Havlin et al., 1999). This is in accordance with the breakdown of fractal physiologic complexity, which may be associated with excessive order (pathologic periodicity), on the one hand, or uncorrelated randomness, on the other (Goldberger, 1996; Goldberger et al., 2002). A unifying theme underlying both routes to pathology is the degradation of correlated, multiscale dynamics.

4.2. Modifications of the LRTC and possible neurophysiopathological interpretations

These alterations of scaling properties indicate that, during sleep, psychiatric disorders may be reflected in the temporal structure of electric neuronal activity. Because of the inverse relationship between LRTC (stage 2 and SWS) and the HAM-D score, it may be stated that during these sleep stages, the severity of depression tends to be reflected by DFA power-law scaling exponents. We have also shown that scaling exponents (during stage 2 and SWS) tend ($p > 0.05$) to be inversely correlated with the total number of sleep stage shifts. Conversely, in REM sleep, scaling exponents are not altered by depression and not related to the HAM-D score or the total number of sleep stage shifts. Our results are in accordance with a recent study performed by Linkenkaer-Hansen (Linkenkaer-Hansen et al., 2005). Despite a different study design used in the above-mentioned reference (wakeful rest with eyes closed, recording frequency of 300 Hz, time series investigated with an amplitude envelope of band filtered time series, time interval for time series investigation being 16 min, range for DFA windows 5–100 s, etc.), we have also demonstrated a decrease of long-range temporal correlations in depressive patients in comparison with the healthy controls.

Large-scale neuronal networks in humans depend on neuronal interactions both at synaptic and network levels. The abnormally decreased LRTC in stage 2 and SWS may therefore depend on a complex set of regulatory mechanisms. Currently, a malfunction of limbic-cortical network is the leading systems-level candidate for mediating depression (Drevets, 2000; Mayberg, 2003), and more specifically neuronal atrophy in the hippocampus (MacQueen et al.,...
Nevertheless, in the present study, different rhythms were recorded non-invasively with three sagitally placed EEG electrodes. Only Cz-Ax was analysed and thus, different recorded rhythms were most likely generated in the neocortex. Because only one lead was analysed, “topographic interpretation” is not possible in this study and requires further investigation. At this level, these observed alterations in scaling properties can be explained as an expression of a global and non-specific modification in the dynamics of neuronal networks in depressed patients. Moreover, some of the results presented above for depressed patients such as total number of sleep stage shifts, mean duration of one continuous stage 2 and SWS (Table 2) and their relations with scaling exponents (Fig. 4) are an illustration of the well-known fragmentation classically observed during a major depressive episode. Despite no statistical significance but only trends (Table 2 and Fig. 6), this description could establish a relationship between the breakdown of LRTC in stage 2 and SWS (i.e., the reduction of the corresponding scaling exponents) and sleep instability in depression. Like the Cyclic Alternating Pattern (CAP), scaling exponent could also reflect the sleep instability (Farina et al., 2003).

It should be noted that excessive stage shifts are not specific to depression and are also observed in other diseases, some of which include, narcolepsy, primary insomnia, and addiction. Currently, a great interest in sleep fragmentation is founded in the unequivocal evidence of clinical inferences in the cognitive, vigilance, metabolic and hemodynamic/autonomic domains (Roehrs et al., 1994; Ekstedt et al., 2004).

Concerning REM sleep, the absence of breakdown of LRTC in our sample can also be interpreted in the context of depression. In fact, besides sleep continuity disturbances and reduction of SWS, sleep in depression is also characterized by abnormalities in REM sleep: shortening of the interval between sleep onset and the first REM period (i.e., REM latency), an increased amount of REM sleep, a prolongation of the first REM period and an increased number of eye movements during sleep (i.e., REM density). The non-modification of the statistical properties of REM sleep, in terms of LRTC, in comparison with stage 2 and SWS could explain its stability. On the other hand, the disinhibition of REM sleep cannot be explained by our analysis and requires further investigation, focussing on sleep transition phenomena.

Recent reports show that many, but not all, functional abnormalities found during a depressive episode recover after pharmacological or psychotherapeutic treatment (Austin et al., 2001; Castren, 2005). Future studies should seek to establish whether the LRTC of the sleep EEG increases (during stage 2 and SWS) with the recovery from a depressive episode, or whether reduction of LRTC represents trait abnormalities.

Limitations of this study are primarily related to methodology. First, it is recognised that major depression is a heterogeneous syndrome and, within patients, other sources of variance may exist (e.g., severity, atypicality, seasonality, number of previous episode, etc.). Second, by excluding patients with more serious forms of psychiatric comorbidity, our conclusions should be interpreted with care. Third, the sample size and the psychopathological assessment of the subjects did not allow for stratifying the patient sample by depressive subtypes.

Replication of our study in larger groups is clearly required in order to further examine the neurophysiological aspects that were revealed in this study. Finally, the confirmation of our findings will have to await a more complete understanding of the neural network dynamics in healthy subjects and patients suffering from major depressive disorder.

In conclusion, we have demonstrated that energy fluctuations of human sleep EEG exhibit LRTC with or without temporal-law behaviour. DFA approach has shown significant deviations during stage 2 and SWS from the normal range of scaling exponents in a sample of patients suffering from major depressive episode. Therefore, these deviations might be an indicator of dysfunction in the dynamics of neuronal networks. These alterations in scaling properties could be an explanation of the well-known sleep fragmentation and instability of acutely depressed patients.

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