THE MODIFICATIONS OF THE LONG-RANGE TEMPORAL CORRELATIONS OF THE SLEEP EEG DUE TO MAJOR DEPRESSIVE EPISODE DISAPPEAR WITH THE STATUS OF REMISSION

S. LEISTEDT, a, c M. DUMONT, a N. COUMANS, a J.-P. LANQUART, a F. JURYSTA a AND P. LINKOWSKI a

aSleep Laboratory, Department of Psychiatry, Erasme Academic Hospital, Université Libre de Bruxelles, Route de Lennik, 808, 1070 Brussels, Belgium
bDepartment of Biological Physics, Université de Mons Hainaut, Belgium
cNational Fund for Scientific Research, Rue d’Egmont 5, 1000 Brussels, Belgium

Abstract—Objective: The aim of the present study is to investigate the scaling properties of the sleep electroencephalogram (EEG) in remitted depressed men, and to evaluate if a past history of major depressive disorder (MDD) could modify significantly and definitively, as a “scar marker,” the dynamics of the sleep EEG time series.

Methodology: Whole night sleep electroencephalogram signals were recorded in 24 men: 10 untreated depressed men in full to partial remission (42.43±5.62 years) and 14 healthy subjects (42.8±8.55 years). Scaling properties in these time series were investigated with detrended fluctuation analysis (DFA) (time range: 0.16–2.00 s). The scaling exponent \( \alpha \) was determined in stage 2, in slow wave sleep (stages 3 and 4), and during rapid eye movement (REM) sleep. Forty-five epochs of 20 s were chosen randomly in each of these stages for each subject in both groups.

Results: We did not observe a significant difference and deviation of the scaling exponents between the two groups during the three sleep stages of interest.

Conclusion: In this study, we do not observe any functional sequelae of a past history of one or more unipolar major depressive episode on the fluctuation properties of the sleep EEG. This finding is a sign of similar underlying neuronal dynamics in healthy controls and patients with a lifetime history of MDD. This study gives an additional argument to the theory that depression does not modify definitively the dynamics of the neuronal networks and is therefore against the “depressive scar hypothesis,” in which permanent residual deficit is created by the acute state of the depressive disease. © 2007 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: sleep, EEG, energy fluctuations, scaling properties, depression, remission.

ARTICLE IN PRESS

Please cite this article in press as: Leistedt S, et al., The modifications of the long-range temporal correlations of the sleep EEG due to major depressive episode disappear with the status of remission, Neuroscience (2007), doi: 10.1016/j.neuroscience.2007.06.032

Neuroscience xx (2007) xxx

An important research strategy in neuroscience is based on the question of determining whether a given abnormality present during the acute phase of a disease process normalizes with remission (reflecting a transient neurobiological process underlying an acute episode, as a “state-marker”), whether it is still detected when the disorder is no longer present (“scar-marker”), or whether it was already present prior to the clinical onset of the disorder and persists throughout the lifespan (“trait” or “vulnerability-marker”). The latter markers suggest an increased risk for occurrence or relapse linked to a genetic transmission of the disorder.

This concept is well illustrated with the pathological model of major depressive disorder (MDD). Nowadays, MDD is considered to be one of the most frequent and prominent causes of sleep disturbances. More than 90% of acutely depressed patients have sleep impairment complaints (Mendelson et al., 1977). Moreover, it is common clinical wisdom that many, if not most, depressed patients continue to have symptoms after treatment. It is now apparent that residual symptoms are common, not only in patients with partial response, but also in patients who meet criteria for full response or remission (Fava, 1999; Nierenberg and Wright, 1999). Nierenberg found that of the patients who successfully or fully responded to antidepressant medication (HAM-D score \( \leq 7 \)), less than 20% reported being symptom-free following treatment (Nierenberg and Wright, 1999). The most common residual symptoms found were sleep disturbances (44%), fatigue (38%), and disinterest (27%).

Systematic sleep electroencephalogram (EEG) investigations in unmedicated depressed patients using formalized diagnostic criteria were initiated by the group of David Kupfer (Kupfer and Foster, 1972; Kupfer 1976). Besides sleep continuity disturbances, sleep in major depressive episodes is also characterized by a reduction of slow wave sleep (SWS), a shortening of the interval between sleep onset and the occurrence of the first rapid eye movement (REM) period (i.e. REM sleep disinhibition), 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). Concerning the remission state of depression, the literature is to a large extent inconclusive and confused regarding the state/trait/scare issue, and, as well, the neuropysiological observations are poor and heterogeneous as well. For extensive reviews of this topic, see Kupfer (1995), Riemann et al. (2001), and Tsun et al. (2005). Moreover, 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; Castrén 2005).

Recent research has demonstrated that a large variety of complex processes, including earthquakes (Bak, 1997), forest fires (Malamud et al., 1998), financial markets (Mantegna and Stanley, 1995), heartbeats (Peng et al., 1995) and most importantly human electroencephalogram time series (Linkenkaer-Hansen et al., 2001; Hwa and Ferree, 2002; Lee et al., 2002; Shen et al., 2003; Stam and de Bruin, 2004; Stam, 2005; Ferri et al., 2005), exhibit unexpected statistical similarities, most commonly power-law scaling behavior. Scaling behavior (or scale-free behavior) means that no characteristic time scale governs the dynamics of the underlying process. Scaling techniques, adapted from statistical physics, can reveal the presence of long-range, power-law correlations, as a part of multifractal cascades operating over a wide range of time scales. Long-range temporal correlations (LRTC) indicate that events in the past affect the development of the process in the future. The fact that long-range correlations obey power-law statistics indicates that the mechanisms contributing to their buildup are similar at different time-scales. Certain pathological conditions are marked by a breakdown of this scale-free dynamics, for instance producing uncorrelated randomness similar to “white noise,” and apparently distinct from deterministic chaos (Goldberger, 1996; Goldberger et al., 2002; Peng et al., 2000). Examples include severe congestive heart failure (Peng et al., 1995), the erratic ventricular response in atrial fibrillation (Goldberger et al., 2002) and the EEG signal during major depressive episode (Linkenkaer-Hansen et al., 2005; Leistedt et al., 2007).

The central question of this study is whether sleep EEG abnormalities described in a previous report during the acute stage of the depressive disease (Leistedt et al., 2007) are “state-dependent” or a “scar-marker,” in patients with a past history of MDD. It would be interesting to derive objective neurophysiological sleep indices that are sensitive to the remission state of depression, and to quantify how well these indices distinguish remitted depressed patients from a control group. The nature of this question is truly fundamental because of various evident practical and therapeutic implications, related to the hypothetical existence of functional cerebral sequelae in patients who have presented with a major depressive episode.

### EXPERIMENTAL PROCEDURES

**Subjects: healthy controls and patients**

Fourteen healthy men and 10 unmedicated male inpatients with MDD in full to partial remission, according to DSM-IV-TR criteria were included in this study. Descriptive clinical features of remitted depressed patients and controls 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 the Erasme Academic Hospital Psychiatric Outpatient Department. They met criteria for depression, were in full to partial remission, and had mild self-reported sleep complaints. Self-reports of sleep were obtained by the Pittsburgh Sleep Quality Index (PSQI). The PSQI (range 0–21, with 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 $\geq 5$ has been found to correctly discriminate between “good” and “poor” sleepers (Buysse et al., 1989). Remitted depressed patients were evaluated initially by a psychiatrist using DSM-IV-TR criteria (American Psychiatric Association, 2000). Full and partial remission statuses were assessed.

<table>
<thead>
<tr>
<th>Demographics and clinical variables</th>
<th>Normal controls (n=14)</th>
<th>Remitted depressed patients (n=10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>42.43 ± 5.62</td>
<td>42.8 ± 8.55</td>
<td>0.899</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.02 (21.25–27.39)</td>
<td>24.56 (21.45–28.41)</td>
<td>0.371</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>0</td>
<td>NA</td>
</tr>
<tr>
<td>Married</td>
<td>6 (42.88)</td>
<td>4 (40)</td>
<td>NA</td>
</tr>
<tr>
<td>Other</td>
<td>8 (57.14)</td>
<td>6 (60)</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>2 (20)</td>
<td>NA</td>
</tr>
<tr>
<td>Employed</td>
<td>10 (71.43)</td>
<td>7 (70)</td>
<td>NA</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (10)</td>
<td>NA</td>
</tr>
<tr>
<td>HRSD-24 items at baseline*</td>
<td>0 (0–3)</td>
<td>9 (1–14)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Remission status, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial remission</td>
<td>NA</td>
<td>7 (70)</td>
<td>NA</td>
</tr>
<tr>
<td>Complete remission</td>
<td>3 (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSQI at baseline*</td>
<td>1 (1–4)</td>
<td>3 (1–4)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Values are expressed as mean±S.D. except as indicated. HAM-D-24 items, 24-item Hamilton Rating Scale for Depression; PSQI, Pittsburgh Sleep Quality Index; NA, nonapplicable.

*Values expressed as median with minimum-maximum range.

---

S. Leistedt et al. / Neuroscience xx (2007) xxx

Please cite this article in press as: Leistedt S, et al., The modifications of the long-range temporal correlations of the sleep EEG due to major depressive episode disappear with the status of remission, Neuroscience (2007), doi: 10.1016/j.neuroscience.2007.06.032
sessed with the 24-item Hamilton Rating Scale for Depression (HAM-D). Patients were included in the present study if they fulfilled the following five criteria: (1) they suffered from at least one major depression episode (unipolar without psychotic features); (2) they were in full or partial remission with a HAM-D score of 14 or lower for at least 6 months (Hamilton, 1967; Frank et al., 1991); (3) they were free of all prescription and nonprescription psychotropic medications; (4) they had a PSQI of 4 or lower; and (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, hematologe profile, thyroid function tests, and urinalysis. They did not show cardiovascular or endocrine abnormalities, or other systemic illness. Subjects or patients with a body mass index (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.

**Recordings and experimental conditions**

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 week, psychotropic medication–free evaluation period. Polysomnographic 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., 1986). 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 1993–2007, Sleep Laboratory, Erasme Hospital, Brussels, Belgium), 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 (BrainnetTM, 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 (Box 3740TM, Ohmeda, Louisville, CO, USA), or-nasal airflow was detected with thermistors (InfinityTM, Sleepmate Technologies, Midlothian, VA, USA), thoracic and abdominal respiratory movements were recorded with piezoelectric sensors (Resp-EZTM, Sleepmate Technologies), and leg movements were detected with ankle piezoelectric movement strain gauges (Moving ImagesTM, Sleepmate Technologies).

To eliminate low frequency artifacts, drifts, and offsets, the following time constants were set in the BrainnetTM 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 antialiasing analog filter, with a cutoff 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-synchronized audio replay through headphones. The Brainnet™ polygraph samples the signals on 12 bits and sends the resulting data to an Ethernet network, via the Netbios protocol. An acquisition program has been developed (Endymion 1993–2007, Sleep Laboratory, Erasme Hospital) to read and store the data in the EDF file format (Kemp et al., 1992). For subsequent analyses, the 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 synchronization problems between the stages and the other calculations. Using the Endymion program, each 20-s epoch was visually scored according to standard criteria (Rechtschaffen and Kales, 1968).

The fast Fourier transform (FFT) was applied to the Cz-Ax recordings to obtain the EEG power spectra. An FFT was computed on each 5-s data window, and the power of the delta (0.5–3 Hz), theta (3–8 Hz), alpha (8–12 Hz), sigma (12–16 Hz) and beta (16–25 Hz) EEG power bands was computed. These values were subsequently averaged over 20 s windows.

**Measurement of long-range correlations in sleep EEG time series**

An important question is whether the “heterogeneous” structure of physiologic time series arises trivially from external and intrinsic perturbations that push the system away from a homeostatic set point. An important alternative hypothesis is that the fluctuations are, at least in part, due to the underlying dynamics of the system. The key problem is how to decompose subtle fluctuations (due to intrinsic physiologic control) from other nonstationary trends associated with external stimuli.

In this way, the specific method we propose to use in this report is the detrended fluctuation analysis (DFA). DFA, as a scaling technique, can be applied to detect LRTC in noisy non-stationary signals, as it is frequently the case in biological systems. In fact, for the reliable detection of long-range correlations, it is essential to distinguish trends from the long-range fluctuations intrinsic in the data. Trends are caused by external effects. Strong trends in the data can lead to a false detection of long-range correlations if only one method is used (non-detrending) or if the results are not carefully interpreted. In this way, detrending allows one to gain insight into the scaling behavior of the natural variability.

The fundamental idea is to determine how the average root-mean-square (rms) of the fluctuations F(n) of the time series around the local trend varies as a function of the time scale n. DFA was first developed to describe the correlation properties in DNA nucleotides (Peng et al., 1992), and was later extended to heartbeat time series (Peng et al., 1995). It has been applied to EEG previously in several forms (Watters 1998; Linkenkaer-Hansen et al., 2001; Shen et al., 2003; Hwa et al., 2003; Parish et al., 2004). In our study, we closely follow the method of Peng et al. (1995).

The analysis is applied to a discrete time series \( x(i) \), \( 1 \leq i \leq N \), which in the present study represents the energy of the EEG signal:

\[
\begin{align*}
\text{where } v(i) & = \text{the EEG signal recorded at time } t_i, \\
\text{in the first step, the mean is subtracted from the time series and the time series is integrated: } \\
y(k) & = \sum_{i=1}^{k} [x(i) - \langle x \rangle], \quad 1 \leq k \leq N
\end{align*}
\]

where \( \langle x \rangle \) is the average of the time series over the range \([1, N]\). Next, the de-meaned integrated time series \( y(k) \) is divided into a
number of contiguous segments with length \( n \) (\( n \) represents the time scale of observation). For each of these segments, the local trend is determined by least-squares linear fit. The ensuing piece wise linear fit is designated \( y_{s}(k) \). Then, the integrated time series \( y(k) \) is detrended by subtracting the local linear trend \( y_{s}(k) \) for each segment. The root mean square fluctuation of this integrated and detrended time series is given by:

\[
F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^{N} [y(k) - y_{s}(k)]^2}
\]

Subsequently, this determination of \( F(n) \) is repeated for a range of different scales \( n \) (most frequently \( n \) ranged from 4 to 10 or 4/4 samples). In order to reduce fluctuations for large \( n \), we used sliding windows, of size \( n \), with the window lower boundary spanning from \( 1 \) to \( N-n \) by steps of \( 1 \) (Buldyrev et al., 1995). In a final step, the logarithm of \( F(n) \) is plotted as a function of the logarithm of the time scale \( n \). If the time series \( x(i) \) has self-similar, scale-free (fractal) properties, this plot will display a linear region, called the scaling region, with a certain slope \( \alpha \). This slope \( \alpha \) of the linear part of the plot of \( \log(F(n))/\log(n) \) is called the scaling or self-similarity exponent as:

\[
F(n) \propto n^\alpha
\]

The scaling exponent \( \alpha \) provides a quantitative measure of the temporal correlations present in the time series. When the signal is completely uncorrelated or in the case of short-range correlations, the calculation of the scaling exponent yields \( \alpha = 0.5 \). When applied to a signal with LRTC and power-law scaling, DFA will generate scaling exponents with either 0 < \( \alpha \) < 0.5 or 0.5 < \( \alpha \) < 1. When 0.5 < \( \alpha \) < 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 \( 0 < \alpha < 0.5 \), 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 \( \alpha = 0.5 \) toward \( \alpha = 1 \), the temporal correlations in the time series become persistent (decay more slowly with time). When \( \alpha > 1 \), however, the correlations no longer exhibit power-law behavior versus time and decay more rapidly with increasing \( \alpha \). A special case of \( \alpha = 1 \) corresponds to 1/f noise (Bak et al., 1987).

1.5, it indicates brownian noise: the integration of white noise. The \( \alpha \) exponent can also be viewed as an indicator that describes the “roughness” of the original time series; the larger the value of \( \alpha \), the smoother the time series. In addition, a large scaling exponent reflects slow fluctuations and a small scaling exponent reflects more rapid fluctuations. In this context, 1/f noise (\( \alpha = 1 \)) can be interpreted as a “compromise” between the complete unpredictability of white noise (very rough “landscape”) and the very smooth “landscape” of brownian noise (\( \alpha = 1.5 \)) (Peng et al., 1992; Buldyrev et al., 1994).

In the present study, we applied DFA analysis to each contiguous 20-s epoch considered for scoring; \( n \) thus ranged from 4 to 500 (i.e. 0.04–5 s). The scaling exponent was determined by least-square 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).

As a methodological summary, we precisely use DFA in this study to index the temporal correlation structure in the time-window range of 0.16–2.00 s.

**Statistical analysis**

For each of the three sleep stages (stage 2, SWS [stages 3 and 4] and REM) and for each subject in both groups, we collected samples of 45 scaling exponents computed on 45 artifact-free 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 conventional sleep analysis and spectral analysis, Student’s t-test or Mann-Whitney test was applied depending on whether the distribution of the variables was Gaussian or non-Gaussian. Spectral analysis was also applied on our sets of randomly chosen epochs in each sleep stage of interest. For scaling exponents’ analyses, the Kruskal-Wallis test was performed because of the small size of the sample and the non-gaussian distribution of the variables. All analyses were performed with \( \alpha \) (type I error) set at 0.05.

**RESULTS**

**Conventional sleep characteristics**

The two groups do not differ significantly in age or in BMI. The principal conventional sleep EEG parameters according to Rechtschaffen and Kales (1968) are summarized in Table 2. Our results do not show significant differences between the two groups. Nevertheless, we can observe some interesting trends in the remitted depressed group, such as, for example, decreased sleep efficiency, lower delta activity, shorter REM latency, and increased REM density. These results are in line with previous works which described a tendency for sleep parameters abnormalities (especially REM sleep abnormalities) to normalize with remission (Cartwright 1983; Knowles et al., 1986; Buysse et al., 1997; Riemann et al., 2001).

**Power spectral analyses**

To the best of our knowledge, there is no primary study investigating the sleep EEG spectral analysis in remitted depressed patients. On the other hand, previous work has investigated and showed various modifications on the sleep EEG spectral analysis characteristics in acutely depressed patients (Lange, 1982; Borbély et al., 1984; Toussaint et al., 2000; Coutin-Churchman et al., 2003).

In our study, power spectral analysis was performed on our sets of randomly chosen epochs in each sleep stage of interest, and each sleep stage was examined using traditional EEG frequency bands. Fig. 1 presents the power spectral analysis of the healthy controls versus to the remitted depressed patients. They are no significant differences between the controls and the remitted depressed patients in each of the frequency bands we have investigated. Therefore, in regard to the studies performed on the acutely depressed patients (Lange, 1982; Borbély et al., 1984; Toussaint et al., 2000; Coutin-Churchman et al., 2003), we may think that our results show a tendency for sleep EEG spectral analysis characteristics to normalize with the status of remission.

**LRTC analyses**

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 remitted depressed patients

<table>
<thead>
<tr>
<th>EEG sleep variables</th>
<th>Healthy controls (n=14)</th>
<th>Remitted depressed patients (n=10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep continuity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in bed (min)</td>
<td>489.78±76.9</td>
<td>498.83±52.91</td>
<td>0.751</td>
</tr>
<tr>
<td>TST (min)</td>
<td>431.81±56.92</td>
<td>395.47±44.05</td>
<td>0.106</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>19.14±11.34</td>
<td>20.77±15.15</td>
<td>0.766</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>85.69 (81.73–93.60)</td>
<td>83.74 (67.93–88.85)</td>
<td>0.064</td>
</tr>
<tr>
<td>No. of awakenings</td>
<td>41.07±15.55</td>
<td>50.80±19.86</td>
<td>0.192</td>
</tr>
<tr>
<td>No. of stages shifts</td>
<td>232.43±41.6</td>
<td>246.6±60.7</td>
<td>0.503</td>
</tr>
<tr>
<td>Mean duration of one continuous stage 2 episode (min)*</td>
<td>3.16 (2.65–6)</td>
<td>3.46 (2.31–5.44)</td>
<td>0.709</td>
</tr>
<tr>
<td>Mean duration of one continuous REM sleep episode (min)*</td>
<td>4.73 (2.57–11.9)</td>
<td>3.72 (1.88–14)</td>
<td>0.709</td>
</tr>
<tr>
<td>Mean duration of one continuous SWS episode (min)*</td>
<td>0.88 (0.4–3.55)</td>
<td>0.89 (0.37–3.27)</td>
<td>0.703</td>
</tr>
<tr>
<td><strong>Sleep architecture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NREM sleep measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 (% TST)</td>
<td>6.84±2.73</td>
<td>8.42±3.62</td>
<td>0.238</td>
</tr>
<tr>
<td>Stage 2 (% TST)*</td>
<td>64.21 (48.29–73.12)</td>
<td>63.64 (53.50–69.66)</td>
<td>0.585</td>
</tr>
<tr>
<td>SWS (% TST)</td>
<td>9.86±5.55</td>
<td>8.66±4.11</td>
<td>0.568</td>
</tr>
<tr>
<td>REM sleep measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REM (TST %)</td>
<td>21.07±3.53</td>
<td>20.28±3.51</td>
<td>0.593</td>
</tr>
<tr>
<td>Latency (min)</td>
<td>76.12±26.31</td>
<td>70.57±27.76</td>
<td>0.623</td>
</tr>
<tr>
<td>Density (units/min)*</td>
<td>2.7 (1.61–13.69)</td>
<td>2.77 (1.16–6.10)</td>
<td>0.472</td>
</tr>
</tbody>
</table>

* Values expressed as mean±S.D. except as indicated. TST, total sleep time; NREM, nonrapid eye movement.

for one of the healthy controls and one of the remitted depressed patients are displayed in Fig. 2. It is clear that visual inspection alone could not discriminate the patient from the control. Fluctuations, F, showed a linear behavior 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 behavior is illustrated, for example, for a remitted depressed patient in Fig. 3.

In order to probe differences between network dynamics of the remitted depressed and control brains, we compared the scaling exponents between the two groups. Medians and minimum to maximum ranges of scaling exponents of healthy controls and remitted depressed patients for the three sleep stages are presented in Table 3. All our scaling exponents values ranged between 0.66 and 1.09, showing that energy fluctuations in both groups have persistent LRTC with (0.5<α<1) or without (α>1) power-law form (Rangarajan and Ding, 2000). As described in previous work (Shen et al., 2003; Lee et al., 2004), we also found in both groups the increase of the scaling exponent values from light sleep to deep sleep and their decrease during REM sleep.

Our analyses show the absence of significant differences and deviations of the scaling exponents between the two groups during the three sleep stages of interest. Fig. 4 shows the grand averages of the fluctuations F(n) in the two groups during the three sleep stages of interest.

**DISCUSSION**

We have investigated the dynamics structure of the human sleep EEG in terms of energy fluctuations in patients with a past history of MDD.

Using DFA, we showed that the energy fluctuations of the human sleep EEG in remitted depressed patients and healthy controls exhibit LRTC with and without power-law behavior (Rangarajan and Ding, 2000). The presence of power-law scaling in the energy fluctuations of the human sleep EEG demonstrates that the fluctuations are not modulated at a characteristic time scale, but that the energy fluctuations occur as a part of a self-similar cascade of events that have a fractal structure. In spite of different study designs, the scaling exponents calculated here are grossly similar to scaling exponents found in other investigations (Watters 1998; Linkenkaer-Hansen et al., 2001, 2005), and provide additional support that LRTC is a fundamental feature of human brain activity.

**Scaling of temporal correlations in the sleep EEG of remitted depressed patients**

In our study, remitted depressed patients do not show significant and evident differences in scaling exponents’ values in comparison to healthy controls during the three sleep stages of interest. These results are in accordance with our conventional and power spectrum analyses, where no significant differences were seen between our two groups.

This finding is interesting because of the well-described modifications of these scaling properties of the sleep EEG during the acute state of the depressive disease (Linkenkaer-Hansen et al., 2005; Leistedt et al., 2007). In these last two studies, and in spite of a different study design in Linkenkaer-Hansen et al. (these authors studied the amplitude envelope of alpha oscillations and not the raw EEG signals), the authors show the existence of a breakdown of LRTC during sleep (Leistedt et al., 2007) and during wakefulness (Linkenkaer-Hansen et al., 2005) in relation to the acute depressive episode.
The absence of characteristic length (or time) scales may confer important biological advantages, related to the adaptability of the physiological response (Goldberger et al., 2002). Support for this related conjecture is provided by observations from severe diseased states such as heart failure where the breakdown of LRTC is often accompanied by the emergence of a dominant frequency mode (e.g. the Cheyne-Stokes frequency) (Goldberger et al., 2002). More precisely, the complete breakdown of normal LRTC in any physiological system could theoretically lead to three possible diseased states: (i) a random walk (brown noise); (ii) highly periodic behavior; or (iii) completely un-

Fig. 1. Histograms of the spectral mean power of the different frequency bands for healthy controls and remitted depressed patients during stage 2 (a), SWS (b) and REM sleep (c). None of the differences between groups were statistically significant.
Fig. 2. Recorded signals for three epochs of various sleep stages of interest for one healthy control (a) and one remitted depressed patient (b). \( V(t) \) in \( \mu V \).

Please cite this article in press as: Leistedt S, et al., The modifications of the long-range temporal correlations of the sleep EEG due to major depressive episode disappear with the status of remission, Neuroscience (2007), doi: 10.1016/j.neuroscience.2007.06.032
correlated behavior (white noise). Pathological examples of analogous transitions have been observed in a wide range of other disease states, including certain malignancies (Stanley et al., 1994), sudden cardiac death (Stanley et al., 1999), epilepsy (Stanley et al., 1994), and fetal distress syndrome (Stanley et al., 1994).

As recent reports suggest that many functional abnormalities found during the acute state of a depressive disease recover after pharmacological or psychotherapeutic treatment (Austin et al., 2001), we demonstrate here the recovery of the LRTC of energy fluctuations of the human sleep EEG in remitted depressed patients. As a consequence, we may think that the breakdown of LRTC during the acute state of the depressive disease (Linkenkaer-Hansen et al., 2005; Leistedt et al., 2007) represents trait abnormalities and not “scar markers.” In line with our results, we may also believe that the underlying dynamics of neuronal networks are not different between healthy controls and remitted depressed patients and that a previous episode of depression alters not “definitively” but only transiently the dynamics of the brain.

The “recovery” of the LRTC in remitted depressed patients as an illustration of brain plasticity in the depressive disease model

Cerebral plasticity is a continuous process allowing short-term, middle-term and long-term remodelling of neuromodulatory maps, to optimize the functioning of brain networks (Duffau, 2005). Plasticity plays a critical role in different areas: (i) during phylogeny; (ii) during ontogeny, with the elaboration of new circuits induced by learning, and the maintenance of neural networks in adults, then in elderly people (Hedden and Gabrieli, 2004): “natural plasticity” (Hertz-Pannier, 1999); and (iii) after damage to the peripheral or CNS, with functional reshaping underlying
a partial or complete clinical recovery: “post-lesional plasticity” (Xerri, 1998). Moreover, these phenomena must be stabilized to enable functioning of the system: “homeostatic plasticity” (Turrigiano and Nelson, 2004).

Major depression is a complex disorder that affects many different brain structures, often to a different extent. Brain changes associated with major depression have been reported in previous works in the hippocampus, amygdala, caudate nucleus, putamen, and frontal cortex; all structures that are extensively interconnected (Drevets, 2003; Campbell and MacQueen, 2004; Fuchs et al., 2004; Fossati et al., 2004). Brain imaging studies have provided a vast amount of information about the neuroanatomic correlates of depression. Change in either size or function of prefrontal cortex, hippocampus, and amygdala is consistently reported in studies of subjects with these disorders. Particularly, the works of Sheline et al. (1996, 2003) showed (i) reduced hippocampal volume in depressed patients, (ii) a correlation of the volume loss with the duration of depression, and mostly importantly (iii) a recovery of volume after antidepressant treatment. In fact, antidepressants may act by restoring structural as well as functional alterations in limbic-cortical circuits and, as a fundamental principle, may affect neural plasticity underlying normal brain functioning (Fuchs et al., 2004). It is well illustrated in this study, where all the cerebral functional abnormalities related to major depressive episode described in previous reports (Linkenkaer-Hansen et al., 2005; Leistedt et al., 2007), recover after pharmacological treatments. The present results are also an illustration of the “post-lesional cerebral plasticity” (Xerri, 1998).

**Physiological and medical implications**

It is well known that the brain is one of the most challenging complex systems. Moreover, depression is also a highly prevalent and complex disease with “labyrinthic reflections” about psychopathological processes implicated in this morbid evolution. In fact, despite extensive investigations, the exact neurobiological and neurophysiological processes leading to depression and the mechanisms responsible for the therapeutic effects of antidepressant drugs are not completely understood (Manji et al., 2001). Recently, it has been proposed that antidepressants may exert their long-term therapeutic effects by triggering cellular mechanisms that promote neuronal plasticity (Manji et al., 2003). Actions on neurotrophic factors and neurogenesis support these neuroprotective effects of antidepressants (Manji et al., 2003). Our investigation fails to detect any specific functional sequelae in the neuronal networks after at least one major depressive episode in remitted depressed patients who have been treated earlier by antidepressants. This observation is very interesting from a “psychiatrist’s point of view.” Effectively, the existence of some scars resulting from a disease process requires therapeutic adaptations, such as assistance or support for the physiological function that has suffered during the acute period. A comparison could be made with myocardial infarction, where the effects of a long-term adaptation to an acute disease process can be assessed through detailed studies of scar formation and functional sequelae. Similarly, the present results suggest that antidepressant treatment may influence the long-term functional sequelae of depression, and that further investigations are needed to understand the mechanisms underlying this process.


dial infarction where some drugs (i.e. β-blockers, diuretics) are essential after the acute incident to assist the cardiac function of concern. In the case of depressive disease and in relation with the concept of cerebral plasticity, more specifically "post-lesional plasticity," we demonstrate here the absence of one specific neurophysiological scar in the sleep EEG after at least one acute depressive episode. Finally this study gives an additional argument to the hypothesis that depression is severe, prolonged and mostly chronic disease but reversible in its structural and functional manifestations. This observation leads to the question of the longitudinal treatment of depression with antidepressants or hypnotics (in the case of the persistence of sleep impairments) as a "pharmacological support," except in those with a history of recurrent depression to prevent relapse. Our results seem to show that these pharmacological supports are not useful in the case of depression.

Another point of reflection is concerning the fact that many depressed patients continued to have symptoms after treatments, as a "symptomatic scar." As it is the case in our sample, it is now apparent that residual symptoms are common (especially sleep impairments), not only in patients with partial remission, but also in patients who meet criteria for full remission (Fava, 1999; Nierenberg and Wright, 1999). As to the sub-syndromal symptoms observed during partial remission of MDD, several authors suggest that they are essentially part of the depressive process, relying for that idea on the nature of the observed symptoms, and their frequent association with depressions initially considered as the most severe (Judd et al., 1998; Paykel, 1998). On a basis of a series of prospective studies, Fava (1999) even suggests that most of these residual symptoms may also be present during the prodromal phase of MDD, and that they recede in a chronologically inverse order from that observed when they set in, a phenomenon he compares with a roller shutter ("rollback phenomenon"). Conversely, the prospective 6-year study conducted by Shea et al. (1996) in 955 healthy relatives of patients with major depressive episode disappear with the status of remission, Neuroscience (2007), doi: 10.1016/j.neuroscience.2007.06.032

by excluding patients with more serious forms of psychiatric comorbidity, our conclusions should be interpreted with care. Third, the small sample size and the psychopathological assessment of the subjects did not allow for stratification of the patient sample by depressive subtypes. Fourthly, in this study, all the patients had been in remission at least 6 months. It is evident that we cannot attest expressly the absence of a functional scar marker 10 or 15 years after the acute episode. Finally, in the present investigation, different rhythms were recorded non-invasively with three sagittally placed EEG electrodes. Only the Cz-Ax results were reported here, and thus, the corresponding recorded rhythms were most likely generated in the neocortex. Otherwise, our analyses have also been performed on the other two leads (Fz and Oz). We did not observe any significant difference between the results obtained by the three different leads (Cz, Fz, and Oz). For this reason, the results obtained with Fz and Oz are not illustrated here and only Cz is considered as well. Because only three leads were analyzed, a complete "topographic interpretation" is not possible at this stage and requires further investigation. At this level, this observed behavior in scaling properties can be explained as an expression of a global and nonspecific dynamics of neuronal networks in healthy controls and remitted depressed patients.

Replication of our investigation in larger groups and for longer periods 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 who have suffered from MDD. Likewise, further clinical and experimental studies are needed to better understand structural and functional plasticity within the neural network regulating mood and affective behavior and to prepare the ground for the development of novel antidepressant treatments. In the past, antidepressants helped inform research into the mechanism of depression; however, in the future, we will have to better understand the neurophysiopathology of depression to develop better antidepressants.

**CONCLUSION**

In conclusion, we have first confirmed that energy fluctuations of the human sleep EEG exhibit LRTC. We have also demonstrated that the dynamics of the neuronal networks were not different between healthy controls and remitted patients who have suffered from at least one major depressive episode. Finally, this study gives additional arguments to the hypothesis that depression does not modify definitively the dynamics of neuronal networks and is therefore against the "depressive scar hypothesis."

Acknowledgments—The authors would like to thank Chantal Kempenaers, Stéphanie Braun, Michèle Dramaix, Jennifer Barr, Boris Leistedt and Bernard Jacques for their assistance. Research reported in this manuscript was supported by the National Fund for Scientific Research (F.N.R.S.).
REFERENCES


Manji HK, Drevets WC, Charney DS (2003) Enhancing neuronal plasticity and cell-

Please cite this article in press as: Leistedt S, et al., The modifications of the long-range temporal correlations of the sleep EEG due to major depressive episode disappear with the status of remission, Neuroscience (2007), doi: 10.1016/j.neuroscience.2007.06.032.
ular resilience to develop novel, improved therapeutics for difficult-to-treat depression. Biol Psychiatry 15:707–742.


(Accepted 27 June 2007)