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Scale-invariant Aspects of Cardiac Dynamics Across Sleep Stages and Circadian Phases

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Abstract— **We review recent attempts to understand the influence of sleep and wake states, sleep-stage transitions during sleep and the endogenous circadian rhythms on the neuroautonomic regulation of cardiac dynamics as represented by the scale-invariant organization of heartbeat fluctuations. We find that the probability distribution, the long-range temporal correlations as well as the nonlinear properties of the heartbeat fluctuations are significantly altered with transition from sleep to wake state, across sleep-stages and circadian phases. These sleep and circadian meadiated changes in cardiac dynamics occur simultaneously over a broad range of time scales, suggesting a more complex then previously known interaction between the neural systems of sleep and circadian regulation with the neuroautonomic cardiac control, beyond rhythmic modulation at a characteristic time scale.**

I. INTRODUCTION

The normal electrical activity of the heart is usually described as a "regular sinus rhythm". However, cardiac interbeat intervals fluctuate in an irregular manner in healthy subjects — even at rest or during sleep. In recent years, the intriguing statistical properties of interbeat interval sequences have attracted the attention of researchers from different fields. Analysis of heartbeat fluctuations focused initially on short time oscillations associated with breathing, blood pressure and neuroautonomic control [1], [2]. Studies of longer heartbeat records revealed 1/f-like behavior [3], [4]. Recent analyses of very long time series (up to 24h) show that under healthy conditions, interbeat interval increments exhibit power-law anticorrelations [5], [6], follow a universal scaling form in their distributions [7], and exhibit turbulence-like dynamics characterized by a broad multifractal spectrum [8]. These scaling features change with disease and advanced age [9], [10].

Sleep-wake cycles and the endogenous circadian rhythms are associated with periodic changes in key physiological processes [11], [12], [13]. Here, we ask the question if there are characteristic differences in the behavior between sleep and wake cardiac dynamics across multiple time scales. We hypothesize that, in addition to the known periodic rhythms with a characteristic time scale, the endogenous mechanisms of sleep and circadian regulation may influence cardiac dynamics over a broad range of time scales, and thus could lead to systematic changes in the scaling properties of the heartbeat fluctuations. Elucidating the nature of these interactions could lead to a better understanding of the neuroautonomic mechanisms of cardiac regulation.

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II. RESULTS

A. Sleep-wake differences in heart rate distributions

Typically the differences in the cardiac dynamics during sleep and wake phases are reflected in the average and standard deviation of the heartbeat intervals [13]. To analyze the statistical properties of human cardiac activity we introduced the 'cumulative variation amplitude analysis' (CVAA), designed to quantify probability distributions of physiologic fluctuations embedded in nonstationary signals [7]. This method comprises sequential application of a set of algorithms based on wavelet and Hilbert transform analyses. The first step is the wavelet transform [14], which extracts the cumulative variations in the heartbeat intervals over a spacific wavelet (time) scale by simultaneously removing polynomial trends associated with the nonstationarity in the data. The second step of the CVAA method is to extract the amplitudes of the variations in the beat-to-beat signal by means of an analytic signal approach (Hilbert transform) [15], which provides a measure for the duration of segments with different amplitudes of heartbeat variations.

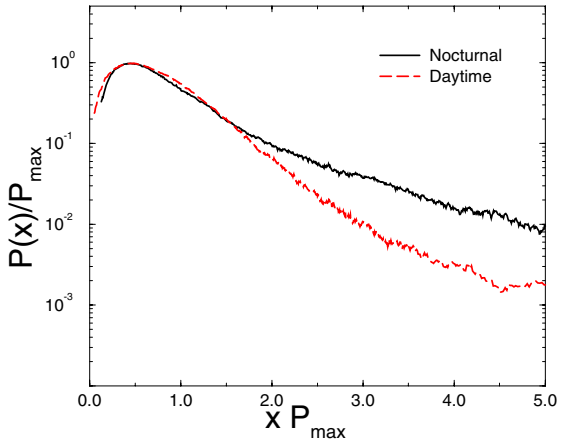

Fig. 1. Plots of the day- and night-phase distributions. Data is averaged over a subset of 18 healthy subjects after rescaling the individual distributions. Adapted from ref. 16.

We studied the distribution of the amplitudes of the beat-to-beat variations for a group of healthy subjects ($N = 18$ 5 males and 13 females; age: $20 - 50$, mean - 34 years). We begin by considering *night* phase records (sleep between midnight-6 AM). Inspection of the distribution functions of the amplitudes of the cumulative variations reveals marked

differences between individuals. To test the hypothesis that there is a possibly universal structure to these heterogeneous time series, we rescale the distributions and find for all healthy subjects that the data conform to a single scaled plot [7]. We find the rescaled data is well fit with a homogeneous Gamma distribution, defined with a single parameter, and that the form of the distribution is preserved when changing the time scale of the analysis. Such robust scaling behavior is reminiscent of a wide class of well-studied physical systems with universal scaling properties [17]. The collapse of the individual distributions for all healthy subjects after rescaling their "individual" parameter is indicative of a "universal" structure, in the sense that there is a closed mathematical scaling form describing in a unified quantitative way the cardiac dynamics of healthy subjects over a broad range of time scales [18].

We next analyzed heart rate dynamics for healthy subjects during the *daytime* (wake state between noon–6 P.M.). The apparently universal behavior we find holds not only for the night phase but for the day phase as well. However, semilog plots of the averaged distributions show a slower decay in the tail for the sleep-state, whereas the wake-state distribution follows the exponential form over practically the entire range [16], [18]. Counterintuitively, the slower decaying tail of the distribution of heartbeat fluctuations for the night phase indicates higher probability of larger variations in the healthy heart dynamics during sleep hours in comparison with the daytime dynamics during wake state [Fig.1].

B. Sleep-wake differences in the correlations of heartbeat fluctuations

As we observed sleep-wake differences in the form of the probability distributions of the amplitudes of the fluctuations in the heartbeat intervals [Fig.1], we next asked the question if there are characteristic differences in the temporal correlations of cardiac dynamics between sleep and wake state. We applied the detrended fluctuation analysis (DFA) method [19]. The advantage of the DFA method over conventional methods, such as power spectrum analysis, is that it avoids the spurious detection of apparent long-range correlations that are an artifact of nonstationarity related to linear and higher order polynomial trends in the data.

We analyzed 30 datasets from 18 healthy subjects, 12 patients with congestive heart failure and 6 cosmonauts during long-term orbital flight. We analyzed the nocturnal and diurnal fractions of the dataset of each subject, which correspond to the 6h from midnight to 6am and noon to 6pm.

We find that at scales above $\approx$ 1min the data during wake hours display long-range power-law correlations over two decades with average exponents $\alpha_W \approx 1.05$ for the healthy group and $\alpha_W \approx 1.2$ for the heart failure patients [20]. For the sleep data we find a systematic crossover at scale $n \approx 60$ beats followed by a scaling regime extending over two decades characterized by a smaller exponent: $\alpha_S \approx 0.85$ for the healthy and $\alpha_S \approx 0.95$ for the heart failure group [20]. We find that for all individuals studied, the heartbeat dynamics during sleep are characterized by a smaller exponent [Fig.2], suggesting *stronger* anticorrelations in heartbeat fluctuations during sleep compared to wake state.

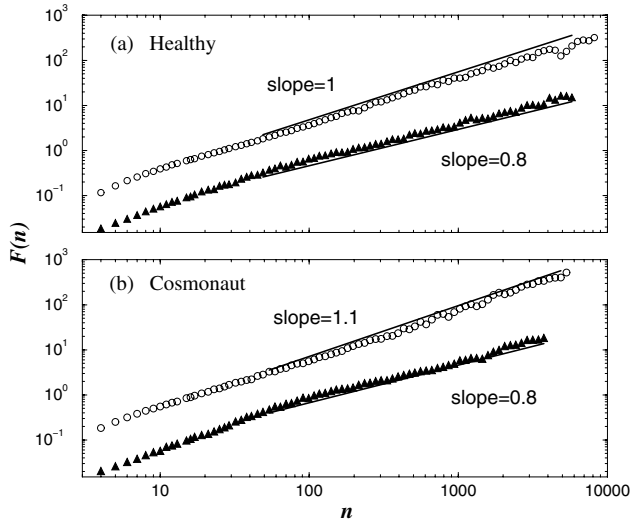

Fig. 2. Log-log plots of the DFA fluctuation function $F(n)$ vs the time scale n (number of beats) for 6h wake records (open circles) and sleep records (filled triangles) of (a) one typical healthy subject; (b) one cosmonaut during orbital flight. The slope indicates the scaling exponent α. Note the systematic lower exponent for the sleep phase (filled triangles), indicating stronger anticorrelations. Adapted from ref. 20.

The findings of stronger anticorrelations [20], as well as higher probability for larger heartbeat fluctuations during sleep [7], [16], [18] suggest that the observed dynamical characteristics in the heartbeat fluctuations during sleep and wake phases are related to intrinsic mechanisms of neuroautonomic control, and support a reassessment of the sleep as a surprisingly *active dynamical* state. Surprisingly, we note that for the regime of large time scales ($n > 60$ beats) the average sleep-wake scaling difference ($\alpha_W - \alpha_S \approx 0.2$ for both healthy and heart failure groups) is comparable to the scaling difference between health and disease. We also note that the scaling exponents for the heart failure group during sleep are close to the exponents observed for the healthy group during wake [20]. Since heart failure occurs when the cardiac output is not adequate to meet the metabolic demands of the body, one would anticipate that the manifestations of heart failure would be most severe during physical stress when metabolic demands are greatest, and least severe when metabolic demands are minimal, i.e., during rest or sleep. The scaling results we obtain are consistent with these physiological considerations: the heart failure subjects should be closer to normal during minimal activity. Of related interest, recent studies indicate that sudden death in individuals with underlying heart disease is most likely to occur in the hours just after awakening [21]. For all cosmonauts the values of the scaling exponent α during wake and sleep are consistent with those found for the healthy terrestrial group [Fig.2].

The sleep-wake changes in the scaling characteristics we observe may indicate different regimes of intrinsic neuroautonomic regulation of the cardiac dynamics, which may "switch" on and off in accordance with circadian rhythms.

These findings raise the intriguing possibility that the transition between the sleep and wake phases is a period of potentially increased neuroautonomic instability because it requires a transition from strongly to weakly anticorrelated regulation of the heart. This hypothesis triggered further investigations as outlined in Subsection D.

C. Temporal correlations in heartbeat fluctuations change with sleep stages

Healthy sleep consists of cycles of approximately 1–2 hours duration. Each cycle is characterized by a sequence of sleep stages usually starting with light sleep, followed by deep sleep, and rapid eye movement (REM) sleep [22]. While the specific functions of the different sleep stages are not yet well understood, many believe that deep sleep is essential for physical rest, while REM sleep is important for memory consolidation [22]. It is known that changes in the physiological processes are associated with circadian rhythms (wake or sleep state) and with different sleep stages. Thus, we next ask how cardiac dynamics of healthy subjects change within the different sleep stages.

A recent study has confirmed our finding of lower value for the scaling exponent during sleep compared to wake and has further shown that different stages of sleep (e.g. light sleep, deep sleep, rapid eye movement stages) could be associated with different temporal correlations in the heartbeat fluctuations [23], suggesting a change in the mechanism of cardiac regulation in the process of sleep-stage transitions.

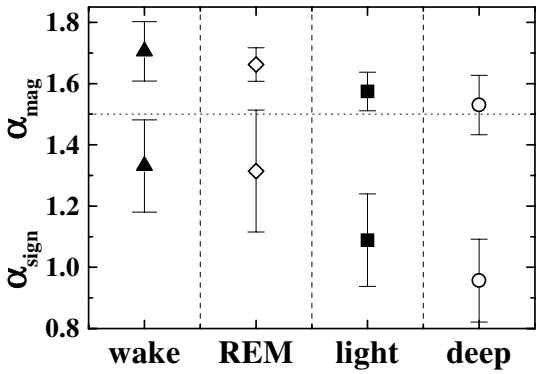

Fig. 3. The average values of the exponents $\alpha_{\rm mag}$ for the integrated magnitude series and $\alpha_{\rm sign}$ for the integrated sign series for the different phases (wake state, REM sleep, light sleep, and deep sleep). For each of the 24 records from 12 healthy subjects the corresponding 2nd order DFA fluctuation functions $F(n)$ have been fit in the range of $8 \leq n \leq 13$ and $11 \leq n \leq 150$ heartbeats for $\alpha_{\rm sign}$ and $\alpha_{\rm mag}$, respectively, where the most significant differences between the sleep stages occur. Adapted from ref. 26.

We employed a recently proposed approach of magnitude and sign analysis [24], [25] to further investigate how the linear and nonlinear properties of heartbeat dynamics change during different stages of sleep. We focus on the correlations of the *sign* and the *magnitude* of the heartbeat increments obtained from recordings of interbeat intervals from healthy subjects during sleep. We apply the DFA method [19] on both the sign and the magnitude time series. We find that the sign series exhibits anticorrelated behavior at short time scales which is characterized by a correlation exponent $\alpha_{\rm sign}$ with smallest value for deep sleep, larger value for light sleep, and largest value for REM sleep [Fig.3]. The magnitude series, on the other hand, exhibits uncorrelated behavior for deep sleep with $\alpha_{\rm mag} \approx 1.5$, and long-range correlations are found for light and REM sleep, with a larger exponent for REM sleep [Fig.3]. The observed increase in the values of both the sign and magnitude correlation exponents from deep through light to REM sleep is systematic and significant [26]. We also observe that the values of the sign and magnitude exponents for REM sleep are very close to the values of these exponents for the wake state.

Our studies suggest that long-range correlated behavior of the magnitude series obtained from a long-range anticorrelated increment series relates to the nonlinear properties of the signal, while the sign series reflects the linear properties [24], [25]. Thus, our finding of positive power-law correlations for the magnitude of the heartbeat increments during REM sleep and of loss of these correlations during deep sleep [Fig.3], indicates a different degree of nonlinearity in cardiac dynamics during different sleep stages. A stochastic model has been subsequently developed to account for the complex changes in the scaling and nonlinear features of heartbeat dynamics with sleep stage transitions [27].

D. Temporal correlations in heartbeat dynamics change with circadian phase

Epidemiological studies have reported a robust day/night pattern in the incidence of adverse cardiovascular events with a peak at $\approx 10AM$ [28]. This peak has been traditionally attributed to day/night patterns in behaviors including activity levels. We hypothesized that these dynamical scaling features of the healthy human heartbeat have an intrinsic circadian rhythm that brings them closer to the features observed under pathologic conditions at specific circadian phases.

We investigated heartbeat dynamics in healthy subjects (4 males, 1 female; age: 20 - 33, mean 25.8 years) recorded throughout a 10-day protocol in which the sleep/wake and activity cycle were desynchronized from the endogenous circadian cycle, enabling separation of internal circadian factors from behavior-related factors. Subjects' sleep-wake behavior cycles are adjusted to 28 hours [29]. This 28-hour recurring sleep/wake schedule is repeated for seven cycles in the absence of bright light, so that the body clock oscillates at its inherent rate. Subjects have been asked to repeat the same schedule in all seven wake periods so that statistically, the same behaviors occur at each circadian phase throughout all seven 28-hour cycles.

We separated all interbeat interval data into 1-hour windows, and for each window we calculate the value of the DFA scaling exponent and the mean heartbeat interval. Since the sleep and wake states have different effects on cardiac dynamics [16], [20], [23], [26], we analyzed wake and sleep-opportunity periods separately. Averaging the data according to the circadian phase yields effects caused by endogenous circadian rhythms independent of behavioral factors, because

in the forced desynchrony protocol each behavior is represented at each circadian phase.

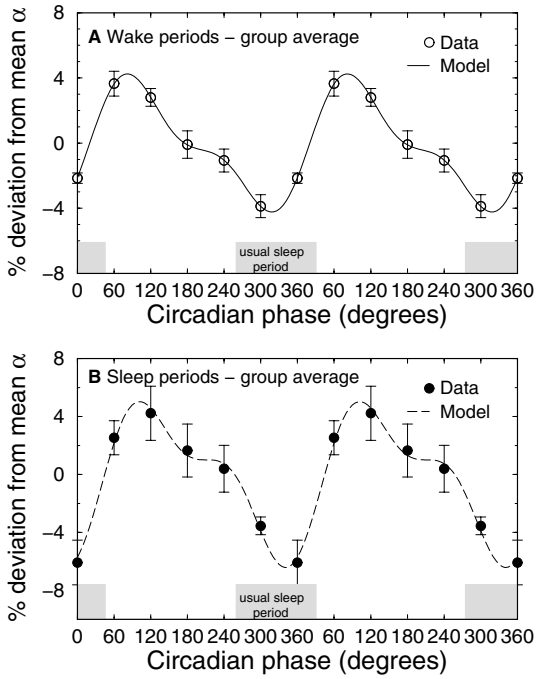

Fig. 4. Circadian rhythms in the group average of the scaling exponent α for (A) wake periods and for (B) sleep-opportunity periods. Consistent and significant circadian rhythms are observed for both wake periods (p-value= 0.01) and sleep-opportunity periods (p-value= 0.0003). Note the well-pronounced peak at between 60 and 90 circadian degrees (9-11AM). Adapted from ref. 29.

We find that the DFA scaling exponent characterizing the temporal correlations in heartbeat dynamics exhibits a significant circadian rhythm, with a sharp peak at the circadian phase corresponding to $\approx 10AM$ [Fig.4], coinciding with the window of cardiac vulnerability reported in clinical studies [28]. We find that this peak in the value of the scaling exponent is independent of the scheduled behaviors and occurs during both sleep and awake periods scheduled across different circadian phases [29]. Since cardiac dynamics under pathologic conditions such as congestive heart failure are associated with a larger value of the scaling exponent, our findings suggest that circadian-mediated influences on cardiac control may be involved in cardiac vulnerability. Further, we find that the peak in the value of the correlation exponen at $\approx 10AM$ is not related to the circadian-mediated influence on the mean activity levels leading to changes in the average heartrate which displays a very different circadian rhythm with a peak in the window 5-9 PM [29].

III. CONCLUSIONS

We find that key scale-invariant features of heartbeat dynamics, which have been previously associated with the underlying mechnisms of cardiac regulation, change significantly with sleep-wake transition, across sleep stages and circadian phases under both healthy and pathologic conditions. Our findings indicate that sleep-wake and circadian cycles do not simply modulate basic physiologic functions by generating rhythms with a fixed periodicity, but also influence the neural regulation of fundamental physiologic systems such as the cardiovascular system over a *broad range* of time scales. Our empirical observations suggest that the neural systems of sleep and circadin regulation play an important role in the scale-invariant fractal organization of cardiac dynamics (and perhaps also of other physiologic dynamics) which has been shown to breakdown with disease and advanced age.

IV. ACKNOWLEDGMENTS

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