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$1/f$ scaling in heart rate requires antagonistic autonomic control

Zbigniew R. Struzik,[1,2,*] Junichiro Hayano,[3] Seiichiro Sakata,[3] Shin Kwak,[4] and Yoshiharu Yamamoto[1,2,†]
[1]*Educational Physiology Laboratory, Graduate School of Education, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*
[2]*PRESTO, Japan Science and Technology Agency, Kawaguchi, Saitama 332-0012, Japan*
[3]*Core Laboratory, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan*
[4]*Department of Neurology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*
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We present systematic evidence for the origins of $1/f$-type temporal scaling in human heart rate. The heart rate is regulated by the activity of two branches of the autonomic nervous system: the parasympathetic (PNS) and the sympathetic (SNS) nervous systems. We examine alterations in the scaling property when the balance between PNS and SNS activity is modified, and find that the relative PNS suppression by congestive heart failure results in a substantial increase in the Hurst exponent H towards random-walk scaling $1/f^2$ and a similar breakdown is observed with relative SNS suppression by primary autonomic failure. These results suggest that $1/f$ scaling in heart rate requires the intricate balance between the *antagonistic* activity of PNS and SNS.

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Healthy human heart rate has long been known to exhibit $1/f$-type fluctuations [1–4] and has recently also been attributed multifractal scaling properties [5]. This complex dynamics, resembling nonequilibrium [6] and/or multiscale [7] dynamics in physics, has been demonstrated to be independent of human behavior—the statistical properties of heart rate remain unaltered even after eliminating known behavioral modifiers [8,9]—suggesting that the origin of heart rate complexity lies in the intrinsic dynamics of the physiological regulatory system. One conjecture previously posed is that $1/f$ (global) scaling and local multifractal scaling in heart rate is caused by the interaction between the activity of sympathetic (SNS) and parasympathetic (PNS) nervous systems [2], leading, respectively, to the increase and the decrease in heart rate. However, the evidence for this is scarce [10].

Here, we present systematic evidence for the origins of $1/f$ scaling and multifractality in human heart rate. We demonstrate that modifying the relative importance of either of the two branches leads to a substantial departure from $1/f$ scaling, showing that $1/f$ scaling in healthy heart rate requires the existence of and the intricate balance between the antagonistic activity of PNS and SNS. It supports the view of the cardiac neuroregulation as a system in a critical state [11], and permanently out of equilibrium, in which concerted interplay of the SNS and PNS is required for preserving momentary "balance." This view of cardiac neuroregulation is coherent with a broad class of models of phenomena which, to a large extent, has been established using the implicit or explicit concept of balance of competing agents or scenarios.

Further, we also observe a hitherto unexplored relationship between the multifractality of the heart rate and variability as measured by interval variance. While it is generally believed that lower variability results in a reduction of multifractal properties (reduced spectrum width), as has been demonstrated in relative PNS suppression both by congestive heart failure (CHF) [5] and by the parasympathetic blocker *atropine* [8], we observe conservation of multifractal properties in relative SNS suppression by primary autonomic failure (PAF) at substantially reduced variability to levels closer to CHF. This suggests the relevance of the intrinsic PNS dynamics for multifractality.

We believe these findings to be important in putting forward the *antagonistic scenario* for complex (multi-) fractal dynamics that has now been observed in a wide variety of real-world signals and also in helping to diagnose the condition of a range of patients having abnormality in their autonomic regulatory system.

We analyze three groups of subjects, of whom long-term heart rate data were measured as sequential heart interbeat intervals. The first group consists of 115 healthy subjects (26 women and 89 men; ages 16–84 yrs) without any known disease affecting autonomic controls of heart rate, who underwent ambulatory monitoring during normal daily life [Fig. 1(a)]. The total number of whole-day data sets is 181, as some of the subjects were examined for two consecutive days, with each data set containing on average 10^5 heartbeats. Details of the recruitment of the subjects, screening for medical problems, protocols, and the data collection are described in Ref. [12]. We analyzed both whole-day data containing sleep and awake periods and daytime only data, with essentially identical results [13]. In this paper, we present daytime results only.

The second group of subjects are 12 patients with CHF, of whom whole-day ambulatory data [Fig. 1(c)] are available from Physionet [15]. This severe heart failure is known to be associated with both increased SNS [16,17] and decreased PNS [16,18] activity. Thus, this data set contains information on how heart rate is (multi-) scaled during relative PNS suppression.

*Electronic address: z.r.struzik@p.u-tokyo.ac.jp
†Electronic address: yamamoto@p.u-tokyo.ac.jp

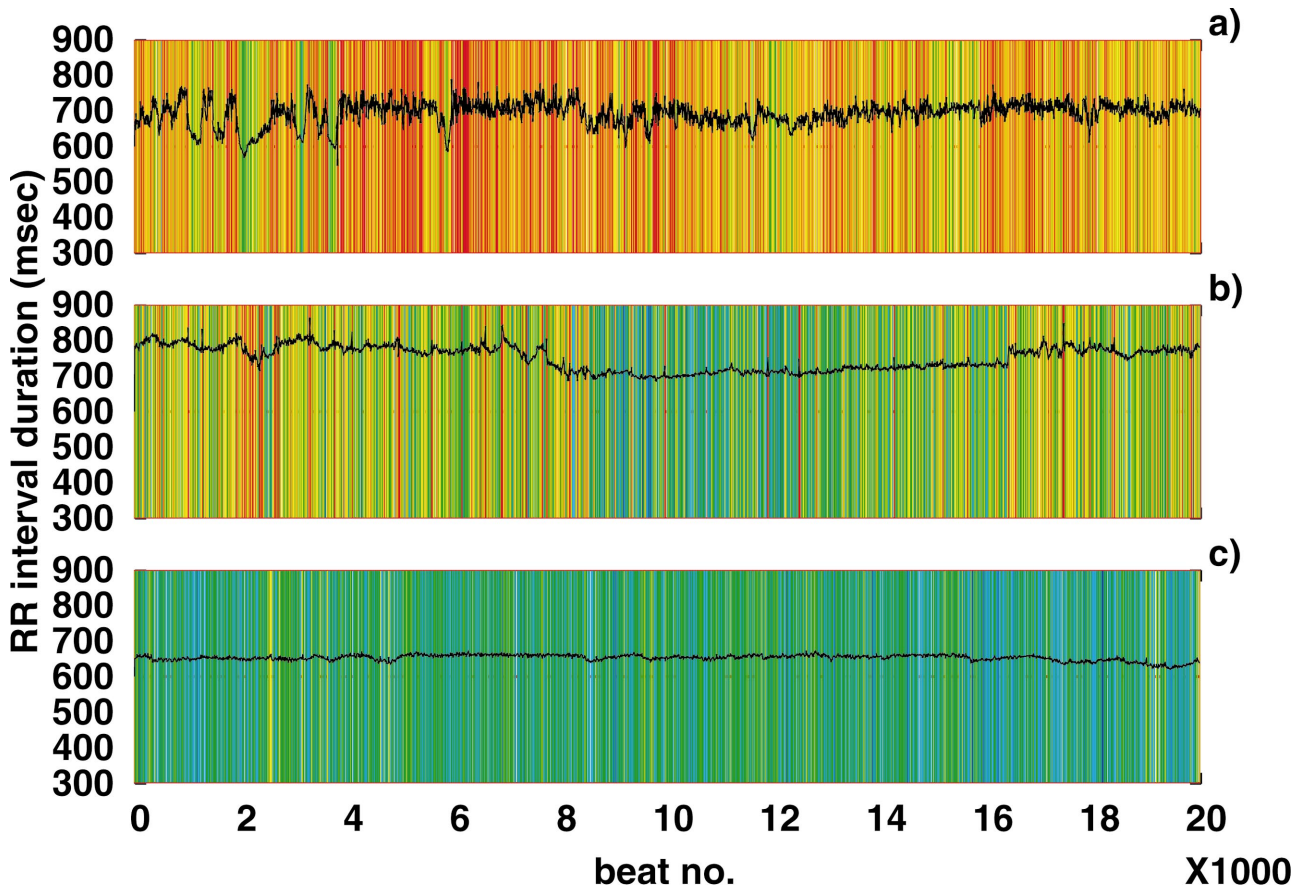

FIG. 1. (Color) Typical traces of daytime heartbeat intervals for (a) a healthy subject, (b) a PAF patient, and (c) a CHF patient. The color coding used shows the local contribution to multifractality—the color spectrum is centered at $h=0.3$ (green), with the strongest singularities in red ($h=0.0$) and the weakest in blue ($h=0.6$) [14].

As the last group, we examined the 24-hour ambulatory heart rate dynamics of 10 PAF patients, aged 54–77 years [19,20], containing on average 10^5 heartbeats [21] [Fig. 1(b)]. PAF is clinically characterized as autonomic dysfunction, including orthostatic hypotension, impotence, bladder and bowel dysfunction, and sweating defects, which primarily result from progressive neuronal degeneration of an unknown cause. The main pathological finding related to autonomic dysfunction in PAF is severe loss of preganglionic and/or postganglionic sympathetic neurons [22]. In contrast to the severe degeneration of the efferent SNS, PNS is believed to remain relatively intact in PAF; we will confirm this below by showing a similar level of high-frequency fluctuations of heart rate, known as a robust indicator of PNS activity [25,26], in our PAF patients to that of healthy subjects. Thus, it is highly possible that this group serves as an example of relative and *neurogenic* SNS suppression.

The mean global scaling exponent (the Hurst exponent H) has been evaluated by using (first-order) detrended fluctuation analysis (DFA) [15,23,24]. We have analyzed the scaling behavior of the mean quantity (group mean) $\overline{M}_{DFA}(s) = L^{-1}\Sigma_{l=1}^{L} \log_{10}[D_{DFA}^{(l)}(s)]$, where l indexes time series in the group. For each scale/resolution s as measured by the DFA window size, and for each integrated, normalized heartbeat interval time series $\{F_i^{(l)} = T_l^{-1}\Sigma_{j=1}^{i} f_j^{(l)}\}_{(i=1,\ldots,N_l),(l=1,\ldots,L)}$, $D_{DFA}^{(l)}(s)$ (total scalewise detrended fluctuation) has been calculated as

$$D_{DFA}^{(l)}(s) = s^{-1}\sqrt{\frac{1}{K^{(l)}(s)}\sum_{k=1}^{K^{(l)}(s)}[F_k^{(l)} - P_k(s)]^2}.$$

$P_k(s)$ denotes the local least-squares linear fit in each DFA window k, and $K^{(l)}(s)$ is the number of windows per scale s. Integration of the input heart rate intervals is performed according to standard DFA practice, and the norm used is the elapsed time $T_l = \Sigma_{i=1}^{N_l} f_i^{(l)}$. The normalization applied allows us to compute group averages of records of different duration, and to compare the mean absolute levels of variability per resolution s; for each resolution s, the quantity $\overline{M}_{DFA}(s)$ measures the (logarithmic) scalewise mean of the normalized DFA—the sum of the logarithm of detrended fluctuations for each group of time series at this resolution. The Hurst exponent was computed from the log-log fit to the group averaged DFA values over the selected range of scales (20–4000 beats).

In Fig. 2, we show the scaling behavior of the $\overline{M}_{\mathrm{DFA}}(s)$ versus $\log_{10}(s)$ for healthy subjects, PAF patients, and CHF patients, with the slopes corresponding to the Hurst exponent H. We find a substantial difference in the scalewise variabil-

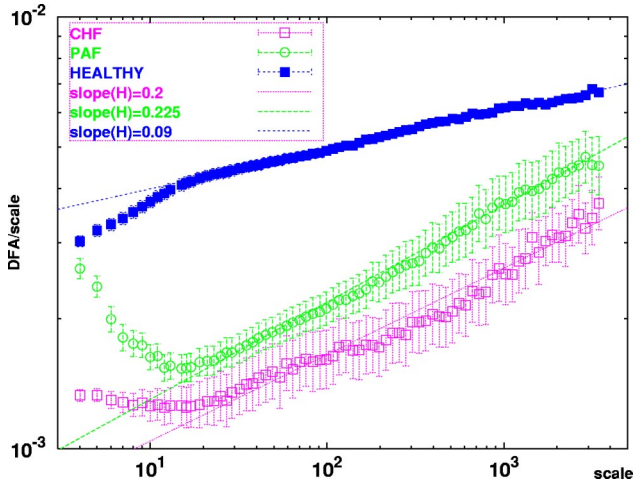

FIG. 2. (Color online) Scale dependency of the mean detrended fluctuation $\bar{M}_{\mathrm{DFA}}(s)$ for healthy subjects, PAF patients, and CHF patients. Detrended fluctuations have been calculated with first-order DFA, i.e., linear trend removal [24]. The vertical bars represent the standard deviations of the group means.

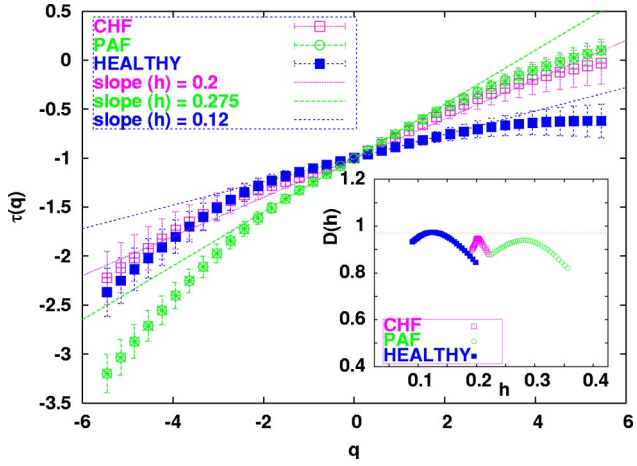

FIG. 3. (Color online) Multifractal $[\tau(q)]$ spectra for healthy subjects, PAF patients, and CHF patients. The vertical bars represent the standard deviations of the linear fit to (the group mean of) the partition function. (Inset) Singularity $[D(h)]$ spectra derived from the avarage $\tau(q)$ curves.

ity levels between controls and PAF and CHF patients. This holds for the entire compared resolution range of 4–4000 beats as measured by the DFA window size s. However, PAF variability reaches normal levels asymptotically for the highest resolutions (and lowest beat numbers), most likely reflecting the preservation of high-frequency fluctuations of heart rate indicative of the intact PNS activity [25,26] in our PAF patients. CHF variability, on the contrary, remains at low levels at all resolutions.

In addition, we find that the relative PNS suppression by CHF results in a substantial increase in the Hurst exponent from $1/f$ range ($H \approx 0.09$ for healthy controls) to $H > 0.2$, i.e., towards random-walk scaling $1/f^2$ ($H=0.5$) (Fig. 2). This effect has been observed for the entire range of resolutions with almost consistent scaling, which for all three groups stretches from about 20 beats up to the maximum resolution used of 4000 beats (DFA window size). The slope within the scaling range obtained for PAF is close to that obtained for CHF and considerably higher than that for the control group. Thus, surprisingly, we observe a similar breakdown in the case of relative and neurogenic SNS suppression by PAF. This is particularly interesting in the context of the recognized effect that β-adrenergic blockers, mainly affecting the response of the heart to nonsuppressed SNS activity and leaving the vascular branch of sympathetic neuroregulation intact, do not result in a breakdown of $1/f$ scaling in heart rate [4,8].

Further, we also tested the multifractal properties of the data using the wavelet-based multifractal methodology [27]. We apply the 2nd derivative of the Gaussian to the data as the mother wavelet before calculating the partition function $Z_q(s)$, defined as the sum of the qth powers of the local maxima of the modulus of the wavelet transform coefficients at scale s. The power-law scaling of $Z_q(s)$ for $13 < s < 850$ then yields the scaling exponents $\tau(q)$—the multifractal spectrum (Fig. 3). The multifractal spectrum is related to the singularity spectrum $D(h)$, where $D(h_o)$ is the fractal dimension of the subset of the original time series characterized by a *local* Hurst exponent $h=h_o$ [28], through a Legendre transform $D(h)=qh-\tau(q)$ with $h=d\tau(q)/dq$ (Fig. 3, inset).

For both PAF patients and control subjects, we obtained comparable curvature of the $\tau(q)$. However, this curvature is nearly lost in the case of CHF patients (Fig. 3). These results imply wider singularity spectra $D(h)$ for both PAF patients and control subjects, indicative of preserved multifractality (Fig. 3, inset), that can also be observed in nonuniform distributions of the local Hurst exponents h (Fig. 1). In addition, we also observe an intriguing relation between the conserved multifractality of the heart rate for the PAF case and the profoundly low absolute variability as measured by normalized DFA (Fig. 2). While it is generally believed that lower variability results in a reduction of multifractal properties (reduced spectrum width), as has been demonstrated in relative PNS suppression both by CHF [5] and the parasympathetic blocker *atropine* [8], in PAF patients we observe conservation of multifractal properties at substantially reduced variability to the levels closer to CHF. This suggests the relevance of the intrinsic PNS dynamics for the multifractality of heart rate.

Amaral *et al.* [8] reported a slightly decreased width of multifractal spectra and an almost unchanged global scaling exponent of healthy heart rate during the administration of the sympathetic blocker *metoprolol*, which reduces sympathetic control by blocking the action of β-adrenergic receptors on the heart. Physiologically, this case is very different from PAF because in healthy subjects, central SNS activity also influences vascular tone of both capacitance and resistance vessels through α-adrenergic mechanisms, and strongly affects blood pressure (through cardiac output and peripheral resistance) and hence heart rate through *baroreflex* control with the intact PNS. In other words, while the *metoprolol* only blocks the β-adrenergically-mediated effects of SNS on the heart in healthy subjects, PAF is associated with a wide range of sympathetic failure affecting various end organs, including the heart and the vasculature [22], and the

breakdown of $1/f$ scaling of heart rate is observed only in the latter case. Thus, we conclude that healthy $1/f$ heart rate indeed requires physiologically antagonistic activity of PNS and SNS within the brain for autonomic neuroregulation.

A relevant question would be why "nature" has implemented an antagonistic control system in one of, if not the, most important instruments in maintaining human life, i.e., the heart. One possible, albeit as of now still speculative, explanation is that the antagonistic control prevents mode locking by ensuring permanent far-from-equilibrium-like, critical state-like operation [6], and thus enhances error tolerance of the system [29]. The importance of this invariant "response" (mode-free operation) may be the result of the optimization of the heart rate control system by evolutionary processes; physiologically antagonistic cardiac control is observed in a wide range of vertebrates [30]. A mode-free response may be important for rapid change of the operating point of the system according to dynamically changing internal and/or external environmental conditions.

Historically, measurements of fluctuations of heart rate have been widely used for monitoring human autonomic controls in health and disease [25,26]. In particular, the heart rate can easily be measured during normal daily life, by ambulatory monitoring devices, enabling us to probe various autonomic pathologies in a natural setting. However, one drawback of this method using short-term fluctuations of heart rate, such as spectral analyses [25,26], is that the statistical properties of heart rate may be affected by behavior (e.g., exercise, diet, postural changes, etc.), as well as by pathological changes in the autonomic nervous system. It is usually very difficult to monitor patients' behavior during normal daily life, and robust identification of autonomic abnormality due to the disease *per se* is difficult. By contrast, the long-term (multi-) scaling properties of ambulatory heart rate have recently been shown to be highly independent of behavioral modifiers [8,9]. This study further shows that the scaling properties do depend on the autonomic pathologies of patients, i.e., one may be able to derive a behavioral-independent marker for PNS suppression by the increased global scaling exponent and the decreased multifractality of heart rate, and for SNS suppression by the increased global exponent, but with preserved multifractality. Thus, our findings could be also important in helping to diagnose a range of patients having abnormality in their autonomic regulations.

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