Correlated and Uncorrelated Regions in Heart-Rate Fluctuations during Sleep

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Healthy sleep consists of several stages: deep sleep, light sleep, and rapid eye movement (REM) sleep. Here we show that these sleep stages can be characterized and distinguished by correlations of heart rates separated by n beats. Using the detrended fluctuation analysis (DFA) up to fourth order we find that long-range correlations reminiscent to the wake phase are present only in the REM phase. In the non-REM phases, the heart rates are uncorrelated above the typical breathing cycle time, pointing to a random regulation of the heartbeat during non-REM sleep.

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In recent years it has been recognized that in many natural sequences the elements are not positioned randomly, but exhibit long-range correlations. Prominent examples include noncoding DNA sequences [1,2], weather records [3], as well as sequences of letters and notes in literature and music [4]. The common feature of all these diverse systems is that the long-range correlations decay by a power law, where a characteristic scale is absent. These findings are useful, e.g., in DNA for distinguishing between coding and noncoding sequences, and in atmospheric science for testing state-of-the-art climate models.

In this Letter we consider heart rate sequences where also long-range correlations have been found [2,5]. Extensive analysis has shown that different long-range correlation exponents characterize the heart rates of healthy subjects and patients suffering from heart diseases, and this feature can be used as a diagnostic tool. Different exponents have been found also for the wake and the sleep periods [6]. Here we concentrate on the heart rate correlations in the different sleep stages, where external stimuli (which might give rise to additional trends) are absent.

It is well known that healthy sleep consists of cycles of roughly 1–2 hours duration. Each cycle is characterized by a sequence of sleep stages starting usually with light sleep and followed by deep sleep (slow-wave sleep) and REM (rapid eye movement) sleep. While the specific functions of the different sleep stages are not well understood, it is believed that the deep sleep stage is essential for physical recreation, while the REM stage is important for mental recreation.

We investigate the heart rhythm within the different sleep stages. We find the intriguing result that during non-REM sleep, which covers about 80% of the total sleep period, the heart rates show almost no correlations. According to our findings, long-range correlations [7] occur solely during REM sleep. The correlations are similar (while less pronounced) to those during wakefulness [6], and it seems likely that they are caused by the enhanced influence of the brain on the autonomous nervous system. When this influence is strongly reduced, as is the case during non-REM sleep, the heartbeat intervals behave in a more random fashion.

In our analysis, we consider 30 interbeat records from 15 healthy individuals and 47 records from 26 individuals suffering from moderate sleep apnea with less than 22 apneas per hour. The average length of the records is 7.5 h with a standard deviation of 45 min. Figure 1(a) shows the

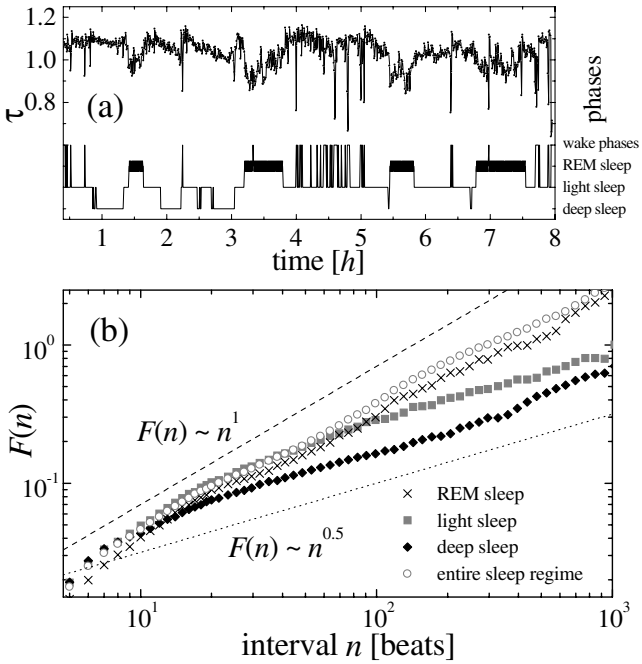

FIG. 1. (a) Representative one-night record for a healthy subject. The τ values shown represent averages of the heartbeat intervals τ_i over 30 heartbeats. The sleep phases have been determined by visual evaluation of electrophysiological recordings of brain activity [14]. (b) Second order detrended fluctuation analysis (DFA2) of the data shown in (a). The fluctuation function $F(n)$ is plotted as a function of window size n for the three sleep stages and compared to the result for the entire sleep regime without sleep stage separation. For comparison, a dotted straight line with slope 0.5 and a dashed straight line with slope 1 are also shown.

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interbeat intervals τ_i and their variations in the sleep stages for a healthy subject. As expected from earlier works [8], the rates are small for light sleep and deep sleep, and quite large for REM sleep. The largest fluctuations of the rate occur usually at the transitions between sleep stages and wake stages, often associated with body movements. These large fluctuations representing local trends are eliminated, if the sleep stages are analyzed separately.

Quantitatively, correlations between interbeat intervals separated by n beats are defined by the (auto)correlation function,

$$C(n) \equiv \langle \Delta\tau_i \Delta\tau_{i+n} \rangle = \frac{1}{N-n} \sum_{i=1}^{N-n} \Delta\tau_i \Delta\tau_{i+n}\,, \quad (1)$$

where N is the number of beats in the considered record, $\Delta\tau_i \equiv \tau_i - \tau$, and τ is the average interbeat interval. If the $\Delta\tau_i$ are uncorrelated, $C(n)$ is zero for n positive. If correlations exist up to a certain number of beats $n_\times$, the correlation function will be positive up to $n_\times$ and vanish above $n_\times$. A direct calculation of $C(n)$ is hindered by the level of noise present in the finite heart rate records, and by possible nonstationarities in the data (see, e.g., [9]). To reduce the noise we do not calculate $C(n)$ directly, but instead study the "profile" $Y_m = \sum_{i=1}^{m} \Delta\tau_i$.

We can consider the profile Y_m as the position of a random walker on a linear chain after m steps. The random walker starts at the origin of the chain and performs, in the ith step, a jump of length $\Delta\tau_i$ to the right, if $\Delta\tau_i$ is positive, and to the left, if $\Delta\tau_i$ is negative. According to random walk theory (see, e.g., [10,11]), the fluctuations (standard deviation; see below) $F(n)$ of the profile in a given "time window" of n beats are related to the correlation function $C(n)$. For the relevant case of long-range power-law correlations $C(n) \sim n^{-\gamma}$, $0 < \gamma < 1$, the fluctuations $F(n)$ increase by a power law,

$$F(n) \sim n^{\alpha}, \qquad \alpha = 1 - \gamma/2\,. \quad (2)$$

For uncorrelated data [as well as for short-range correlations represented by exponentials $C(n) \propto \exp(-n/n_\times)$ or an exponent $\gamma \geq 1$], we have $\alpha = 1/2$.

To avoid spurious detection of correlations that are artifact of nonstationarities in the data, we calculate the time-dependent fluctuation function $F(n)$ by employing the detrended fluctuation analysis (DFA) [11,12] up to fourth order. We divide the profile Y_m into nonoverlapping segments of size n. In first order DFA (DFA1) we determine, in each segment, the best linear fit of the profile. The standard deviation of the profile from these straight lines represents the fluctuation function $F(n)$. Linear trends in the profile are eliminated by this procedure. In second order DFA (DFA2) we determine, in each segment, the best quadratic fit of the profile, and the standard deviation of the profile from these parabolas represents the fluctuation function $F(n)$. The higher order DFAs are straightforward extensions: In qth order DFA, trends of order q in the profile and of order $q-1$ in the original data are eliminated.

We begin by applying DFA2 to the data of Fig. 1(a). The results are shown in Fig. 1(b). The analysis reveals that the fluctuations in the three different sleep stages are significantly different. (i) In the deep sleep, apart from very short times, the slope of $F(n)$ in the double-logarithmic representation is close to $1/2$, indicating the *loss* of correlations. (ii) In the light sleep, we observe a similar pattern, but the loss of correlations appears at larger times. (iii) In the REM sleep, we observe a slope of $\alpha \approx 0.85$ in a regime of at least up to 500 beats, characterizing long-range correlations.

Figure 1 also shows the fluctuation function $F(n)$ obtained for the entire sleep regime (whole night), without distinguishing between the different sleep stages. In the double logarithmic presentation, the slope α is about 0.85 for the entire sleep regime, in substantial agreement with earlier findings [6]; see also [7]. In order to detect the origin of these correlations, we have again considered the whole sleep regime, but excluded the transition regimes (one minute each) between the different stages, and calculated the fluctuation function for this reduced data set. We find that the resulting $F(n)$ (not shown in the figure) is very close to $F(n)$ for light sleep. This indicates that the strong long-range correlations found for the whole night do not originate from the REM stages but from the *transition regimes* between the sleep stages and between sleep and wake stages.

Figure 2 shows the fluctuation functions of four more records. The characteristic features (long-range correlations for REM sleep, loss of correlations for deep sleep and light sleep) are the same as in Fig. 1(b). This is also

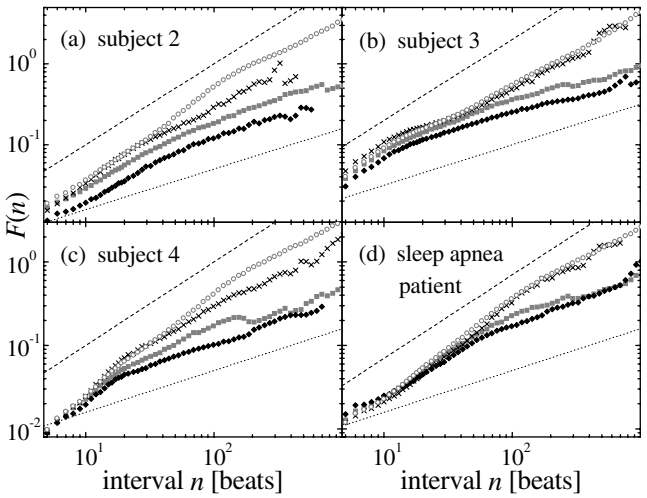

FIG. 2. Detrended fluctuation analysis (DFA2) of heartbeat intervals of four records, three from healthy subjects (a)–(c) and one from a subject suffering moderate sleep apnea (d). The fluctuation functions [same symbols as in Fig. 1(b)] show the same characteristic features as described in Fig. 1(b), but with an enhanced crossover in the case of sleep apnea.

true for the subject with moderate sleep apnea [Fig. 2(d)]. Even though the subject awakes quite often the characteristic features of the fluctuation functions remain unchanged, but with an enhanced crossover time.

To ensure that the results are not affected by trends, we applied also DFA3 and DFA4 to all our data, and compared them with DFA1 and DFA2. Representative results, again for the data of Fig. 1(a), are shown in Figs. 3(a), 3(c), and 3(e). The figure clearly supports the conclusions drawn from DFA2. Moreover, it shows that crossovers due to trends that appear in DFA1 and DFA2 at large n values [Figs. 3(c) and 3(e)] disappear in DFA3 and DFA4.

To estimate the crossover times, we have generated control sequences with $\alpha = 0.85$. To generate a crossover from correlated to uncorrelated behavior at $n_\times$, we have divided the sequence into subsequences of length $n_\times$ and shuffled randomly the subsequences. We found that the best $n_\times$ representing the data are $n_\times = 3 \pm 1$ for deep sleep [see Figs. 3(e) and 3(f)] and $n_\times = 6 \pm 1$ for light sleep [see Figs. 3(c) and 3(d)]. REM sleep [Figs. 3(a) and 3(b)] is well reproduced by the original control sequence with $\alpha = 0.85$, but we cannot exclude the possibility of a crossover to a larger exponent α for small n values. The crossover times in deep sleep and light sleep are close to the typical breathing time [13].

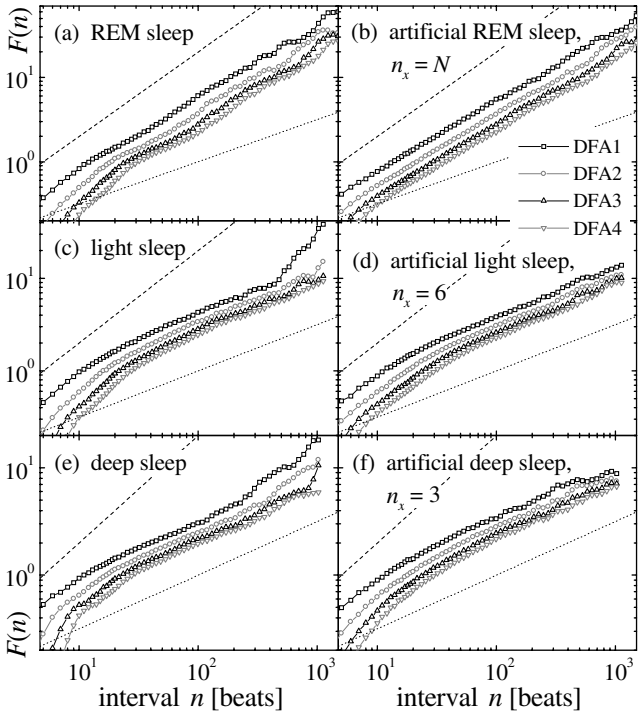

FIG. 3. The fluctuation function $F(n)$ for (a) REM sleep, (c) light sleep, and (e) deep sleep obtained from DFA1 (squares), DFA2 (grey circles), DFA3 (triangles up), DFA4 (grey triangles down) compared with results from artificial data (b),(d),(f). The artificial data consist of correlated random numbers with $\alpha = 0.85$ below $n_\times$. Above $n_\times$ the data are uncorrelated. The lengths and numbers of the control sequences are identical with the lengths and numbers of the sleep stages in the real recordings. The best $n_\times$ values representing the real data are $n_\times = N$ for REM sleep (b), $n_\times = 6$ for light sleep (d), and $n_\times = 3$ for deep sleep (f). To allow for a comparison of the data, the standard deviation of the τ_i values was set equal to 1 in all cases.

This points at an intimate relation between heart rhythm and breathing, which is further indicated by the fact that in the case of sleep apnea the crossover is enhanced [see Fig. 2(d)]. To clarify this point further, we studied the power spectrum of the heart rates in the different sleep stages. In deep sleep, a pronounced narrow peak occurs around the frequency $\nu \approx 1/4$ (corresponding to four heartbeats) that can be identified with the breathing cycle. In light sleep, a less pronounced and broader peak occurs at the same frequency. In REM sleep, the peak is even broader and weaker. These findings are in agreement with our DFA analysis and support our conclusion that the crossover seen in deep and light sleep is due to the coupling of the heartbeats with breathing. At lower frequencies, in both light and deep sleep, the power spectrum becomes almost flat, with large fluctuations, which is consistent with the loss of long-range correlations we observed by DFA. While we can identify the influence of the breathing cycle, i.e., respiratory sinus arrhythmia on the Fourier transform and the DFA results, we could not identify crossover times related to Mayer waves or to influences of temperature regulation.

We have obtained similar findings for all healthy subjects and sleep apnea patients. The results are summarized in Figs. 4(a)–4(c) where the histograms for the exponents α in the three sleep stages are shown. For light and deep sleep, the histograms are centered around $\alpha \approx 0.5$ and show a large overlap. Both histograms are well separated from the histogram of REM sleep, which is centered around $\alpha \approx 0.85$. A simple measure of the significance is obtained from the student t-test. The fluctuation exponents for light and deep sleep are well separated from REM sleep, with p values smaller than 10^{-7} for both.

In order to test further the significance of the DFA results, we have generated artificial control sequences for each of the 77 records in the same way we did in Figs. 3(b), 3(d), and 3(f). In the procedure, the lengths of the sleep stages were chosen identical to those of the real records, but the interbeat intervals were replaced by correlated random numbers (REM sleep) or shuffled correlated random numbers with subsequence sizes $n_\times = 6$ (light sleep) and $n_\times = 3$ (deep sleep). The histograms of the exponents α obtained from the fluctuation functions for the control sequences are shown in Figs. 4(d)–4(f). The exponents have been determined in exactly the same way as for the real records. For deep sleep [Fig. 4(e)] the original histogram [Fig. 4(b)] is nearly exactly reproduced. This strongly supports our conclusion of uncorrelated interbeat intervals in deep sleep. In light sleep, the histogram for the control sequences [Fig. 4(d)] is centered around $\alpha \cong 0.55$ just as

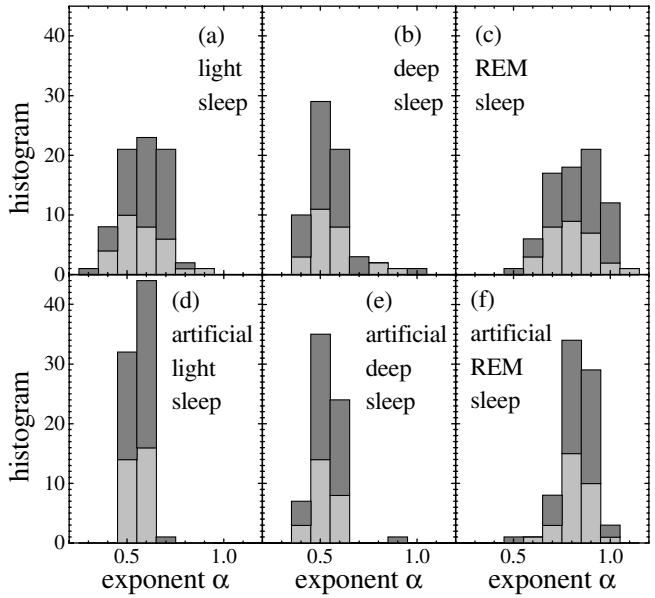

FIG. 4. (a)-(c) Histograms of the fluctuation exponents α obtained from linear fits to log-log plots of $F(n)$ versus n in the regime $70 < n < 300$ for (a) light sleep, (b) deep sleep, and (c) REM sleep. The fitting range has been chosen to be above the regime of short-range correlations related to breathing and below the n values where the statistical errors become too large due to the finite length of the sleep stages. The data in (a) are based on all 30 records from healthy subjects (light grey) and on all 47 records from patients with moderate sleep apnea (dark grey). In (b) ten records have been dropped since they where too short while in (c) only one record was too short and has been dropped. (d)–(f) The corresponding results for artificial control data sets. The artificial data for the sleep stages have been generated in the way described below Fig. 3 and in the text.

in the original histogram [Fig. 4(a)]. This suggests that the slight deviation from uncorrelated behavior is related to the crossover at $n_\times = 6$ and not to slight long-range correlations, which are actually absent in the control sequences due to the shuffling.

In summary, we have studied the heart rhythm in the different sleep stages (deep, light, and REM sleep) that reflect different brain activities, for both healthy subjects and patients with moderate sleep disorder. We have found that when the brain is very active as in the "dream"-REM stage, the heart rates have a long-time memory, as in the wake phase. In contrast, in deep sleep the memory of the heart rates vanishes after a small number of beats that is below the order of the breathing cycle time. In light sleep, finally, the heart rates seem to become uncorrelated as well, but the crossover occurs slightly above the breathing time. We believe that these findings will be useful to develop a sleep phase finder that is based on the different heart rhythm in the different sleep stages, supplementing the quite tedious evaluation of the sleep phases by the standard electrophysiological procedures.

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