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Behavioral-Independent Features of Complex Heartbeat Dynamics

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Abstract

We test whether the complexity of cardiac interbeat interval time series is simply a consequence of the wide range of scales characterizing human behavior, especially physical activity, by analyzing data taken from healthy adult subjects under three conditions with controls: (i) a “constant routine” protocol where physical activity and postural changes are kept to a minimum, (ii) sympathetic blockade, and (iii) parasympathetic blockade. We find that when fluctuations in physical activity and other behavioral modifiers are minimized, a remarkable level of complexity of heartbeat dynamics remains, while for neuroautonomic blockade the multifractal complexity decreases.

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Healthy free-running physiologic systems have complex self-regulating mechanisms which process inputs with a broad range of characteristics [1], and may generate signals that have scale-invariant dynamics [2]. Many physiologic time series are extremely “patchy” and nonstationary, fluctuating in an irregular and complex manner. This observation suggests that some physiologic signals are sufficiently inhomogeneous that a single fractal exponent may not be sufficient to characterize them.

Time series of healthy human interbeat intervals belong to a special class of complex signals that display multifractal properties [3]. Multifractal signals—such as those generated by binomial multiplicative processes or turbulent fluctuations— can be decomposed into many subsets characterized by different *local* Hurst [4] exponents h , which quantify the local singular behavior and thus relate to the local fractal properties of the time series [4,5]. The statistical properties of the different subsets characterized by the different exponent values of h are quantified by the function $D(h)$. Here $D(h_o)$ is the fractal dimension of the subset of the original time series characterized by the local Hurst exponent h_o [4,5]. For heart rate time series from healthy individuals, the function $D(h)$ is “broad” (implying multifractality), but “narrow” (implying monofractality) for subjects with heart failure [3], a life-threatening condition.

An intriguing question, with implications for basic signalling and feedback mechanisms, is what gives rise to multifractality in healthy human heartbeat dynamics? Two distinct possibilities can be considered. The first is that the observed multifractality is primarily a consequence of the response of neuroautonomic control mechanisms to activity-related fractal stimuli [2]. If this were the case, then in the absence of such correlated inputs the heartbeat dynamics would not generate such a heterogeneous multifractal output. The second is that the neuroautonomic control mechanisms—in the presence of even weak external noise— *endogenously* generate multifractal dynamics. Here, we present evidence from three new experiments which supports the latter possibility.

The procedure to calculate the values of h and their corresponding fractal dimensions has been described elsewhere [3,6–8]. We calculate the experimental $\tau(q)$, which is related

to $D(h)$ through a Legendre transform [4,9,10],

$$D(h) = q \frac{d\tau(q)}{dq} - \tau(q). \quad (1)$$

We first analyze datasets from six healthy, non-smoking male subjects [11] (ages: 21–30 yr). We obtained two datasets per subject, the first under constant routine conditions, and the second under usual daily activity conditions [12,13]. Figure 1a displays the average multifractal spectra $\tau(q)$ for the six subjects under both regimens. The nonlinearity of $\tau(q)$ does not appear altered by constant routine conditions. Indeed, our analysis indicates that major reductions in external stimulation and physical activity do not reduce the multifractal properties of healthy cardiac dynamics, supporting the hypothesis that the multifractality in healthy heartbeat dynamics is endogenous to the neuroautonomic regulation of the heart rate [14,15].

To test the possibility that the multifractality in healthy heartbeat dynamics is related to neuroautonomic control, we analyze data from six subjects [11] (4 male, 2 female, ages: 21–34 yr) who were administered a beta-blocking drug [16] which reduces sympathetic control. We analyzed eight datasets from the six subjects from the the second and/or third day of beta-blocker administration [13,17]. As a control, we also analyzed eight datasets for the same subjects but for the second and/or third day of placebo administration [17]. Figure 2a shows the multifractal spectra for the two groups. The curve for the group corresponding to the administration of the the beta-blocker drug is more linear than that for the control group. This result is consistent with decreased multifractality due to the suppression of sympathetic control (Fig. 2b).

As a further test, we also analyze the multifractal properties of the heartbeat dynamics of healthy individuals who were administered atropine [18] which suppresses parasympathetic control of the heartbeat. We analyze six datasets from six different healthy males [11] (ages: 21–26 yr). As a control, we utilize datasets from subjects in the beta-blockade experiment after administration of the placebo. Figure 3a shows the multifractal spectra for the two groups. The curve for the group under parasympathetic blockade is nearly linear

—indicating a marked loss of multifractality— even more apparent than with sympathetic blockade (Fig. 3b). These results are consistent with the possibility that multifractality in healthy heartbeat dynamics may arise, at least in part, from the interplay between the two branches of the neuroautonomic system.

The major finding of this study is the strong evidence supporting the idea that (multi)fractality in heartbeat dynamics is related to intrinsic properties of the control mechanisms, and is not simply due to changes in external stimulation, degree of physical activity or other apparent behavioral modifiers—such as postural changes, food intake and sleep-phase transitions (See Table I). Understanding how the interaction of neuroautonomic, and possibly other, control mechanisms generates the complex multiscale dynamics of the heartbeat will be a major challenge to future efforts to model “real-world” signalling mechanisms [19].

Our results are also of note for a number of other reasons. First, as shown in Figs. 1-3, the singularity spectrum $D(h)$ during sympathetic blockade has a narrower range of allowed values of h than the singularity spectra for the control groups. However, the position of the peak in $D(h)$ during sympathetic blockade is not substantially modified from its position for the same subjects when given a placebo. This suggests that sympathetic blockade may not have a major effect on the linear correlations in the dynamics, that is, it does not change the average Hurst exponent substantially [20].

Second, we find that during parasympathetic blockade there is a marked loss of multifractality (see Fig. 3b), much as occurs for patients with severe heart failure [3]. Indeed, as with heart failure, the peak of the singularity spectra is located to the right of the healthy control group, indicating weaker anticorrelations [2]. This finding is consistent with the hypothesis that both the monofractality and “weaker” anti-correlations for heart failure dynamics may be related, at least in part, to impaired parasympathetic control in congestive heart failure patients, in agreement with recent studies [21].

Third, our finding of the impact of neuroautonomic control on the multifractal properties of heart rate variability during waking hours raises the question of how transitions during

sleep might affect these properties. The present study using a constant routine protocol was not designed to elucidate this intriguing possibility. Recent reports of differences in heartbeat scaling exponents—related to two-point correlations—between daytime and nighttime hours [22] and also during different sleep stages [23] support the need for future investigation of multifractal properties in different physiologic states.

Finally, we note that for many of the systems which generate multifractal signals there are no mathematical equations describing the dynamics, and even for those for which such equations exist, their analytical solution is not feasible. Thus, the understanding and modeling of the intrinsic control mechanisms for heart rate may offer new opportunities to explore multifractal dynamics in the natural sciences [24].

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- [8] See [3] and [7] for details.
- [9] Monofractal signals display a linear $\tau(q)$ spectrum: If $\tau(q) = qH - 1$ is linear, then $D(h = H) = 1$, and $D(h \neq H) = 0$, indicating that there is a single global Hurst exponent [4]. For a more complete description of the multifractal formalism see [<http://argento.bu.edu/~amaral/Multifractal.html>] and references therein.

- [10] Physiologic signals and the algorithms for their analysis are freely available at the *PhysioNet* website [<http://www.physionet.org>].
- [11] Each subject gave informed consent to participate in this study after the test protocol was fully described. This study was reviewed and approved by the ethics committee of the Graduate School of Education of The University of Tokyo.
- [12] The constant routine protocol was originally used in chronobiology research to investigate endogenous circadian rhythms as a means of minimizing environmental and behavioral influences [C. A. Czeisler, J. S. Allan, and S. H. Strogatz, *Science* **233**, 667 (1986); C.A. Czeisler *et al.*, *Science* **244**, 1328 (1989); J. N. Mills, D. S. Minors, and J. M. Waterhouse, *J. Physiol. (London)* **285**, 455 (1978)]. Subjects were instructed to keep their regular sleep schedules (00:00–00:20 h and 07:00–09:00 h for sleep onset and wake-up, respectively) during the week prior to the study. They were required to refrain from vigorous exercise or alcohol consumption during a week prior to testing, when they reported to the laboratory at about 08:00 h after an overnight fast. Data collection started at 09:00–11:30 h, and subjects were kept awake for 27 h in a constant semi-recumbent posture with minimal physical activity. They were allowed to work on a laptop computer, read, listen to the radio, and talk quietly to the staff, in the controlled laboratory environment (temperature: 24–25°, light intensity: <250 lx). Isocaloric meals were given every 2 h to minimize dietary-induced changes in heart rate. As a control, heart rate data were also collected for each of the 7 subjects —with the same experimental settings as for constant routine— during usual activities of daily living, but without vigorous exercise or alcohol consumption.
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- [15] Our results do not preclude the possibility that even very slight movements may affect heart rate dynamics and contribute to the observed multifractal properties. However,

it is not feasible to prevent all motion in a controlled way. Further, attempts to impose such restraints would be stressful and alter neuroautonomic tone. Moreover, many small movements, such as those required for balance, are of an involuntary nature, which would support our conclusion that voluntary physical activity is not responsible for the observed complexity of heart rate variability.

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[17] In the sympathetic blockade study, 6 subjects were randomly assigned into two groups and continuously monitored for seven days. The first group of 3 subjects took a long-acting β_1 -selective adrenergic antagonist, metoprolol tartrate, in single-blind fashion, 120 mg once daily in the morning for the first three days. After a wash-out day without any medication, the subjects were given a placebo drug for the last three days. The second group of 3 subjects took the placebo first, followed by the metoprolol.

[18] In the parasympathetic blockade study, data were collected for 60 min under sustained suppression of the vagal influence on heart rate by a primed (0.75 mg) constant intravenous infusion (0.009 mg/min) of atropine sulfate. The infusion rate was determined so that steady-state increases in heart rate of about 20 beats/min were achieved. The subjects were examined on a tilt table while the tilt angle was changed every 10–15 min to investigate cardiovascular responses to the orthostatic challenge, the original purpose of the experiment. These transient changes in posture introduce an additional nonstationarity in the data which, however, can be eliminated by the application of wavelet analysis. The smaller number of data points ($\approx 6,000$ beats) obtained in this experiment is nonetheless sufficient, as the largest wavelet scale we use is only 400 beats. Heart rate was measured continuously from a surface ECG by use of standard bipolar leads with an ECG device (AT-601G, Nihon-Koden). The analog output of the ECG device was differentiated to yield a train of rectangular impulses corresponding to the QRS spikes, and the impulse train was processed at a sampling frequency of 1,000 Hz

to yield beat-to-beat RR intervals.

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FIGURES

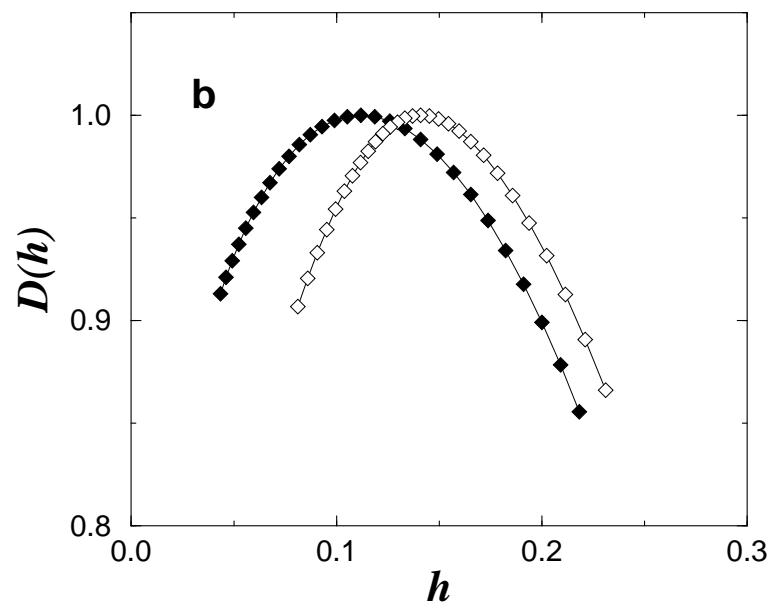
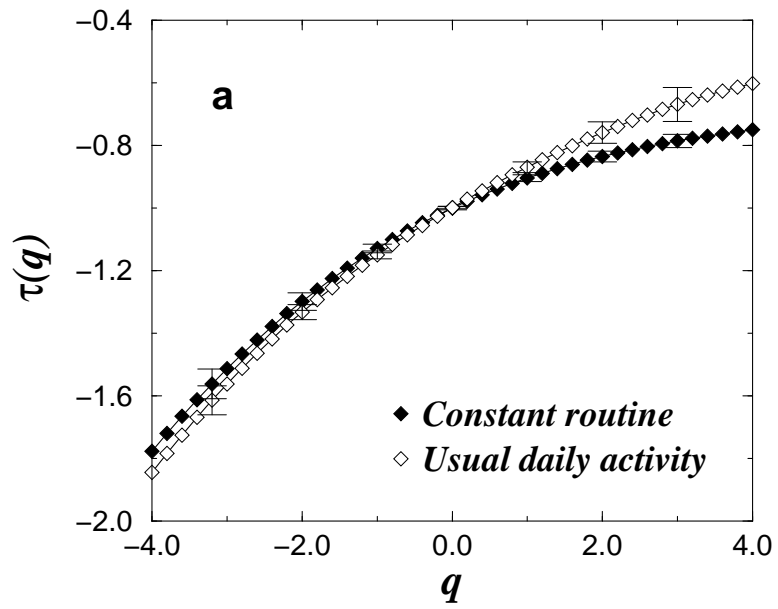
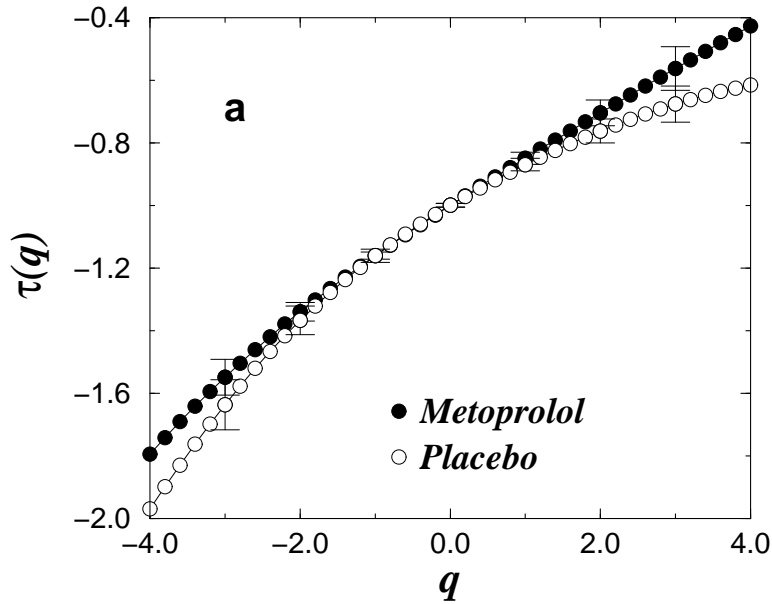


FIG. 1. Constant routine study. The average heart beat interval for constant routine is 0.951 s (0.820 s for controls) and the average standard deviation is 0.117 s (0.129 s for controls). (a) Multifractal spectra $\tau(q)$ for constant routine and control (usual daily activity) protocols ($n = 6$). In this and following figures, the error bars indicate the standard error of the group average $\tau(q)$. The two curves have nearly identical curvature but appear to be slightly rotated around a vertical axis going through $q = 0$, which suggests that there are no major differences in the multifractal properties of control and constant routine groups. (b) Singularity spectra $D(h)$ for the two groups. $D(h)$, which is obtained as the Legendre transform of $\tau(q)$, measures the fractal dimension of the subsets of the signal characterized by local Hurst exponents h . Note that the two curves have nearly identical widths indicating a similar degree of multifractality. This result is consistent with the possibility that the activities of daily living do not account for the multifractal complexity of heart rate dynamics.



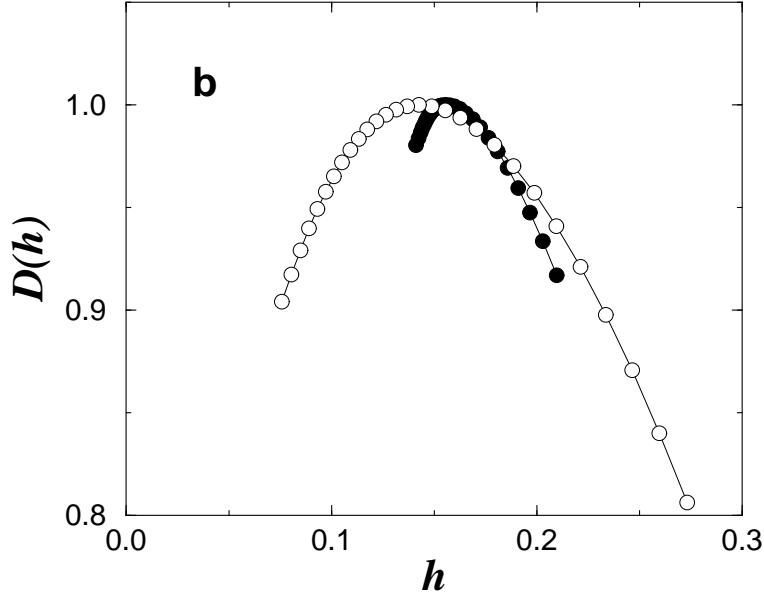


FIG. 2. Sympathetic blockade study. The average heart beat interval for beta-blocker intake is 0.885 s (0.750 s for placebo intake) and the average standard deviation is 0.115 s (0.092 s for placebo intake). (a) Group average $\tau(q)$ for datasets ($n = 8$) during sympathetic (beta) blockade with metoprolol [16]. Note that the curve for the beta blocker administration remains above the placebo curves for all q , indicating a more marked curvature —i.e., *nonlinearity*— of $\tau(q)$ for the control group. (b) Singularity spectra $D(h)$ for the two groups. The singularity spectrum is obtained by a Legendre transform of the multifractal spectrum. Note that the peaks for the two curves appear to be at somewhat different positions. However, our analysis indicates that the variation from group to group and subject to subject is wider for the position of the peak than for its width, so that no change in peak position can be inferred. Heartbeat dynamics during sympathetic blockade display a change in the singularity spectrum, namely decreased multifractality as evidenced by the narrower distribution $D(h)$. The “weaker” nonlinearity of $\tau(q)$ during sympathetic blockade indicates less pronounced multifractality, suggesting that suppression of sympathetic control decreases the multifractal complexity of cardiac dynamics.

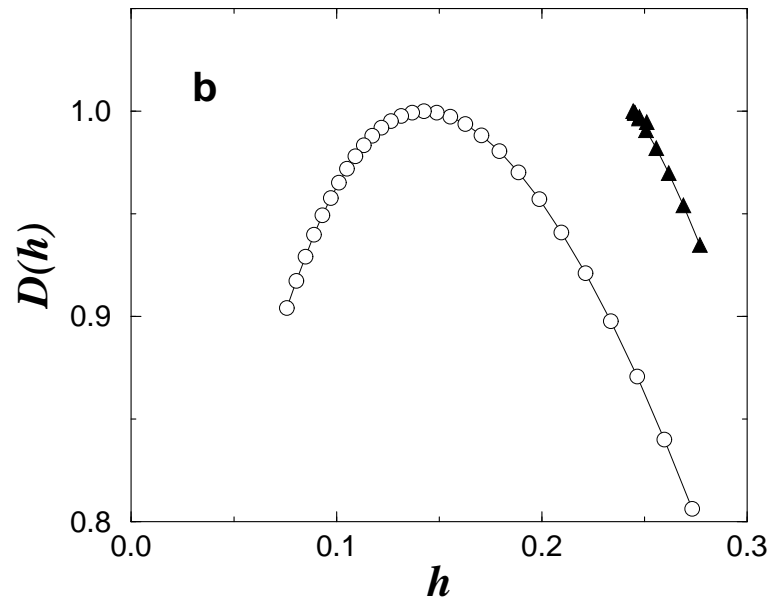
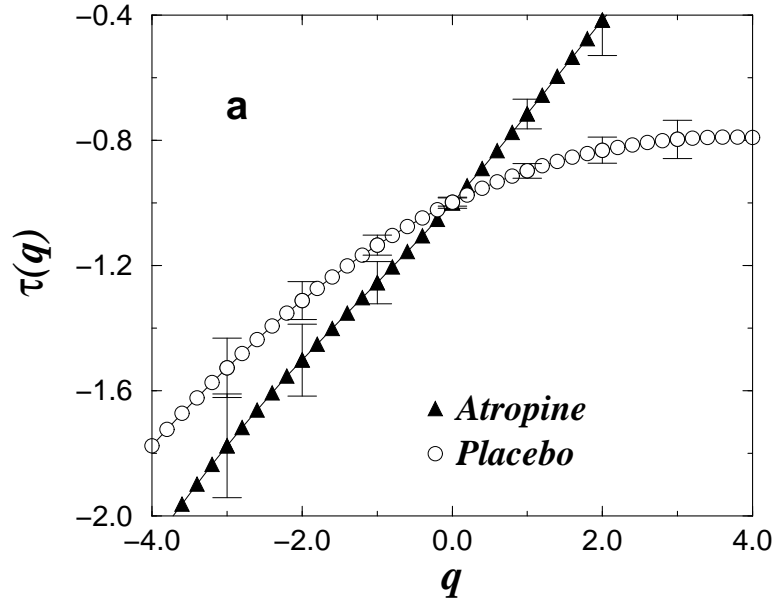


FIG. 3. Parasympathetic blockade study. The average heart beat interval for atropine intake is 0.703 s and the average standard deviation is 0.078 s. (a) Group average $\tau(q)$ for datasets obtained during parasympathetic (vagal) blockade with atropine ($n = 6$). Because of the potential adverse effects associated with very prolonged parasympathetic blockade, these datasets are shorter than the others, consisting of only about 6,000 interbeat intervals. As a control, we analyze the first 6,000 data points from the subjects being administered the placebo in the sympathetic blockade experiments. Our analysis suggests (i) that the dynamics become monofractal under parasympathetic blockade —note that $\tau(q)$ becomes nearly linear— and (ii) that the typical Hurst exponent increases towards less anti-correlated values as previously observed for severe heart failure ($h_{HF} \approx 0.25$) [2] —note the increase in the slope for q close to zero which is closely related to the single exponent obtained by a standard (mono)fractal analysis [2]. (b) Singularity spectra $D(h)$ for the two groups. The singularity spectrum is obtained by a Legendre transform of the multifractal spectrum. The figure shows that the heart rate dynamics after parasympathetic blockade becomes nearly monofractal.

TABLES

TABLE I. Width and peak position for $D(h)$ spectra for the different protocols studied.

| Protocol | Width | Peak |
|--------------------------|-----------------|-----------------|
| Usual daily activity | 0.16 ± 0.04 | 0.14 ± 0.04 |
| Constant routine | 0.18 ± 0.04 | 0.11 ± 0.04 |
| Placebo | 0.20 ± 0.04 | 0.14 ± 0.04 |
| Sympathetic blockade | 0.08 ± 0.04 | 0.16 ± 0.04 |
| Parasympathetic blockade | 0.03 ± 0.03 | 0.24 ± 0.02 |