On the Motions of Our (Non-Heavenly) Bodies

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Outline

- Introduction: fundamental properties of physiological signals
- Complexity measures: MSE and GMSE
- Application of MSE/GMSE to heart rate dynamics
- Novel dynamical biomarker of biological age: definition and applications to the prediction of 1) cardiovascular events (heart attack, stroke, etc), 2) all-cause mortality, and 3) cognitive decline
- Future work: assessing links between autonomic dysfunction and balance impairment/falls

Main Focus: Physiologic Outputs

- There is information of explanatory and predictive power encoded in the fluctuations of physiological signals.
- Dynamical biomarkers are used for:

  (i) risk stratification

  (ii) predict outcomes (e.g. falls, cognitive decline, cardiovascular events, etc)

Harnessing Physiologic Signals

Physiologic Signal

Time Series Analysis

Dynamical Biomarkers
(Dynamical Assays)

Basic Science

Mechanisms of physiologic control: health, disease, aging, and biotoxicity

Precision Medicine

- *Track disease progression*
- *Monitor & tailor interventions*
- *Assess risk & predict outcomes*

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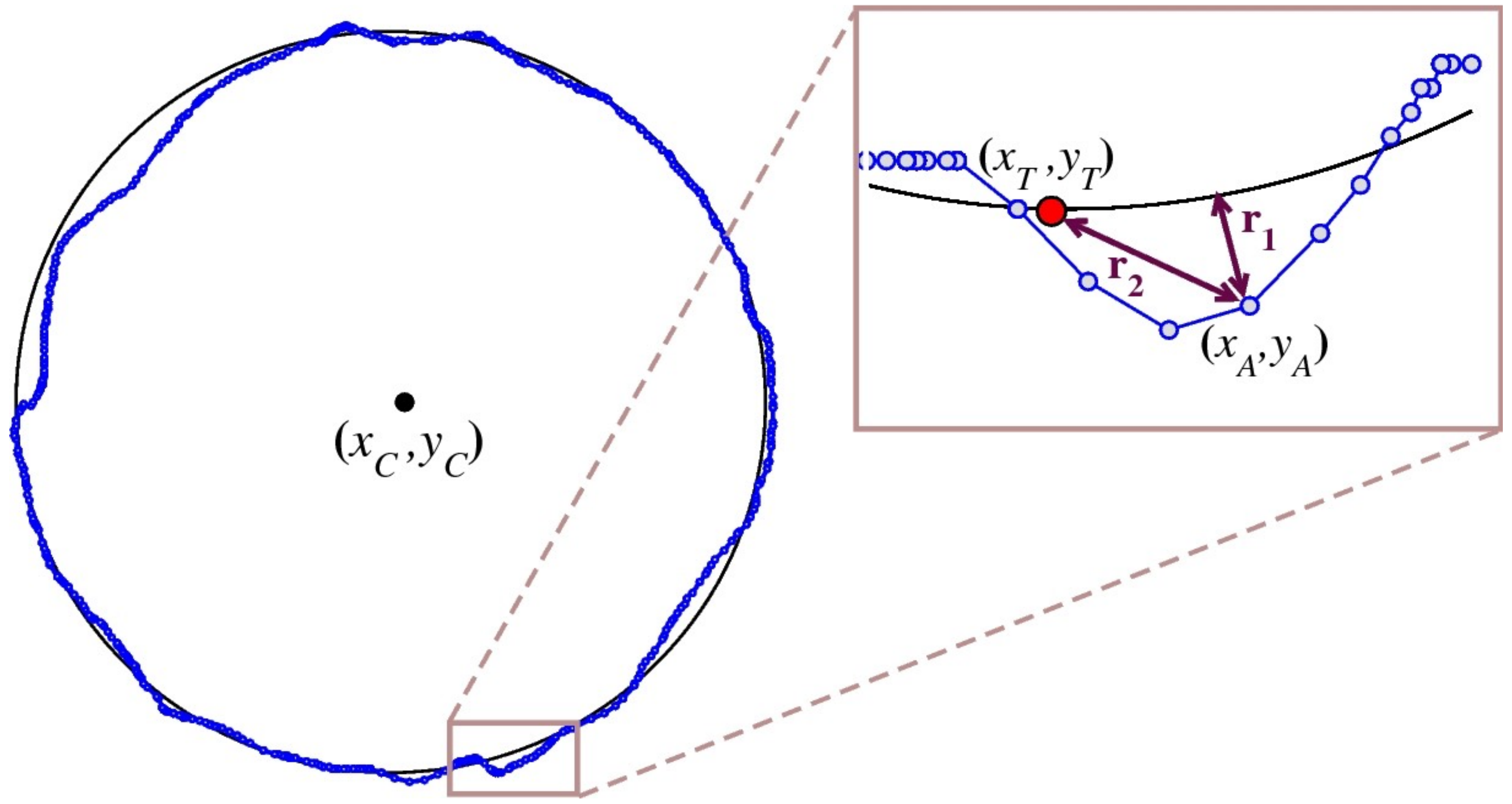
Visuo-motor tracing task

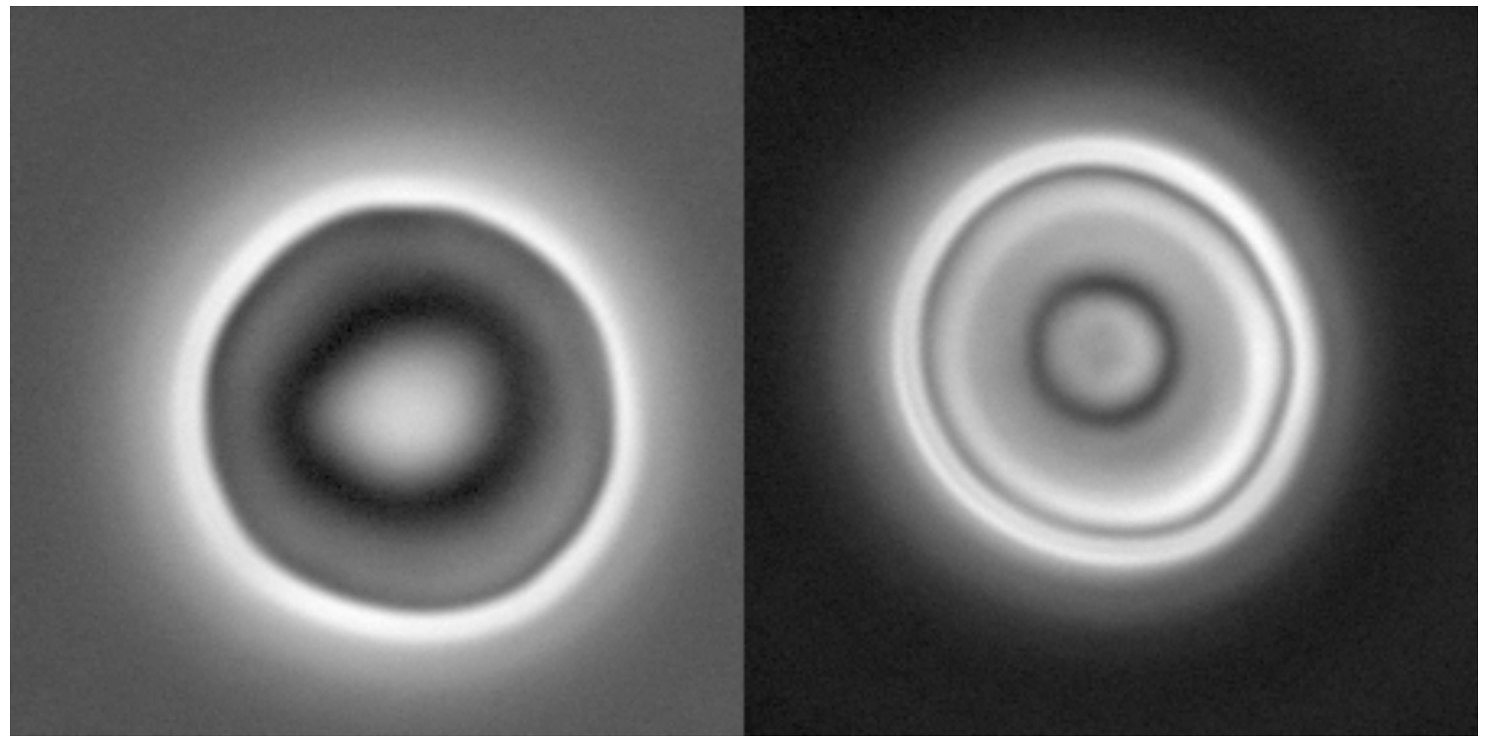
$$\sqrt{((x_A - x_C)^2 + (y_A - y_C)^2)} - r$$



Red blood cell membrane flickering

Newly formed RBC

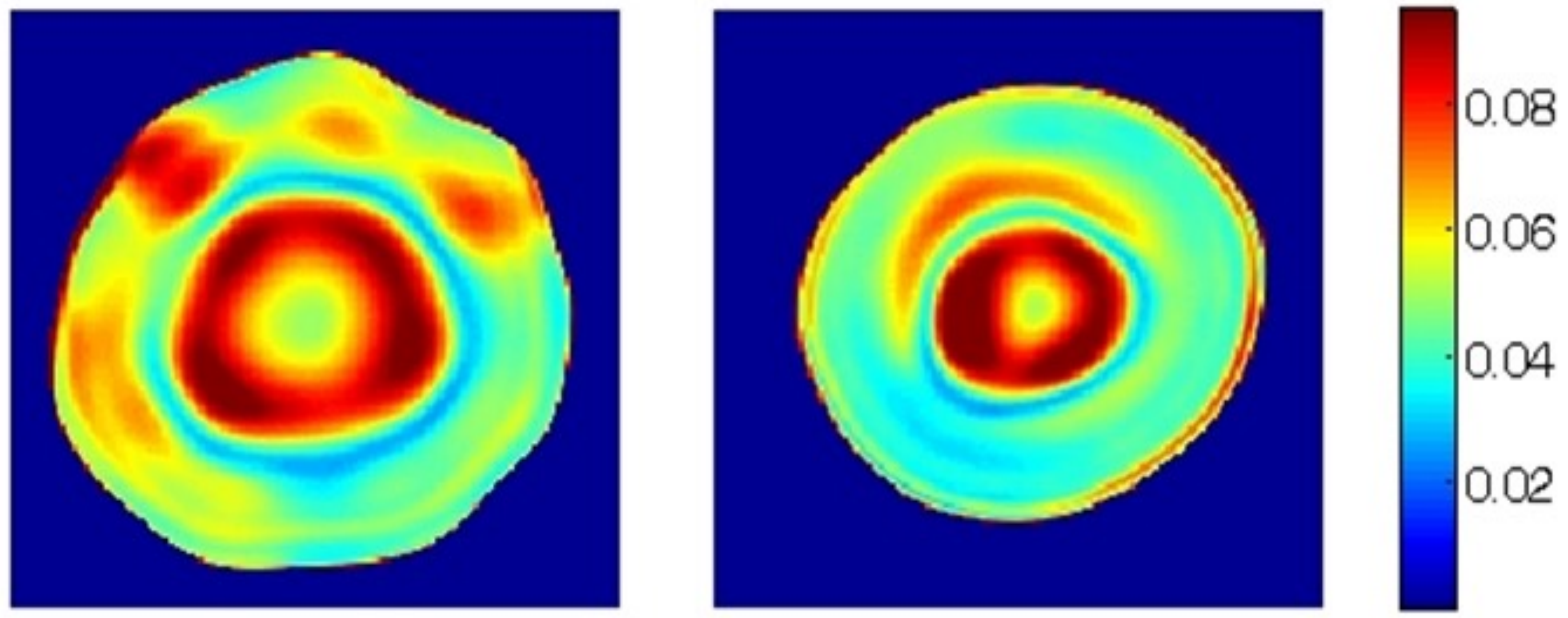
Older cell



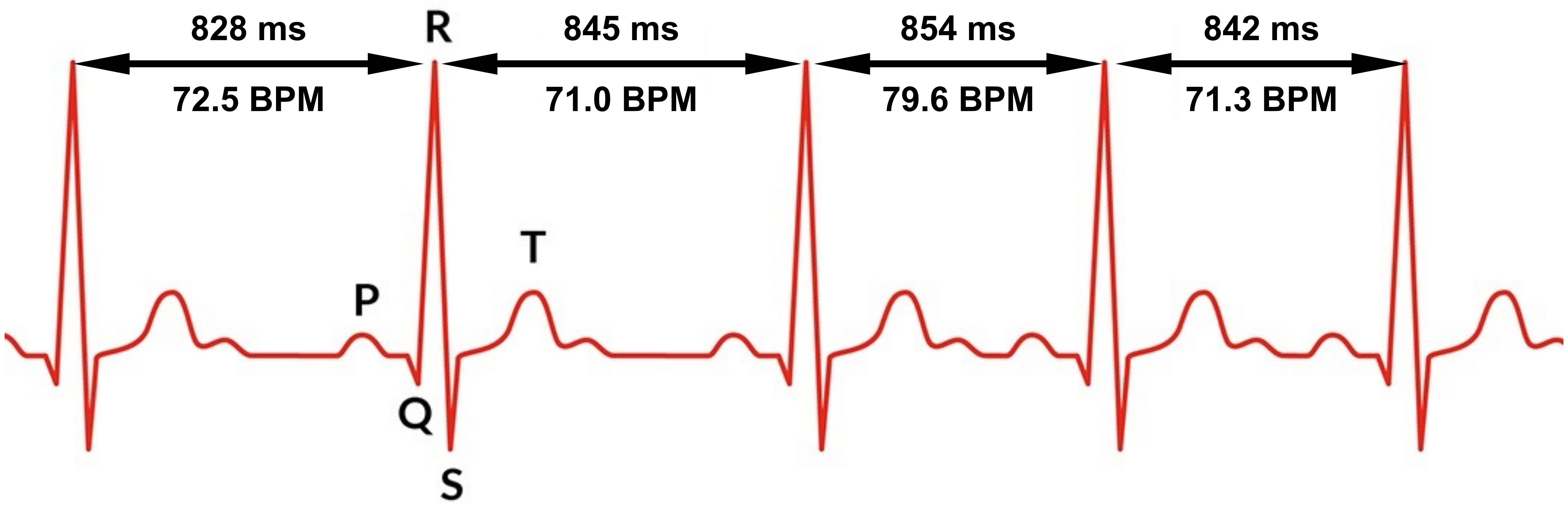
Newly formed RBC

Older RBC

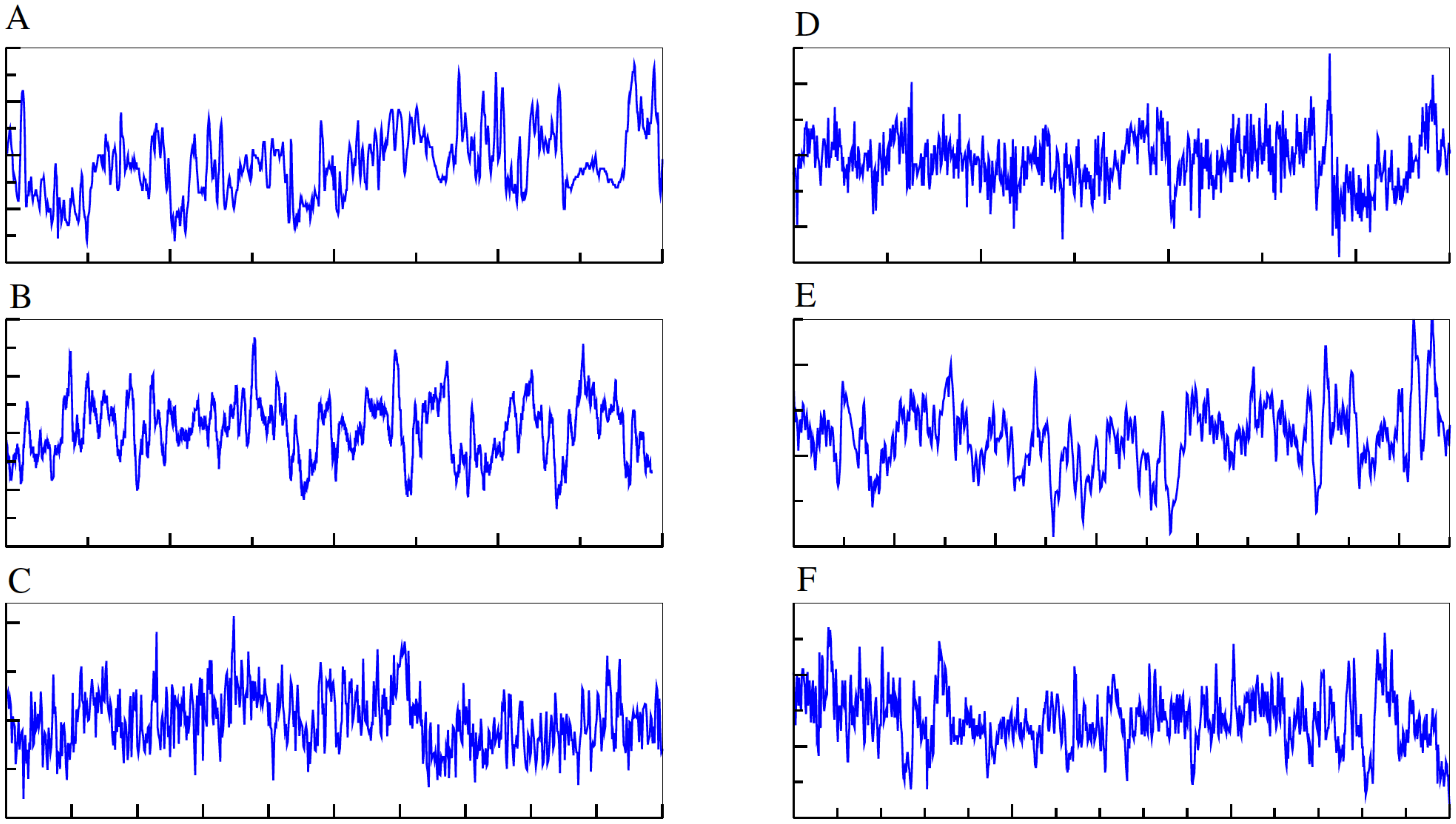
Coefficient of variation



From the ECG to the Interbeat Interval (RR or NN) Time Series

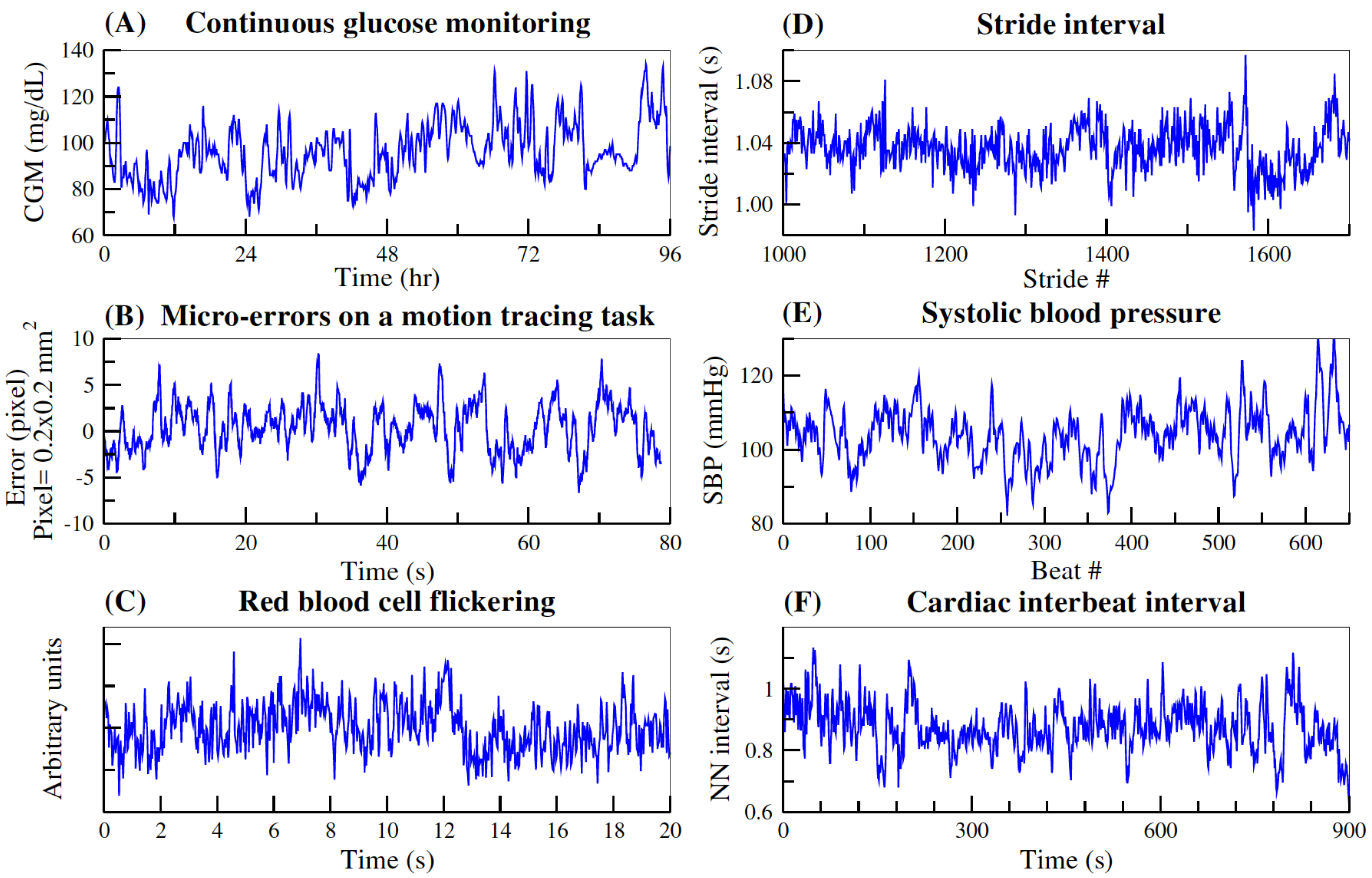


HR (bpm) = 60/NN (sec)



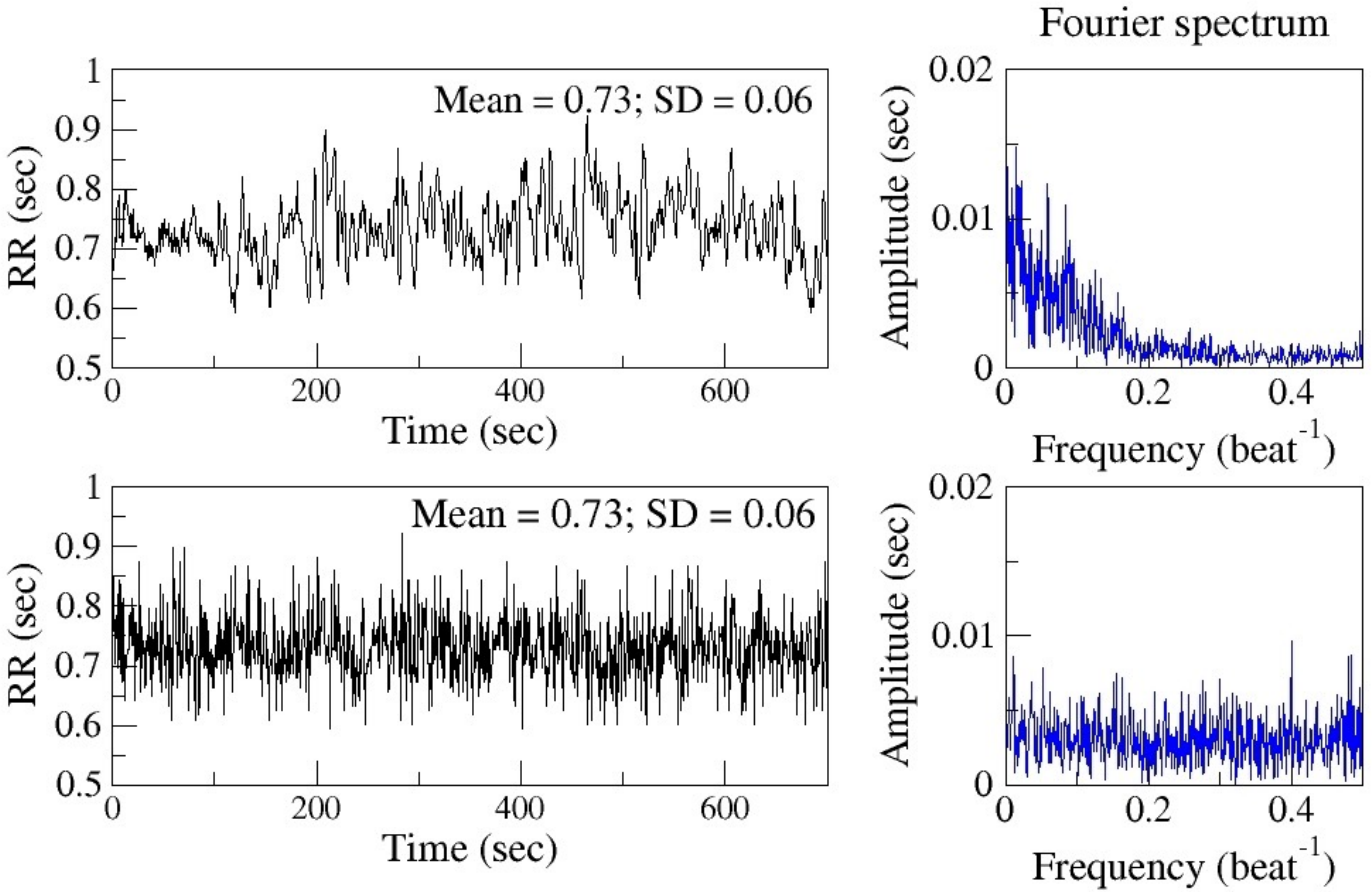
- Blood glucose
- Cardiac interbeat interval
- Red blood cell membrane flickering

- Systolic blood pressure
- Micro-errors from visuomotor tracing task
- Interstride interval



(A) Continuous glucose monitoring
CGM (mg/dL)
Time (hr)
(B) Micro-errors on a motion tracing task
Error (pixel)
Pixel= 0.2x0.2 mm2
Time (s)
(C) Red blood cell flickering
Arbitrary units
Time (s)
(D) Stride interval
Stride interval (s)
Stride #
(E) Systolic blood pressure
SBP (mmHg)
Beat #
(F) Cardiac interbeat interval
NN interval (s)
Time (s)

What does uncorrelated randomness look like?



Fundamental property of physiologic/biologic dynamical systems

COMPLEX VARIABILITY:

- Information over multiple time scales (fractal-like structure)
- Nonlinearity
- Possible time irreversibility
- Nonstationarity

Complexity Tutorials & Software Freely Available at PhysioNet (www.physionet.org)

Multiscale Entropy Analysis (MSE)

Madalena Costa, Ary L. Goldberger and C.-K. Peng

Beth Israel Deaconess Medical Center, Boston, USA

A detailed description of the multiscale entropy algorithm and its application can be found in:

- Costa M., Goldberger A.L., Peng C.-K. Multiscale entropy analysis of biological signals. *Phys Rev E* 2005;**71**:021906.
- Costa M., Goldberger A.L., Peng C.-K. Multiscale entropy analysis of physiologic time series. *Phys Rev Lett* 2002; **89**:062102.

Multiscale Entropy (MSE) Algorithm

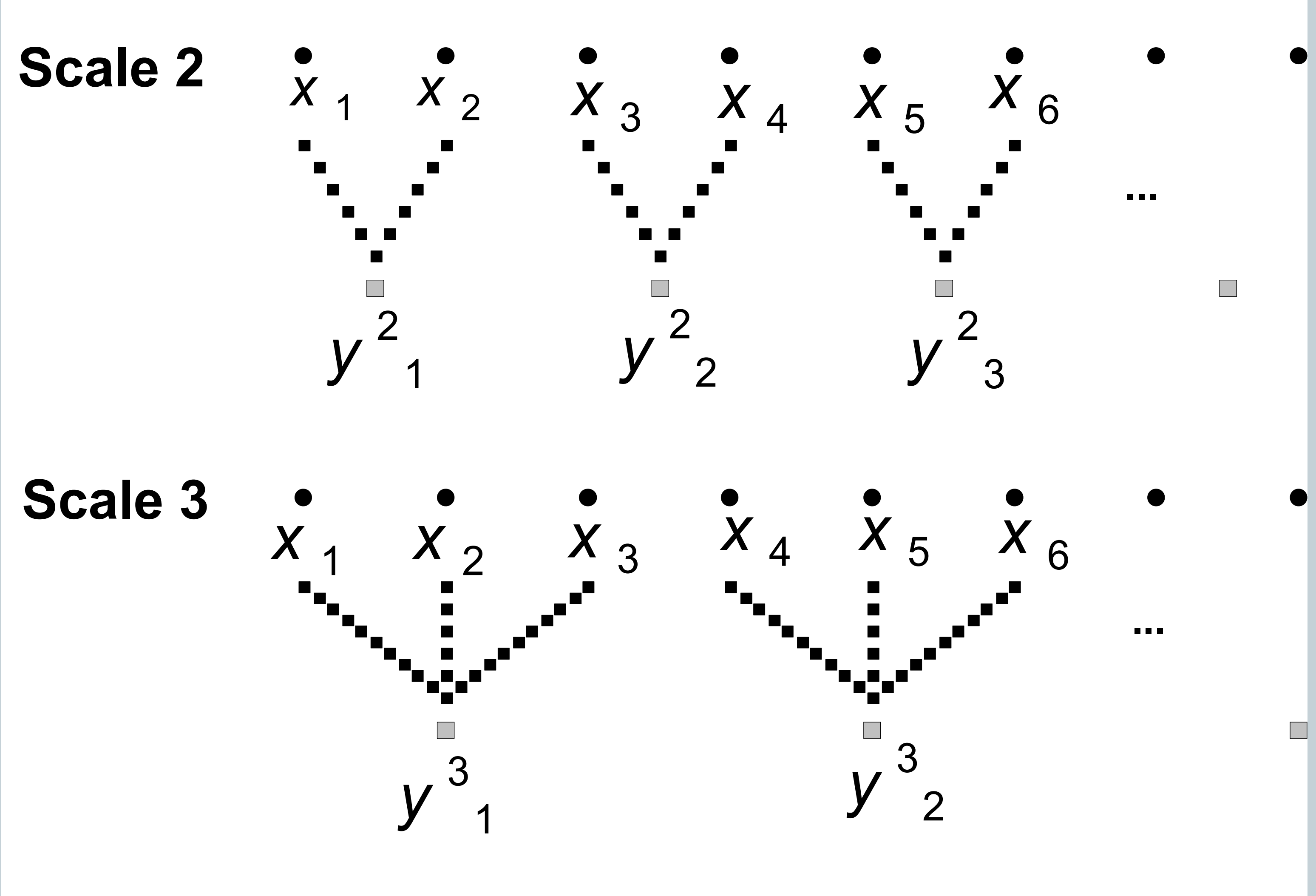
Step 1. Coarse-grain the time series for looking at different scales

Step 2. Calculate entropy for each coarse-grained series

Step 3. Plot entropy as a function of scale factor

Step 4. Analyze the MSE curve profiles

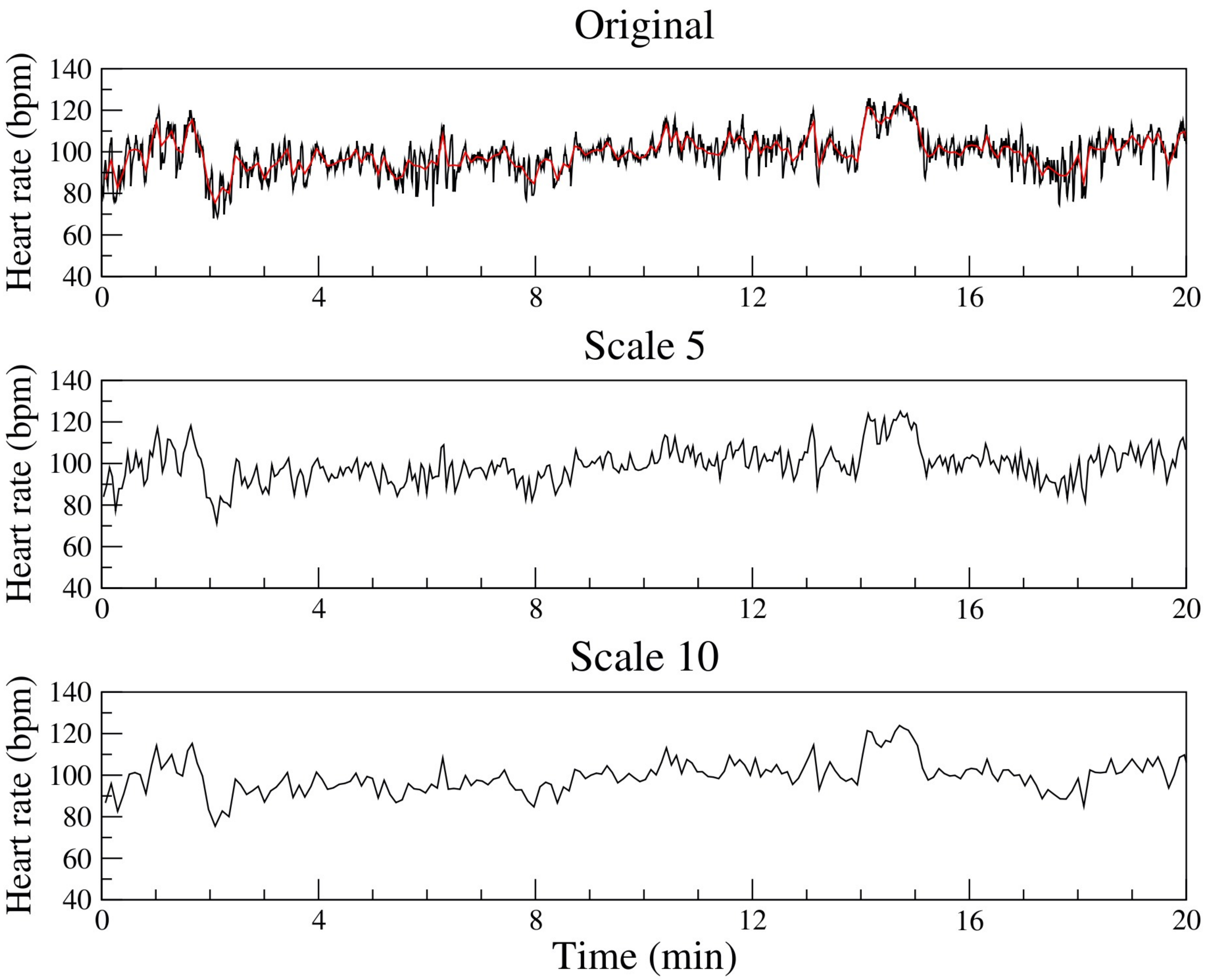
Coarse-graining schematic



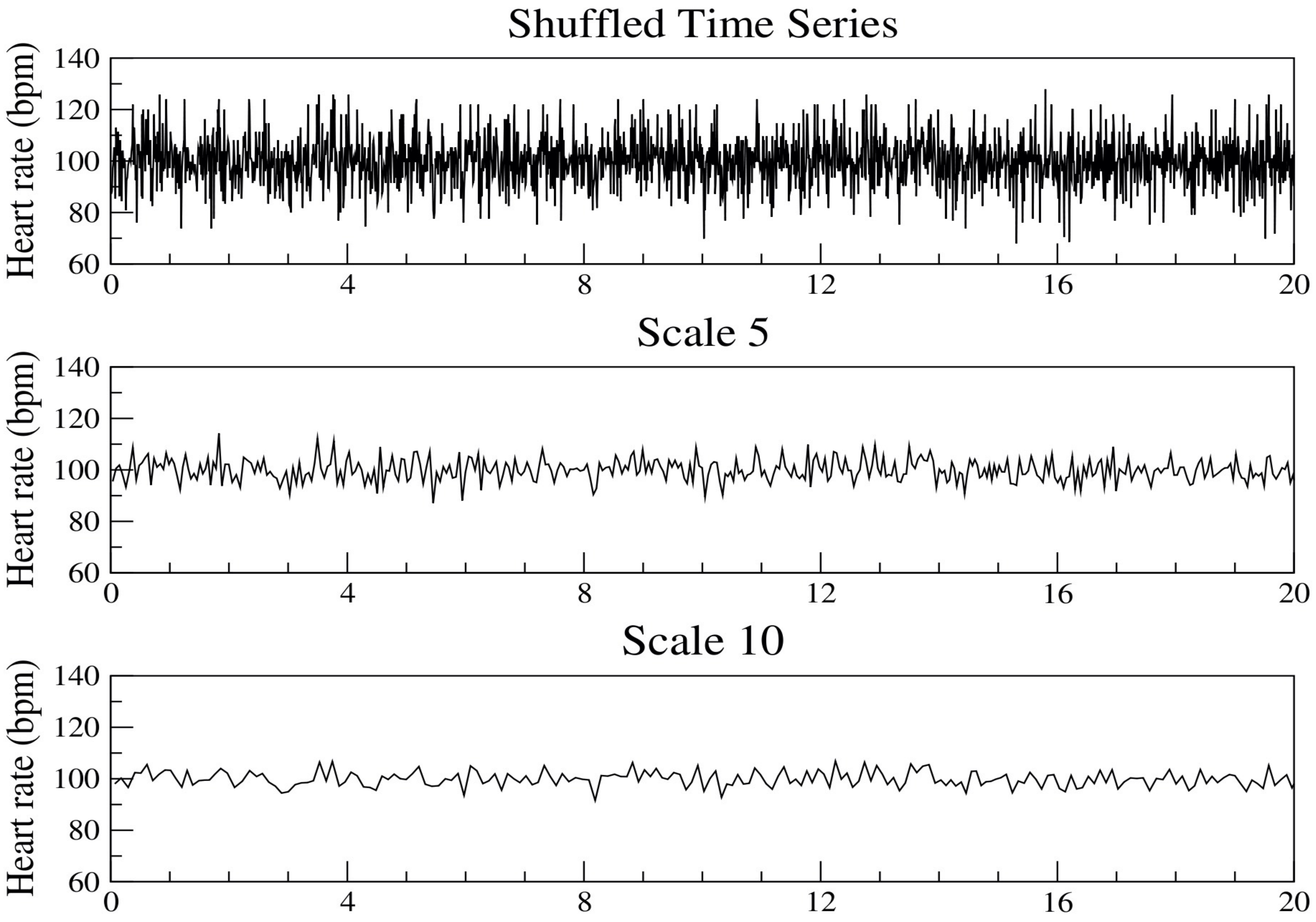
References:

M. Costa, A.L. Goldberger, C.-K. Peng. *Physical Review Letters* 2002;89:068102
M. Costa, A.L. Goldberger, C.-K. Peng. *Physical Review E* 2005;95:198102
M. Costa, A.L. Goldberger. *Entropy* 2015;17:1197-1203.

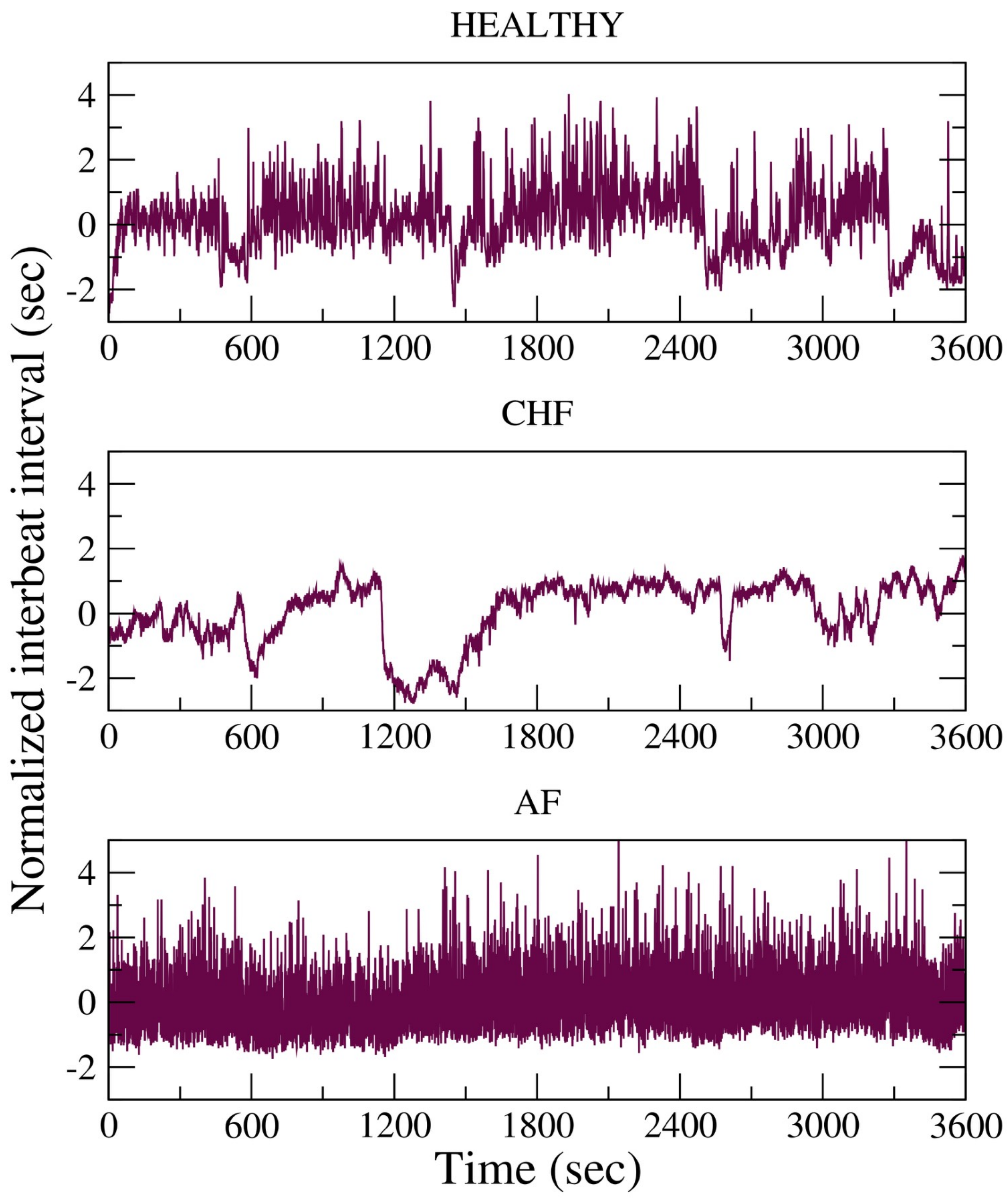
Coarse-graining of a Heart Rate Time Series

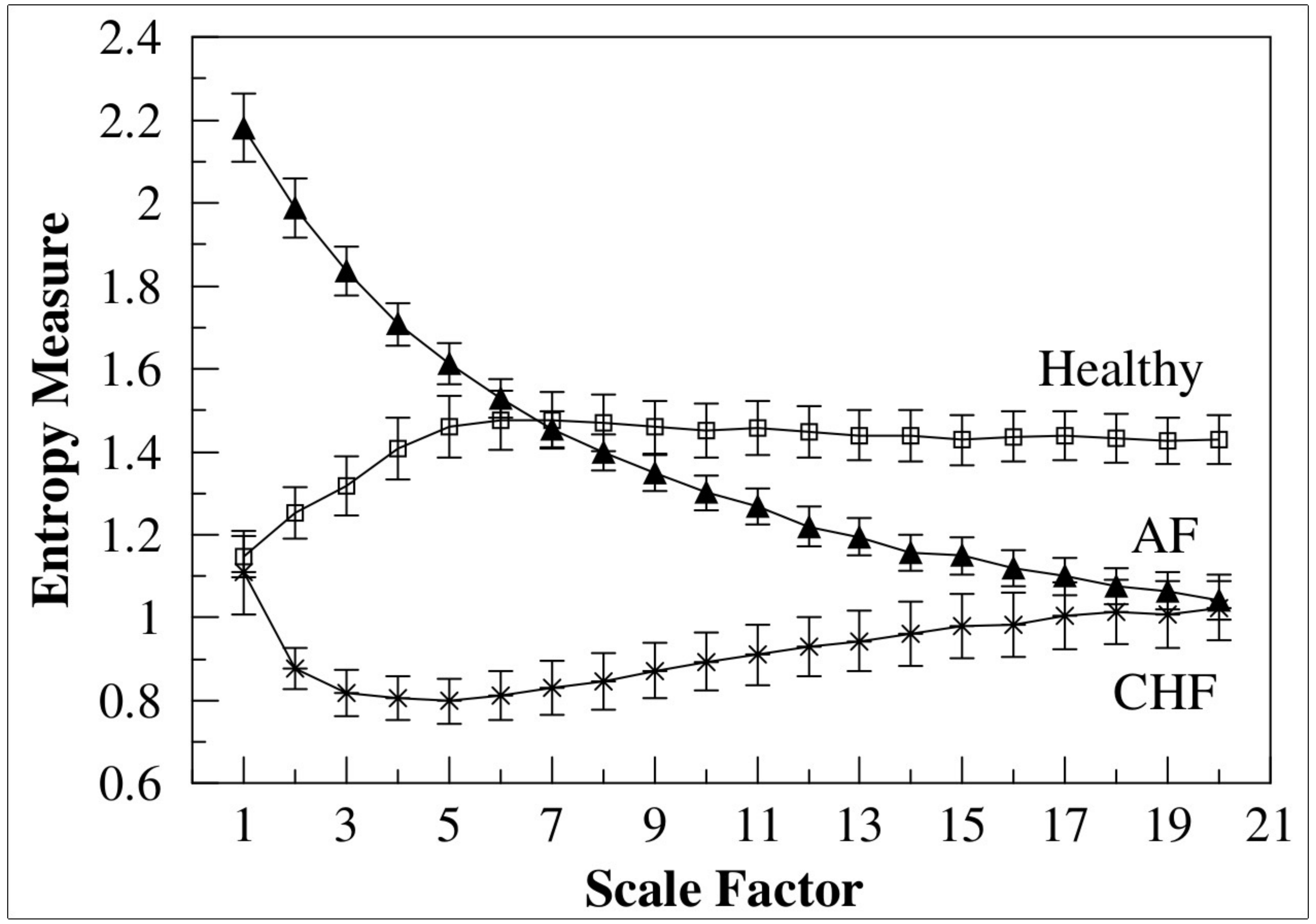


What Happens if the Original Time Series is Uncorrelated Random Noise?



Multiscale Entropy (MSE) of Heart Rate Dynamics





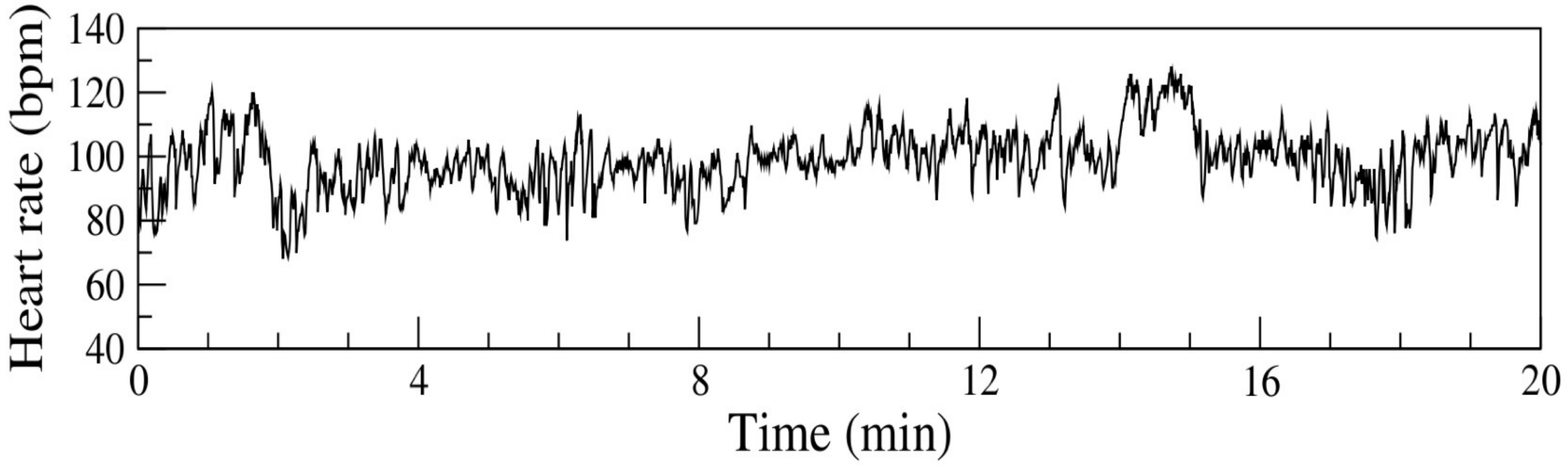
- Healthy (n=18)
- Chronic Heart Failure (CHF; n=15)
- Atrial Fibrillation (AF; n=9)

Costa *et al.*, PRL 2002;89:068102.

Collapse of Complexity with Aging and Disease

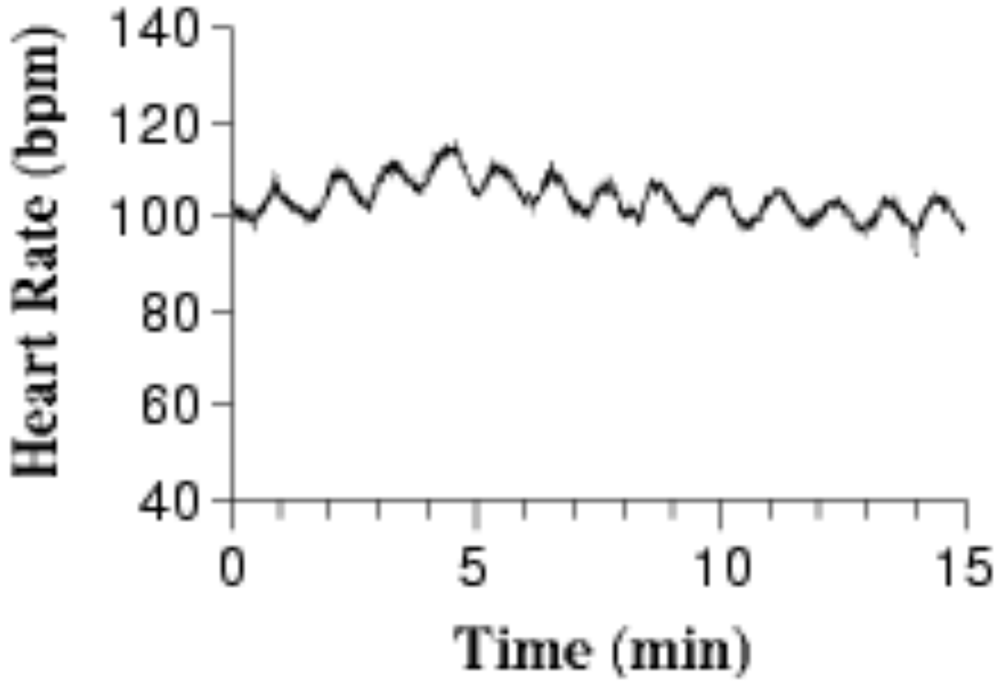
Adapted from: Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. Lancet 1996;347:1312-1314.

Healthy Dynamics: Multiscale Variability

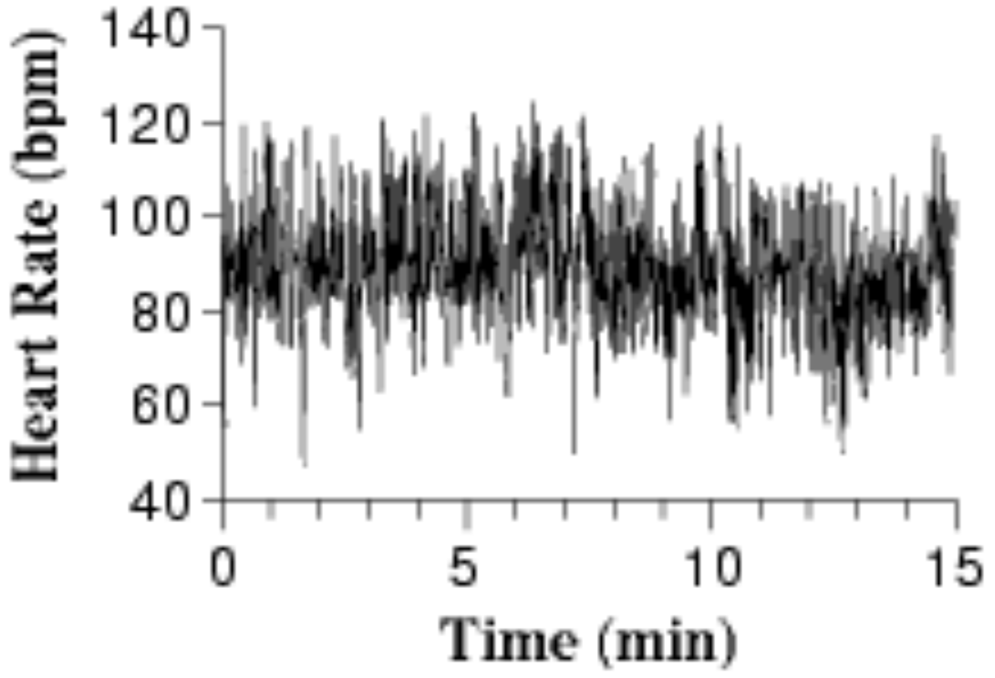


Two Patterns of Pathologic Breakdown

Single Scale Periodicity



Uncorrelated Randomness

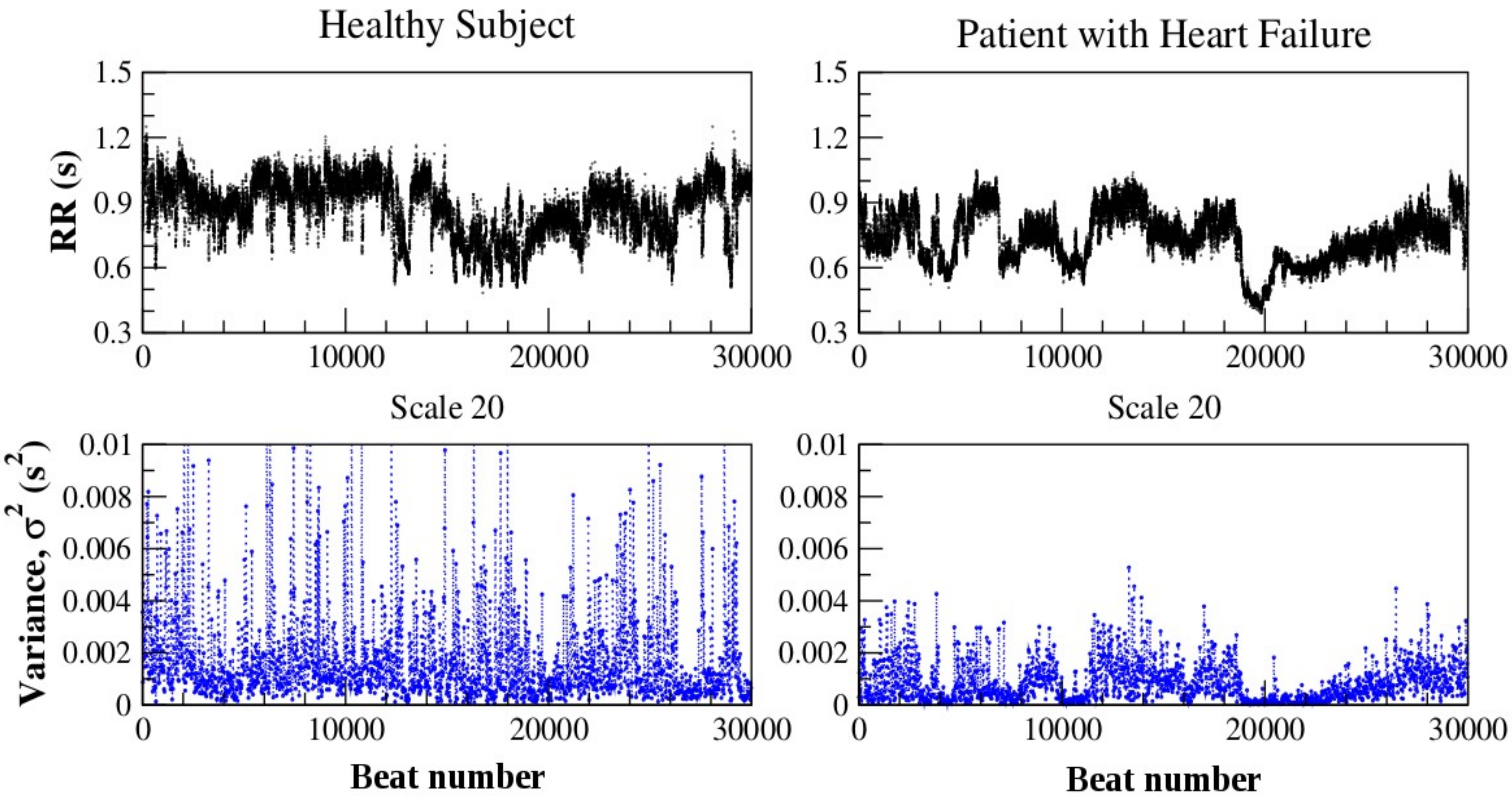


Healthy dynamics poised between too much order and total randomness

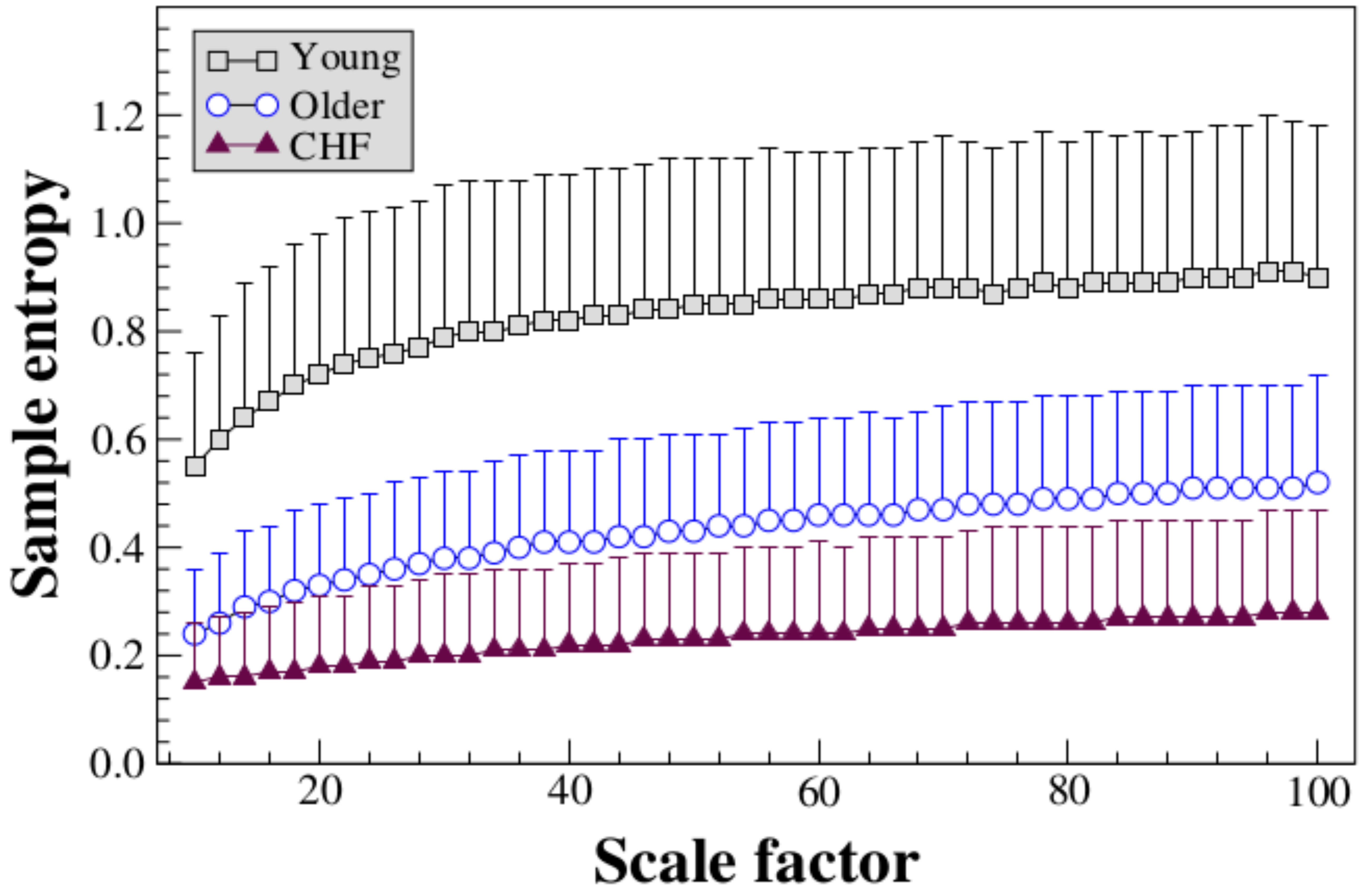
Costa MD *et al*. Multiscale entropy analysis of complex physiologic time series. Phys Rev Lett 2002;89:68102.

Goldberger AL *et al.* Fractal dynamics in physiology: alterations with disease and aging. Proc Natl Acad Sci USA. 2002;99(Suppl 1):2466.

MSEσ: Coarse-Graining Using Variance



MSEσ (Measure of Multiscale Volatility): Analysis of Heart Rate Time Series



- Healthy young (n = 26)
- Healthy elderly (n = 46)
- Chronic heart failure (n = 43)

M. Costa, A.L.Goldberger. *Entropy* 2015;17:1197-1203.

Selected MSE Applications

- **2003: Gait dynamics**
  Costa M et al. “Multiscale entropy analysis of human gait dynamics.” Physica A vol. 330,1-2 (2003): 53-60.
- **2007: Sway dynamics and quantification of improvement in postural stability with a stochastic-resonance-based therapy**
  Costa M et al. “Noise and poise: Enhancement of postural complexity in the elderly with a stochastic-resonance-based therapy.” Europhysics letters vol. 77 (2007): 68008.
- **2008: RBC membrane dynamics**
  Costa M et al. “Complex dynamics of human red blood cell flickering: alterations with in vivo aging.” Physical review. E, Statistical, nonlinear, and soft matter physics vol. 78,2 Pt 1 (2008): 020901.
- **2009: Quantification of the impact of a cognitive task on the dynamics of postural control (sway)**
  Kang HG et al. “Frailty and the degradation of complex balance dynamics during a dual-task protocol.” The journals of gerontology. Series A, Biological sciences and medical sciences vol. 64,12 (2009): 1304-11.

  Manor B et al. “Physiological complexity and system adaptability: evidence from postural control dynamics of older adults.” Journal of applied physiology (Bethesda, Md. : 1985) vol. 109,6 (2010): 1786-91.
- **2013: Quantification of age, sex and handedness on visuomotor performance**
  Stirling LA et al. “Use of a tracing task to assess visuomotor performance: effects of age, sex, and handedness.” The journals of gerontology. Series A, Biological sciences and medical sciences vol. 68,8 (2013): 938-45.
- **2017: Prediction of falls based on complexity of sway**
  Zhou J et al. “The Complexity of Standing Postural Sway Associates with Future Falls in Community-Dwelling Older Adults: The MOBILIZE Boston Study.” Scientific reports vol. 7,1 (2017): 2924.

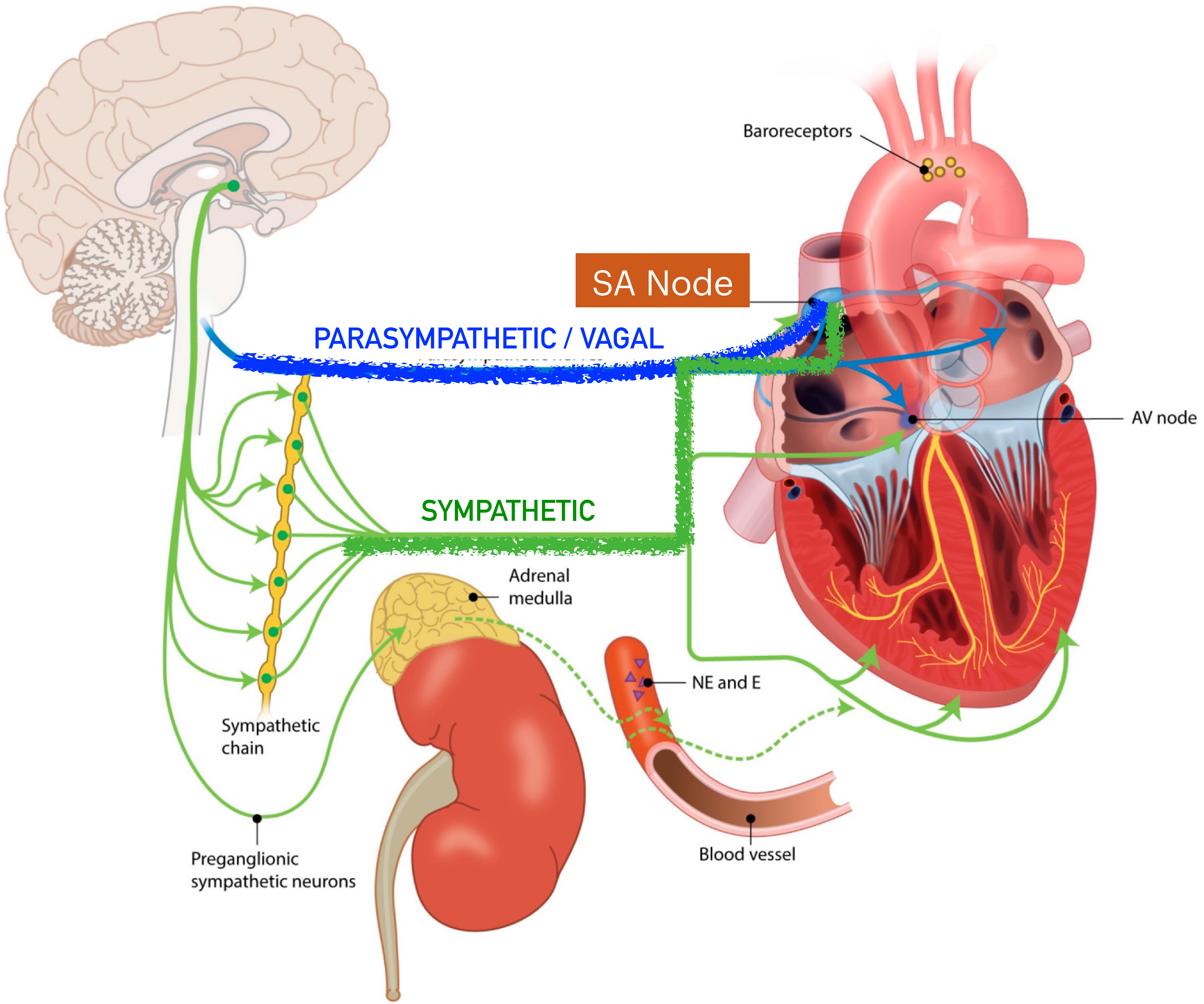
Development of a Metric of Biological Age

Focus: Quantification of autonomic nervous system (ANS) function

Why this focus: The ANS is involved in the control of virtually all (voluntary & involuntary) physiologic processes

How: Through the analysis of heart rate dynamics: changes with aging and disease in neuroautonomic control ***imprint dynamical signatures*** on heart rate fluctuations that can be exploited in relation to the quantification of biological age.

Heart Rate Dynamics is Mainly Controlled by the ANS

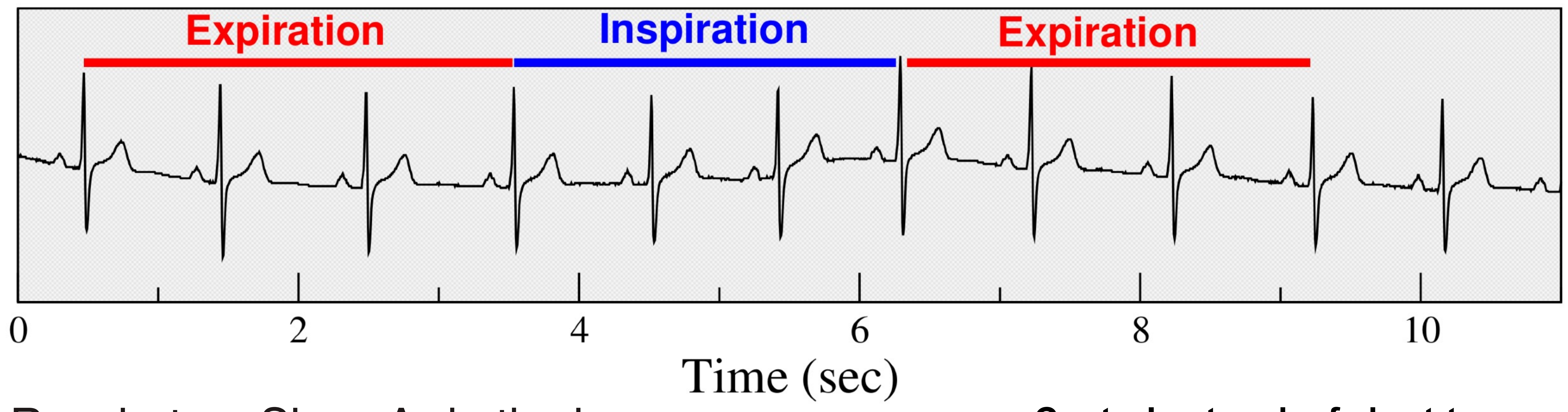


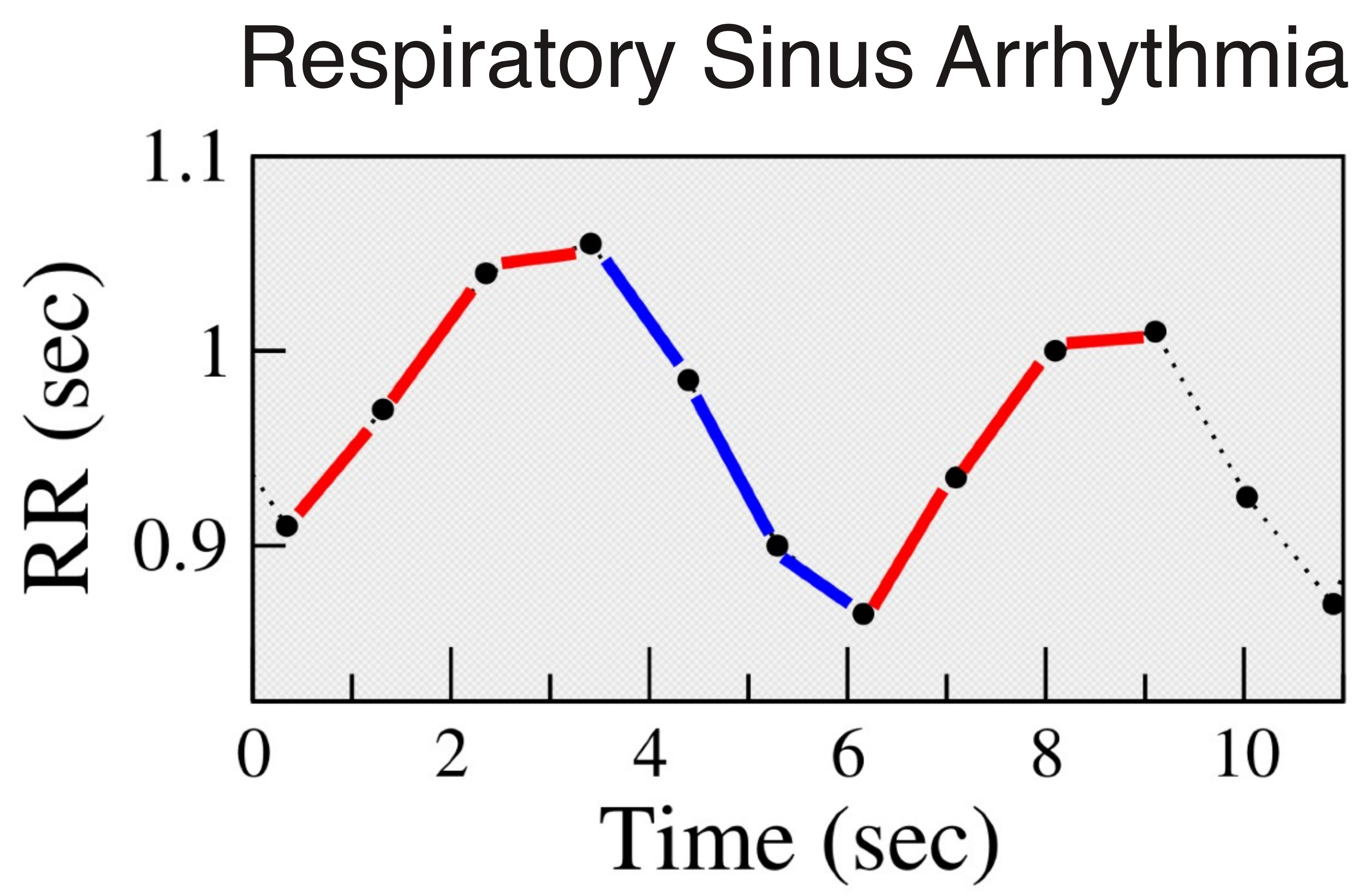
Long ECG recordings are easily obtainable and their acquisition is noninvasive.

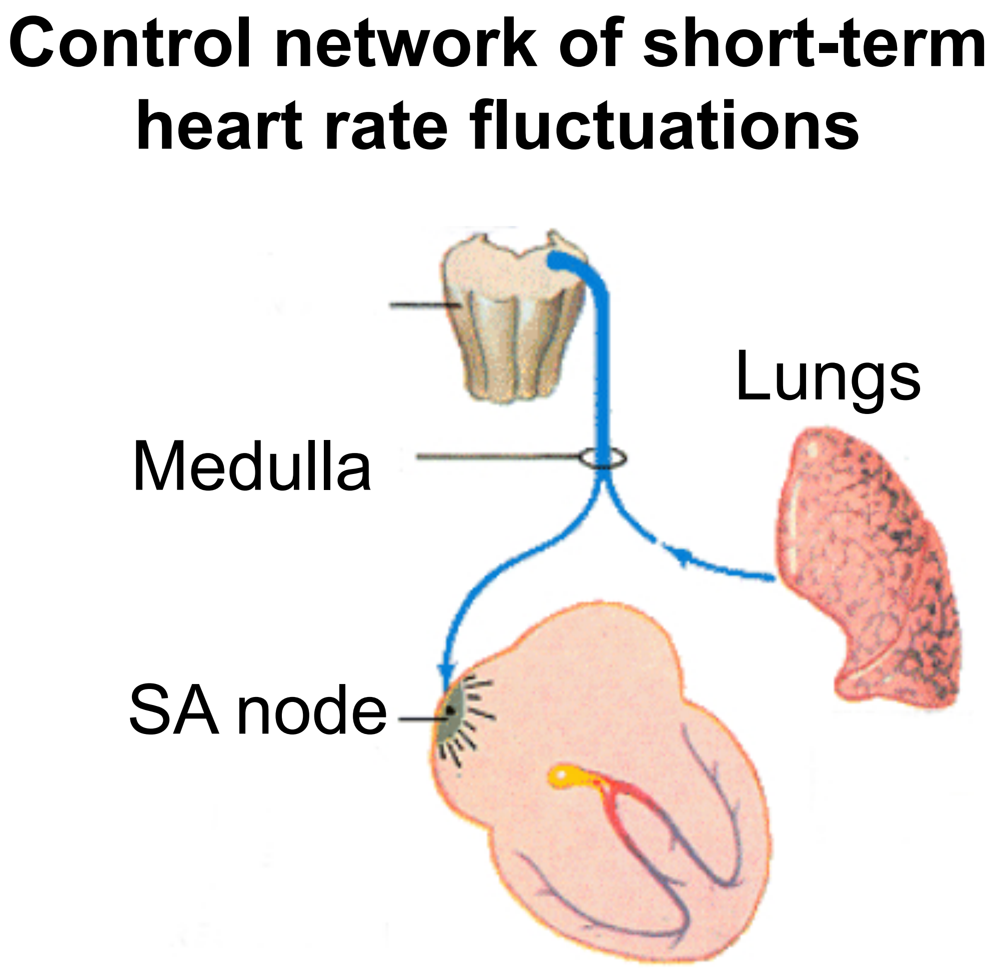
Beat-to-beat fluctuations in heart rate provide a window into the integrity of the neuroautonomic system.

The ANS is the major “orchestrator” in the body, integrating information from virtually all processes, physiological and psychological.

Fastest Physiologic Fluctuations in Heart Rate are due to Vagal Tone Modulation



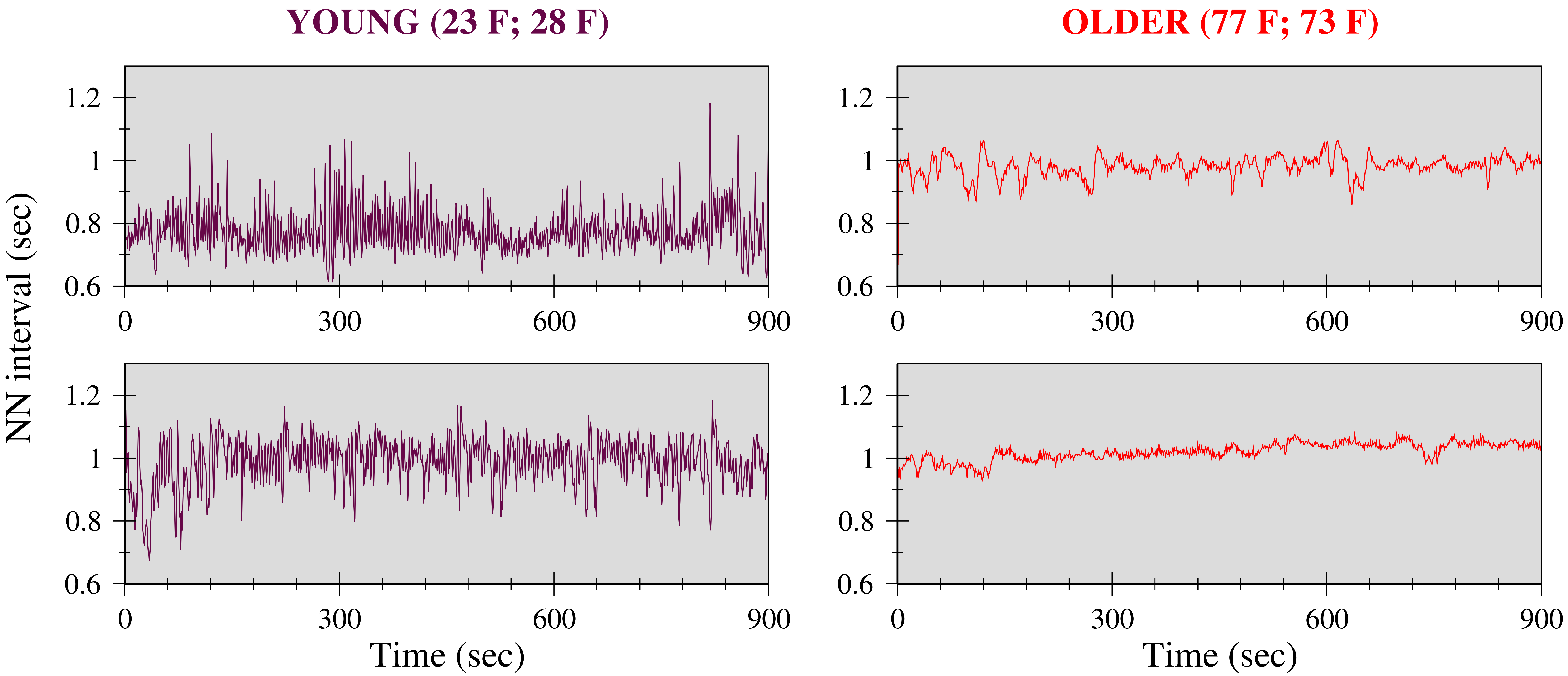




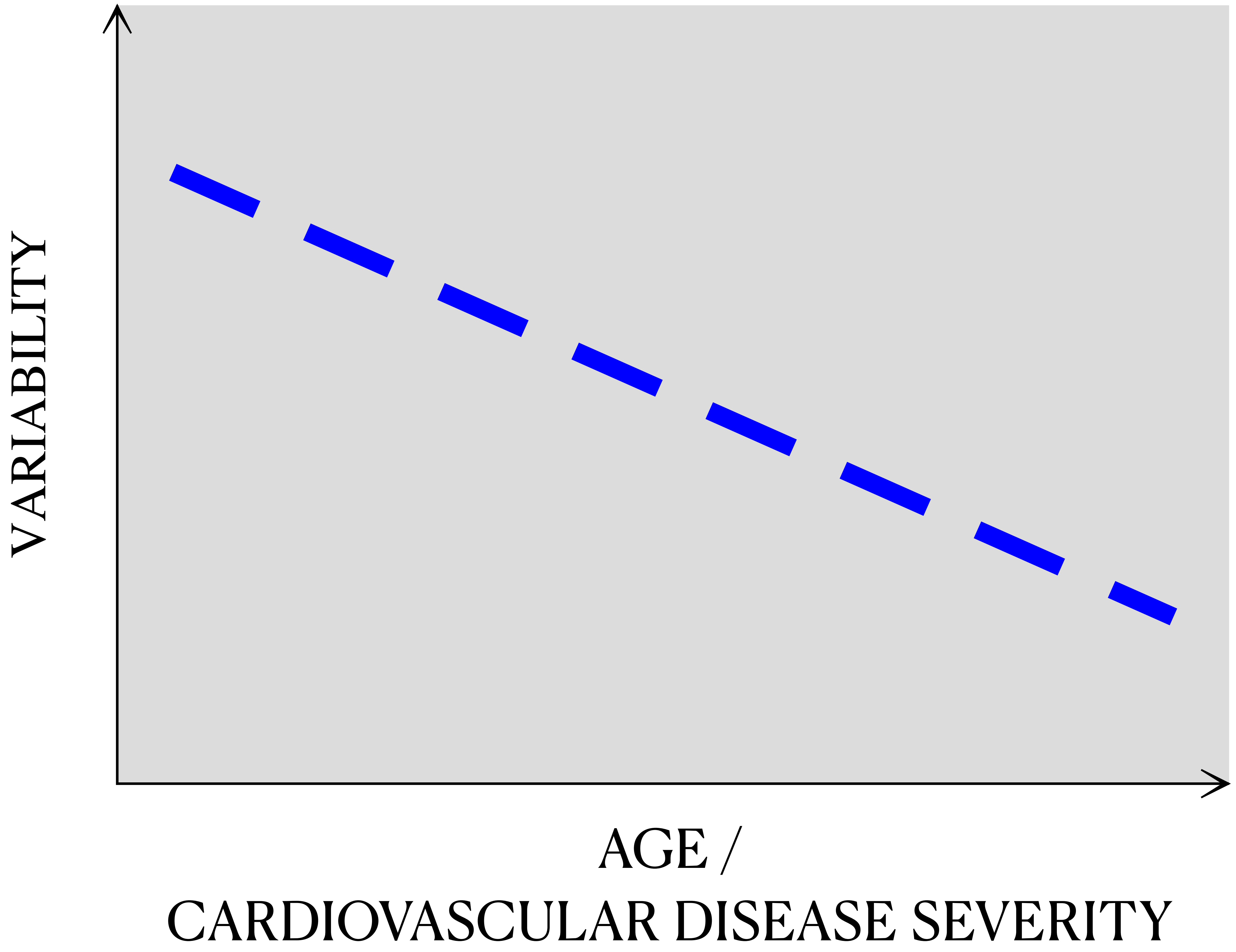
Parasympathetic/vagal modulation of heart rate decreases with **age** and **heart disease, as well as other pathologies** (multiple sclerosis, dementia, etc). **Repeatedly documented.**

What Happens to Heart Rate Fluctuations as a Consequence of the Decrease in Vagal Tone Modulation with *Healthy* Aging?

15-min Long NN Interval Time Series

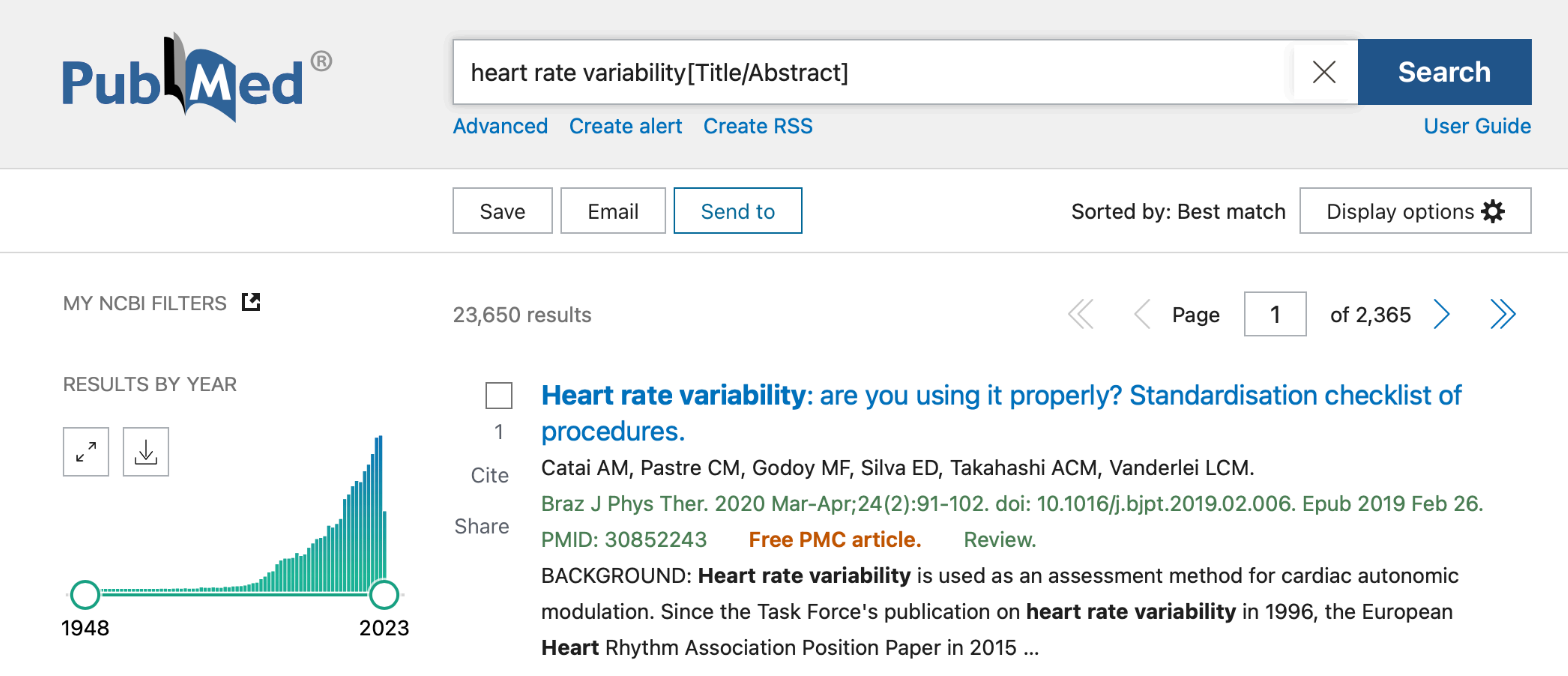


Heart Rate Variability (HRV) Framework



Variability decreases with aging and disease, reflecting the decrease in autonomic control.

> 20,000 Publications!



The Multi-Ethnic Study of Atherosclerosis (MESA)

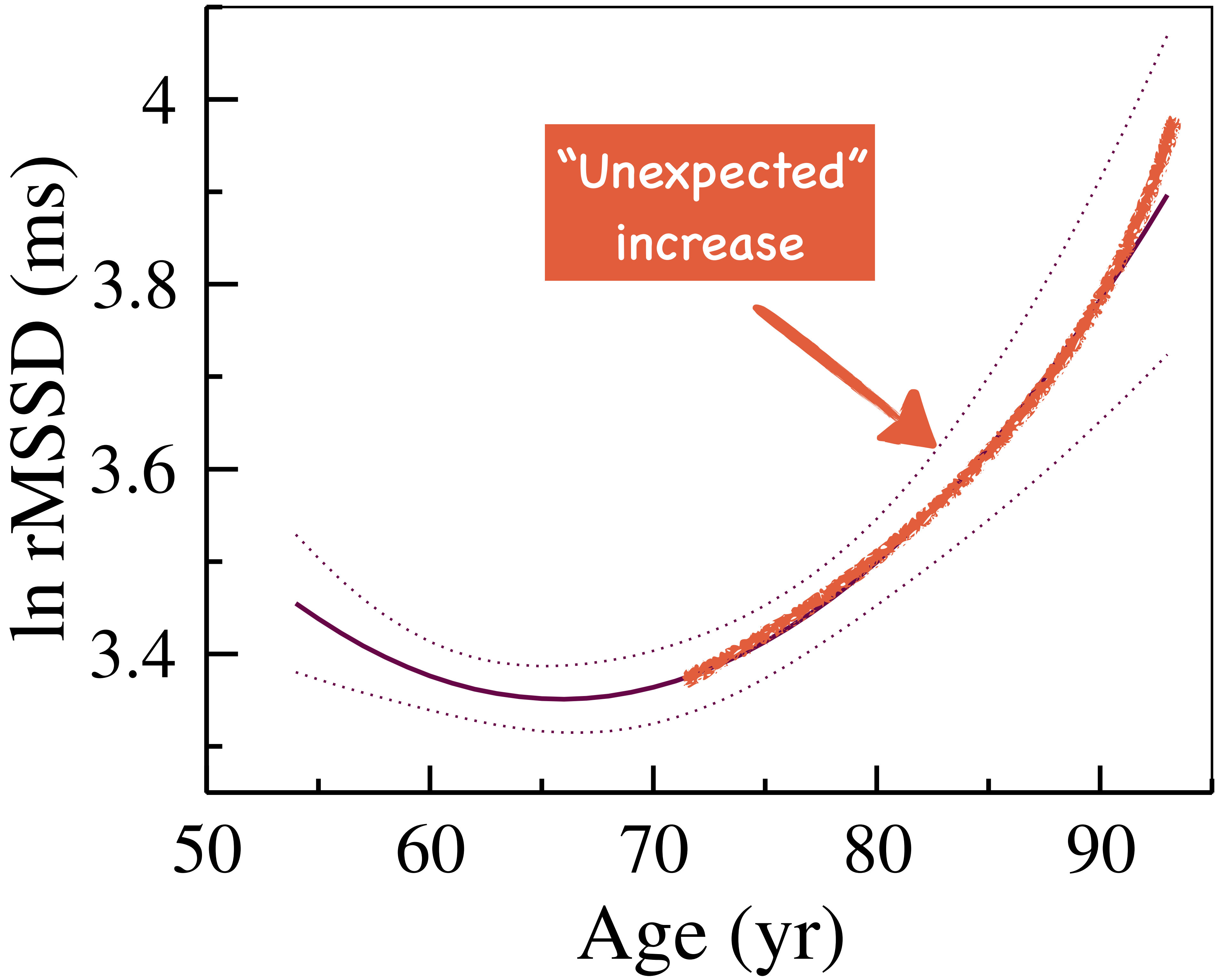
- On-going large NIH-sponsored longitudinal study of the onset of overt cardiovascular disease and of the risk factors that predict its progression.
- Enrolled 6,814 asymptomatic men and women aged 45-84 from six centers across the US.
- 38% participants were white, 28% African-American, 22% Hispanic, and 12% Asian.
- 1st exam: July 2000 – July 2002. 5th exam April 2010 – January 2012. Participants are contacted every 9 to 12 months throughout the study to assess clinical status.
- Major adverse outcomes: death (all, cardiovascular), stroke, MI, coronary bypass graft, heart failure, angioplasty, etc.

- ***Focus:*** heart rate time series derived from the ECG channel of an ancillary polysomnographic (PSG) study conducted between 2010 and 2013 that enrolled 2,057 participants.

How does HRV Change with Age in MESA?

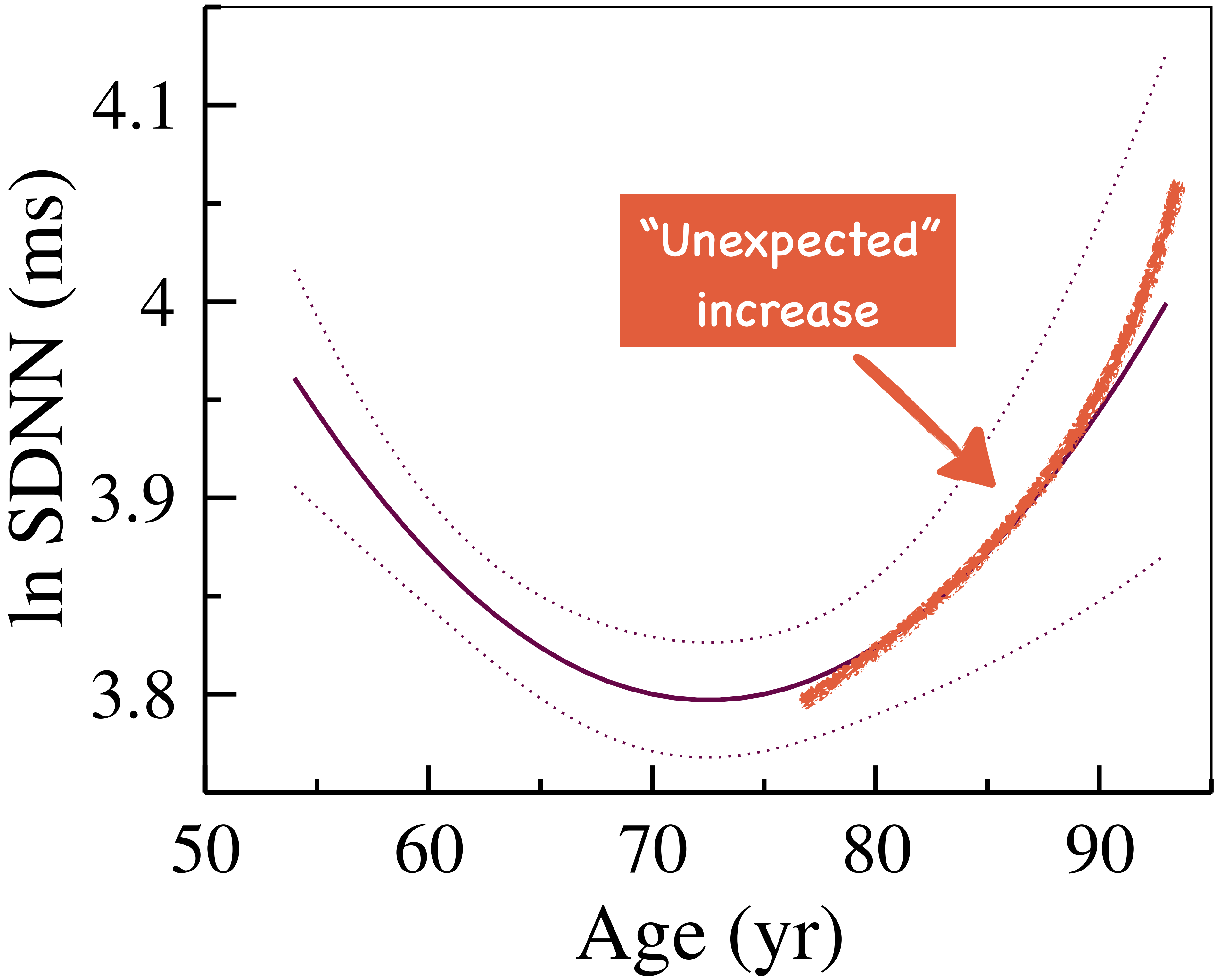
Short-term (beat-to-beat) variability

$$rMSSD = \sqrt{\sum \frac{1}{N-1}(RR_{i+1} - RR_i)^2}$$



Overall degree of variability

$$SDNN = \sqrt{\sum \frac{1}{N-1}(RR_i - \overline{RR})^2}$$



Costa MD, et al. Front Physiol 2017;8:255; Costa MD, et al. Front Aging Neurosci. 2021;13:708130.

We know autonomic control decreases with age and disease. So, what is “inflating” traditional variability measures (SDNN, rMSSD, HF), especially in older (and sicker) individuals?

Symbolic Dynamical Analysis

Mapping of the NN interval time series: 3 symbols

- Heart rate **acceleration**:

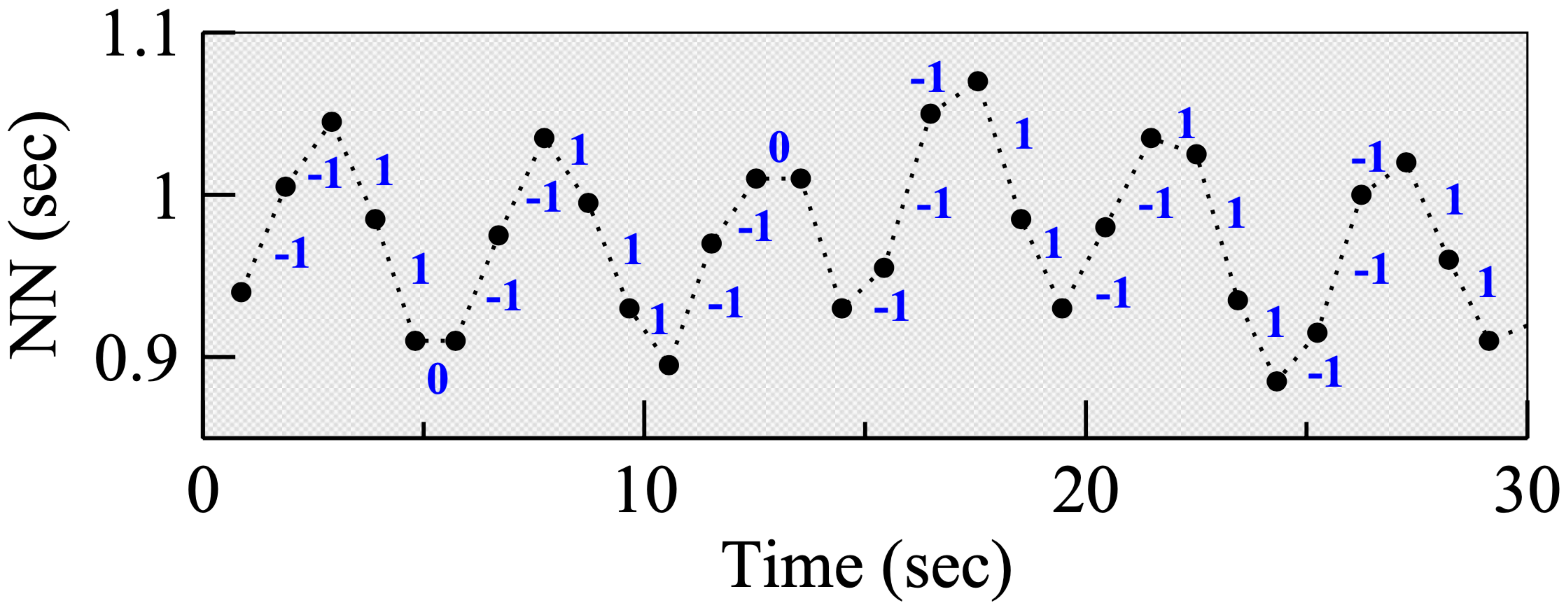
  ΔNN < 0: "−1"

- Heart rate **deceleration**:

  ΔNN > 0: "1"

- **No change**:

  ΔNN = 0: "0"



−1 −1 1 1 0 −1 −1 1 1 1 0 −1 −1 0 1 −1

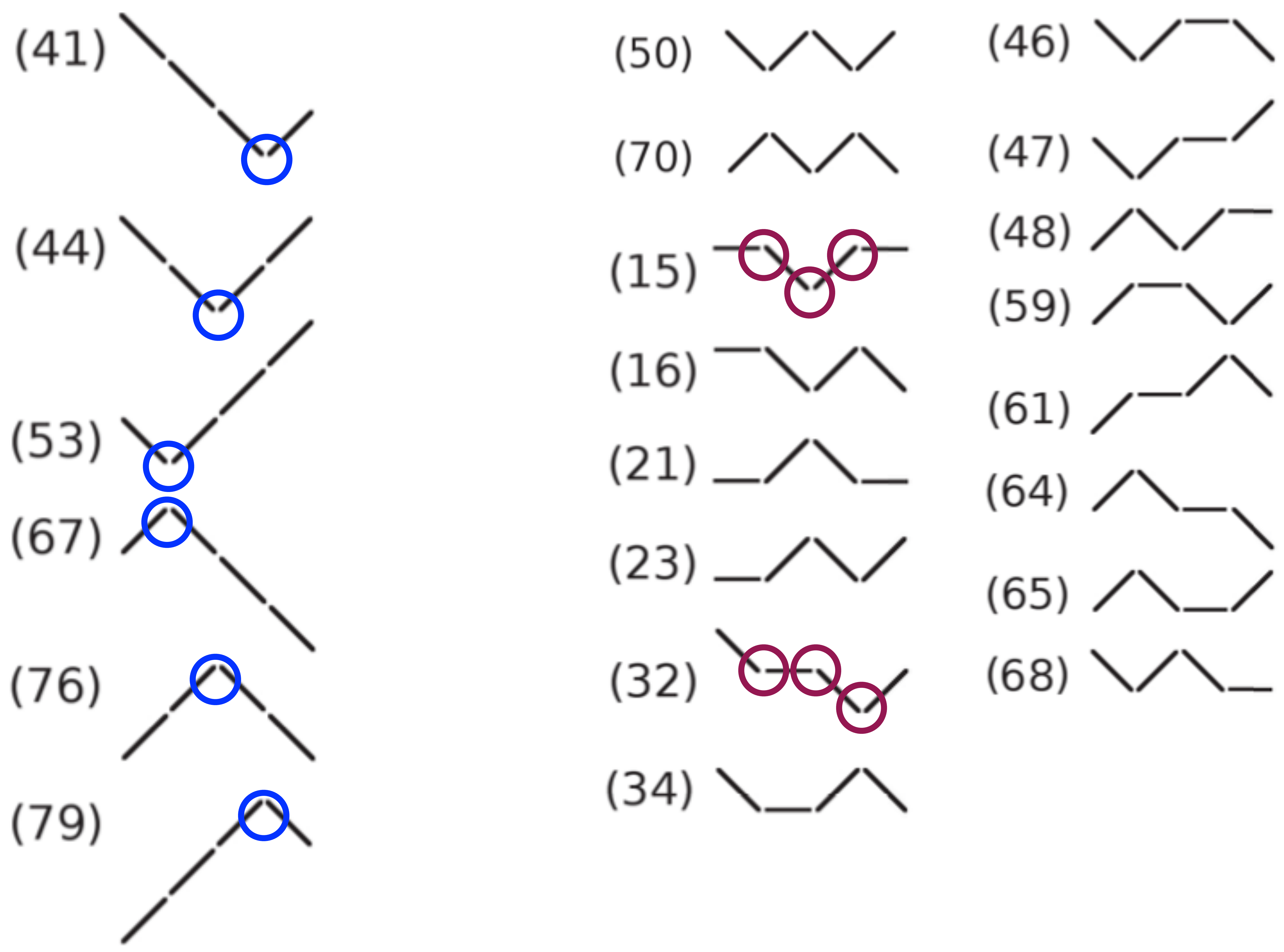
Key Questions

1. How does the frequency of each word change with age?
2. What do words that increase (decrease) with age have in common?
3. What is the physiologic meaning of the shared dynamical property?
4. Is that property useful for the prediction of cardiovascular events (CVEs) and overall assessment of health status?

Associations of Words' Frequency with Cross-sectional Age

Examples of patterns that **DECREASE** with age:

Example of patterns that **INCREASE** with age:



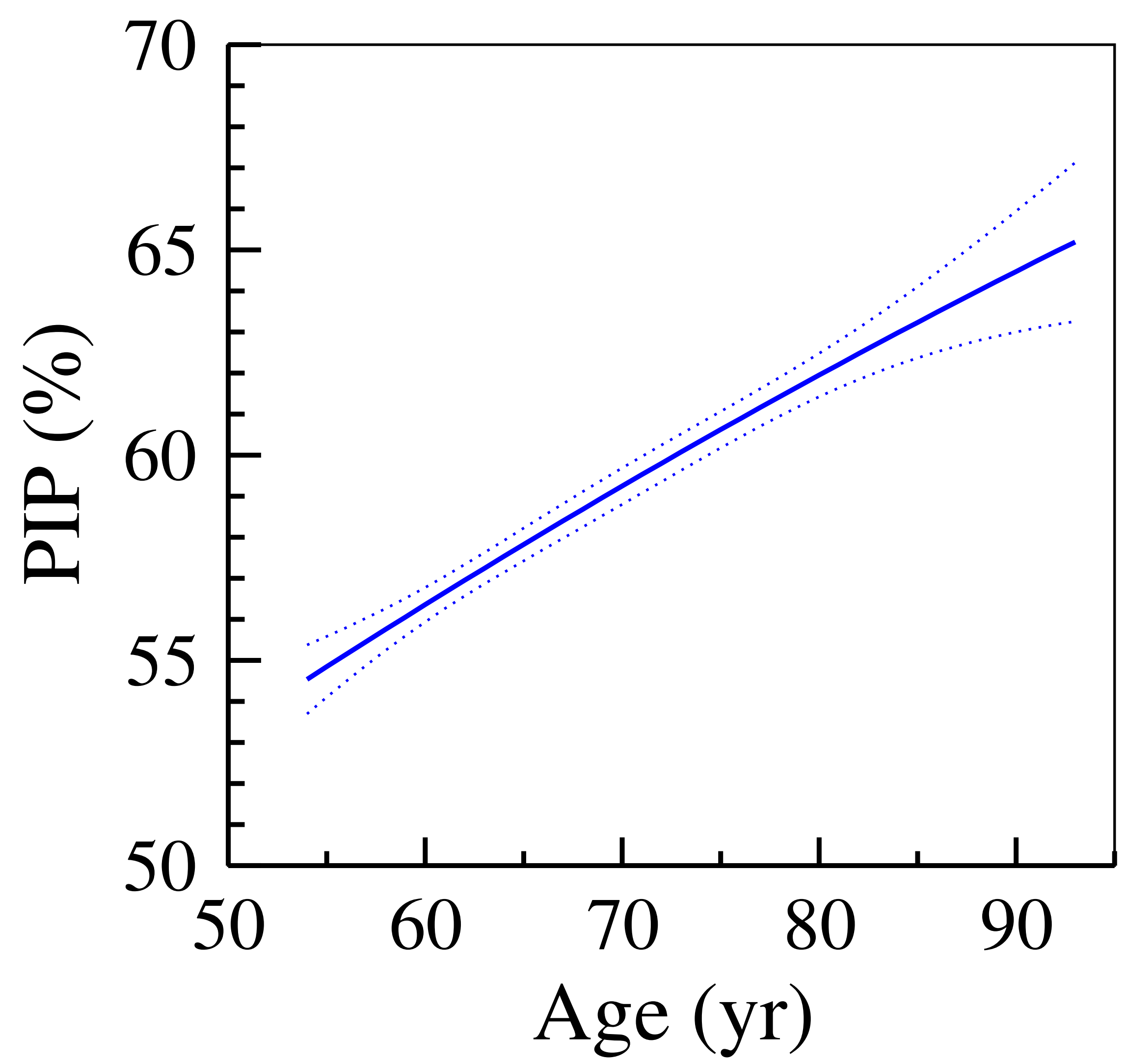
Patterns that **decrease** with age have a **single** "inflection point."

Patterns that **increase** with age have **multiple** inflection points.

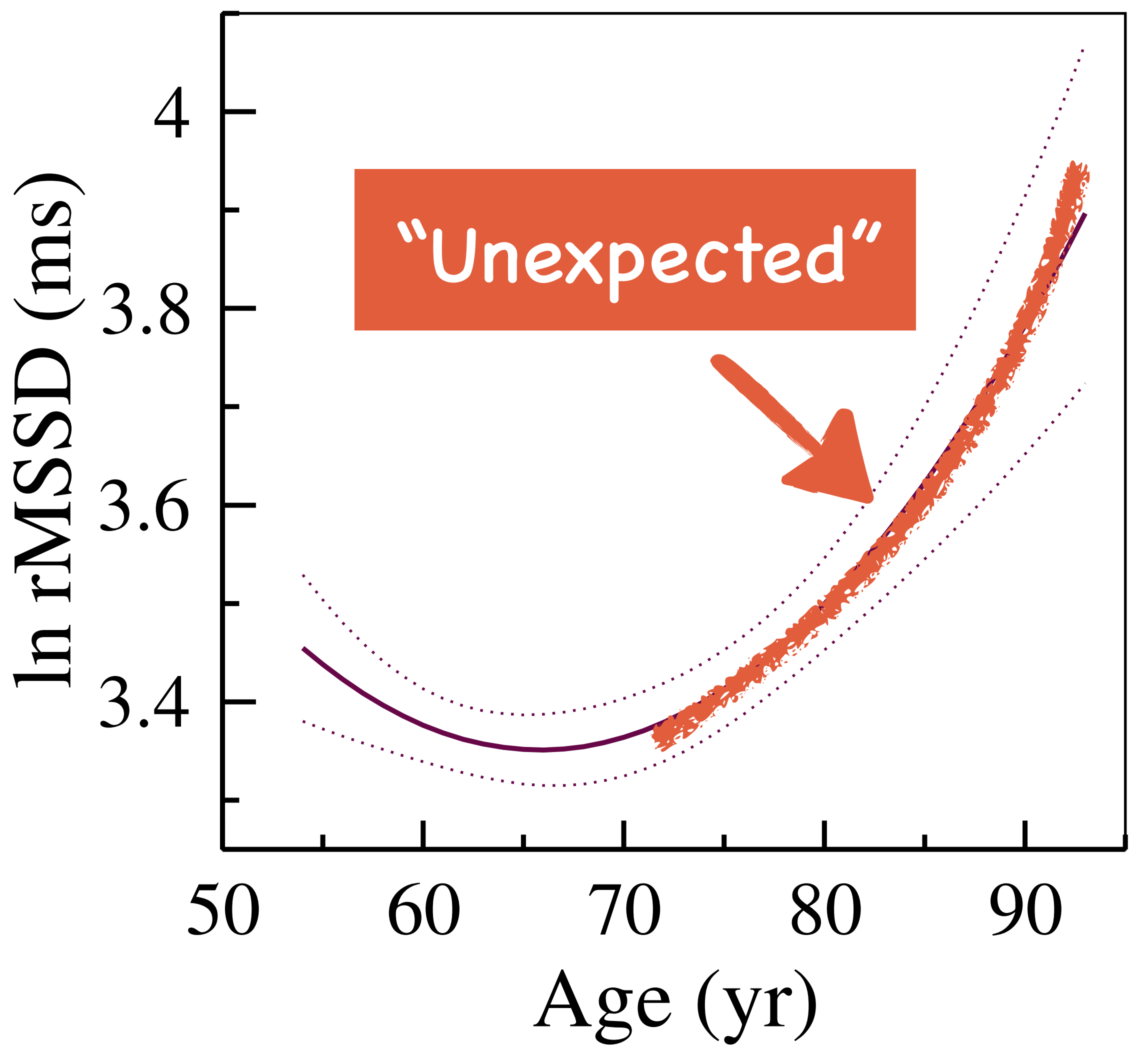
PIP: % of Inflection Points

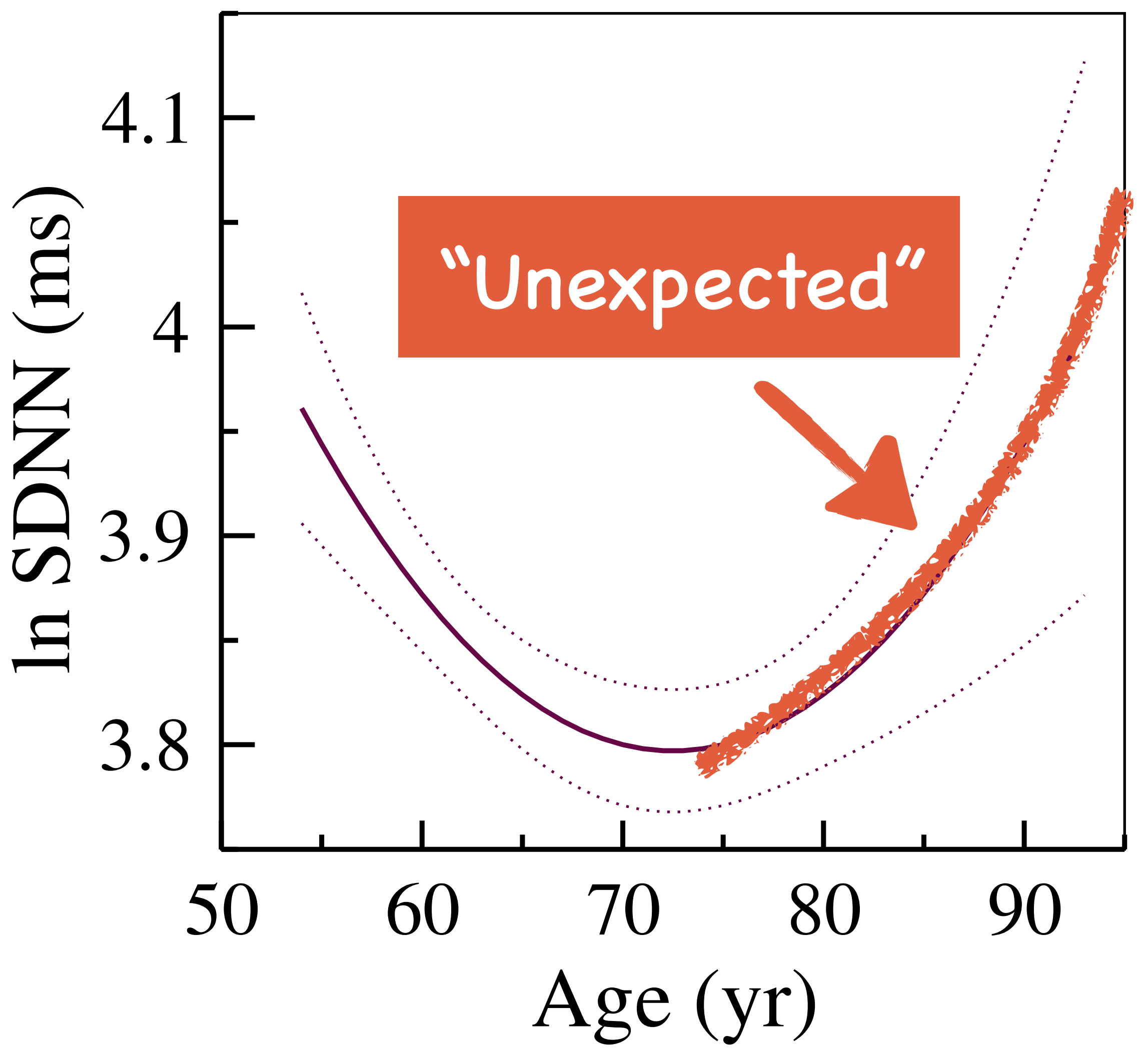
- Mathematical definition of inflection point: $\Delta NN_{i+1} \times \Delta NN_i \leq 0, \;\; \Delta NN_{i+1} \neq \Delta NN_i$
- Inflection points represent changes in heart rate (HR) acceleration sign, i.e., transitions from heart rate (HR) acceleration to deceleration and vice-versa, and from HR acceleration/deceleration to no change in HR and vise-versa
- PIP quantifies the property termed **heart rate fragmentation** (HRF)

Results in MESA

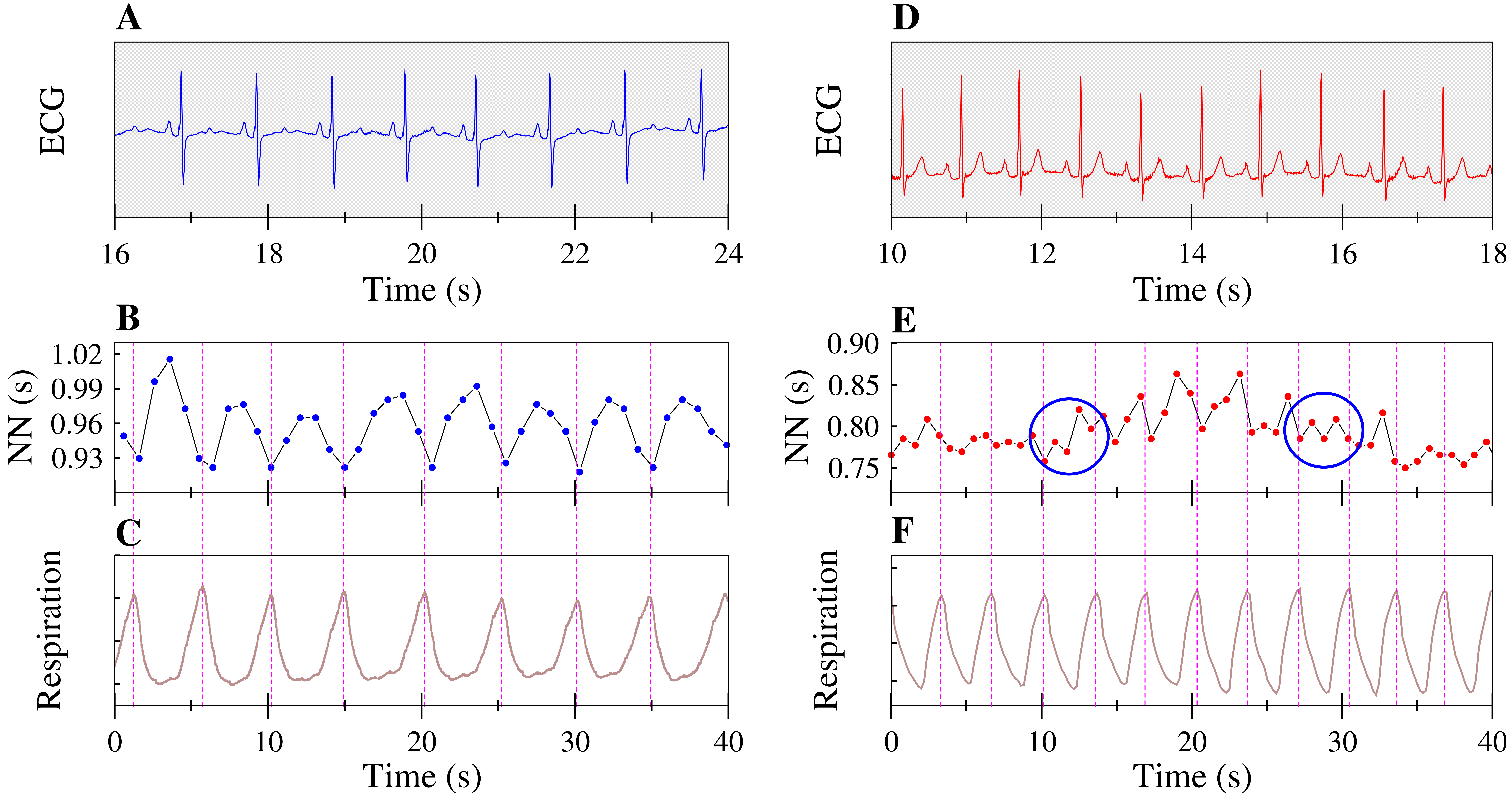


HRF monotonically increases with cross-sectional age





Costa MD, Redline S, Hughes TM, Heckbert SR, Goldberger AL. Prediction of Cognitive Decline Using Heart Rate Fragmentation Analysis: The Multi-Ethnic Study of Atherosclerosis. Front Aging Neurosci. 2021;13:708130.



Costa MD, et al. Am J Physiol Heart Circ Physiol 320: H256–H271, 2021.

Why are traditional variability measures (SDNN, rMSSD, HF) not "good" probes of neuroautonomic control, especially in older individuals?

Because heart rate fragmentation may inflate variability measures.

PIP vs. rMSSD

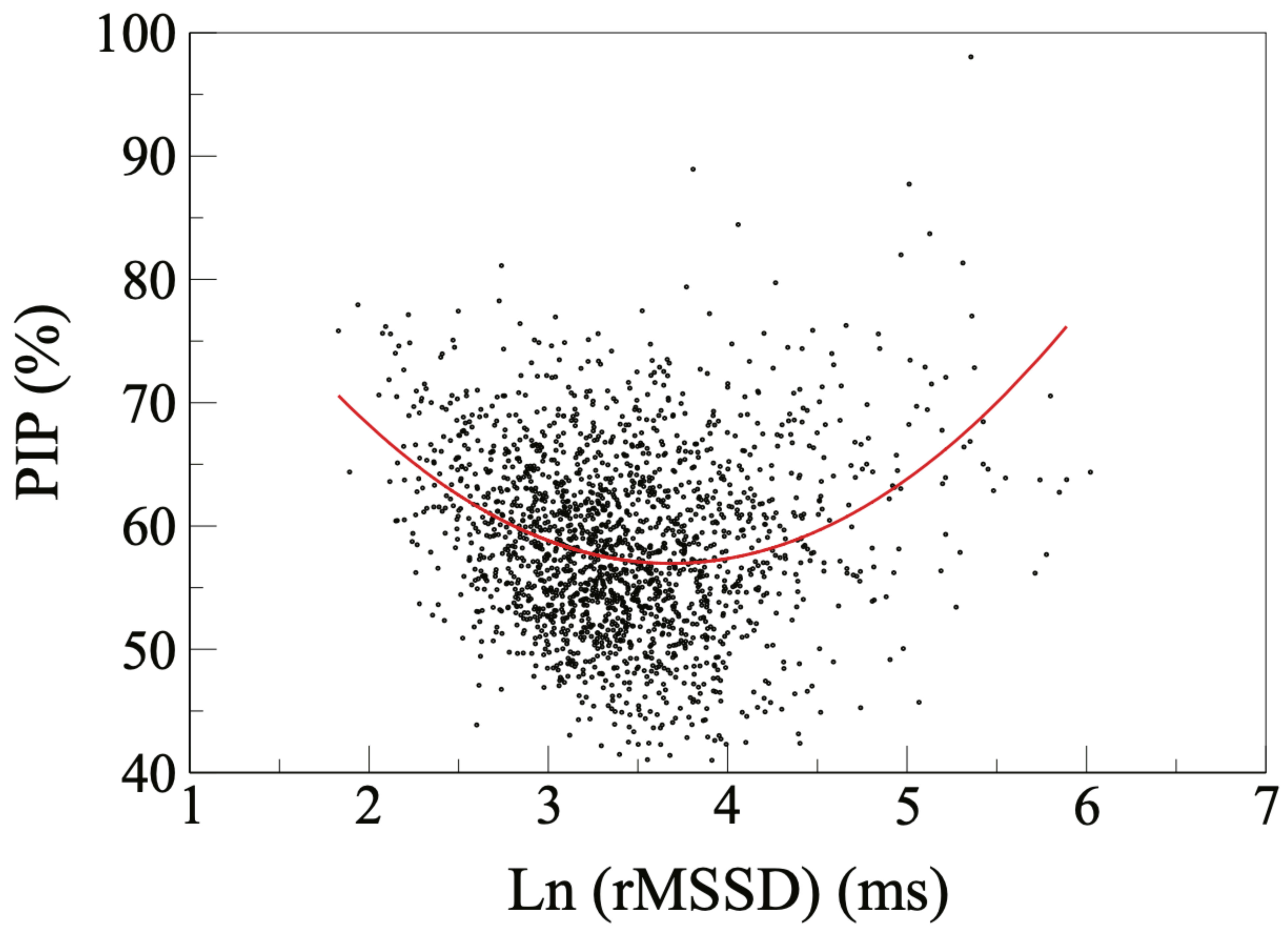


FIGURE 4 | Scatter plot of PIP vs. the natural logarithm of rMSSD. The fitting line is described by the equation:
$\text{PIP} = -26.2 * \ln(\text{rMSSD}) + 3.54 * [\ln(\text{rMSSD})]^2 + 105.3$. The 95% CI for the 1st, 2nd and 3rd terms are: (−30.0 – −22.5), (3.03–4.05) and (98.5–112.1), respectively. PIP, percentage of inflection points; rMSSD, root mean square of the successive differences.

Two independent sources of short-term fluctuations: vagal tone modulation (physiologic) and HRF (pathologic).

Caution!

HRF can confound amplitude-based measures of HR dynamics.

Costa MD, Redline S, Davis RB, Heckbert SR, Soliman EZ, Goldberger AL. Heart rate fragmentation as a novel biomarker of adverse cardiovascular events: The Multi-Ethnic Study of Atherosclerosis. Front Physiol. 2018; 9:1117.

Is HRF a measure of biological age?

If that is the case, HRF should be predictive of adverse outcomes such as CVEs and cognitive decline.

The Framingham CV Risk Score

The FRS estimates the 10 year risk of manifesting clinical CVD (CAD, Stroke, PVD, CHF, cardiac death)

- Age
- Sex
- Anti-hypertensive medication
- Systolic blood pressure
- Total cholesterol
- HDL
- Diabetes
- Smoking

Cardiovascular risk scores had been used to determine who should be offered preventive drugs such as drugs to lower blood pressure or lower cholesterol levels.

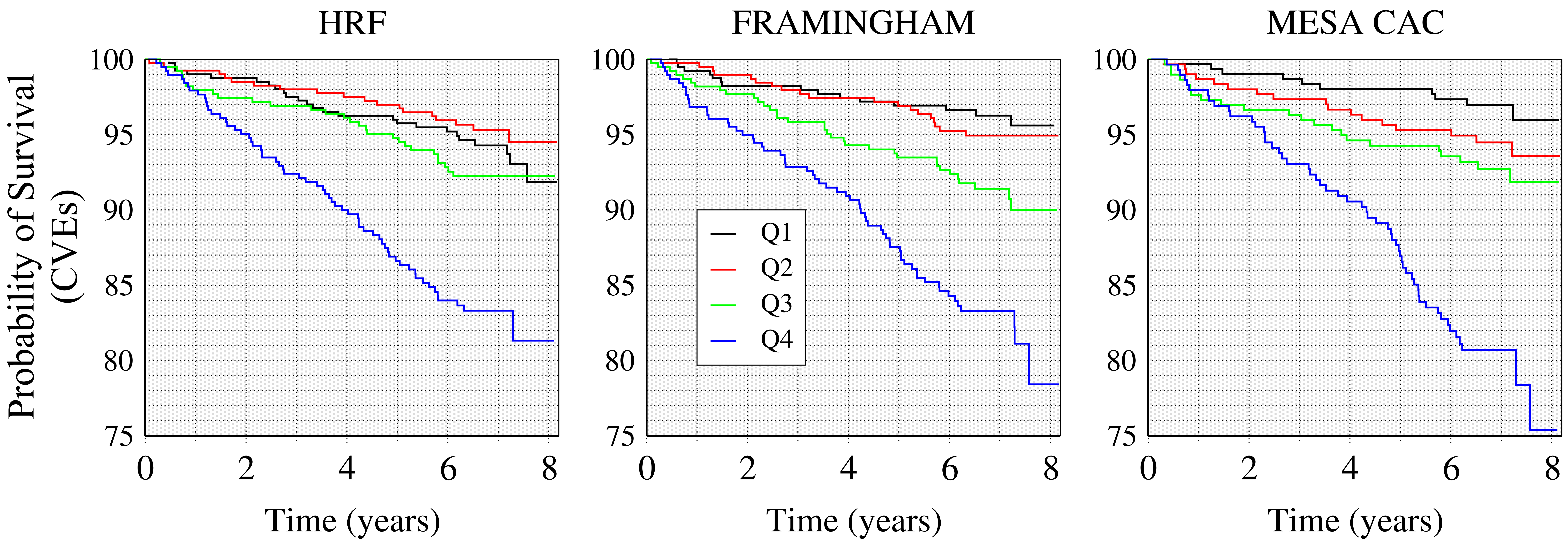
The Multi-Ethnic Study of Atherosclerosis

MESA 10-Year CHD Risk with Coronary Artery Calcification Back to CAC Tools

1. Gender	Male	Female			
2. Age (45-85 years)		Years			
3. Coronary Artery Calcification		Agatston			
4. Race/Ethnicity	**Choose One**				
	Caucasian				
	Chinese				
	African American				
	Hispanic				
5. Diabetes	Yes	No			
6. Currently Smoke	Yes	No			
7. Family History of Heart Attack (History in parents, siblings, or children)	Yes	No			
8. Total Cholesterol		mg/dL	or		mmol/L
9. HDL Cholesterol		mg/dL	or		mmol/L
10. Systolic Blood Pressure		mmHg	or		kPa
11. Lipid Lowering Medication	Yes	No			
12. Hypertension Medication	Yes	No			

Calculate 10-year CHD risk

Prediction of Cardiovascular Events in MESA



Costa MD, et al. Heart Rate Fragmentation as a Novel Biomarker of Adverse Cardiovascular Events: The Multi-Ethnic Study of Atherosclerosis. *Front Physiol*. 2018;9:1117.

Association between nocturnal heart rate variability and incident cardiovascular disease events: The HypnoLaus population-based study

Mathieu Berger, PhD,[*,†] Vincent Pichot, PhD,[†] Geoffroy Solelhac, MD,[*] Pedro Marques-Vidal, MD, PhD,[‡] José Haba-Rubio, MD,[*] Peter Vollenweider, MD,[‡] Gérard Waeber, MD,[‡] Martin Preisig, MD,[§] Jean-Claude Barthélémy, MD, PhD,[†] Frédéric Roche, MD, PhD,[†] Raphael Heinzer, MD[*]

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BACKGROUND Although heart rate variability (HRV) is widely used to assess cardiac autonomic function, few studies have specifically investigated nocturnal HRV.

OBJECTIVE The purpose of this study was to assess the association between nocturnal HRV and cardiovascular disease (CVD) incidence over 4 years in a population-based sample.

METHODS A total of 1784 participants (48.2% men; 58 ± 11 years) from the HypnoLaus population-based cohort free of CVD at baseline were included. Polysomnography-based electrocardiograms were exported to analyze time- and frequency-domain HRV, Poincaré plots indices, detrended fluctuation analysis, acceleration capacity (AC) and deceleration capacity (DC), entropy, heart rate fragmentation (HRF), and heart rate turbulence. Multivariable-adjusted Cox regression analysis was used to assess the association between HRV indices and incident CVD events.

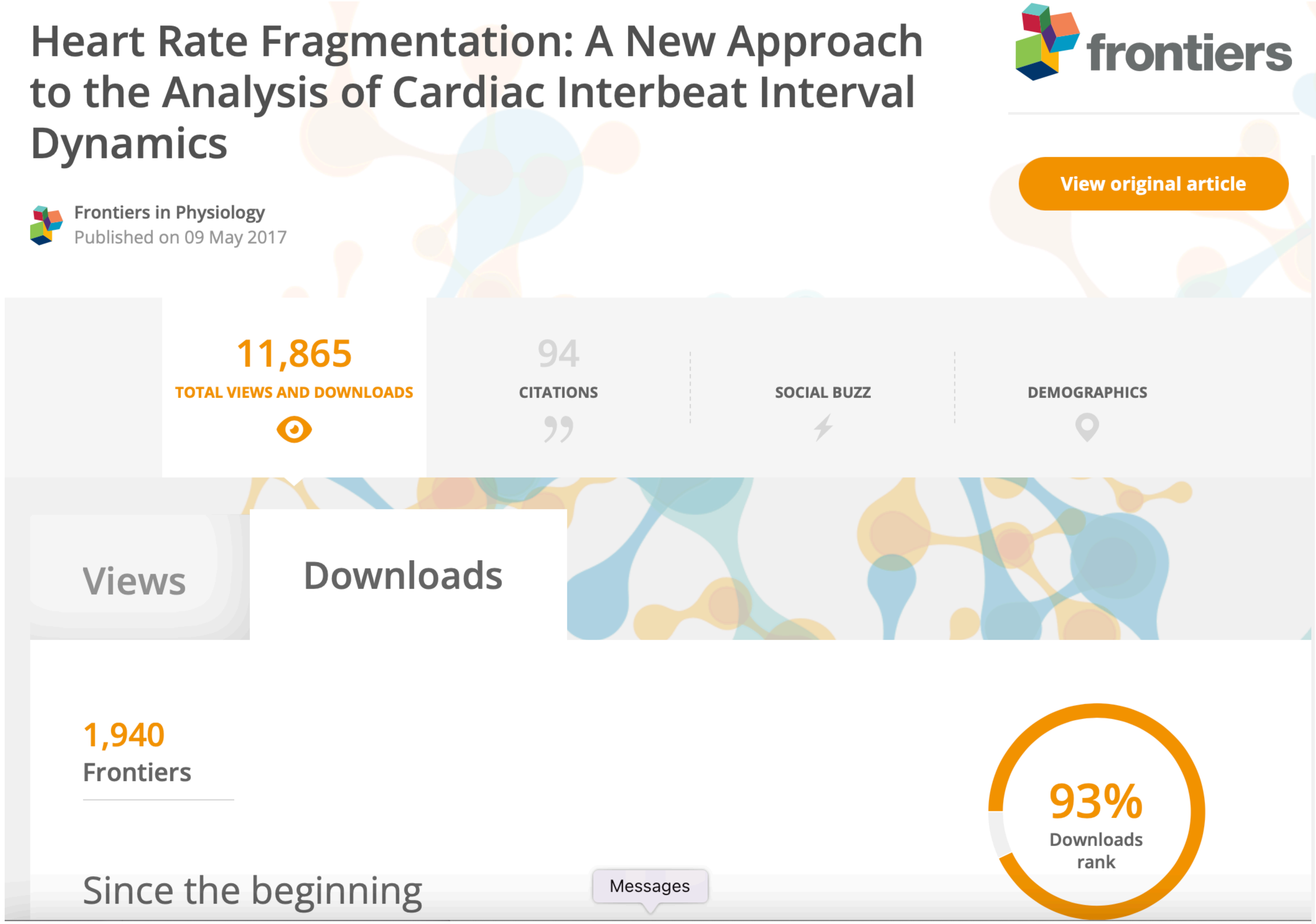
RESULTS Sixty-seven participants (3.8%) developed CVD over mean follow-up of 4.1 ± 1.1 years. In a fully adjusted model, AC (hazard ratio per 1-SD increase; 95% confidence interval: 1.59; 1.17–2.16; $P = .004$), DC (0.63; 0.47–0.84; $P = .002$), and HRF (1.41; 1.11–1.78; $P = .005$) were the only HRV metrics significantly associated with incident CVD events after controlling for false discovery rate.

CONCLUSION Nocturnal novel HRV parameters such as AC, DC, and HRF are better predictors of CVD events than time and frequency traditional HRV parameters. These findings suggest a form of dysautonomia and fragmented rhythms, but further experimental studies are needed to delineate the underlying physiological mechanisms of these novel HRV parameters.

KEYWORDS Cardiovascular disease; Electrocardiogram; Heart rate fragmentation; Heart rate variability; Prospective study; Sleep

(Heart Rhythm 2021;■:1–8) © 2021 Heart Rhythm Society. All rights reserved.

Article's impact



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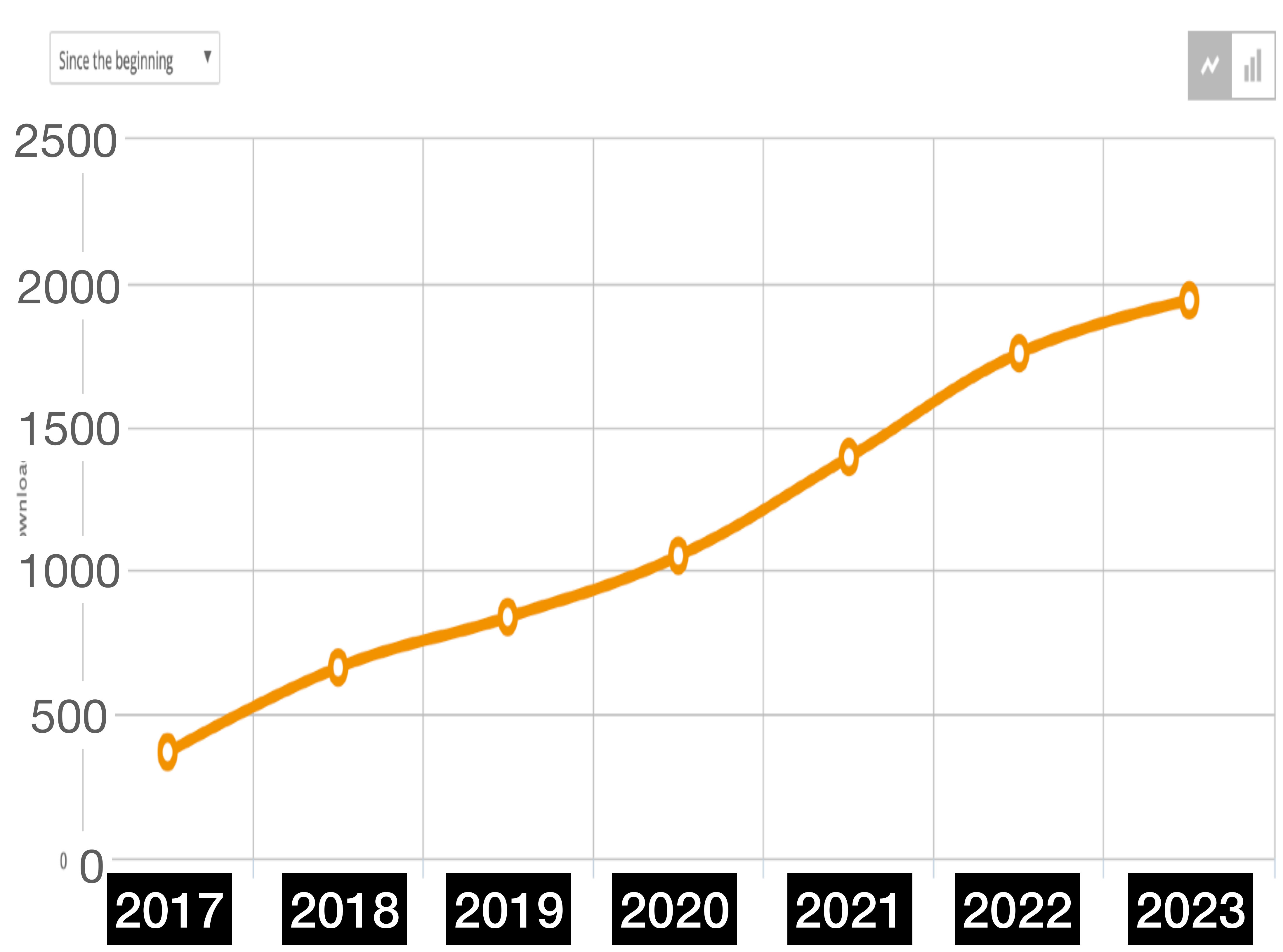
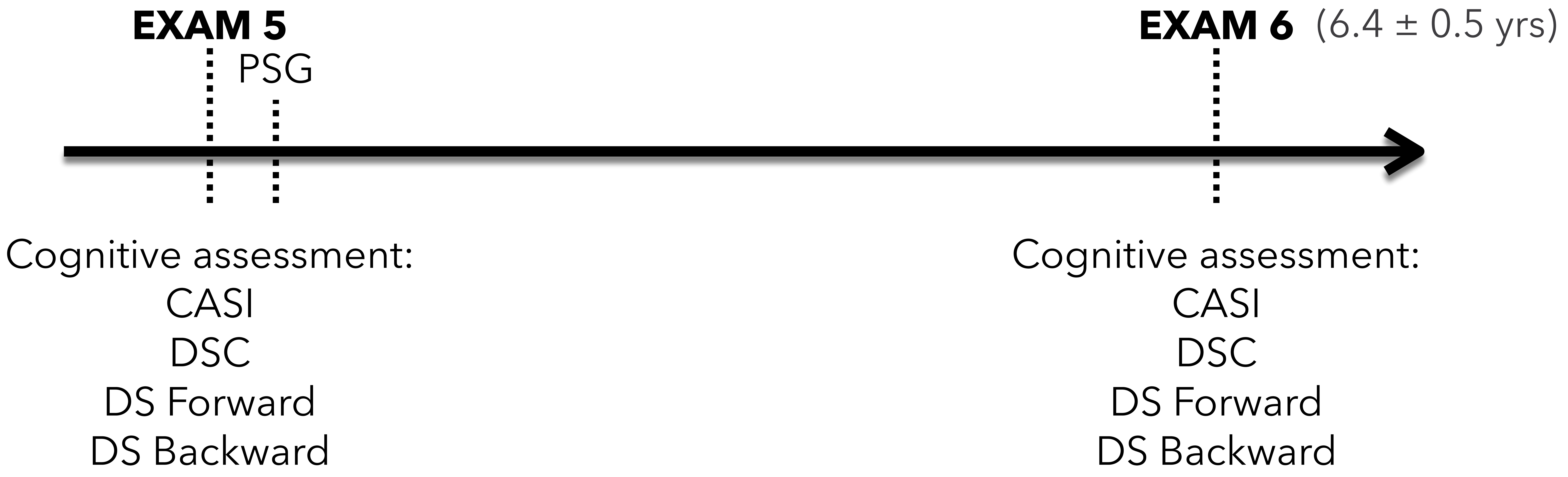
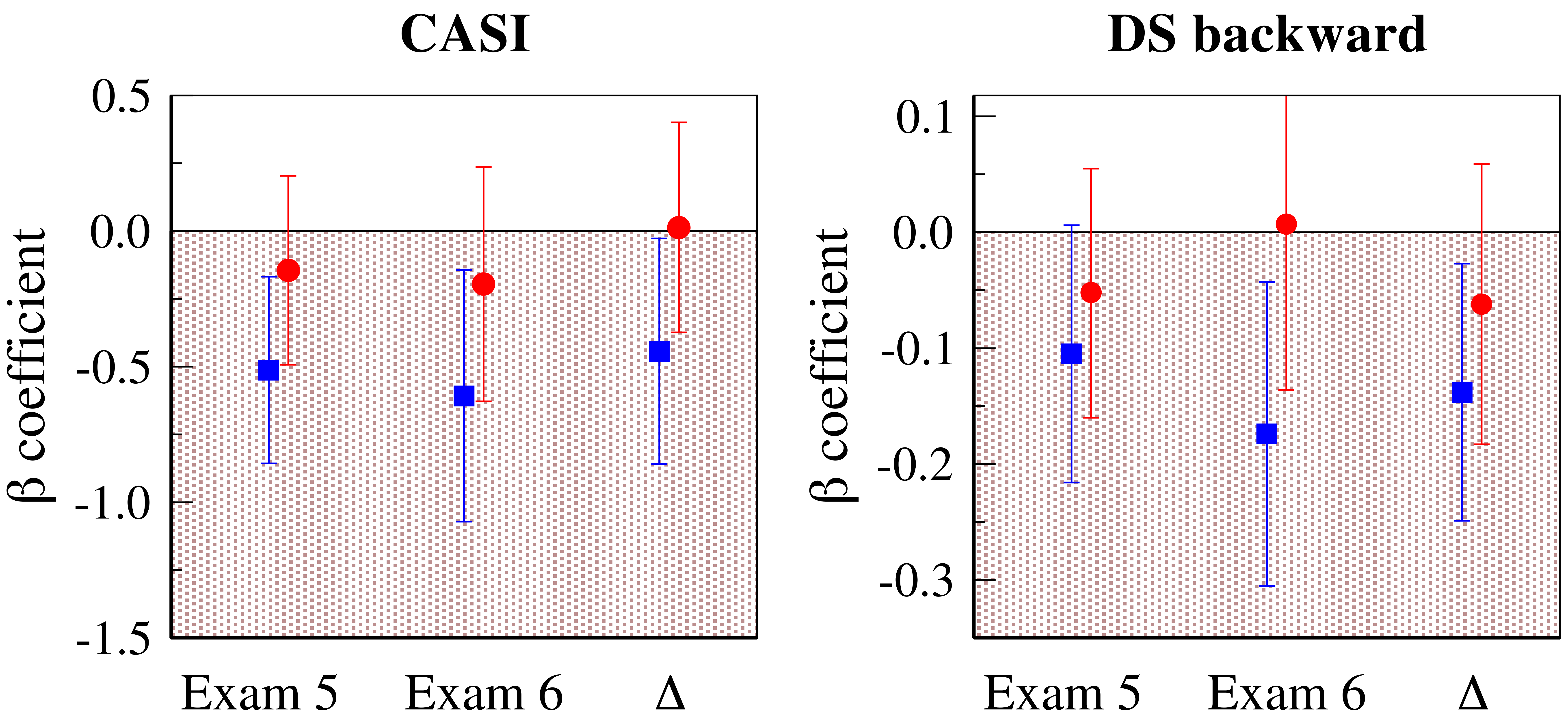


Association of HRF with Concurrent and Future Cognitive Performance



Association of HRF with Cognitive Performance Metrics: Multivariable Linear Regression Models

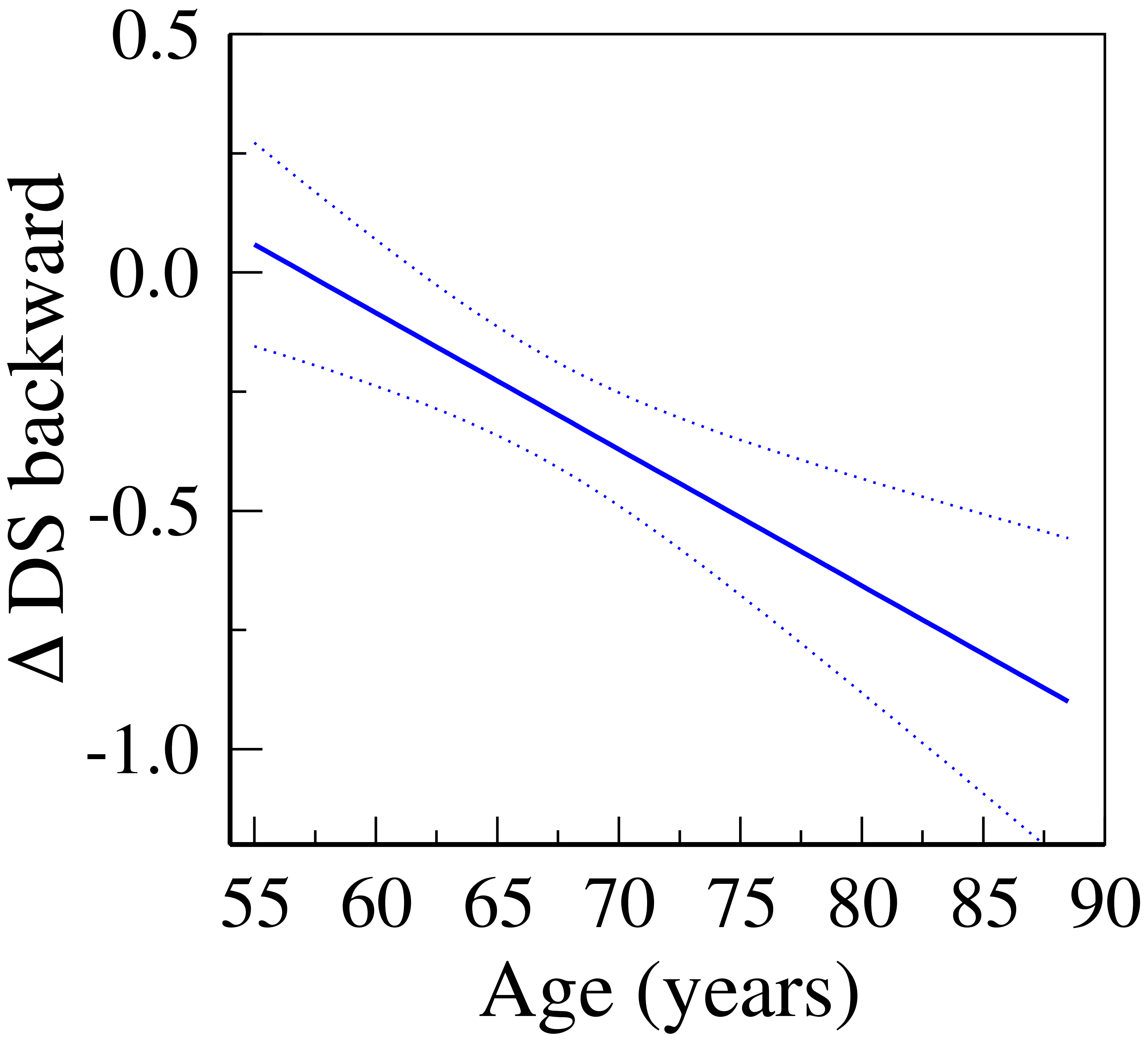


Blue symbols are the results for HRF; **red** symbols are the results for ln rMSSD.

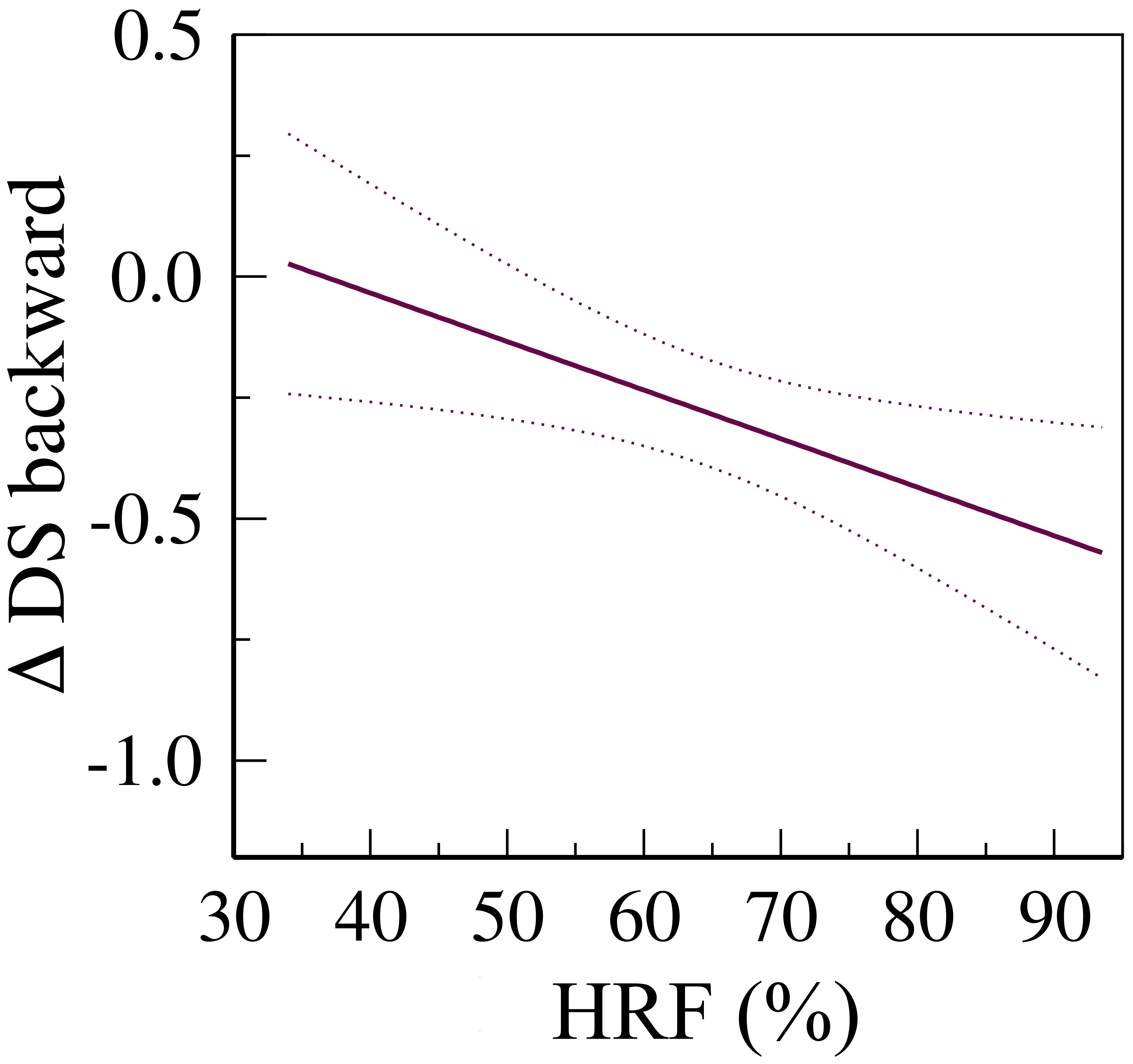
Costa MD et al. Prediction of Cognitive Decline Using Heart Rate Fragmentation Analysis: The Multi-Ethnic Study of Atherosclerosis. *Front Aging Neurosci. 2021;*13:708130.

Cognitive Decline Accelerates with Age as well as with HRF

(A)



(B)



Costa MD et al. Prediction of Cognitive Decline Using Heart Rate Fragmentation Analysis: The Multi-Ethnic Study of Atherosclerosis. *Front Aging Neurosci. 2021;*13:708130.

Older age was associated with larger decrements in cognitive scores.

Higher HRF was associated with larger decrements in cognitive scores.

What does HRF have to do with Balance & Motor Control?

- HRF is an index of parasympathetic functionality
- Breakdown of vagal control, in turn, is a biomarker of biological aging (predictive of cognitive decline, atrial fibrillation and major adverse CVEs, independent of chronological age)
- Autonomic dysfunction is linked to impaired balance and falls through mechanisms that may involve instability of blood pressure control and impaired immune function
- Increased HRF may precede postural instability (hypothesis)

Going back to maxims of our everyday language

“Stay young at heart"