Full title: Fractal scale-invariant and nonlinear properties of cardiac dynamics remain stable with advanced age: A new mechanistic picture of cardiac control in healthy elderly

Running title: Fractal and nonlinear stability of cardiac dynamics with aging

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The outputs of physiologic systems under neural regulation exhibit (a) high degree of variability, (b) spacial and temporal fractal organization which remains invariant at different scales of observation, as well as (c) complex nonlinear properties. These inherent features of physiologic dynamics change significantly with different physiologic states such as wake and sleep, exercise and rest, circadian rhythms, as well as with pathologic conditions. As different physiological states and pathologic perturbations correspond to changes or even breakdown in the mechanism of the underlying neural regulation, alterations in certain dynamical properties of physiologic signals have been found to be reliable markers of changes in physiologic control.

Aging is traditionally associated with the process of decline of physiologic function and reduction of physiologic complexity. One major hypothesis is that physiologic aging results from a gradual change in the underlying mechanisms of physiologic control — a regulatory network of neural and metabolic pathways interacting through coupled cascades of nonlinear feedback loops on a range of time and length scales — leading to changes of physiologic dynamics. Under this hypothesis even ostensibly healthy elderly subjects would exhibit: (i) Loss of sensitivity and decreased responsiveness to external and internal stimuli, leading to reduced physiologic variability; (ii) Breakdown of certain feedback loops acting at different time scales in the regulatory mechanism of various physiologic systems. This breakdown would lead to loss of physiologic complexity as reflected in certain scale-invariant and nonlinear temporal characteristics of physiologic dynamics. This hypothesis of a breakdown of physiologic complexity with healthy aging has recently been challenged. Further, earlier studies have linked various pathologic states with breakdown of the scale-invariant fractal organization in physiologic dynamics, which is likely to result from disintegration of coupled feedback loops in the regulatory mechanism. Thus, based on this hypothesis, mechanistically, physiologic processes under healthy aging would be categorized in the same class as pathologic dynamics where fractal organization and nonlinear complexity is lost.

A second hypothesis is that while aging may lead to reduced variability, certain temporal fractal, scale-invariant and nonlinear structures embedded in physiologic dynamics may remain unchanged. These two alternative hypotheses represent different notions about which aspects of the physiologic control mechanisms are expected to change in the process of aging in contrast to the changes accompanying certain pathologic conditions.

To test these two hypotheses we analyze cardiac dynamics — a typical example of an output of an integrated physiologic system under autonomic neural regulation. Previous studies have shown that heart rate variability decreases with certain pathologic conditions, as well as with advanced age. Studies based on approaches from statistical physics and nonlinear dynamics
revealed that heartbeat fluctuations in healthy subjects possess a self-similar fractal structure characterized by long-range power-law correlations over a range of time scales (43, 60, 62). The scaling exponent associated with these power-law correlations was shown to change significantly with rest and exercise (16, 11, 51), posture (11, 76, 82), sleep and wake state (34), across sleep stages (10, 37, 38, 61, 62, 72) and circadian phases (27, 28, 52), and to be a reliable marker of cardiac vulnerability under pathologic conditions (2, 12, 28, 59). Further, studies have found that turbulence-like multifractal and nonlinear features in heartbeat dynamics are reduced and even lost with disease (30, 32, 45, 71). Several studies have also reported reduced heart rate variability (77) (as also shown in Fig. 1), apparent loss of fractal organization, as well as breakdown of scale-invariant correlations and certain nonlinear properties with advanced age (20, 21, 36, 47, 64), suggesting that healthy aging is associated with changes in the neuroautonomic mechanism of cardiac regulation related to disintegration of coupled feedback loops across a range of time scales.

Here, we investigate how cardiac dynamics change with advanced age by analyzing scale-invariant, linear, and nonlinear characteristics of heartbeat fluctuations recorded from subjects during rest and sleep from two independent databases.

I. DATA AND METHODS

We analyze heartbeat interval recordings from two independent databases.

**Fantasia Database:** The Fantasia database (63) contains 20 young and 20 elderly subjects. We carefully selected 19 healthy young subjects (9 male; 10 female) with an average age of 25.7 years (youngest 21; oldest 34) and 16 healthy elderly subjects (6 male; 10 female) with an average age 73.8 years (youngest 68; oldest 85). All subjects were recorded while watching the movie Fantasia (Disney, 1940) in a relaxed supine or semi-recumbent posture. These conditions were chosen to avoid the effect which differences in the level of physical activity between young and elderly subjects during daily routine might have on cardiac dynamics (Fig. 1). The continuous ECG and respiration signals were digitized at 250 Hz. Each heartbeat was annotated using the ARISTOTLE arrhythmia detector (53), and each beat annotation was verified by visual inspection. Only intervals between two normal beats were considered. One young and four elderly subjects (shown in Fig. 5) were excluded from our analysis due to artefacts in the data.

**Sleep Heart Health Study (SHHS) Database:** The Sleep Heart Health Study (SHHS) is a prospective cohort study designed to investigate the relationship between sleep disordered breathing and cardiovascular disease. Subjects were recorded during their habitual sleep periods of $\approx 8 \text{ h}$, and continuous ECG were recorded with 250 Hz (Fig. 2). Full details of the study design and cohort are provided in (46, 65). Details about obtaining the ECG and polysomnographic recordings are outlined in (68). Sleep apnea episodes were annotated, and heart rate data during apnea (obstructive and central) were excluded from our analysis (Fig. 2). We selected a subset of 29 subjects (8 males; 21 females) average age at the time of the first recording 75.9 years (youngest 72; oldest 84). The recordings were repeated 5 years later when the subjects were again screened and categorized as healthy.

**Detrended Fluctuation Analysis (DFA):** We use the DFA method (58), which has been developed to quantify fractal correlations embedded in nonstationary signals, to estimate dynamic scale-invariant characteristics in heartbeat fluctuations. Compared with traditional correlation analyzes such as autocorrelation, power-spectrum analysis, and Hurst analysis, the advantage of the DFA method is that it can accurately quantify the correlation property of signals masked by polynomial trends, and is described...
in detail in [12, 13, 26, 34, 80].

The DFA method quantifies the detrended fluctuations $F(n)$ of a signal at different time scales $n$. A power-law functional form $F(n) \sim n^\alpha$ indicates the presence of self-similar organization in the fluctuations. The parameter $\alpha$, called the scaling exponent, quantifies the correlation properties of the heartbeat signal: if $\alpha = 0.5$, there is no correlation and the signal is white noise; if $\alpha = 1.5$, the signal is a random walk (Brownian motion); if $0.5 < \alpha < 1.5$, there are positive correlations, where large heartbeat intervals are more likely to be followed by large intervals (and vice versa for small heartbeat intervals).

One advantage of the DFA method is that it can quantify signals with $\alpha > 1$, which cannot be done using the traditional autocorrelation and R/S analyses [17]. In contrast to the conventional methods, the DFA method avoids spurious detection of apparent long-range correlations that are an artefact of nonstationary [73]. Thus, the DFA method is able to detect subtle temporal structures in highly heterogeneous physiologic time series.

An inherent limitation of the DFA analysis is the maximum time scale $n_{\text{max}}$ for which the fluctuation function $F(n)$ can be reliably calculated. To ensure sufficient statistics at large scales it was shown that $n_{\text{max}}$ should be chosen $n_{\text{max}} \leq N/6$, where $N$ is the length of the signal [13, 26, 80]. For time scales $n < n_{\text{max}}$ there is no bias in estimating the scaling exponent $\alpha$. Thus, recordings longer than 1 hour ($N \approx 3600$ beats) are sufficient to reliably quantify $\alpha$ up to time scales $n = 600$ beats, and differences in the length of the recordings between the Fantasia database (2 hours) and SHHS database (8 hours) do not affect the estimate of $\alpha$. Recent studies have tested the performance of the DFA method, when applied to correlated signals with patches of missing data, random spikes, superposed trends related to different activity levels and patches with different standard deviation and local correlations, as often found in heartbeat data [13, 26].

Both the Fantasia database and the NIH Sleep Heart Health Study database have used 250 Hz sampling rate for the ECG recordings. A precision of 0.004 sec (250 Hz) is more than sufficient for our analysis, since the DFA method as well as the MSA and FDA analyses we employ (see below) are robust in that respect. Using a lower sampling rate (i.e., lower precision in the estimate of the RR-intervals) acts effectively as added random noise with an amplitude proportional to the sampling interval — in our case the amplitude of this “sampling noise” is more than two orders of magnitude smaller than the RR interval. It has been shown that adding noise with such a small amplitude to a fractal correlated signal does not effect the correlation scaling and fractal properties [13].

**Magnitude and Sign Analyzes (MSA):** Since the DFA method quantifies linear fractal characteristics related to two-point correlations, we have selected the MSA method to probe for long-term non-linear properties in the data. Specifically, it has been shown that signals with identical temporal organization, quantified by the DFA-scaling exponent $\alpha$, can exhibit very different non-linear properties captured by the MSA method [10].

The MSA method [4, 5] consists of the following steps: (i) given RR$_i$ series we obtain the increment series, $\Delta RR_i = RR_{i+1} - RR_i$; (ii) we decompose the increment series into a magnitude series $|\Delta RR|$ and a sign series $\text{sign}(\Delta RR)$; (iii) to avoid artificial trends we subtract the average from the magnitude series; (iv) because of limitations in the accuracy of the DFA method for estimating the scaling exponents of anti-correlated signals ($\alpha < 0.5$), we integrate the magnitude series [26]; (v) we perform a scaling analysis using DFA; (vi) to obtain the scaling exponents for the magnitude series we measure the slope of $F(n)/n$ on a log-log plot, where $F(n)$ is the fluctuation function and $n$ is the time scale of analysis.

This approach is sensitive to nonlinear features in signals [74]. We find that positive correlations in the magnitude series ($\alpha_{\text{mag}} > 0.5$) are a reliable marker of long-term nonlinear properties. Thus, we employ the MSA as a complementary method to the DFA, because it can distinguish physiologic signals with identical long-range correlations, as quantified by the DFA method, but with different nonlinear properties and different temporal organization for the sign($\Delta RR$) series.

**Fractal Dimension Analysis (FDA):** The fractal dimension $D(k)$ is a local nonlinear measure used to quantify the irregularity of a time series [50]. We estimate the fractal dimension using an algorithm proposed in [23].

Starting from a discrete time series, $x(i)$, with $i \in [1, N]$, a new sparse time series $x_k^m$ is constructed in the following way

$$x_k^m; x(m), x(m + k), \ldots, x\left(m + \left\lfloor \frac{N - m}{k} \right\rfloor k \right), \quad (1)$$

with $m \in [1, k]$ where $m$ and $k$ are integers, and $\left\lfloor \frac{N - m}{k} \right\rfloor$ denotes the largest integer number smaller than $\frac{N - m}{k}$. Then a length measure for this sparse time series is defined as

$$L_m(k) = \frac{N - 1}{h k^2} \left( \sum_{i=1}^{h} |x^m_{ik} - x^m_{(i-1)k}| \right), \quad (2)$$

with $h \equiv \left\lfloor \frac{N - m}{k} \right\rfloor$. For a time series $x(i)$ with a fractal dimension $D$ the length $L_m(k)$ averaged over $m$ is a power-law function of the scale $k$: $L(k) \equiv \langle L(k) \rangle_m \sim k^{-D}$. In the general case $D$ can depend on the scale $k$. In this case, the local fractal dimension $D(k)$ of the time series $x(i)$ is defined as the negative local derivative of $\log L(k)$ as a function of $\log k$. 
TABLE 1: Overview of measures used.

| Abbreviation | Measure                                      | Significance                                      |
|--------------|----------------------------------------------|--------------------------------------------------|
| $\langle RR \rangle$ (AVNN) | mean of RR intervals  | inversely proportional to heart rate              |
| $\sigma_{RR}$ (SDNN) | std. deviation of RR  | para- and sympathetic HRV measure sensitive to trends |
| $\sigma_{\Delta RR}$ (RMSSD) | std. deviation of $\Delta RR$ | parasympathetic HRV measure insensitive to trends |

**II. RESULTS**

**A. Variability in heartbeat intervals and their increments**

We first test the possibility that advanced age in ostensibly healthy subjects would lead to an increase in the average heart rate and to a significant reduction in heart rate variability — a behavior previously observed in subjects with congestive heart failure where under suppressed vagal tone increased heart rate is associated with reduced heart rate variability \[19, 79, 81\]. We find that both young and elderly healthy subjects in the Fantasia database exhibit very similar group average interbeat intervals: \(\langle RR \rangle \pm \sigma = 0.9 \pm 0.14\) for the young group and \(\langle RR \rangle \pm \sigma = 1.06 \pm 0.17\) for the elderly group, where \(\sigma\) is the standard deviation (Table 2). This is in agreement with previous studies \[14, 36, 64\]. A Student’s t-test shows no significant difference between the two groups with a \(p\)-value = 0.11. A very similar average heartbeat interval we observe for the healthy elderly subjects in the SHHS database with \(\langle RR \rangle \pm \sigma = 0.92 \pm 0.075\), indicating no significant difference \(p\)-value = 0.07) compared to the group of young Fantasia subjects (Table 2). Further, comparing the group average heartbeat interval of the elderly subjects from the SHHS database with the same subjects recorded 5 years later, we find again no significant difference: \(\langle RR \rangle \pm \sigma = 0.92 \pm 0.08\) at the first recording and \(\langle RR \rangle \pm \sigma = 0.92 \pm 0.1\) after 5 years \(p\)-value = 0.92, Table 2). Thus, we do not observe a significant change in the average heart rate with advanced age.

To test whether there is a reduction in heart rate variability with aging, we next estimate for each subject the standard deviation of the heart rate intervals \(\sigma_{RR}\) (often denoted as SDNN) and the standard deviation of the increments in the consecutive heartbeat intervals \(\sigma_{\Delta RR}\) (often denoted as RMSSD) (Table 2). For the young and elderly subjects in the Fantasia database we find a statistically significant difference with (i) a higher value for the group average \(\langle \sigma_{RR} \rangle\), and (ii) larger inter-subject variability for the young group: \(\langle \sigma_{RR} \rangle \pm \sigma = 0.089 \pm 0.034\) for the young compared to \(\langle \sigma_{RR} \rangle \pm \sigma = 0.051 \pm 0.017\) for the elderly subjects \(p\)-value = 3.3 \cdot 10^{-04}\) (Table 2). Similarly, we observe a significantly higher value for the group average \(\langle \sigma_{\Delta RR} \rangle\) for the young subjects in the Fantasia database \(\langle \sigma_{\Delta RR} \rangle \pm \sigma = 0.061 \pm 0.031\) compared to the elderly subjects \(\langle \sigma_{\Delta RR} \rangle \pm \sigma = 0.027 \pm 0.012\) \(p\)-value = 9.9 \cdot 10^{-5}\), again with a larger inter-subject variability for the young group (Table 2). We note that the sampling rate of 250 Hz does not effect the significance of the difference in \(\sigma_{\Delta RR}\) between the young and elderly groups, as this difference is approximately 0.034 sec, i.e., one magnitude larger than the sampling precision of 0.004 sec.

For the group of healthy elderly subjects from the SHHS database we find a higher value of \(\langle \sigma_{RR} \rangle \pm \sigma = 0.077 \pm 0.027\) compared to the elderly group from the Fantasia database — a difference which could be attributed to the fact that the SHHS subjects were recorded during sleep where transitions between sleep stages are associated with trends and larger fluctuations in the interbeat interval time series \[37, 61, 62\], while the elderly Fantasia subjects were recorded during rest. In contrast, for \(\langle \sigma_{\Delta RR} \rangle\) we do not observe a significant difference between the elderly groups from the Fantasia and SHHS database \(p\)-value = 0.74) (Table 2). However, we find a significant difference between young and elderly subjects, indicating a clear reduction in the heart rate variability with aging.

**B. Fractal Correlations**

We next test whether the temporal organization in the heartbeat fluctuations changes in ostensibly healthy elderly compared to young subjects. Earlier studies have shown that heartbeat fluctuations exhibit self-similar power-law correlations over a broad range of time scales ranging from seconds to many hours \[41, 69\], and that
the scaling exponents associated with these power-law correlations change significantly with sleep and wake state (43) and with pathologic conditions (60, 80), reflecting changes in the underlying mechanism of cardiac regulation. Specifically, heartbeat fluctuations of healthy subjects during daily activity exhibit 1/f-like power spectrum (43, 60, 82) with a scaling exponent \( \alpha \approx 1 \) (see Section I). During sleep this behavior changes to exponent \( \alpha \approx 0.8 \) at time scales above 60 beats, indicating stronger anti-correlations in the interbeat increments \( \Delta RR \) during sleep compared to wake state (34) (Fig. 3(a)). In contrast, for pathologic conditions such as congestive heart failure earlier studies have reported a value for the exponent \( \alpha \) closer to 1.5 — typical for random walk behavior (Brownian motion) and associated with loss of cardiac control (54).

Applying the DFA method we obtain a very similar scaling behavior for a representative healthy young and a healthy elderly subject from the Fantasia database, both characterized by a scaling exponent \( \alpha_2 \approx 0.8 \) at intermediate and large time scales (Fig. 3(b) and 3(c)). At small time scales for both representative subjects we observe a crossover to a higher exponent of \( \alpha_1 \approx 1.1 \) (Fig. 3(b) and 3(c)). While there is certain inter-subject variability in the scaling functions \( F(n) \), this crossover behavior remains robust with a group average scaling exponent \( \alpha_1 \approx 1.1 \) at small scales and \( \alpha_2 \approx 0.75 \) at large scales for the young subjects, and respectively \( \alpha_1 \approx 1.2 \) and \( \alpha_2 \approx 0.8 \) for the elderly subjects (Appendix, Fig. 12). Our analysis indicates no significant difference in the scaling behavior between healthy young and healthy elderly subjects under the resting conditions in the Fantasia study protocol (Table 2). We note that our findings for the young and elderly Fantasia subjects (Fig. 3(b) and 3(c)) are very similar to the scaling behavior in heartbeat fluctuations previously reported for healthy subjects during sleep (34), which exhibit a crossover from \( \alpha_1 \approx 1.2 \) at small time scales to \( \alpha_2 \approx 0.8 \) at intermediate and large time scales (Fig. 3(a)). This similarity in the scaling properties of heartbeat dynamics of healthy subjects during sleep (Fig. 3(a) and the Fantasia database subjects (Fig. 3(b) and 3(c)) may be attributed to the fact that under the Fantasia study protocol subjects are resting in a semi-recumbent/supine posture, watching a relaxing movie — physiologic conditions which more closely resemble sleep than daytime activity.

To confirm the validity of these findings, we further investigate the scale-invariant correlation properties of cardiac dynamics for healthy elderly subjects from the SHHS database, where heart rate data were recorded during sleep — a protocol which differs from the Fantasia study (see Section I). In Fig. 3 we show the DFA scaling curves for a representative SHHS subject with a crossover in the scaling behavior from \( \alpha_1 \approx 1.1 \) at small time scales to \( \alpha_2 \approx 0.9 \) above 60 beats. This scaling behavior is very similar to the one we find for both young and elderly subjects from the Fantasia database (Fig. 3). Further, comparing the scaling behavior of the elderly subjects from the SHHS database to the same subjects recorded five years later, we do not find a significant difference in the correlation scaling exponents \( \alpha_1 \) and \( \alpha_2 \) (Fig. 4 and Table 2). The results shown in Figs. 3, 4 and in Appendix, Fig. 12 indicate that the fractal correlation properties of healthy heartbeat dynamics remain stable and do not significantly change with advanced age.

![Fluctuation function](image_url)

**FIG. 3**: Fluctuation function \( F(n) \) vs. time scale \( n \) (in heartbeat number) obtained using DFA-2 for (a) 6h-long record of RR heartbeat intervals during wake and sleep from a representative healthy subject (MIT-BIH Normal Sinus Rhythm Database (63)), as well as 2h-long records of a representative (b) healthy young subject and (c) healthy elderly subject from the Fantasia database. A very similar scaling behavior is observed for the representative (b) young and (c) elderly subjects, which closely resemble the scaling behavior of the healthy subjects during sleep shown in (a) (MIT-BIH Normal Sinus Rhythm Database (63)), indicating no change in the scale-invariant temporal correlations of heartbeat intervals with advanced age under healthy resting conditions. Scaling curves for all individuals are shown in Appendix, Fig. 12.

C. Magnitude and sign scaling analysis (MSA)

Recent studies have demonstrated that scale-invariant processes with identical long-range power-law correlations may be characterized by very different dynamics for the magnitude and sign of their fluctuations (6, 37), and that the information contained in the temporal organization of the magnitude and the sign time series is independent from the correlation properties of the original time series (4). Specifically, for cardiac dynamics of healthy
subjects it was shown (6) that heartbeat intervals during routine daily activity exhibit correlation properties at intermediate and large time scales characterized by scaling exponent \( \alpha_2 \approx 1 \), while at the same time scales the magnitude series of the increments in consecutive heartbeat intervals is characterized by \( \alpha_{\text{mag}} \approx 0.8 \). Further, while correlations reflect the linear properties of heartbeat dynamics, the temporal structure of the magnitude of interbeat increments has been shown to relate to the nonlinear properties encoded in the Fourier phases (4, 8, 12). For certain pathologic conditions such as congestive heart failure previous studies have reported loss of nonlinearity (65) associated with a breakdown of the multifractal spectrum (30), and reduced scaling exponent \( \alpha_{\text{mag}} \) for the magnitude series (4).

For the magnitude time series of the interbeat increments we obtain \( \alpha_{\text{mag}} \approx 0.53 \) at small time scales and \( \alpha_{\text{mag}} \approx 0.68 \) at intermediate and large time scales for a representative young subject (Fig. 5(a)), and very similar results with \( \alpha_{\text{mag}} \approx 0.53 \) and \( \alpha_{\text{mag}} \approx 0.72 \) for a representative elderly subject from the Fantasia database (Fig. 5(b)). The DFA scaling functions \( F(n) \) for all young and elderly subjects, shown in Appendix, Fig. 12, which is not consistent with the hypothesis of a gradual loss of scale-invariant complexity in the process of aging.

To confirm these findings, we next calculate the magnitude scaling exponent of the interbeat increments for the elderly subjects from the SHHS database. Again we observe a crossover from \( \alpha_{\text{mag}} \approx 0.52 \) at small scales to \( \alpha_{\text{mag}} \approx 0.7 \) at large time scales shown in Fig. 5(c) for a representative elderly subject — a behavior very similar to the one observed for both young and elderly Fantasia subjects shown in Fig. 5(a–b). Our analysis does not show a statistically significant difference in the group average magnitude scaling exponents \( \alpha_{\text{mag}} \) (with \( p\text{-value}=0.71 \)) and \( \alpha_{\text{mag}} \) (with \( p\text{-value}=0.57 \)) between the elderly SHHS subjects and the elderly Fantasia subjects. Moreover, we find no significant difference in \( \alpha_{\text{mag}} \) (with \( p\text{-value}=0.24 \)) and \( \alpha_{\text{mag}} \) (with \( p\text{-value}=0.16 \)) between the elderly SHHS subjects and the young Fantasia subjects.

For the sign of the interbeat increments time series we again find no significant difference in the scaling behavior between the young and elderly subjects in the Fantasia database with practically identical exponents of \( \alpha_{\text{sgn}} \approx 0.2 \) at short time scales and \( \alpha_{\text{sgn}} \approx 0.4 \) at intermediate and large time scales (Fig. 6(a–b)). A consistently similar behavior we observe for all subjects in the young and elderly group in the Fantasia database (Appendix, Fig. 13), where the scaling function \( F(n) \) exhibits a crossover from strongly anti-correlated behavior at short time scales to weaker anti-correlations at larger scales, respectively characterized by group average sign exponents \( \alpha_{\text{sgn}} \approx 0.24 \) for the young and \( \alpha_{\text{sgn}} \approx 0.3 \) for the elderly subjects at small scales, and \( \alpha_{\text{sgn}} \approx 0.47 \) for the young and \( \alpha_{\text{sgn}} \approx 0.43 \) for the elderly subjects at large scales. These results indicate no significant difference in the temporal organization of the sign series between the young and the elderly subjects in the Fantasia database (Table 2).

Repeating our sign scaling analysis for the SHHS database we observe a crossover from strongly anti-correlated behavior with an exponent \( \alpha_{\text{sgn}} \approx 0.2 \) at small time scales to weaker anti-correlations with \( \alpha_{\text{sgn}} \approx 0.4 \) at intermediate and large time scales, as shown in Fig. 6(c–d). This crossover behavior is very similar to the one we find for both young and elderly Fantasia subjects (Fig. 6(a–b) and Appendix, Fig. 13). Moreover, we do not find a significant difference in the scaling of the sign series for the elderly SHHS subjects and the same subjects five years later (Fig. 6(c–d) and Table 2).

D. Fractal Dimension Analysis

Finally, we employ the FDA method (see Section 11) to estimate the fractal dimension \( D(k) \) of a time series (17, 23, 50). It has been demonstrated that the fractal dimension is a measure which represents the nonlinear properties in the output of a dynamical system, so that two signals with identical scale-invariant correlations may be quantified by different scale-invariant fractal dimension depending on the degree of nonlinearity encoded in the
FIG. 5: Fluctuation function $F(n)$ vs. time scale $n$ (in beat number) obtained for the magnitude of the interbeat increments $|\Delta R R|$ using DFA-2 for a representative (a) healthy young and (b) healthy elderly subject from the Fantasia database, and for a representative (c) healthy elderly subject from the SHHS database and (d) the same subject recorded 5 years later. All subjects exhibit a very similar scaling behavior characterized by an exponent $\alpha_{mag} \approx 0.7$ at intermediate and large time scales, very different than $\alpha_{mag} = 0.5$ characteristic for linear processes with no correlations in the Fourier phases $\{4, 6\}$, which indicates that the long-term nonlinear properties of heartbeat dynamics do not break down with advanced age under healthy resting conditions. This is in contrast to the hypothesis linking the process of healthy aging with a gradual loss of nonlinearity. Scaling curves for all individuals from the Fantasia database are shown in Appendix, Fig. 13.

FIG. 6: Fluctuation function $F(n)$ vs. time scale $n$ (in beat numbers) obtained for the sign of the interbeat increments $\text{sign}(\Delta R R)$ using DFA-2 for a representative (a) healthy young and (b) healthy elderly subject in the Fantasia database, and for (c) representative healthy elderly subject from the SHHS database and (d) the same elderly SHHS subject recorded 5 years later. All subjects exhibit a very similar scaling behavior for the sign with a crossover from strong anti-correlations with $\alpha_{sgn} \approx 0.2$ at small time scales to weaker anti-correlations with $\alpha_{sgn} \approx 0.4$ at large scales, indicating a similar fractal organization of sympathetic and parasympathetic control in both young and elderly subjects under healthy resting conditions. Scaling curves for all individuals in the Fantasia database are shown in Appendix, Fig. 14.
Fourier phases [24, 74]. Our analysis shows no significant difference in the group average of the nonlinear fractal dimension $D(k)$ between the young and the elderly subjects in the Fantasia database for the whole range of time scales except for a very short time interval of 6 to 8 heartbeats (Fig. 7(a) — time scales typical for sleep apnea (see Fig. 8). At smaller and larger time scales the average fractal dimension $D(k)$ converges for both groups (Fig. 7(a)). Furthermore, we do not observe a statistically significant difference between the elderly subjects from the SHHS database and the same subjects recorded five years later (Fig. 7(b)). These findings do not support the hypothesis that nonlinearity is reduced in healthy elderly subjects.

FIG. 7: Group average nonlinear fractal dimension $D(k)$ versus time scale $\log_2 k$, where $k$ is measured in beat numbers. (a) For young and elderly healthy Fantasia subjects; (b) healthy elderly SHHS subjects and the same subjects 5 years later. There is no significant difference in the group averages indicated by the overlapping standard deviations except for the interval of scales $k \in [3, 6]$ marked in (a) by the symbol (*) ($p$-value $= 1.94 \times 10^{-4}$ and $6 \times 10^{-3}$ correspondingly). Note the very similar profile of $D(k)$ for all groups indicating no apparent loss of nonlinearity with aging, in agreement with our findings for the long-term nonlinear properties represented by the magnitude exponent $\alpha^\text{mag}_2$ shown in Fig. 8.

E. Summary of the results

In agreement with previous studies [14, 56, 64, 73] we observe a certain degree of reduction in heart rate variability, as measured by $\sigma_{\text{HR}}$ (SDNN) and $\sigma_{\Delta \text{RR}}$ (RMSSD), when comparing young to elderly subjects (Table 2). In contrast to previous studies [36, 47, 64], however, we do not find a significant difference in the scaling exponents $\alpha_1$ and $\alpha_2$, characterizing the fractal scale-invariant temporal organization of heartbeat fluctuations, between young and elderly subjects (Table 2). For the scaling properties of the magnitude and the sign of heartbeat fluctuations — which have been shown to carry additional independent information about the nonlinear and linear properties of a time series [1, 2, 37] — we find that these measures also remain unchanged when comparing young and healthy elderly subjects (Table 2). Finally, for the fractal dimension $D(k)$ of the heartbeat interval time series — an independent nonlinear measure — again contrary to previous reports [21], we do not find significant differences between young and elderly subjects. Furthermore, comparing longitudinal data from a group of elderly subjects who were also recorded five years later, we find that the heart rate variability is not further reduced (Table 2), and that the scaling exponents $\alpha_1$ and $\alpha_2$ of the heartbeat fluctuations, as well as the nonlinear features as measured by the magnitude exponent $\alpha^\text{mag}_2$ and the fractal dimension $D(k)$, remain stable.

These findings indicate that in the process of aging the alterations in the underlying mechanisms of cardiac autonomic regulation are not likely to involve breakdown of coupling between feedback loops at different time scales or dominance of a particular feedback loop at a given time scale, as often observed with pathologic perturbations [22, 31, 33, 44, 44, 54]. Rather, our findings suggest a reduced reflexiveness of the neuroautonomic regulation with aging, while the nonlinear feedback interactions across time scales between elements of the cardiac regulatory system remain unchanged.

III. INTERPRETATION AND MODELING

Our findings indicate that scale-invariant correlation and nonlinear properties do not significantly change in healthy elderly subjects compared to young subjects. This is in contrast to some earlier studies, based on the same Fantasia database (or on a subset of it), which have reported loss of fractal organization in heartbeat fluctuations — a behavior resembling Brownian motion (random walk process) with $\alpha = 1.5$ at small scales and white noise with $\alpha = 0.5$ over large scales [36, 64], as well as a significant loss of nonlinearity [21] with healthy aging. A possible reason for these different findings may be the presence of artefacts in the data such as segments of corrupted recordings or certain periodic patterns (Fig. 8). These periodic patterns strongly resemble episodes of sleep apnea, as shown in Fig. 9 (Top panel). Indeed, sleep apnea may be present in the elderly subjects from the Fantasia database, since they have not been specifically screened for sleep apnea. Further, ECG recordings were taken when subjects were watching a calming movie for 2 hours in a semi-recumbent or supine posture during which subjects may have fallen asleep for periods of time, when apnea episodes are likely to occur.
TABLE 2: Average values and standard deviation of \( \langle RR \rangle, \sigma_{RR} \) (SDNN), \( \sigma_{\Delta RR} \) (RMSSD), and DFA-2 scaling exponents for subjects from the Fantasia database and the SHHS database. For the Fantasia database, \( F(n) \) was fitted in the interval \( n \in [6, 16] \) for \( \alpha_1 \) and \( n \in [60, 2500] \) for \( \alpha_2 \). For the SHHS database, \( F(n) \) was fitted in the interval \( n \in [6, 16] \) for \( \alpha_1 \) and \( n \in [60, 600] \) for \( \alpha_2 \). A two-tailed Student’s t-test was performed to obtain the p-values.

| Measure | Fantasia Database | SHHS Database |
|---------|-------------------|---------------|
| \( \langle RR \rangle \) | 0.9 ± 0.14 | 0.92 ± 0.08 |
| \( \sigma_{RR} \) | 0.089 ± 0.034 | 0.077 ± 0.027 |
| \( \sigma_{\Delta RR} \) | 0.061 ± 0.031 | 0.028 ± 0.015 |
| \( \alpha_1 \) | 1.09 ± 0.24 | 1.12 ± 0.27 |
| \( \alpha_2 \) | 0.76 ± 0.08 | 0.88 ± 0.12 |
| \( \alpha_1^{\text{mag}} \) | 0.53 ± 0.1 | 0.57 ± 0.13 |
| \( \alpha_2^{\text{mag}} \) | 0.64 ± 0.11 | 0.70 ± 0.12 |
| \( \alpha_1^{\text{sgn}} \) | 0.24 ± 0.15 | 0.23 ± 0.19 |
| \( \alpha_2^{\text{sgn}} \) | 0.47 ± 0.09 | 0.38 ± 0.07 |
| Young | Elderly | p-value | Elderly | Elderly + 5y | p-value |
| 0.11 | | | 0.92 | 0.92 | 0.50 |
| 3.3 · 10^{-4} | | | 0.90 | 0.024 | 0.74 |
| 9.9 · 10^{-5} | | | 0.78 | | |
| 0.16 | | | 0.01 | 0.12 | 0.01 |
| 0.36 | | | 0.49 | | |
| 0.45 | | | 0.58 | | |
| 0.28 | | | 0.74 | | |
| 0.37 | | | 0.77 | | |

The periodic patterns we observe in wide segments of the interbeat interval recordings shown in Fig. S and Fig. 10(a) have a period of approximately 30 to 60 seconds, typical for apnea episodes (Fig. 10(b)). Similar apnea-like patterns are also present in the breathing records of some Fantasia subjects (Figs. S and 10(a)). These periodic patterns have a very strong effect on the scaling analysis, as shown in earlier studies [36, 66], leading to a pronounced crossover at the time scale corresponding to the period of the patterns. This crossover separates a regime of apparent Brownian-motion-type behavior with \( \alpha \approx 1.5 \) at smaller scales from a second regime of apparent white noise behavior \( \alpha \approx 0.5 \) at larger scales (Figs. 10(f) and 11) — a behavior which in earlier studies [31, 35, 66] has spuriously been attributed to changes in the cardiac neuroautonomic control due to aging.

To model the effect which periodic patterns of sleep apnea have on the scaling properties of heartbeat intervals, we first generate a fractal correlated signal \( X_\eta \) using the Makse et. al. algorithm [43]. To account for the statistical properties observed in heartbeat intervals, we rescale the signal to have the mean value \( \langle X_\eta(i) \rangle = 1 \), standard deviation \( \sigma_{X_\eta} = 0.05 \), and correlation scaling exponent \( \alpha_{X_\eta} = 0.8 \) (Fig. 10(a)), which match the group mean \( \langle RR \rangle \), standard deviation \( \sigma_{RR} \) (Table 2), and scaling exponent \( \alpha_2 \) (Appendix, Fig. 12(c, d)) of the elderly subjects in the Fantasia database. To model the periodic influence of sleep apnea on the heartbeat intervals, we generate a sinusoidal signal, \( X_s(i) = A \sin(2\pi n/T) \), with a period \( T = 50 \) (similar to the average period of 50 heartbeats in apnea patterns) and amplitude \( A = 0.1 \) (as observed in apnea patterns) (Fig. 10(b)), and we superpose the sinusoidal signal \( X_s \) with the fractal correlated signal \( X_\eta(i) \) to obtain \( X_{\eta s}(i) = X_\eta(i) + X_s(i) \) (Fig. 10(c)). We note that \( X_{\eta s}(i) \) strongly resembles the data shown in Fig. S and Fig. 9.

Applying the DFA analysis to the fractal signal \( X_\eta \) we obtain the scaling function \( F_\eta(n) \) with a slope of...
0.8 across all scales — in agreement with the scaling exponent $\alpha = 0.8$ we have found for healthy subjects (Fig. 10(d)). For the sinusoidal signal $X_s$, the scaling function $F_s(n)$ exhibits a crossover at scale $n_x \approx T$, corresponding to the period of $X_s$. For scales $n_x < T$, the fluctuation function $F_s(n)$ exhibits an apparent scaling, $F_s(n) \sim A T n^{\alpha_s}$, with an exponent $\alpha_s = 2$. For scales $n_x > T$, due to the periodic property of the sinusoidal signal $X_s$, the fluctuation function $F_s(n)$ is constant and independent of the scale $n$, i.e., $F_s(n) \sim 1$, where $\alpha_s = 0$. Thus, changing the amplitude $A$ leads to a vertical shift in $F_s(n)$ (Fig. 10(e)) (26).

Applying the DFA analysis to our model signal $X_{ns}$, we observe that $F_{ns}(n)$ exhibits a very pronounced kink (not present in $F_{ns}(n)$) with a crossover at $n_x \approx T$ due to the sinusoidal trend (Fig. 10(f)). The behavior of $F_{ns}(n)$ around the kink is very similar to $F_s(n)$ around $n_x \approx T$. At small scales $n_x < T$ and at large scales $n_x > T$ the fluctuation function $F_{ns}(n)$ converges to the scaling behavior expected for $F_s(n)$. Testing our model for signals $X_s$ with different values for $\alpha$, we find that the position of the crossover $n_x$ for $F_{ns}(n)$ does not depend on $\alpha$. Thus, this type of crossover behavior in the scaling for different subjects depends only on the period $T$ of the periodic patterns embedded in the heartbeat signals.

We find that our model in Fig. 10(f) reproduces well the crossover behavior in $F(n)$ observed for the sleep apnea subject (Apnea-ECG Database (63)) shown in Fig. 11(b). Indeed, a very similar kink in $F(n)$ is observed at scale $n \approx 50$ beats for this apnea subject, as shown in Fig. 11. Moreover, we find that this behavior is also closely followed (as shown in Fig. 11) by the Fantasia subject in Fig. 8(a). Adding the same sinusoidal trend to a real heartbeat signal from a healthy subject (MIT-BIH Normal Sinus Rhythm Database (63)) also leads to a very similar kink in $F(n)$ (Fig. 11).

As we demonstrate in Fig. 11, the excluded Fantasia subject shown in Fig. 8(a) exhibits a scaling curve very similar to the curve obtained from a recording during sleep from a subject diagnosed with sleep apnea (Apnea-ECG Database (63)). Further, our model reproduces well the crossover in the scaling behavior of $F(n)$ and demonstrates that this crossover is due to the superposition of healthy heart rate dynamics and a sinusoidal trend with approximately the same period and amplitude as the periodic apnea patterns shown in Fig. 8. Our model reproduces also the scaling curve $F(n)$ obtained for the elderly Fantasia subject excluded from this study and shown in Fig. 8(a), suggesting that artifacts may have been the reason why earlier studies (21, 36, 64) have reported scaling differences in heartbeat dynamics between young and elderly subjects.

Our modeling results confirm that the presence of pronounced crossovers for some of the elderly subjects in the Fantasia database are due to periodic patterns embedded in the heart rate which strongly resemble sleep apnea episodes, and thus, cannot be attributed to changes in the underlying mechanism of cardiac neuroautonomic regulation associated with healthy aging. Since apnea is more prominent in elderly subjects, our modeling results (Figs. 10 and 11) explain why earlier studies using the same Fantasia database have reported higher values for the scaling exponent $\alpha_1$ at small scales $n$ and lower values for $\alpha_2$ at large scales $n$ for the elderly subjects compared to the group of young subjects (21, 36), claiming changes in cardiac regulation with healthy aging.

IV. DISCUSSION

Our investigations demonstrate the presence of robust correlation, fractal and nonlinear properties in cardiac dynamics of healthy elderly subjects which remain surprisingly stable when compared to healthy young subjects. Specifically, we find that key dynamical characteristics such as the correlation scaling exponent of heart beat fluctuations, the scaling exponent of the magnitude and sign of interbeat increments, and the nonlinear fractal dimension measure do not significantly change with advanced age. Because the scaling exponents $\alpha$ and the fractal dimension measure $D$ quantify a robust scale-invariant fractal and nonlinear structure in heartbeat fluctuations (50, 51, 53, 54), and have been shown to reflect underlying mechanisms of cardiac control (4, 10, 32, 33), our findings indicate that important aspects of heartbeat regulation do not break down with healthy aging. Moreover, we observe no significant change in these scaling and nonlinear measures when comparing healthy elderly subjects with the same subjects recorded five years later.

**FIG. 9:** Segments of interbeat RR interval time series for (a) an elderly subject from the Fantasia database excluded from this study (shown in Fig. 8 top panel), and (b) a subject diagnosed with sleep apnea from the apnea-ECG database (63). Both subjects show very similar and pronounced periodic patterns with a period of about 50 beats, matching the periodic patterns in the breathing record (top panel (a)). These patterns strongly affect the scaling analysis as demonstrated in Figs. 10 and 11.
FIG. 10: Modeling crossover behavior in the scaling of heartbeat dynamics associated with periodic patterns. (a) Artificially generated fractal signal $X_\eta$ with long-range power-law correlations, average value and standard deviation as observed in healthy heartbeat data. (b) A sinusoidal signal $X_s$ with period and amplitude matching the period $T$ and amplitude $A$ of typical sleep apnea patterns embedded in heartbeat interval time series as shown in Fig. 9. (c) Superposition of the signals $X_\eta$ in (a) and $X_s$ in (b). Note the apparent similarity between the signal $X_{\eta s}$ and the time series shown in Fig. 9. (d) Fluctuation function $F_\eta(n)$ obtained using DFA-1 for the signal $X_\eta$ in (a). (e) Fluctuation function $F_s(n)$ obtained using DFA-1 for the signal $X_s$ in (b). The position of the crossover $n_\times$ corresponds to the period $T$ in $X_s$. Changing $A$ leads to a vertical shift of $F_s(n)$. (f) Fluctuation function $F_{\eta s}(n)$ obtained using DFA-1 for the signal $X_{\eta s}$ in (c). Note the appearance of a kink with a crossover at $n_\times \approx T$ as observed in (e).
heart interval using DFA (Fig. 11).

A period of $T = 50$ beats and an amplitude of $A = 0.1$ sec were chosen for the sinusoidal signal to model the effect of periodic patterns due to sleep apnea on the scaling function $F(n)$. This effect leads to a change in the scaling exponent to $\alpha \approx 1.5$ (left of the crossover) and to $\alpha \approx 0.5$ (right of the crossover), which may be the reason why earlier studies have reported loss of fractal organization in heartbeat fluctuations with healthy aging.

These findings do not support the hypothesis that healthy aging may be associated with such a change in the mechanism of cardiac neuroautonomic control that would lead to a loss of all aspects of physiologic complexity. In contrast, we find that fundamental scale-invariant and nonlinear properties of heartbeat dynamics remain unchanged. Further, our findings do not support the hypothesis of a gradual change of cardiac dynamics under healthy conditions with advanced age, as key properties of these dynamics, including heart rate variability (Table 2), remain stable in healthy elderly subjects with advancing age. Indeed, in agreement with previous studies (14, 36, 64, 75), we find a significant reduction in heart rate variability as measured by $\sigma_{RR}$ (SDNN) and $\sigma_{\Delta RR}$ (RMSSD) (although not in the average heart rate) in healthy elderly subjects compared to healthy young subjects (Table 2). The observed reduction in heart rate variability is also in agreement with decrease of the commonly used Approximate Entropy (ApEn) measure with aging, as reported earlier (14), and often interpreted as loss of complexity. However, comparing elderly subjects with the same subjects years later we do not find a further reduction in interbeat variability. Moreover, we do not observe a loss in the scale-invariant fractal and nonlinear features in healthy elderly compared to healthy young subjects, indicating that the process of aging, even in elderly healthy subjects, may not result in a gradual change of the mechanism of control. Our findings support the hypothesis that (i) only certain aspects of cardiac regulation may change with advanced age: these aspects are related to decreased responsiveness to external and internal stimuli, leading to reduced heart rate variability; (ii) other fundamental features of the neuroautonomic cardiac control may remain stable and unchanged with healthy aging: These features are related to the network of nonlinear feedback loops responsible for the neuroautonomic regulation at different time scales, leading to scale-invariant cascades in heartbeat fluctuations (32, 33, 45).

This new emerging picture of healthy aging is fundamentally different from the changes in neural regulation of cardiac dynamics under pathologic conditions (23, 24, 54, 55), and also differs from previous studies reporting breakdown of the scale-invariant and nonlinear features of heartbeat dynamics in elderly (24, 21, 36, 47). Indeed, suppression of parasympathetic tone and dominance of sympathetic inputs, typical for subjects with congestive heart failure, lead to changes in cardiac dynamics associated with higher heart rate (70, 81), lower heart rate variability (79), relative loss of the scale-invariant long-range correlations in the heartbeat fluctuations with scaling exponent $\alpha$ between 1.25 and 1.4 (closer to $\alpha = 1.5$ corresponding to Brownian motion, i.e., random walk) (59), reduced responsiveness (8), as well as breakdown of nonlinearity and multifractality (1, 30, 32, 65). In contrast to such pathologic perturbations, healthy aging appears to be accompanied only by a reduction in heart rate variability as measured by $\sigma_{RR}$ and $\sigma_{\Delta RR}$, while the heart rate, the scaling and nonlinear properties remain on average unchanged. This important dissociation between heart rate variability on one side and the scale-invariant and nonlinear temporal organization of heartbeat fluctuations on the other side may be specific for the process of aging, and suggests that the alterations in the cardiac control mechanism with advanced age differ conceptually from the mechanistic changes in the autonomic regulation associated with pathologic conditions. More specifically, the reduced heart rate variability with advanced age suggests a reduced responsiveness of cardiac control to external and internal stimuli, and thus a reduced strength of feedback interactions. However, the cascade of nonlinear feedback loops controlling the dynamics across different time scales may remain intact in healthy elderly subjects without breaking down at a particular scale or across a range of scales, as the scale-invariant fractal and nonlinear properties appear to remain stable with advanced age (Table 2). This is not the case with pathologic conditions such as congestive heart failure, where the self-organization of neural feedback interactions indeed breaks down across time scales, shifting the dynamics closer to a process which is more random (loss of long-range power-law correlations) and is closer to a linear process (loss of nonlinearity and multifractality).
The value of the correlation exponent $\alpha_2 \approx 0.8$ we observe at intermediate and large time scales for both young and elderly Fantasia subjects (Figs. 3 and 4) is consistent with earlier reports of a very similar value of $\alpha_2 \approx 0.85$ for healthy subjects during sleep, compared to $\alpha \approx 1$ for the same subjects during wake and daily activity (34). This is also in agreement with studies of heartbeat dynamics of healthy subjects during rest and exercise, with $\alpha \approx 0.8$ for rest and $\alpha \approx 1.1$ during exercise (16, 41, 51). Indeed, the Fantasia subjects were recorded under conditions of rest (see Data and Methods Section I) (63). Our findings of $\alpha \approx 0.8$ consistently for both healthy young and healthy elderly subjects from the Fantasia database are further supported by our analysis of data from the longitudinal SHHS study, where the same elderly subjects were recorded during sleep several years later. These observations of $\alpha < 1$ are not due to artefacts in the heartbeat time series related to sleep apnea, as full polysomnographic data were recorded for the SHHS subjects indicating the apnea episodes, and we have excluded the apnea segments in the data from our analysis. Moreover, our preliminary results (a focus of a subsequent study) indicate no significant differences between young and elderly subjects even when we account for REM and NREM sleep stages. Since there is no statistically significant difference in the value of the scaling exponent $\alpha$ between the young and elderly subjects from both databases, the $\alpha$-value lower than 1 is not likely to be related to a mechanistic breakdown of cardiac control with advanced age as previously suggested (36, 41). Rather, this decrease in $\alpha$ is most likely to be related to the normal regime of cardiac regulation during rest and sleep when parasympathetic tone dominates during NREM sleep stages, leading to stronger anti-correlations with $\alpha \approx 0.8$ in the heartbeat fluctuations (14, 33, 34, 38, 41).

We find very similar results for the scaling exponent $\alpha_{\text{mag}}$ for the magnitude of the interbeat increments between young and elderly subjects in the Fantasia database (Table 2), as well as between the young Fantasia subjects and the elderly subjects from the SHHS database (see p-values reported in Results Section I1C). These findings do not support the hypotheses that the nonlinear properties, as measured by the magnitude scaling exponent $\alpha_{\text{mag}}$ and encoded in the Fourier phases (74), are lost with advanced age in healthy subjects under resting conditions. We note that our results for the magnitude exponents for the young and elderly subjects from both databases are in agreement with previous studies reporting nonlinear magnitude correlations in healthy heartbeat dynamics (6), and more specifically with the magnitude exponent values found in the heartbeat fluctuations of healthy subjects during sleep (37, 38).

Further, as the dynamics of the sign (directionality) of the interbeat increments is directly related to inputs of the sympathetic and parasympathetic branches of the autonomic nervous system modulating the heart rate in opposite directions, our findings of similar scaling for the sign series for both young and elderly healthy subjects (Table 2) indicate that fundamental features of the cardiac control mechanism remain unchanged with advanced age. We also note that our results for the sign scaling exponent $\alpha_{\text{sim}}$ for the young and elderly subjects from both databases are in agreement with the values reported in previous studies for healthy subjects during rest (41) and sleep (37).

While our results do not show a significant difference in the scaling and nonlinear properties of heartbeat dynamics between healthy young and healthy elderly subjects during rest and sleep, we note that under conditions of high levels of physical activity and stress, which are associated with a different regime of the neuroautonomic control, these properties may differ between young and elderly subjects.

In summary, the observations reported here do not support the hypothesis of a continuous gradual loss of the scaling and nonlinear properties of cardiac dynamics with advanced age under healthy conditions, as we do not find a statistically significant change in these properties between the young and elderly subjects from the Fantasia and the SHHS databases, as well as for the elderly subjects from the SHHS database and the same subjects recorded five years later. While cardiac dynamics in healthy elderly subjects is characterized by markedly reduced variability compared to healthy young subjects, the stability we observe in key fractal and nonlinear characteristics with advanced age does not support the mechanistic view of a breakdown of specific feedback loops at given time scales in the neuroautonomic regulation (which would lead to appearance of dominant time scales in the dynamics), or of a breakdown of the feedback interactions in cardiac control across multiple time scales (which would lead to random-like behavior in the dynamics). Indeed, both dominant time scales and close-to-random behavior in cardiac dynamics, have been observed under various pathologic conditions. In contrast, cardiac dynamics under healthy aging appears not to belong to this class of processes. Instead, our results indicate that the inherent structure and temporal organization in the cascades of nonlinear feedback loops underlying the cardiac neuroautonomic regulation remains intact in healthy elderly subjects, thus preserving the fractal and nonlinear features in heartbeat dynamics across all time scales. The coupling strength of these neuronal feedback interactions, however, is likely to diminish with advanced age, leading to the observed reduction in heart rate variability and dampened reflexive-type responsiveness in elderly compared to young healthy subjects.

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APPENDIX A

Results of our DFA and MSA analyses for the heartbeat interval recordings for all young and elderly subjects in the Fantasia database.

All subjects show a consistent behavior with:

1. A smooth crossover from $\alpha_1 \approx 1.1$ at small time scales to $\alpha_2 \approx 0.8$ at large scales for the heartbeat intervals $RR$ for both the young and the elderly group (Fig. 12).

2. A smooth crossover from $\alpha_{mag}^1 \approx 0.6$ at small time scales to $\alpha_{mag}^2 \approx 0.7$ at large scales for the magnitude of the interbeat increments $|\Delta RR|$ for both the young and the elderly group (Fig. 13).

3. A crossover from $\alpha_{sgn}^1 \approx 0.3$ at small time scales to $\alpha_{sgn}^2 \approx 0.45$ at large scales for the sign of the interbeat increments $\text{sign}(\Delta RR)$ for both the young and the elderly group (Fig. 14).

The results show that these fractal correlation and nonlinear properties of heartbeat dynamics do not break down with healthy aging.
FIG. 12: Scaling curves $F(n)$ versus time scale $n$ (in beat numbers) obtained for the RR heartbeat intervals using DFA-2 for (a–b) 19 young healthy subjects and (c–d) 16 elderly healthy subjects in the Fantasia database. Despite certain inter-subject variability, there is a very common scaling behavior with a crossover from a higher average slope $\alpha_1$ at small time scales to a lower average slope $\alpha_2$ at large scales as represented by the solid lines and consistent with Fig. 3 and Fig. 4. Individual curves are vertically shifted to aid visual comparison. Group average statistics are presented in Table 2. Vertical dashed lines indicate the range of fit.
FIG. 13: Scaling curves $F(n)$ versus time scale $n$ (in beat numbers) obtained for the magnitude of the interbeat increments $|Δ RR|$ using DFA-2 for (a–b) 19 healthy young subjects and (c–d) 16 healthy elderly subjects in the Fantasia database. Despite certain inter-subject variability, there is a common scaling behavior characterized by a group average exponent $α_2 ≈ 0.7$ at large scales for all groups as represented by the solid lines, indicating presence of long-term nonlinear properties encoded in the Fourier phases of the heartbeat time series similar to those shown in Fig. 5. Curves are vertically shifted for clarity. Vertical dashed lines indicate the range of fit.
FIG. 14: Scaling curves $F(n)$ versus time scale $n$ (in beat numbers) obtained for the sign time series of the interbeat increments $\text{sgn}(\Delta RR)$ using DFA-2 for (a–b) 19 healthy young subjects and (c–d) 16 healthy elderly subjects in the Fantasia database. All subjects exhibit a crossover from strongly (at small scales) to weakly (at large scales) anti-correlated behavior with no significant statistical difference between the young and elderly groups (Table 2). Scaling curves are vertically shifted for clarity. Vertical dashed lines indicate the range of fit.