Influences of the Circadian System on Fractal Patterns of Heart Rate Fluctuations

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Outline

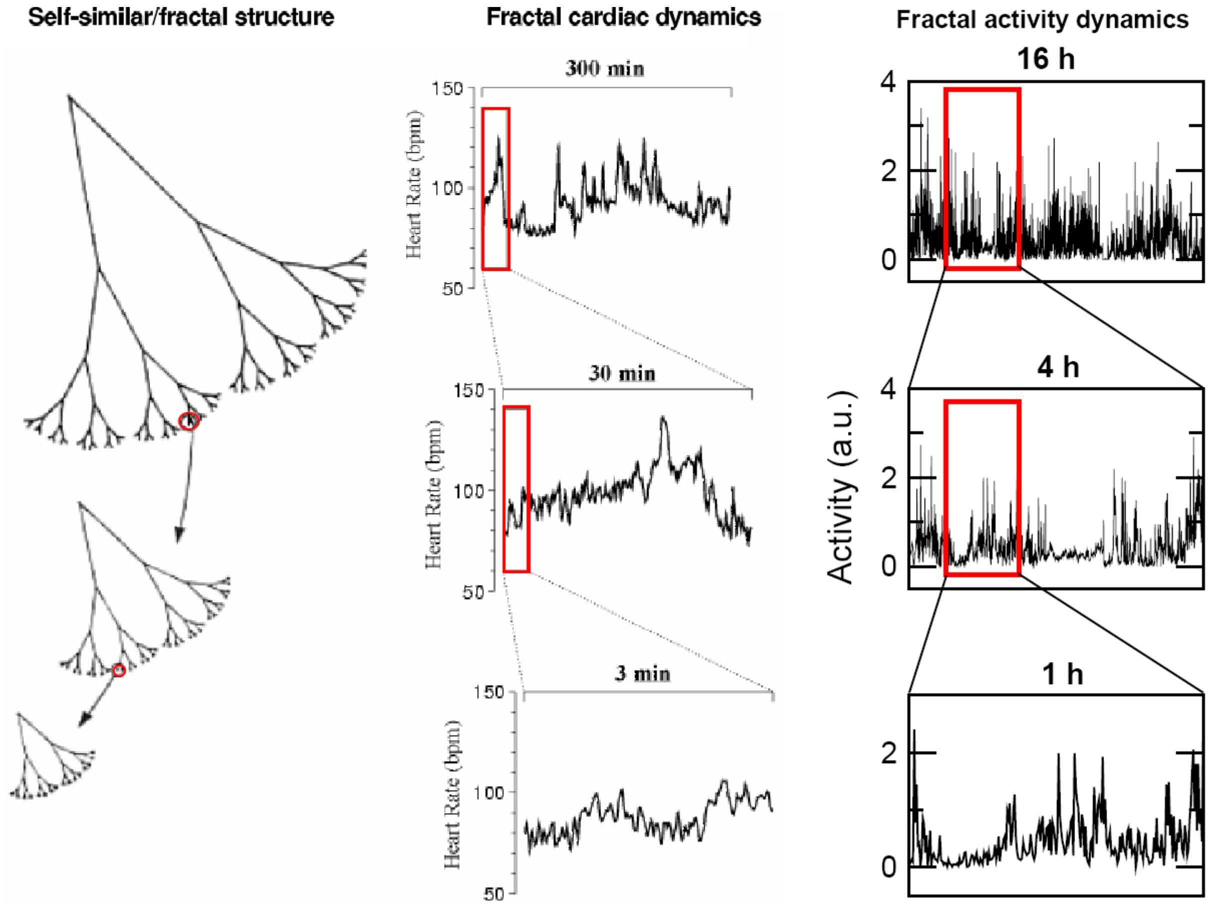
- Concept of *fractal*
- Fractals in physiology (heart rate and motor activity fluctuations)
- Relevance of the circadian system to fractal physiological controls
  - Circadian rhythms of heart rate fractal properties in humans and rats
  - Effects of lesioning the master clock of the circadian system
  - Conceptual neurobiological model of fractal controls

What is fractal?

Fractal: A tree-like object or **process**, composed of sub-units (and sub-sub-units, etc) that resemble the larger scale structure

This internal look-alike property is known as *self-similarity* or *scale invariance*.

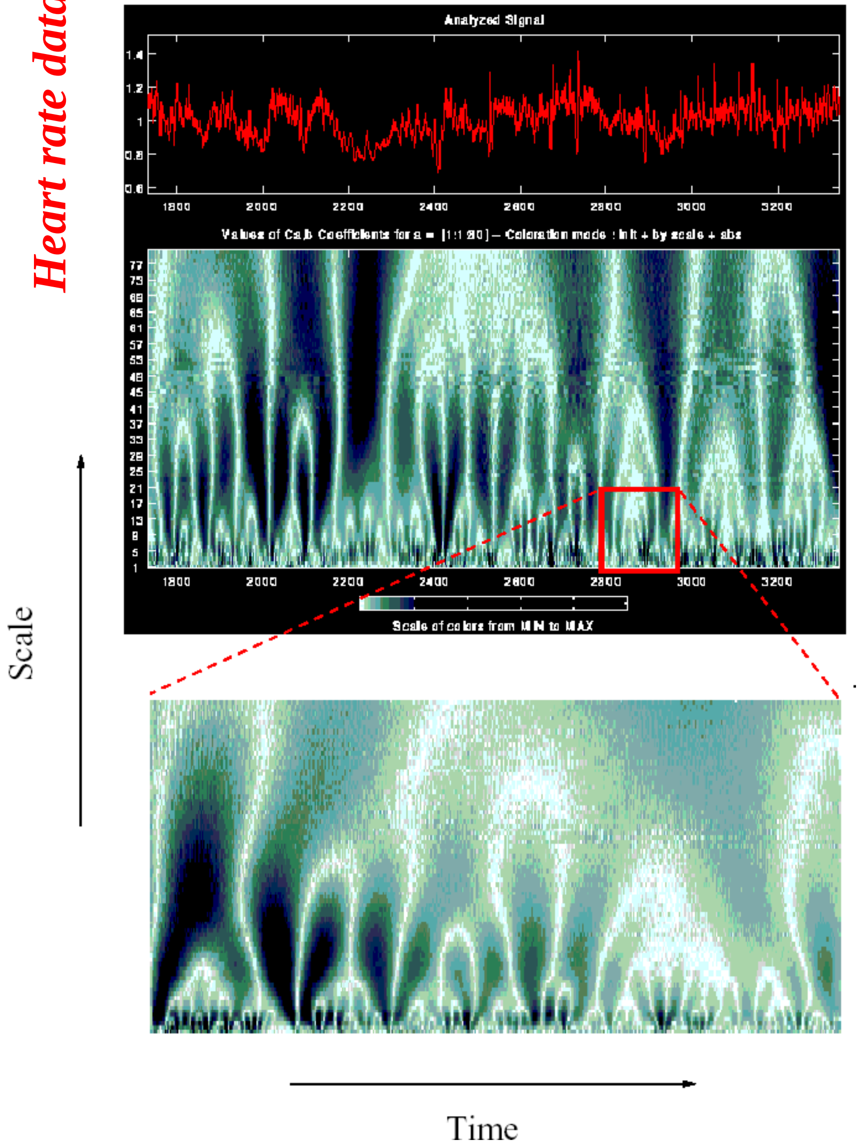
Fractals in Physiology

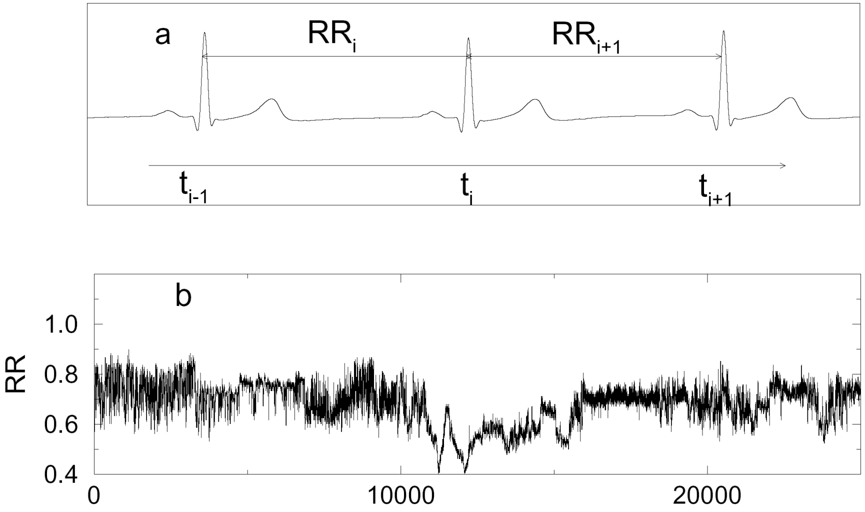


Fractal may be a property of dynamics as well as structure. Fractal fluctuations were observed in a wide range of physiological outputs.

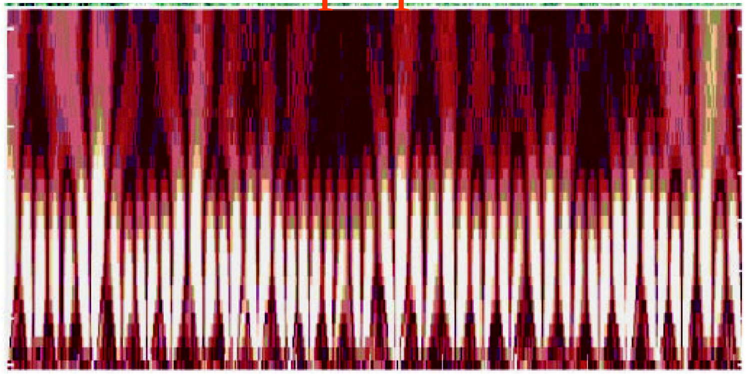
Fractals in heart rate fluctuations

Self-similar cascades





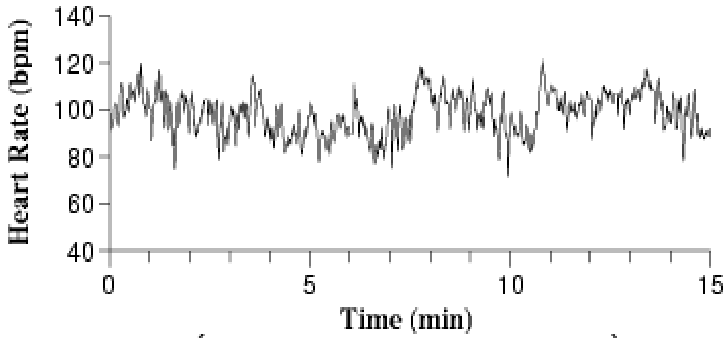
Sleep apnea



P.Ch. Ivanov *et al. Nature* **383**:323 (1996).
P.Ch. Ivanov *et al. Physica A* **249**: 587 (1998).
P.Ch. Ivanov *et al. Chaos* **11**: 641 (2001).

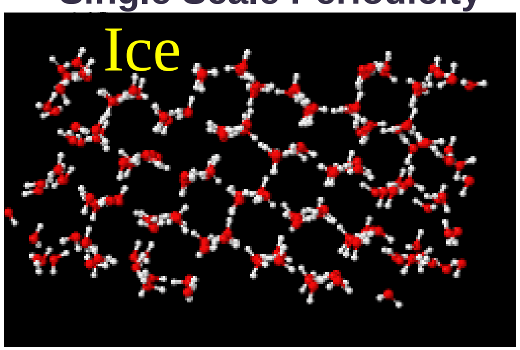
Fractal Complexity Degrades with Disease

Healthy Dynamics: Multiscale Fractal Variability

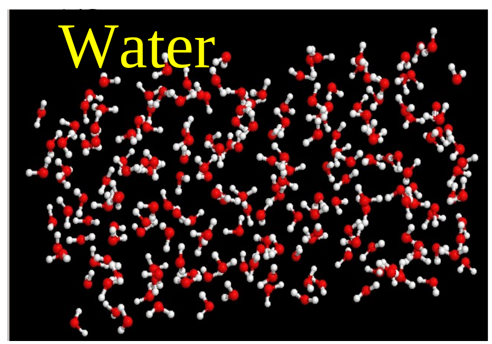


Two Patterns of Pathologic Breakdown

Single Scale Periodicity



Uncorrelated Randomness



- Healthy Heart dynamics poised between too much order and total randomness
- Change or break down under pathologic conditions

Ivanov PCh.*et al.*, Nature 1999; 399:461; Phys Rev Lett 2002; 89 : 068102.
Goldberger AL *et al.*, Proc Natl Acad Sci U S A 2002; 99, 2466-2472.

Homeostasis Revisited

PHYSIOLOGICAL REVIEWS

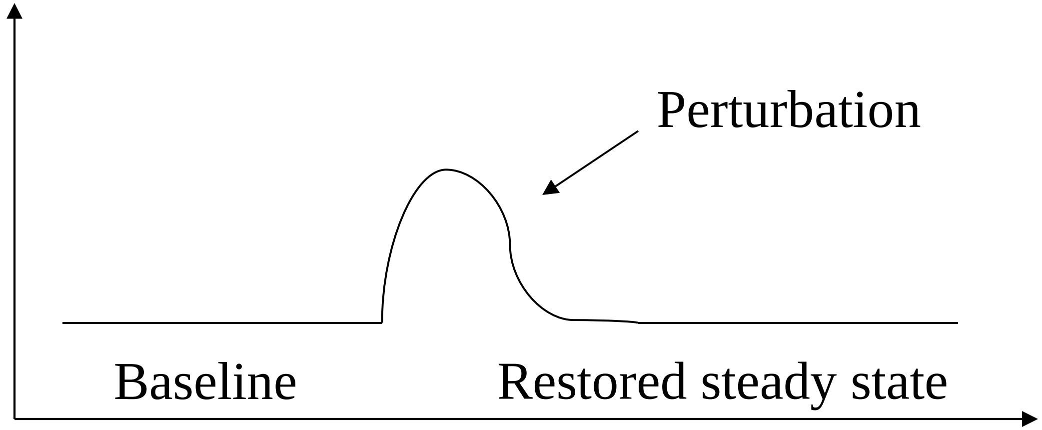
Vol. IX JULY, 1929 No. 3

ORGANIZATION FOR PHYSIOLOGICAL HOMEOSTASIS

WALTER B. CANNON

Body as servo-mechanism type machine

- Importance of corrective mechanisms to keep variables “in bounds.”
- Underlying notion of “constant,” “single steady-state,” equilibrium-like” conditions.



…OR

Homeostasis Revisited

…OR

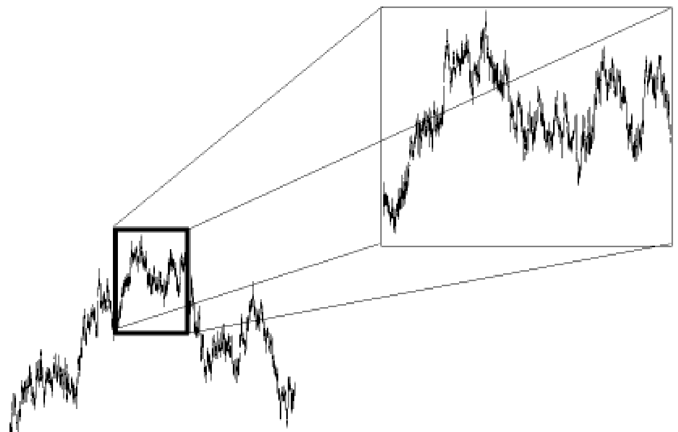
- Is complex spatio-temporal variability a *mechanism* of healthy stability?

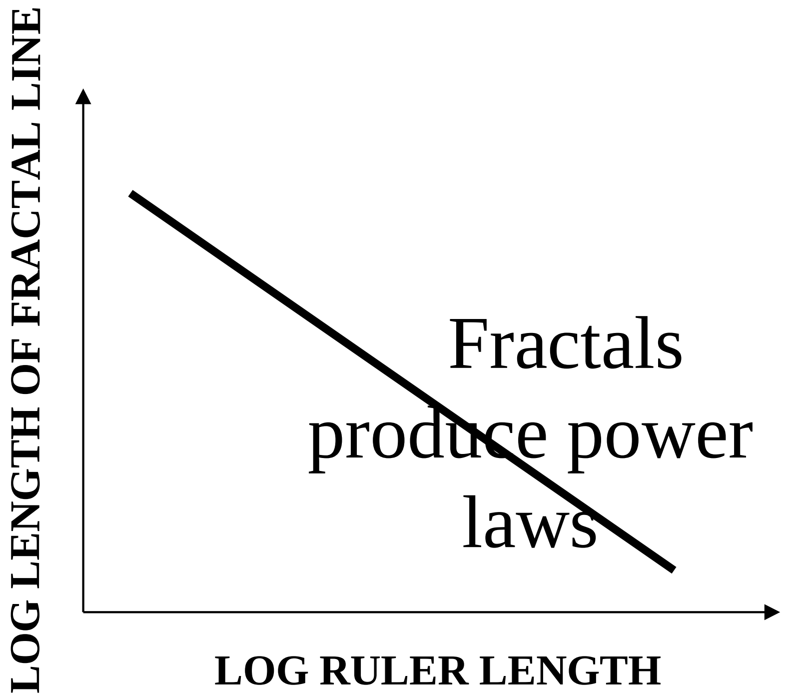
- And, therefore, do we need fundamentally to rethink all notions of mechanisms and causality in physiology

Healthy Dynamics: An Equilibrium State?

Another fallacy. *But* there is an equilibrium state…
…death

Fractals and Power Laws





Method for quantification of fractals

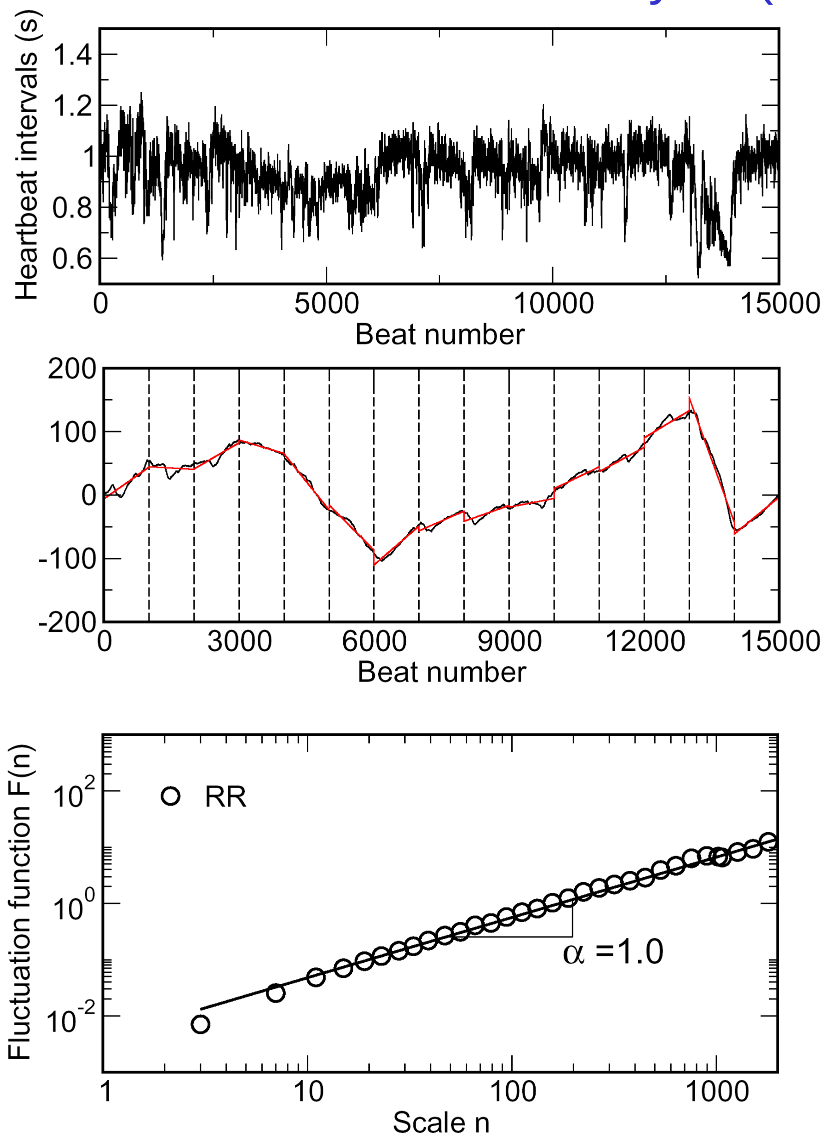
- Box counting (fractal dimension)
- Power spectral analysis
- Hurst analysis
- Root mean fluctuation analysis
- Detrended fluctuation analysis (DFA)
- Detrended moving average analysis
- Wavelet-based multifractal analysis

…

Hu K, *et al.*, *Phys. Rev. E* **64**, 011114 (2001)
Chen Z, *et al.*, *Phys. Rev. E* **65**, 041107 (2002)
Chen Z, et al., Phys. Rev. E **71,** 011104 (2005)
Xu L, et al., Phys Rev E **71**:851101 (2005)

Method for quantification of fractals:

Detrended fluctuation analysis (DFA)



Peng CK, *et al.*, *Phys. Rev. E* **49,** 1685-89, 1994.

Quantification of fluctuations at different window size

- Remove mean
- Integrate
- Detrend using polynomial functions in all windows
- Obtain average fluctuations

Log-log plot (power-law form indicates scale invariance)

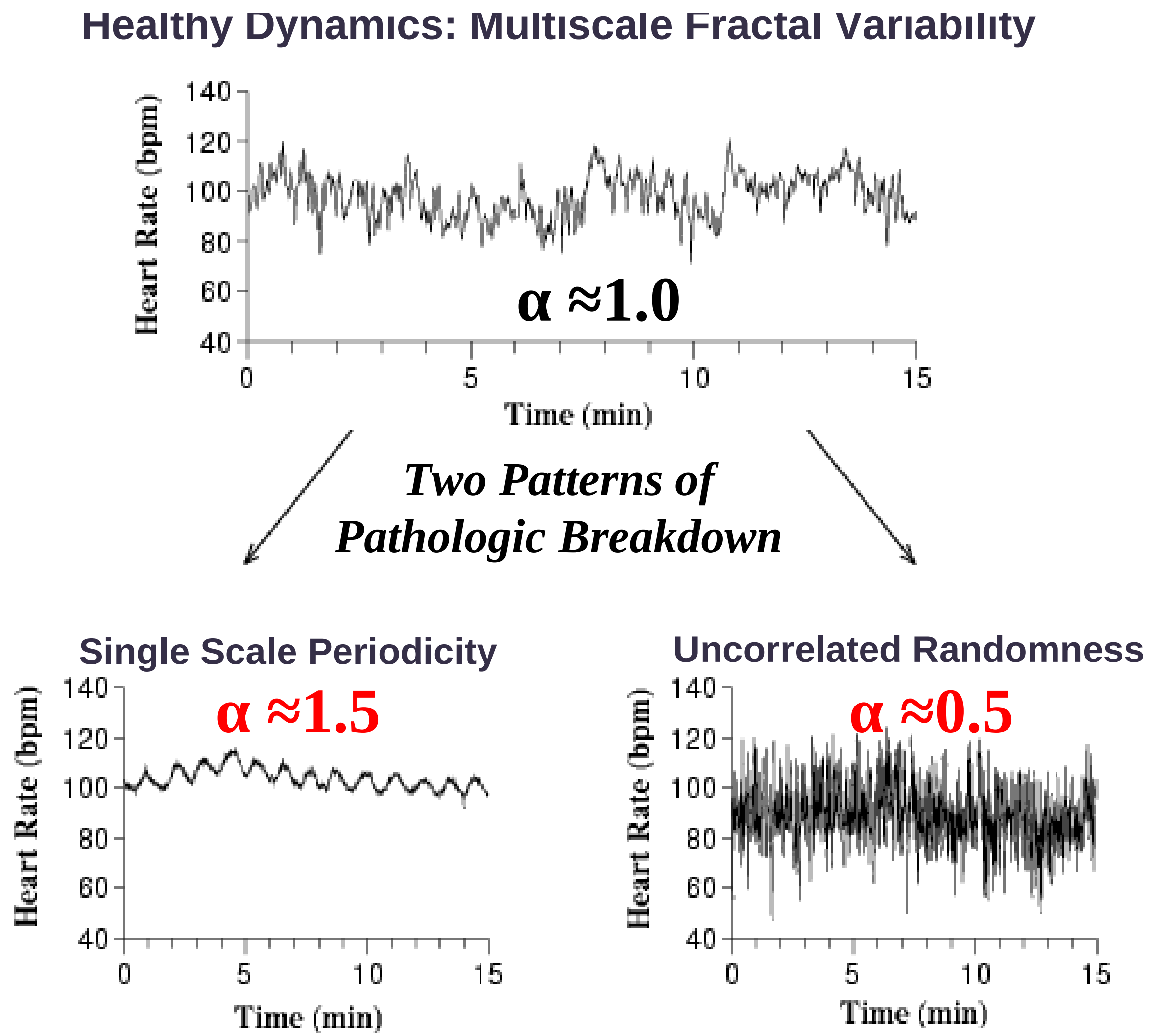
Scaling exponent reveals correlation property:

α=1.0 : the most complex fractal correlations

α=1.5: a random walk (Brownian noise)

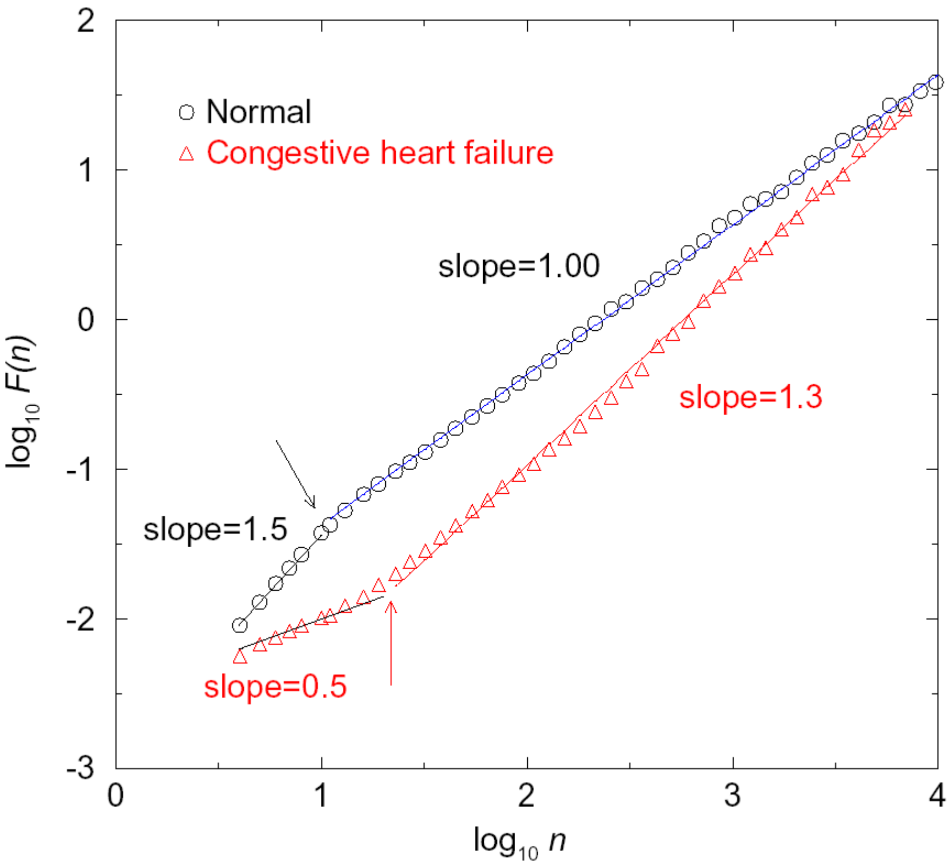
α=0.5 : a white noise

Scaling exponent as an index of fractal correlation properties



Scaling exponent α indicates correlation properties in fluctuations.

Degraded fractal correlations under pathologic conditions



Congestive heart failure :

$\alpha \approx 1.3$ for $30\sim10^4$ beats

closer to a random walk.

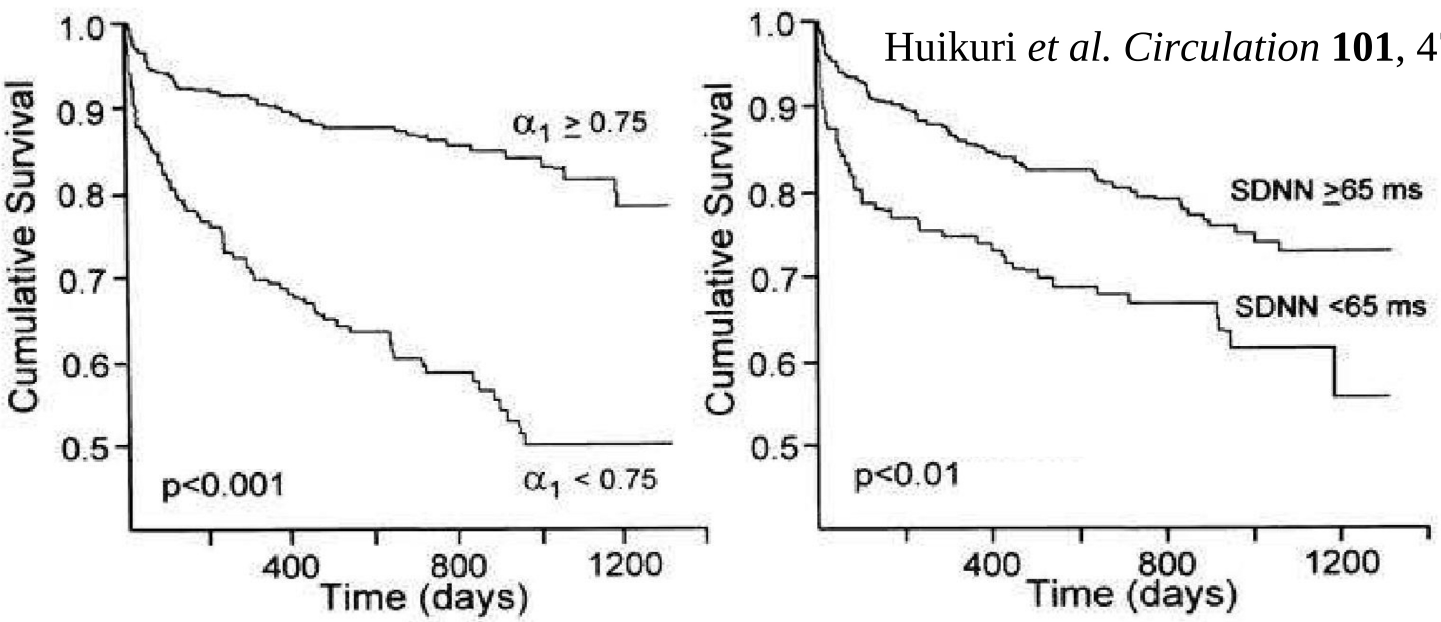
Peng CK. *et al., Chaos* **5**, 82 (1995);

Peng CK *et al., J. Electrocardiol.* **28,** 59 (1996).
Turcott RG, Teich MC, *Ann. Of Biomed. Eng.* **24**, 269 (1996).
Ho KKL. *et al., Circulation* **96**, 842 (1997).
Mietus JE *et al., Comp. Cardiol.* **27,** 753 (2000).

Clinical Utility of DFA:

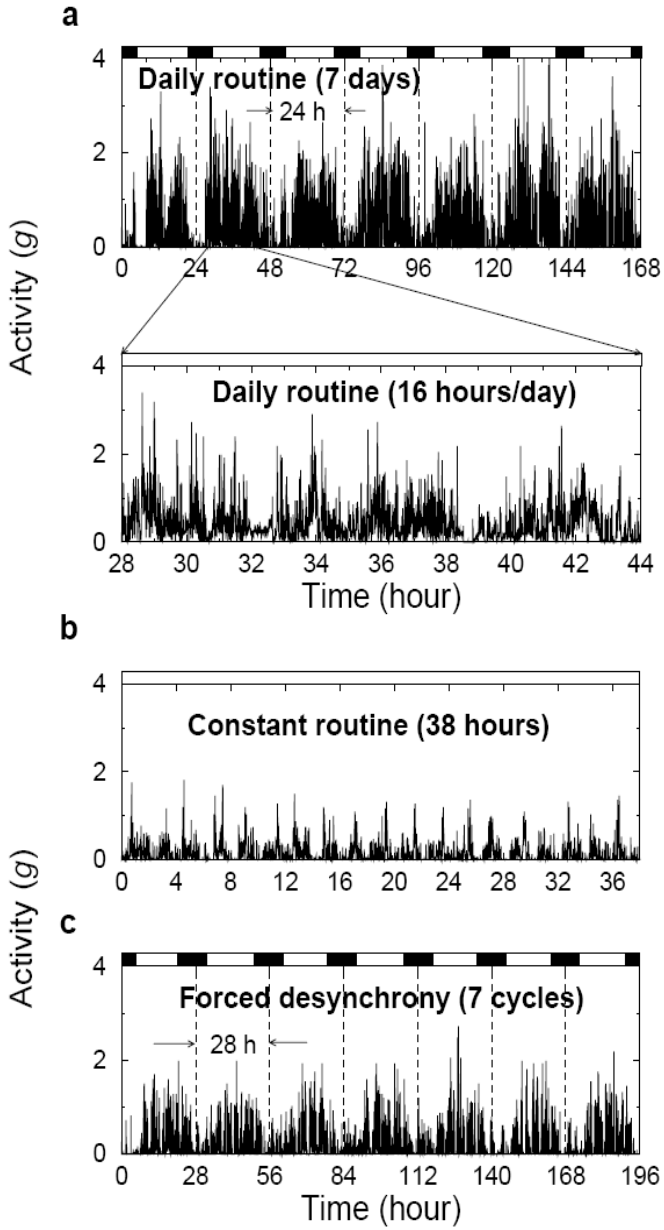
Fractal cardiac dynamics (DFA) can also predict

- survival rate of patients after myocardial infarction (Huikuri *et al. Circulation* **101**, 47, 2000).
- mortality of patients after stroke (Makikallio AM *et al. Neurology* **62**, 1822-1826, 2004)
- successful defibrillation in patients with out-of-hospital cardiac arrest (Lin LY *et al. Resuscitation* **81**, 297-301, 2010)

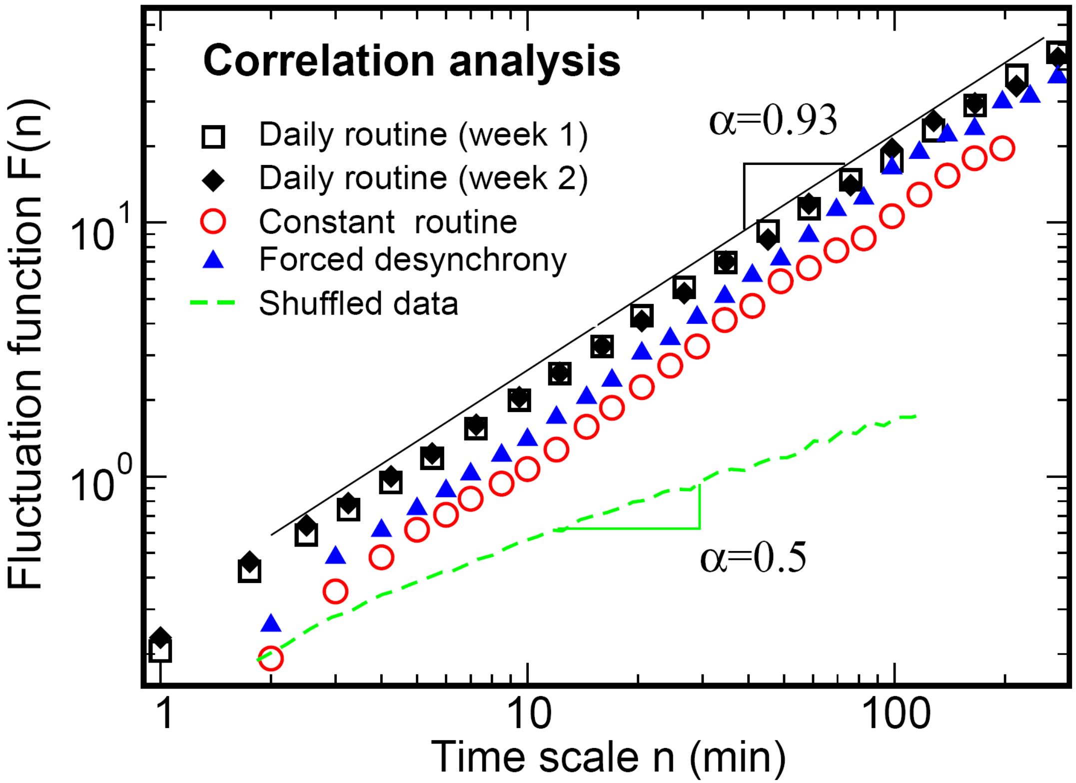


Huikuri *et al. Circulation* **101**, 47, 2000

Human motor activity fluctuations



Fractal correlations in human motor activity fluctuations



- Strong correlations (α > 0.5 and close to 1)
- Stable over a wide range of time scales
- Independent of scheduled events and mean activity levels

Hu *et al.*, Physica A **337**, 307-18 (2004).

Human studies

1. Young control :

2. Elderly control:

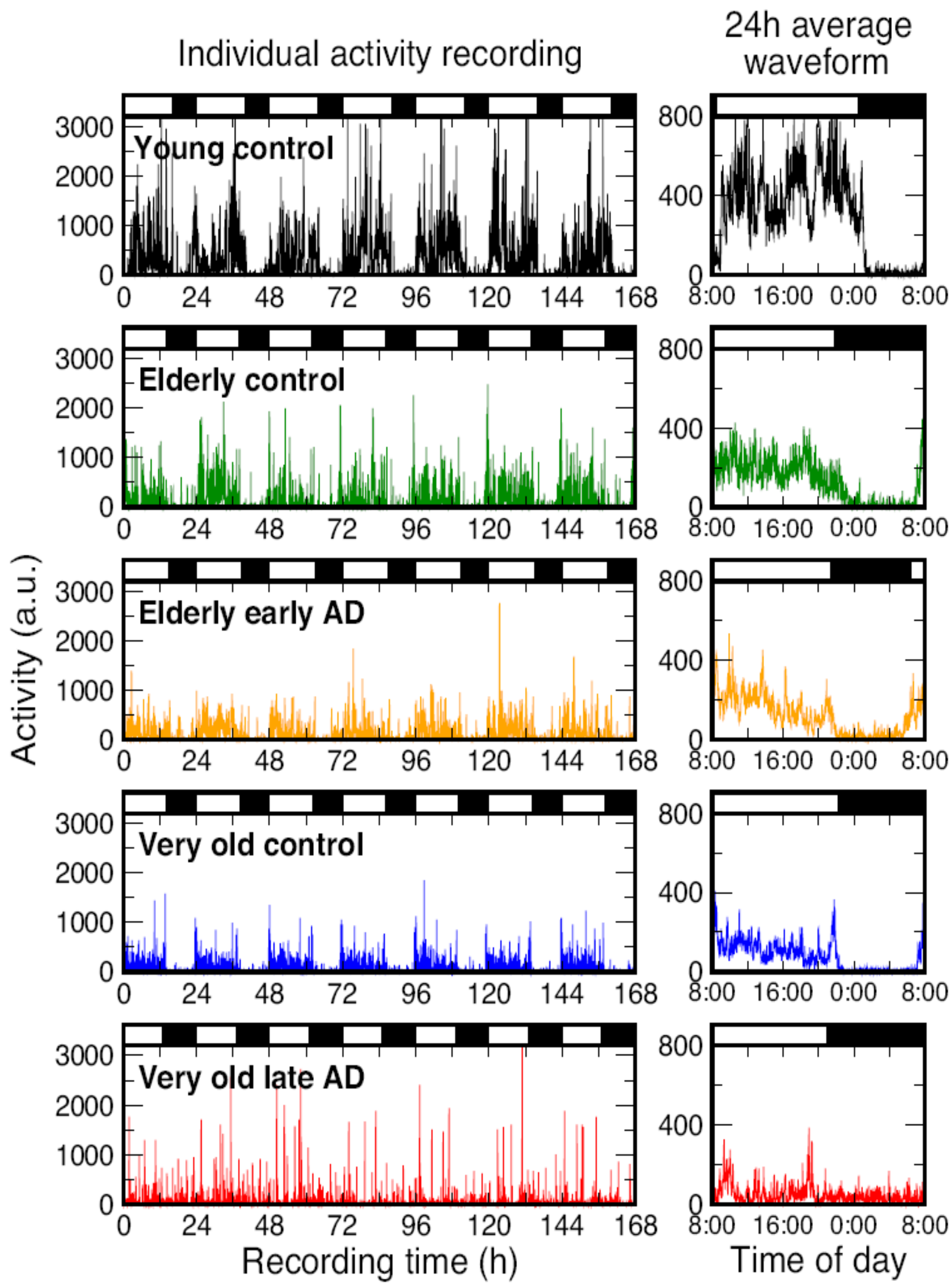
Age-matched

3. Elderly Early-stage AD:

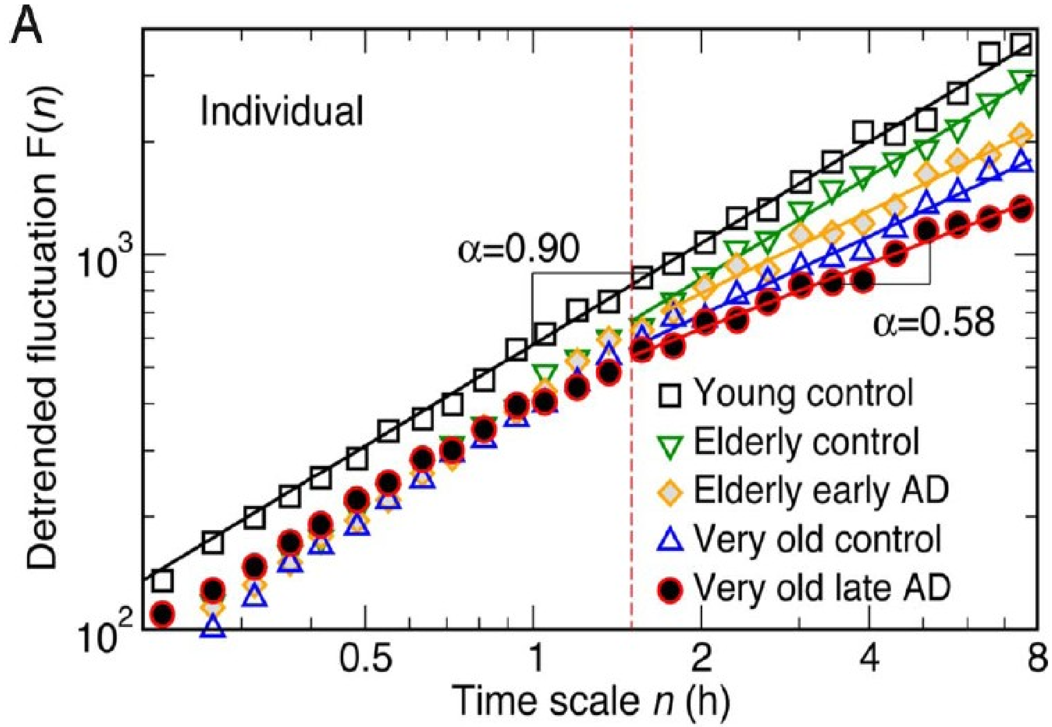
4. Very old control:

Age-matched

5. Very old Late-stage AD:



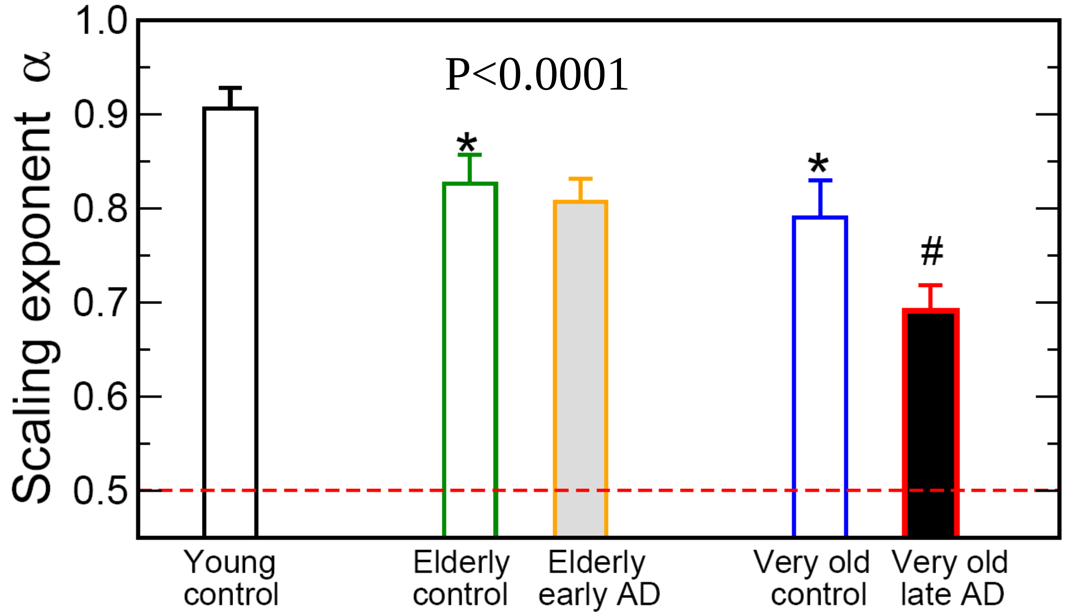
Altered activity fractal fluctuations with aging and AD



- Robust scale-invariant patterns at time scales from minutes to 10 h in young control
- Similar patterns in other groups at small time scales (<1 h)
- Reduction in fractal correlations at >~2h with aging and AD

Hu K *et al*. Proc Natl Acad Sci. 2009; 106(8): 2490-2494

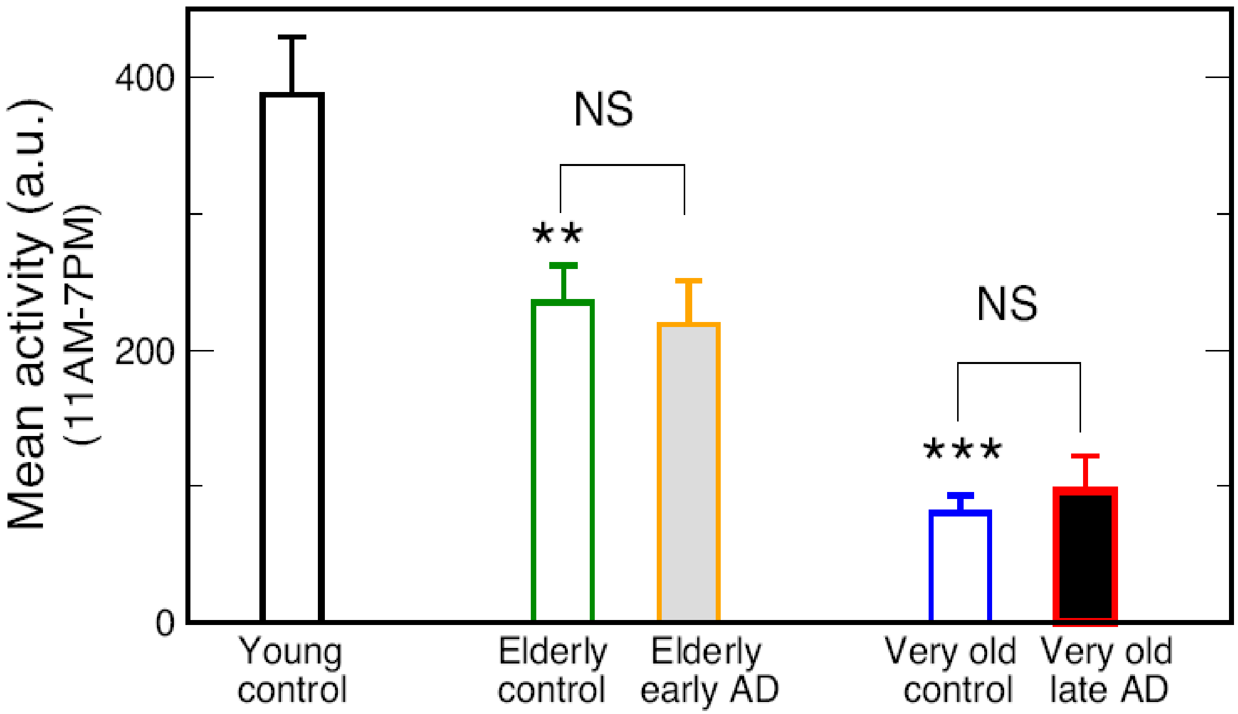
Effect of aging and AD on fractal activity correlations



- There was significant group effect ($p<0.0001$)
- The elderly control and very old control subjects had smaller α values than young controls, as indicated by * ($p<0.05$).
- Early-stage AD subjects and age- and living condition-matched elderly controls showed no significant difference.
- Late-stage AD subjects has significantly smaller α than the age- and living condition-matched very old controls, as indicated by # ($p<0.05$).

Hu K *et al*. Proc Natl Acad Sci. 2009; 106(8): 2490-2494

Effect of aging and AD on the scale-invariant activity regulation



Why is it healthy to be fractal?

- Healthy function requires capability to cope with the unpredictable
- Scale-invariant systems generate broad repertoire of responses & long-range correlations $\rightarrow$ adaptability & plasticity
- Absence of characteristic time scale helps prevent mode-locking (pathologic resonances)

Neurobiological circuitry unknown and meaningful models lacking!

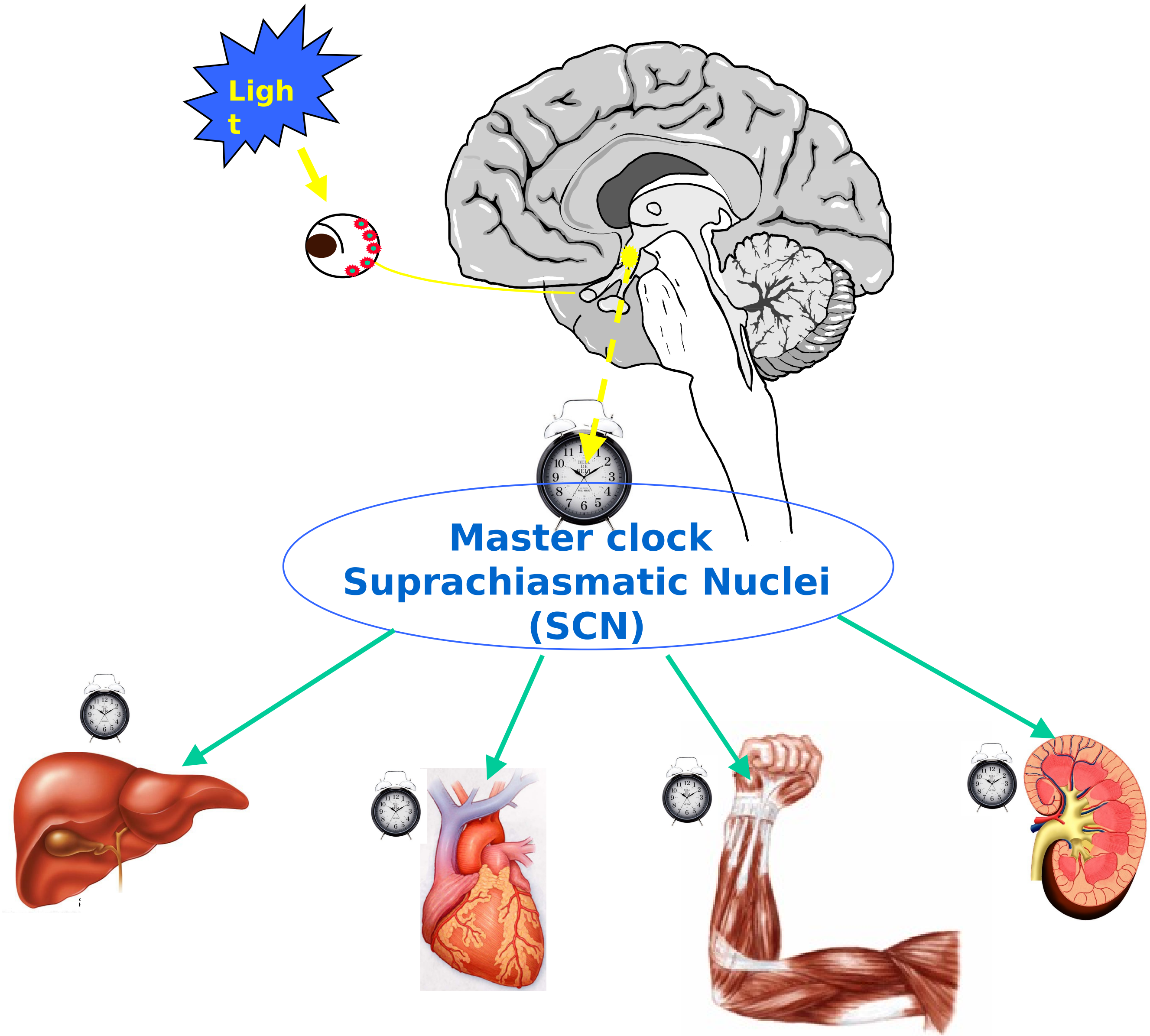
"Understanding scale invariance (fractal) *is one of the top five great ideas in biology ..."*

Sir Paul Nurse,

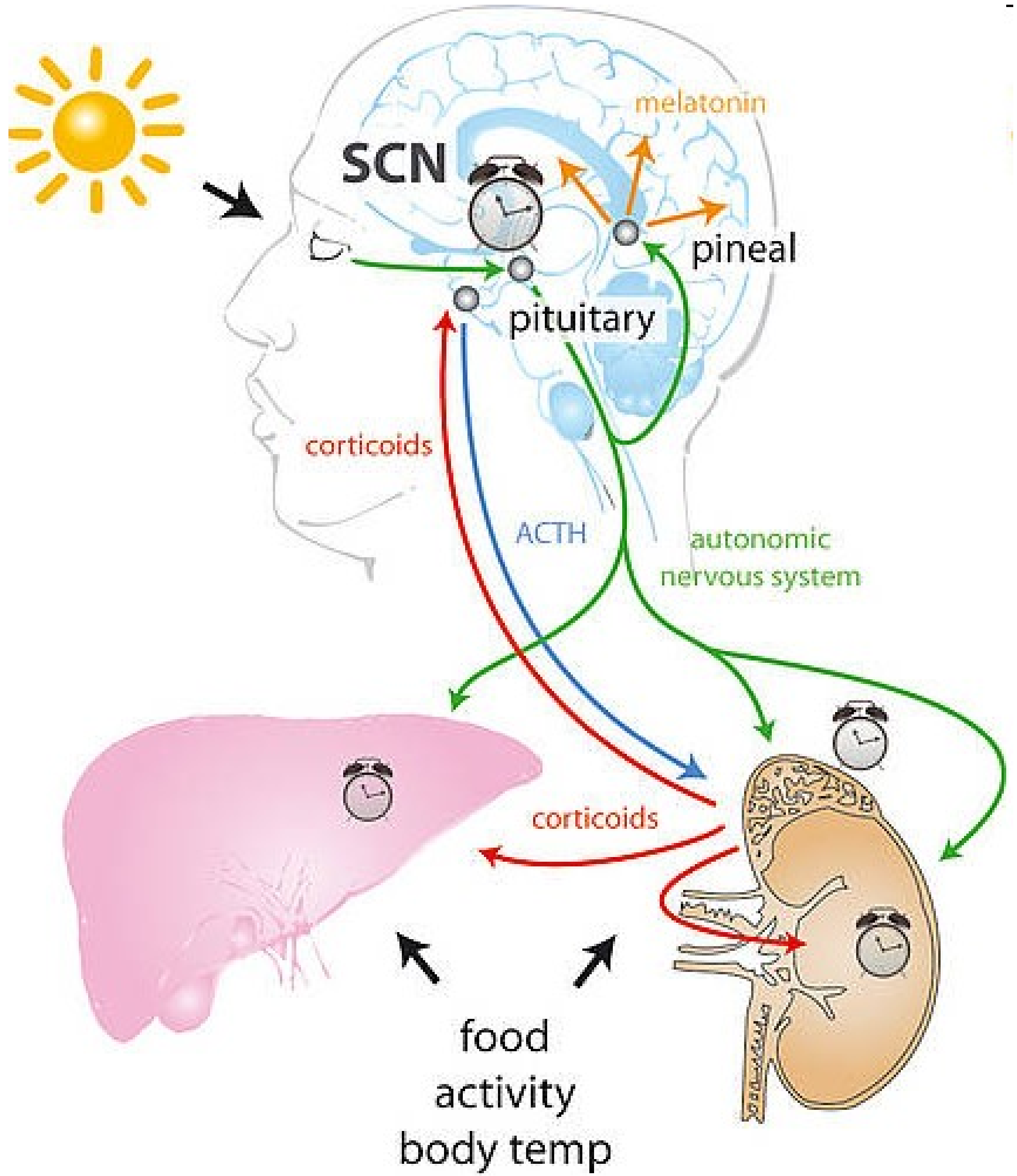
(winner of the 2001 Nobel Prize in Physiology or Medicine)

http://estream.med.harvard.edu:8080/ramgen/Content/CustomVideo/Leaders_in_Biomedicine/C_03202007105445.rm

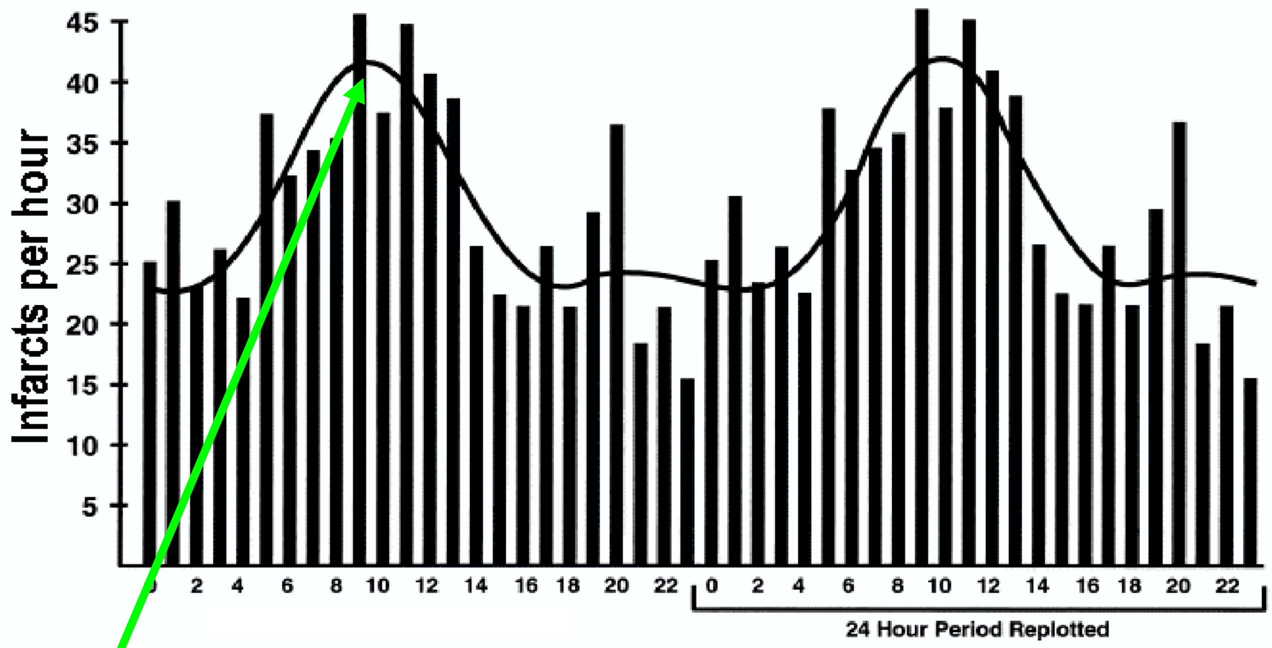
Effects of the circadian system on physiological functions



Coordinated rhythms of ~24 h in Physiological functions


melatonin
SCN
pineal
pituitary
corticoids
ACTH
autonomic
nervous system
corticoids
food
activity
body temp

Daily pattern of cardiac risk



Muller JE, *et al., N. Eng. J. Med.* **313,** 1315 –1322 (1985).

Highest cardiac vulnerability/heart attacks at 9-11 AM

Internal physiologic factors

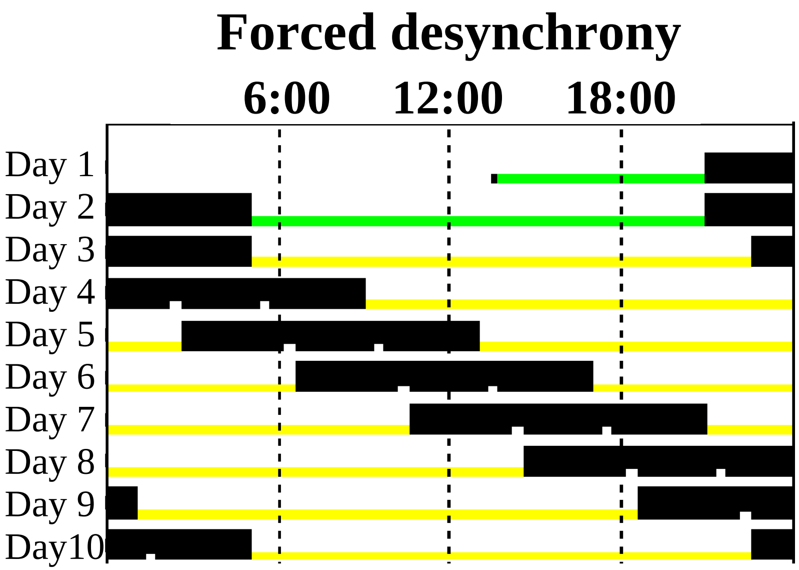
External activity factors

How to separate these two factors ?

Experimental methods to distinguish the effects of intrinsic circadian system from behaviors

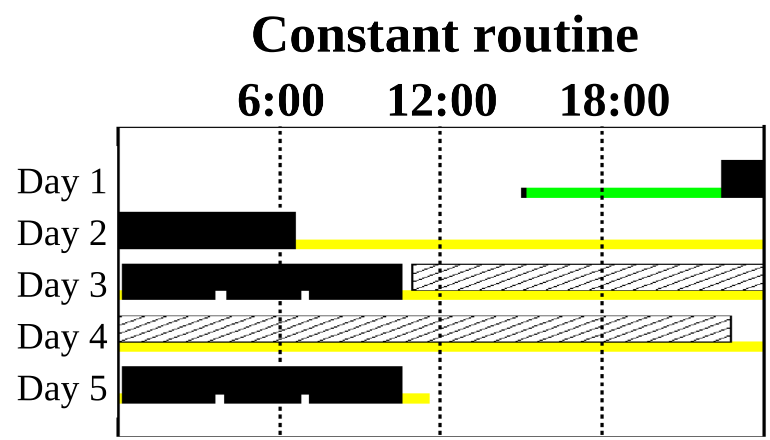
Data was collected in two complementary protocols performed in dim light:

Behavior cycles were uniformly distributed across all circadian phases



5 healthy subjects; Sleep period delayed 4 hours each day; Same scheduled behavior in 28-h sleep/wake cycles.

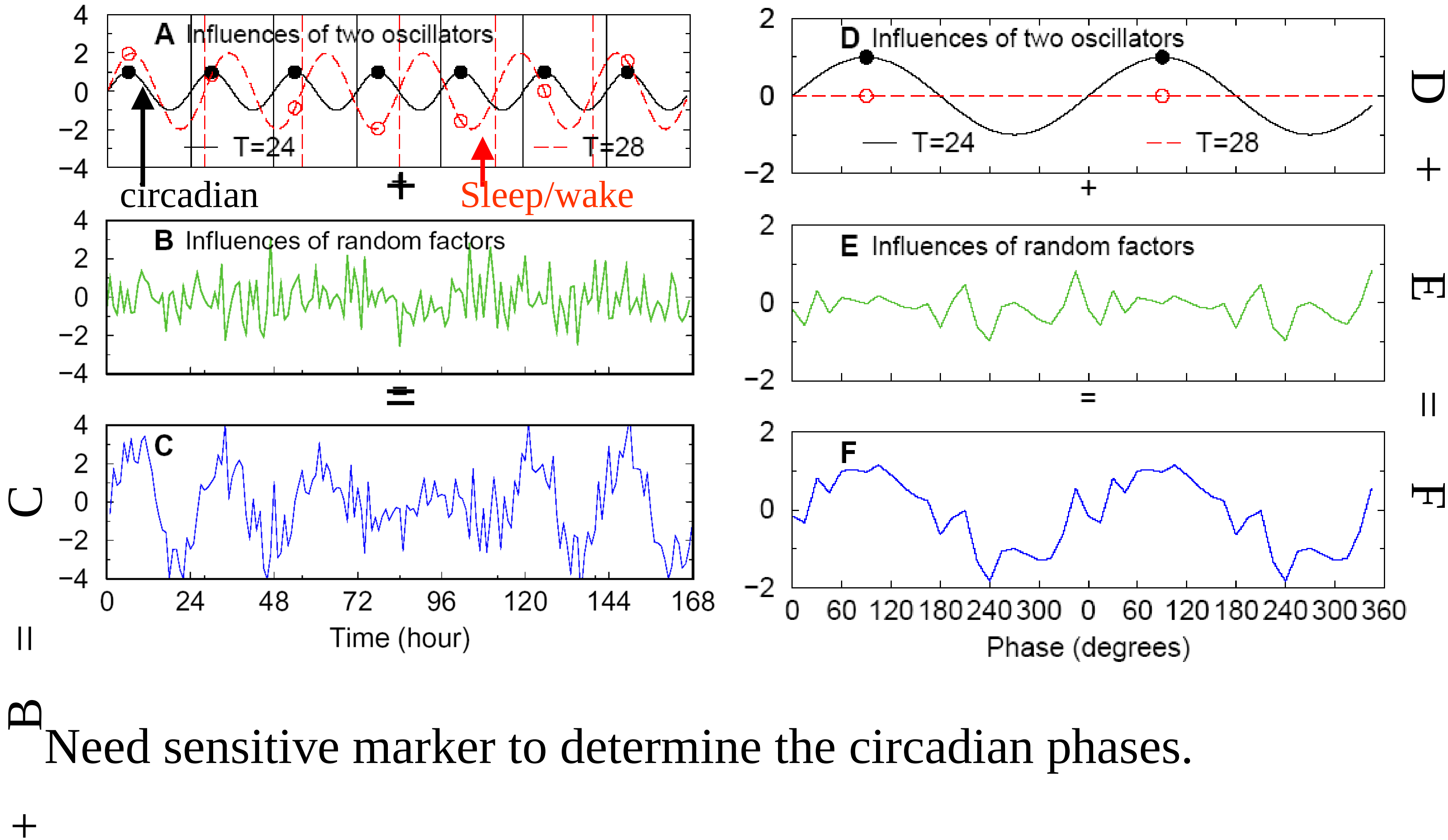
Behavior was kept constant



9 healthy subjects; Semi-recumbent and awake for 38 hours; identical snacks provided every 2 h.

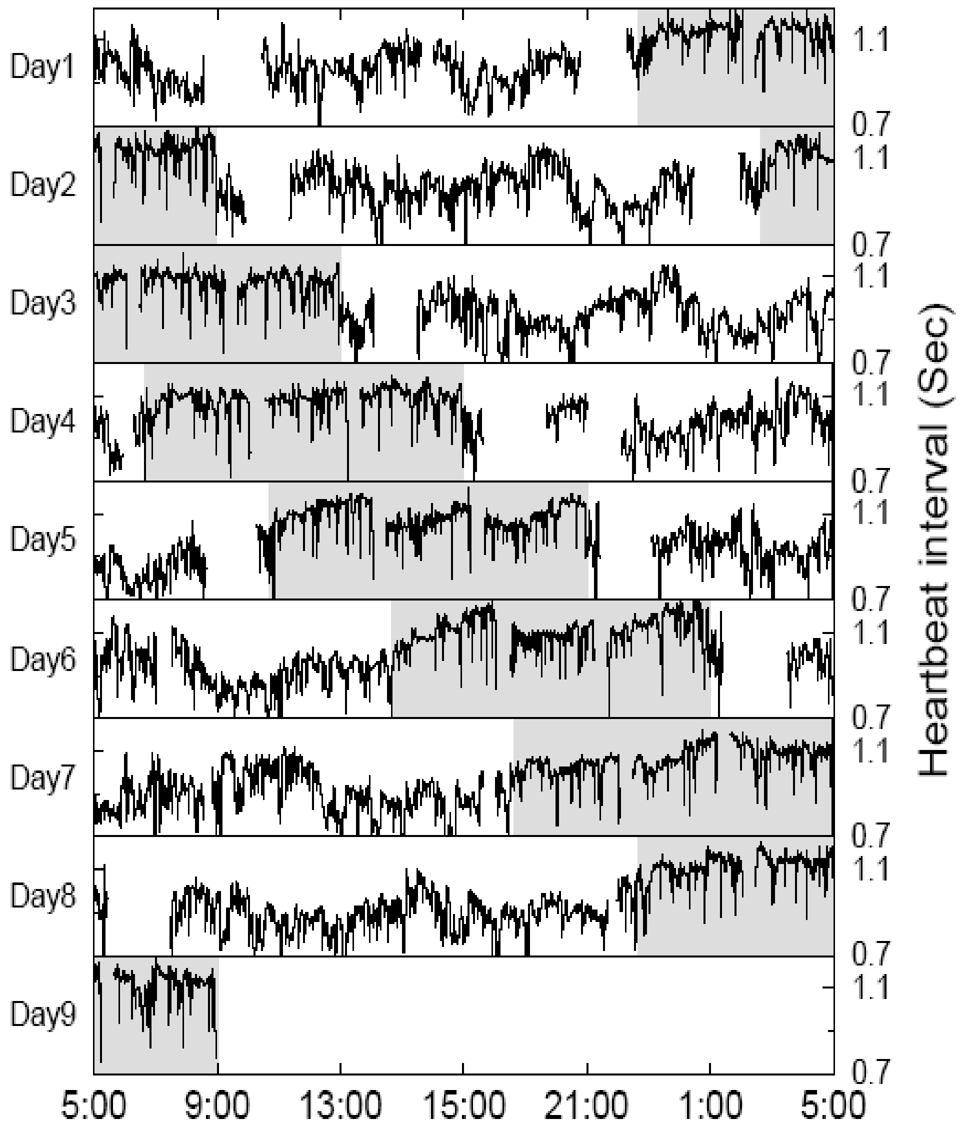
Czeisler CA *et al.*, *Science* **284,** 2177–2181 (1999).
Dijk DJ. & Czeisler CA, *Neurosci. Lett.* **166**, 63–68 (1994).

Schematic illustration of methods of assessing endogenous circadian rhythm



Need sensitive marker to determine the circadian phases.

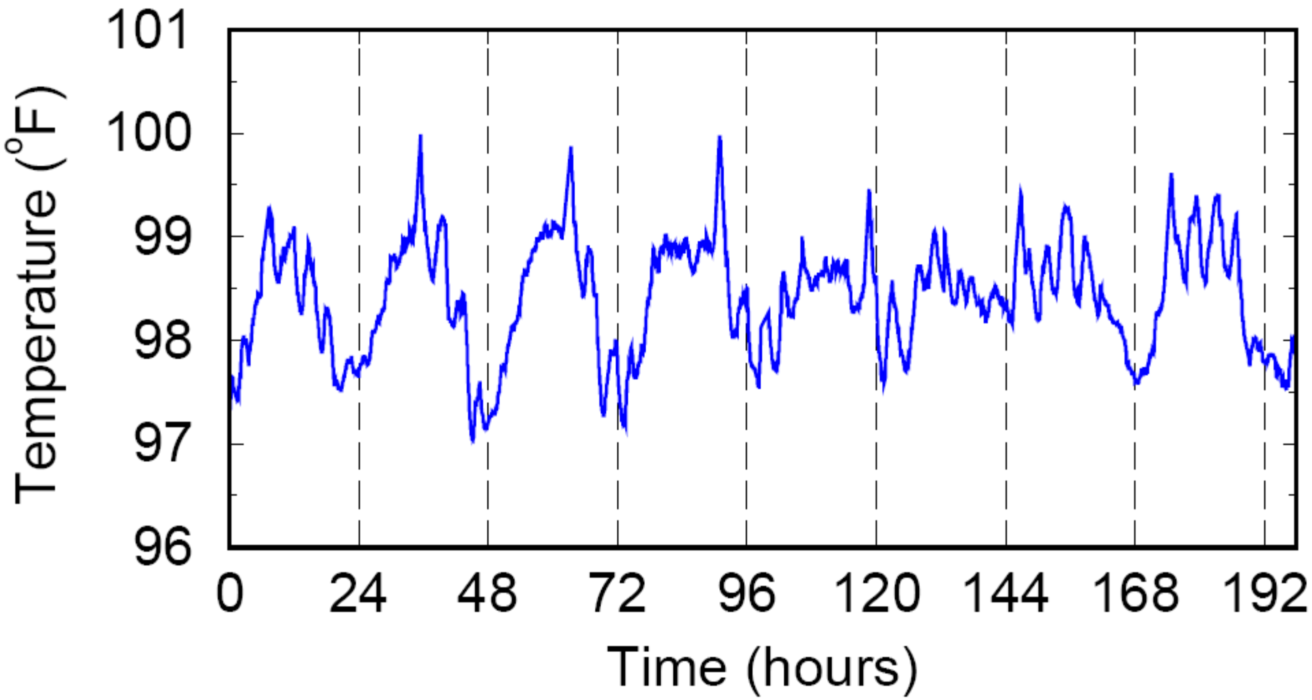
Forced desynchrony protocol: a heartbeat recording



0 60 120 180 240 300 360

Czeisler CA *et al.*, *Science* **284,** 2177–2181 (1999)

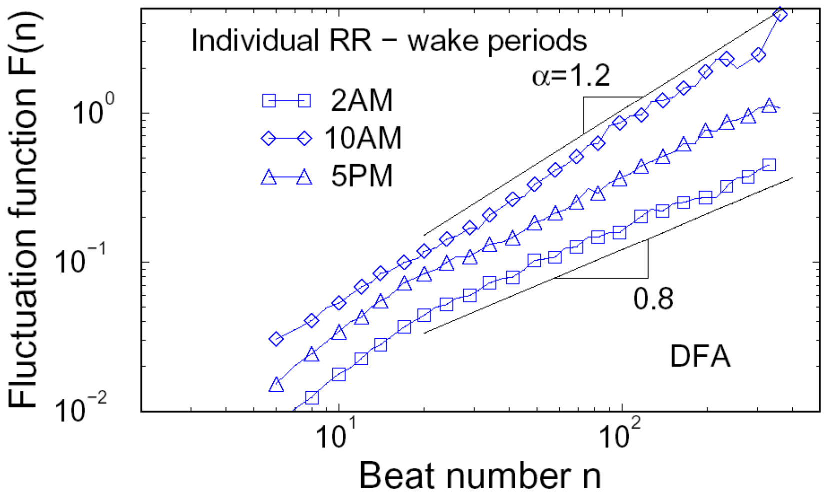
Estimation of internal circadian phases

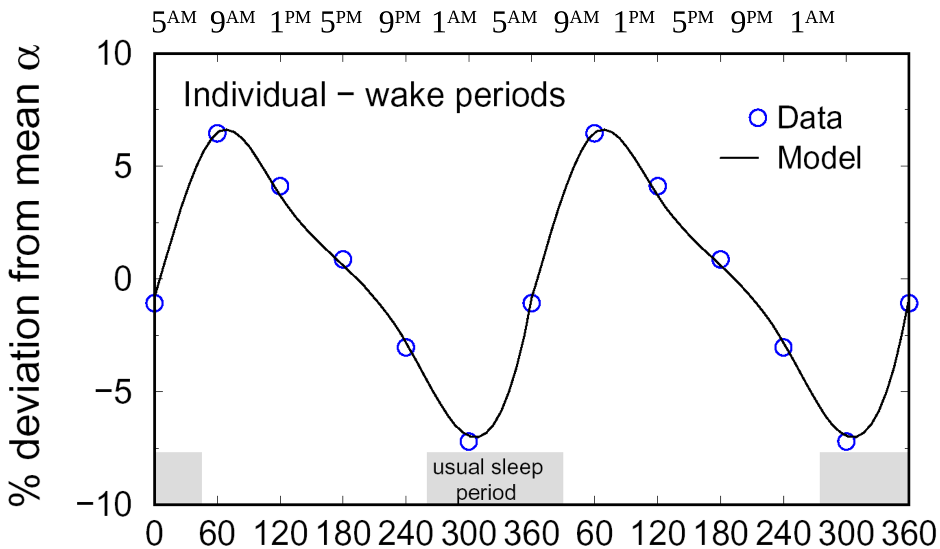


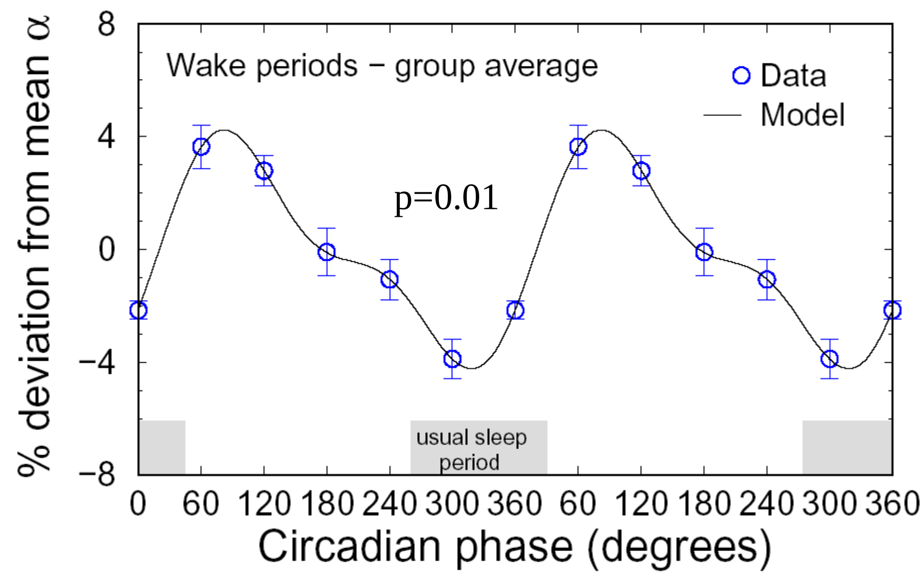
- Body temperature as the marker;
- Phase = 0 for the minimum of body temperature.

Dijk DJ & Czeisler CA. *Neurosci. Lett.* **166**, 63–68 (1994).
Brown EN & Czeisler CA. *J. Biol. Rhythms*;**7**, 177–202 (1992)
Khalsa SB, et al. *J. Biol. Rhythms* **15**, 524–530 (2000).

Circadian rhythms in cardiac fractal correlations: wakeful periods



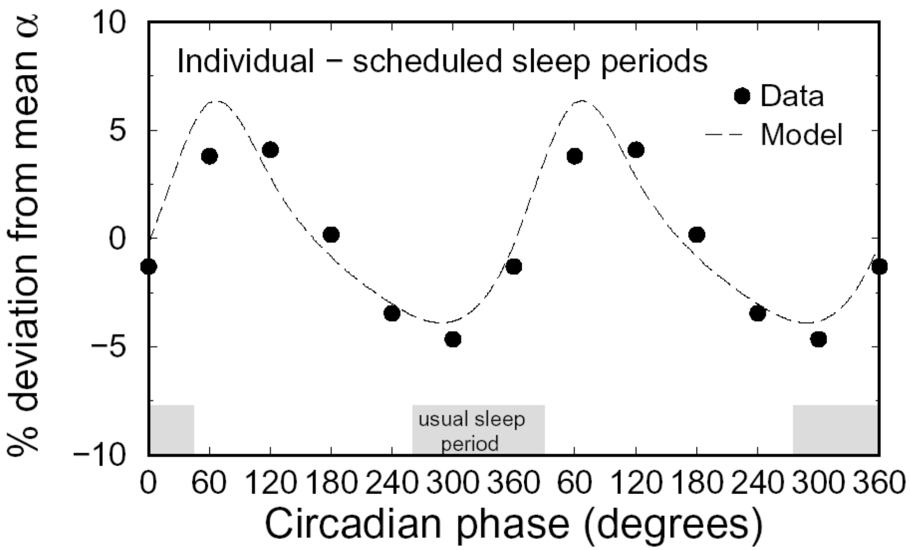


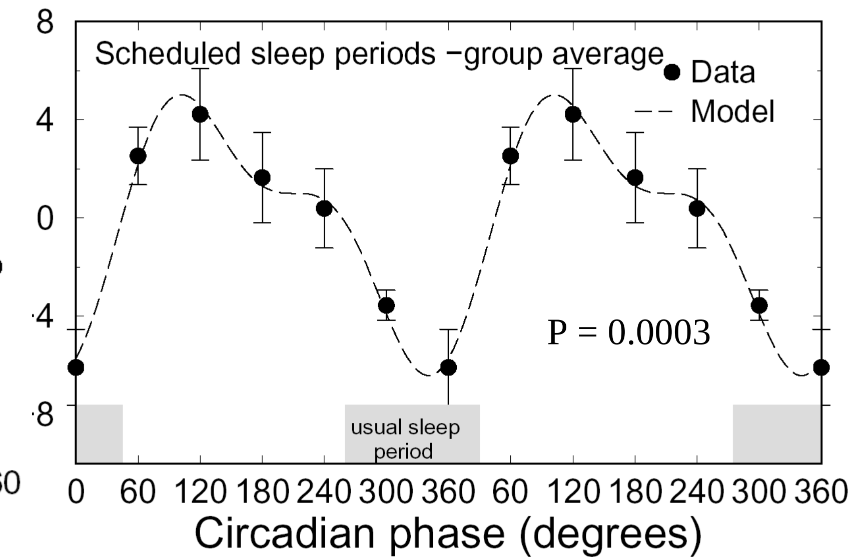


- Fractal: $F(n) \sim n^{\alpha}$
- Circadian rhythms in α
- A sharp peak at 60-90 degrees (corresponding to 9-11 AM);
- A minimum at 300-330 degrees (corresponding to 1-4 AM).

Hu *et al.*, *PNAS* **101**, 18223 (2004).

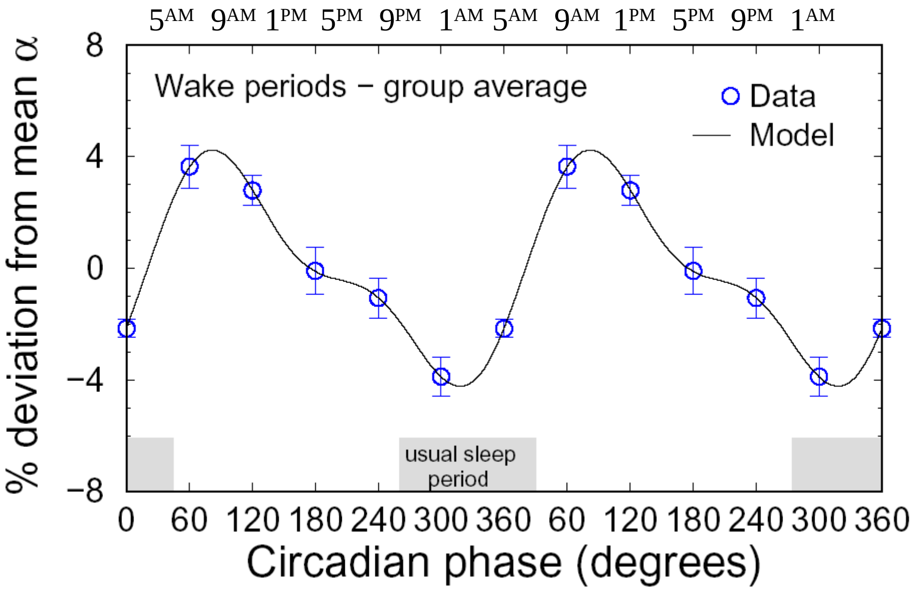
Circadian rhythms in cardiac fractal correlations: sleep periods

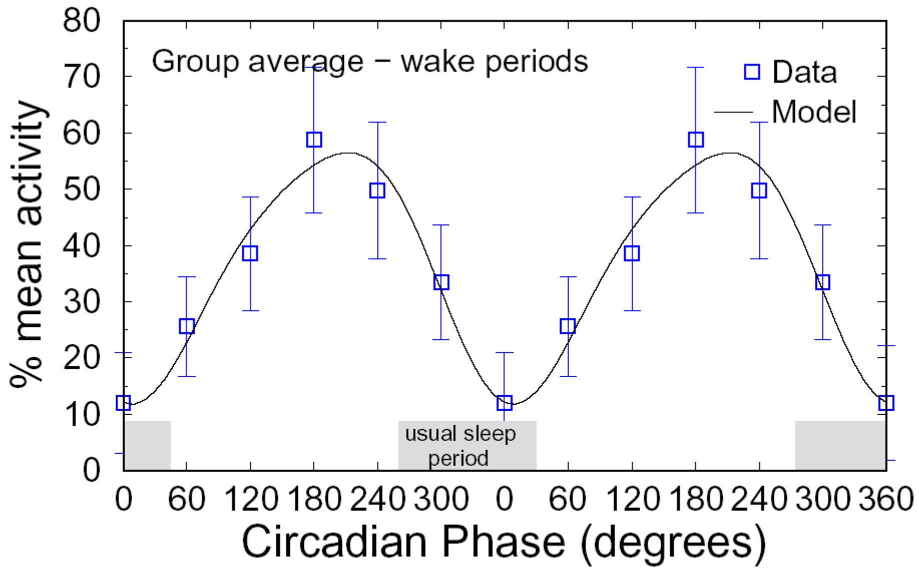




Consistent and significant circadian rhythms during sleep periods.

Circadian rhythm in motor activity

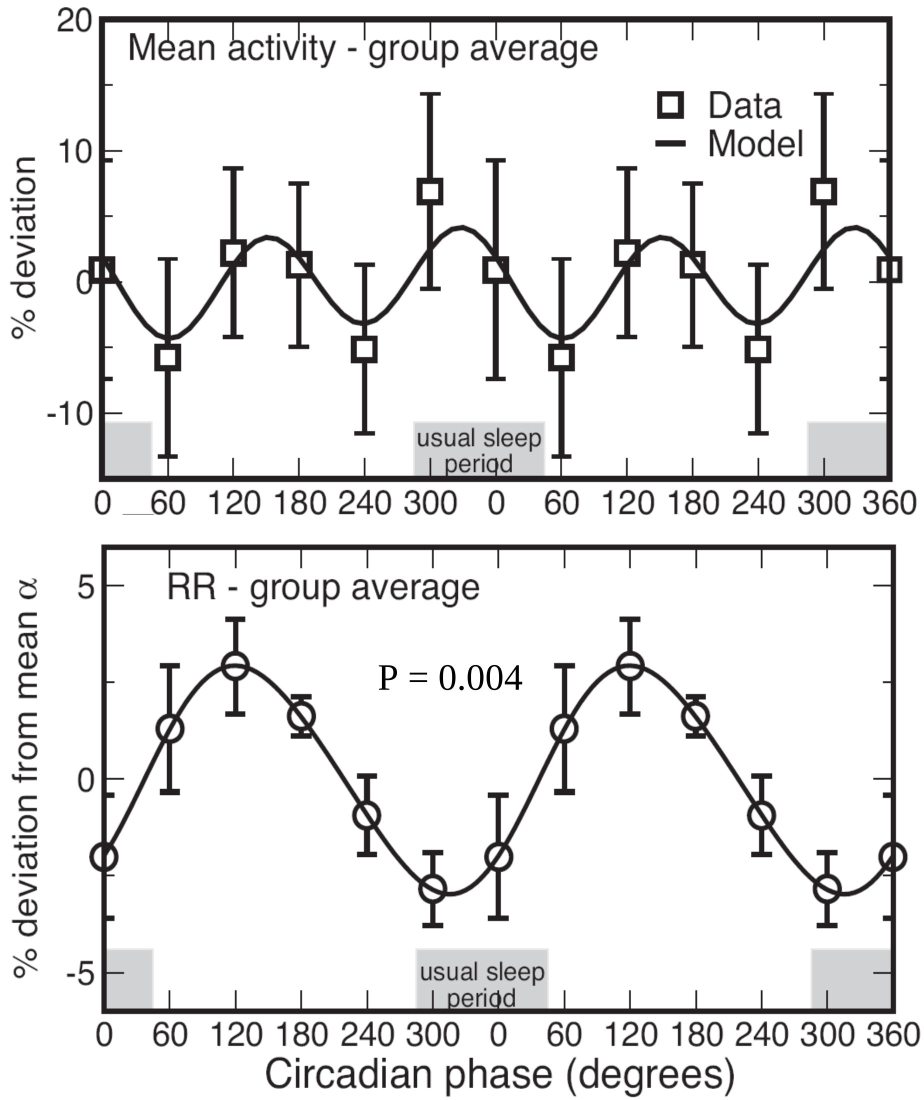




- Significant circadian rhythms in mean activity.

- The circadian pattern in α with a peak at 9-11 AM is very different from the pattern in activity with a peak at 5-9 PM.

Consistent circadian rhythms in cardiac fractal correlations during the constant routine protocol

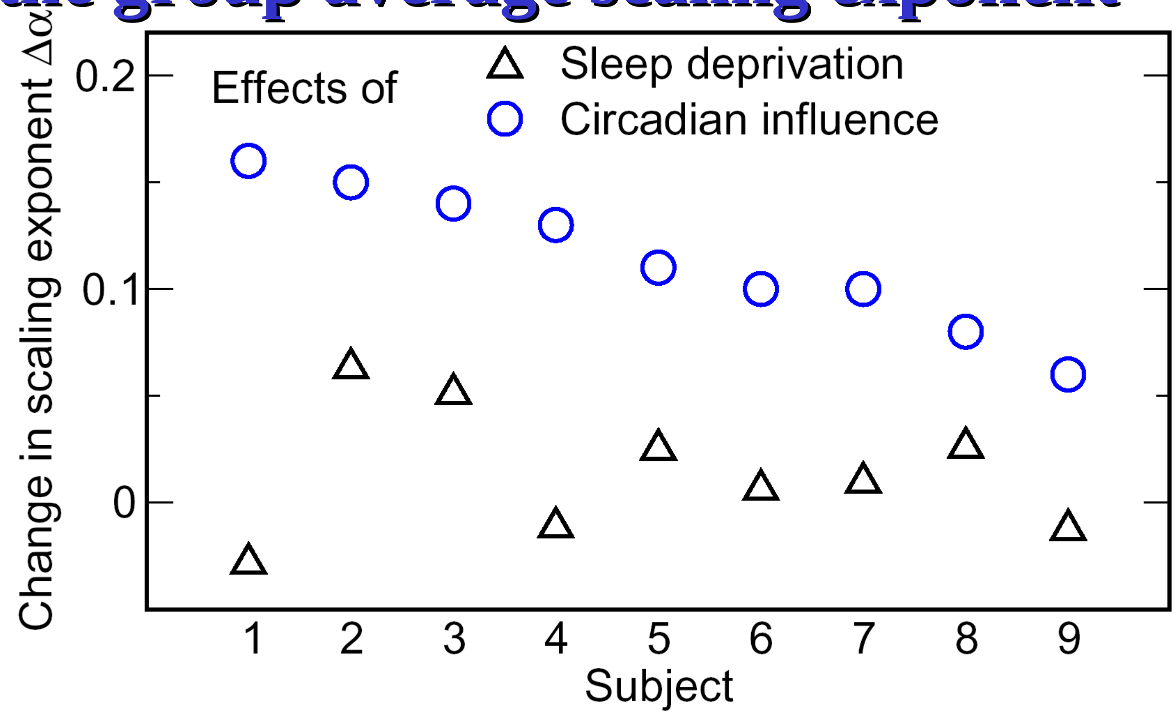


- Abolished circadian rhythms in mean activity

- Circadian rhythms in cardiac fractal correlations persist

Ivanov *et al.*, PNAS **104**, 10702 (2007)

No significant influence of acute sleep deprivation on the group average scaling exponent



- The changes of the scaling exponent along the linear trend in 12 hours were much smaller than the peak to trough amplitude of circadian rhythms.

- Linear trends of the scaling exponent ($P<0.05$) were significant only in 3 out of 9 subjects.

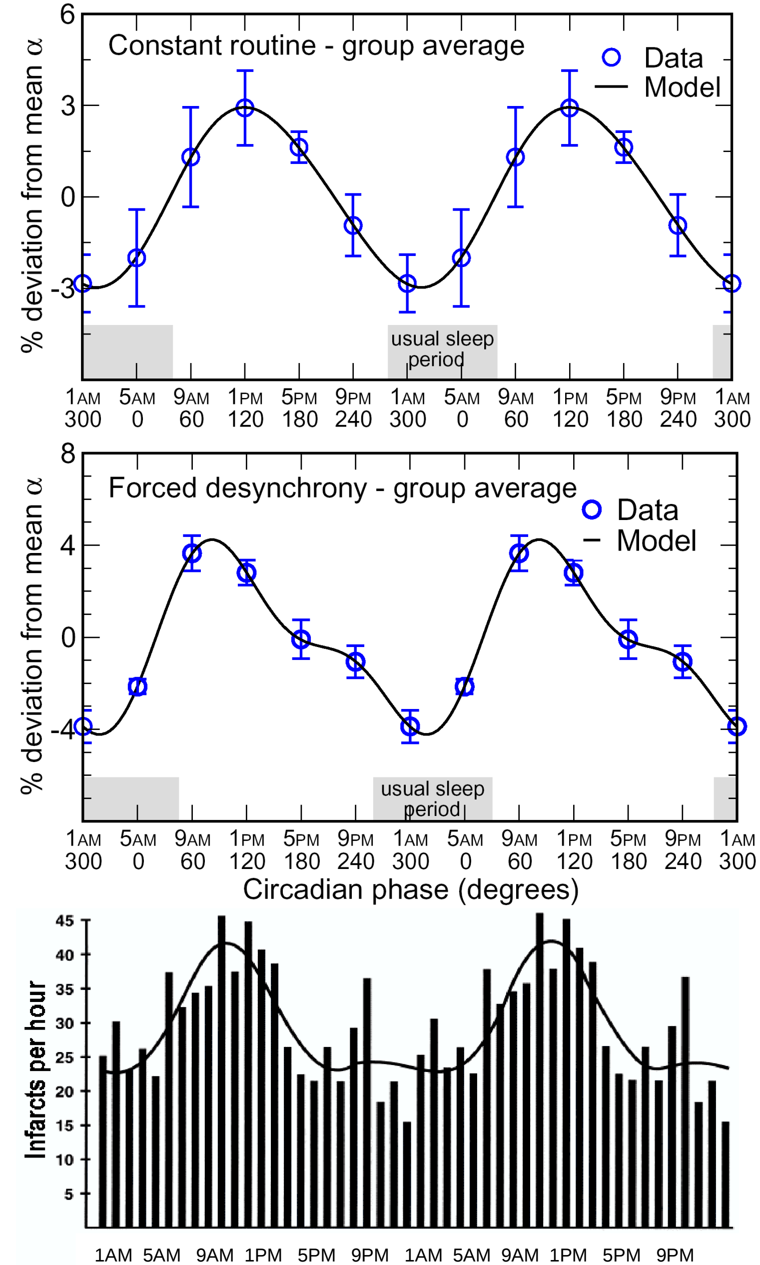
- No significant changes in the group average of the scaling exponent throughout the constant routine protocol.

Circadian rhythms in fractal heartbeat correlations

• Similar circadian rhythms in α during both protocols

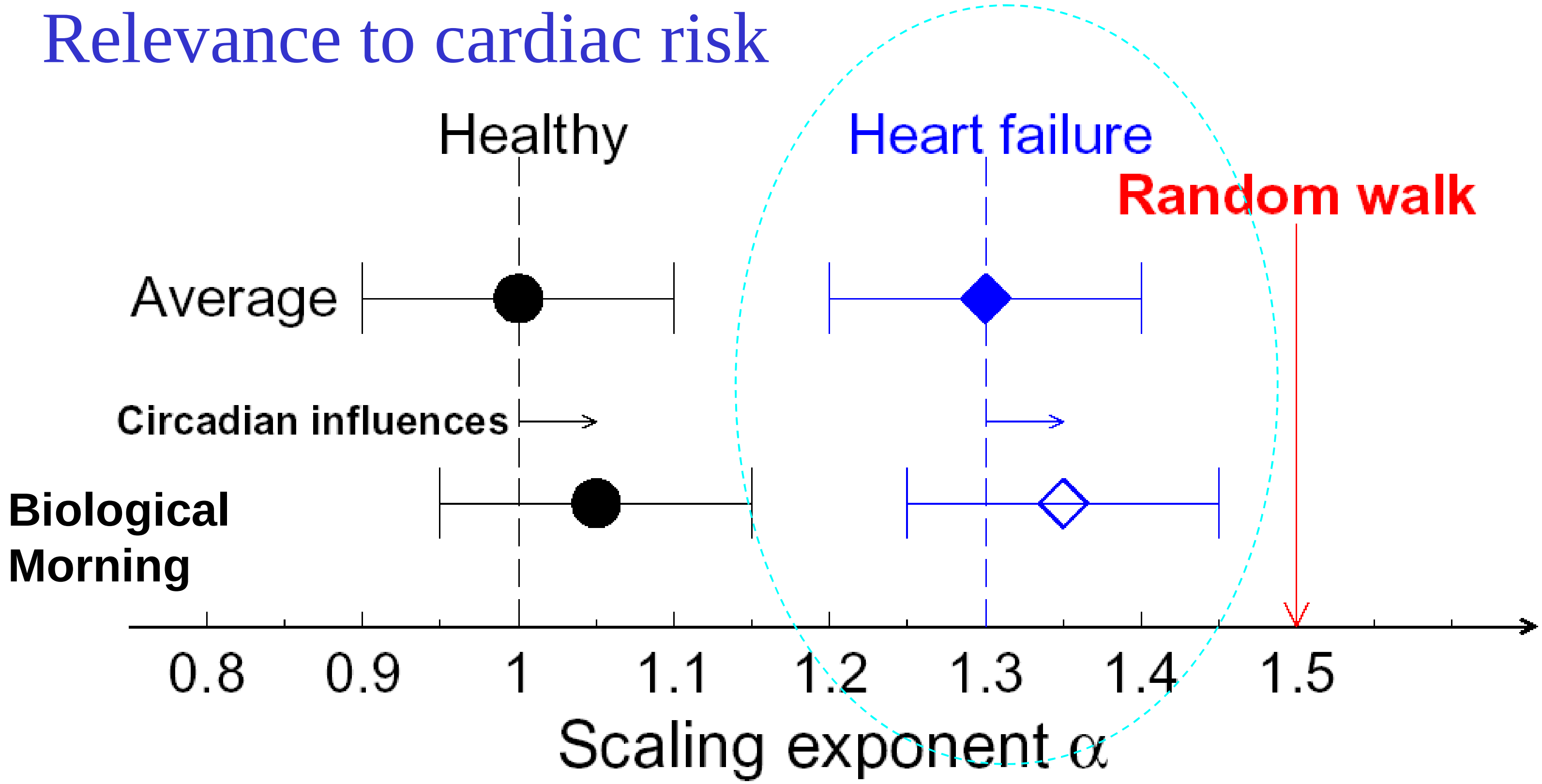
• Maximum α during biological morning

• Circadian peak of α close to the time window of highest cardiac risk observed in epidemiological studies.



Muller *et al.*, *N. Eng. J. Med.* **313,** 1315 (1985).

Hypothesis:
Relevance to cardiac risk



A similarly circadian effect in subjects with congestive heart failure may bring the value of their exponent α even closer to the critical value of 1.5 at specific time window during biological morning.

Animal study

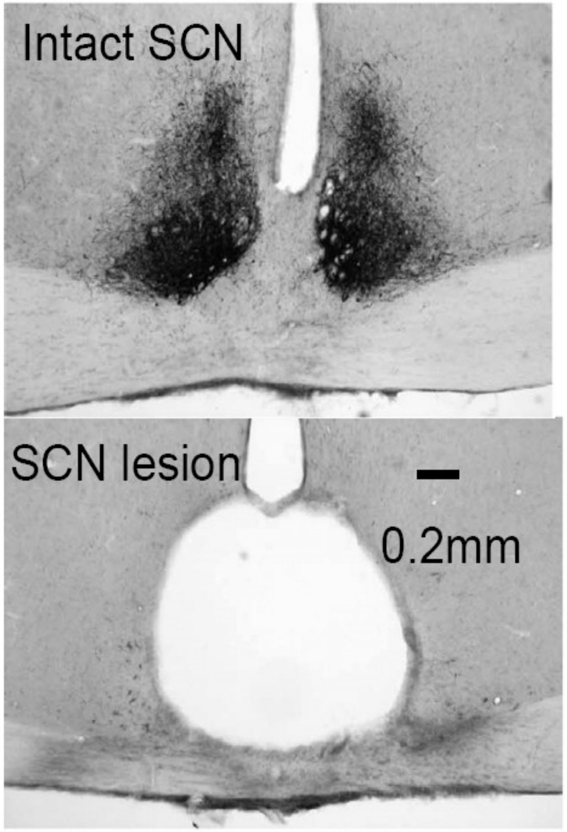
• 8 control and 6 SCN-lesion (SCNx) Wistar rats

• Under 10-day 12-hour:12-hour light/dark condition (LD) followed by10-day constant dark condition (DD)

• Movements cross the space in a cage 39x38x38 cm

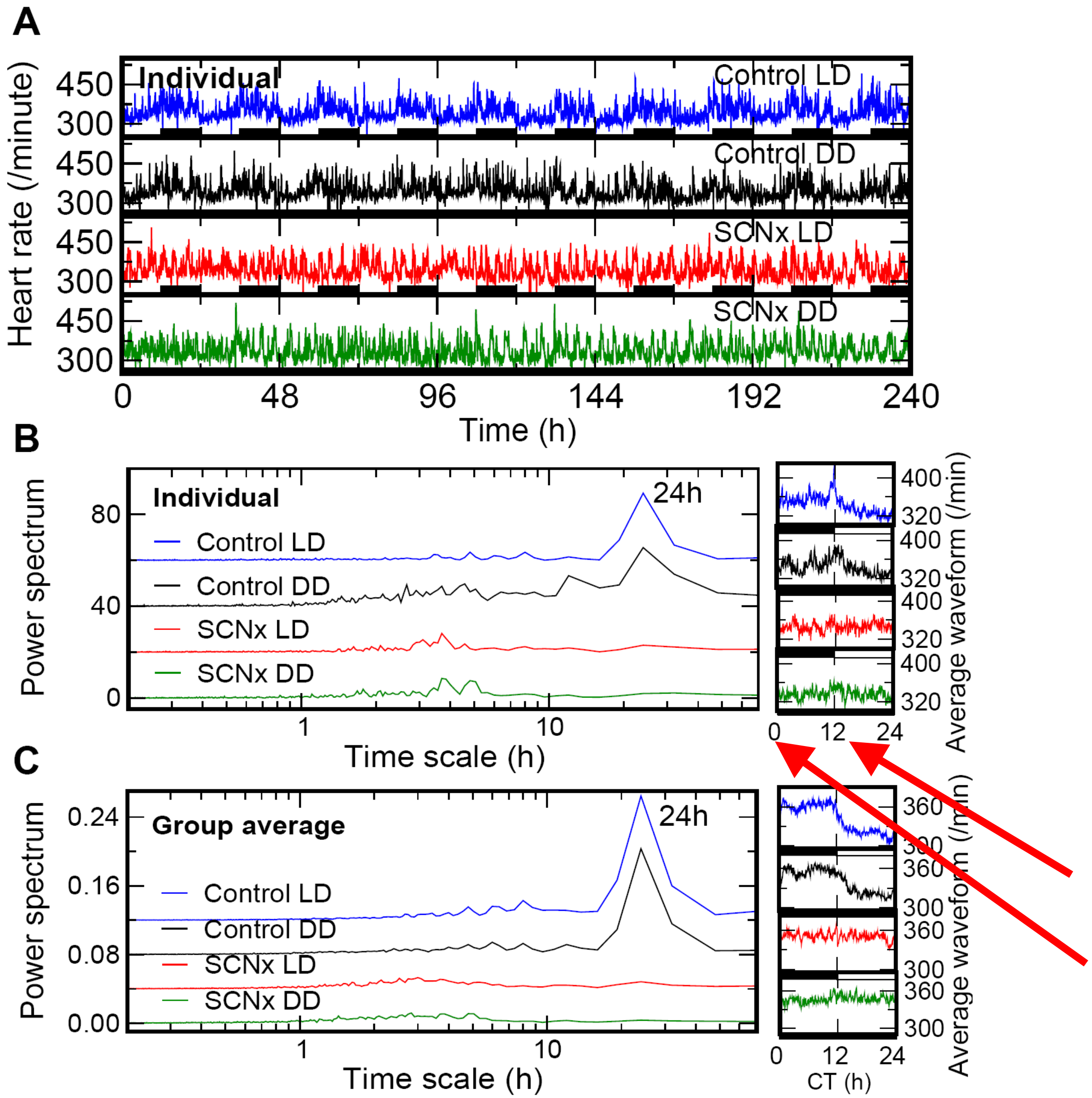
• One data point every 4 minutes (10 sec sampling at 500Hz)

• Core body temperature as circadian phase marker. Mean circadian period of control rats (24.1h) was used for SCNx rats



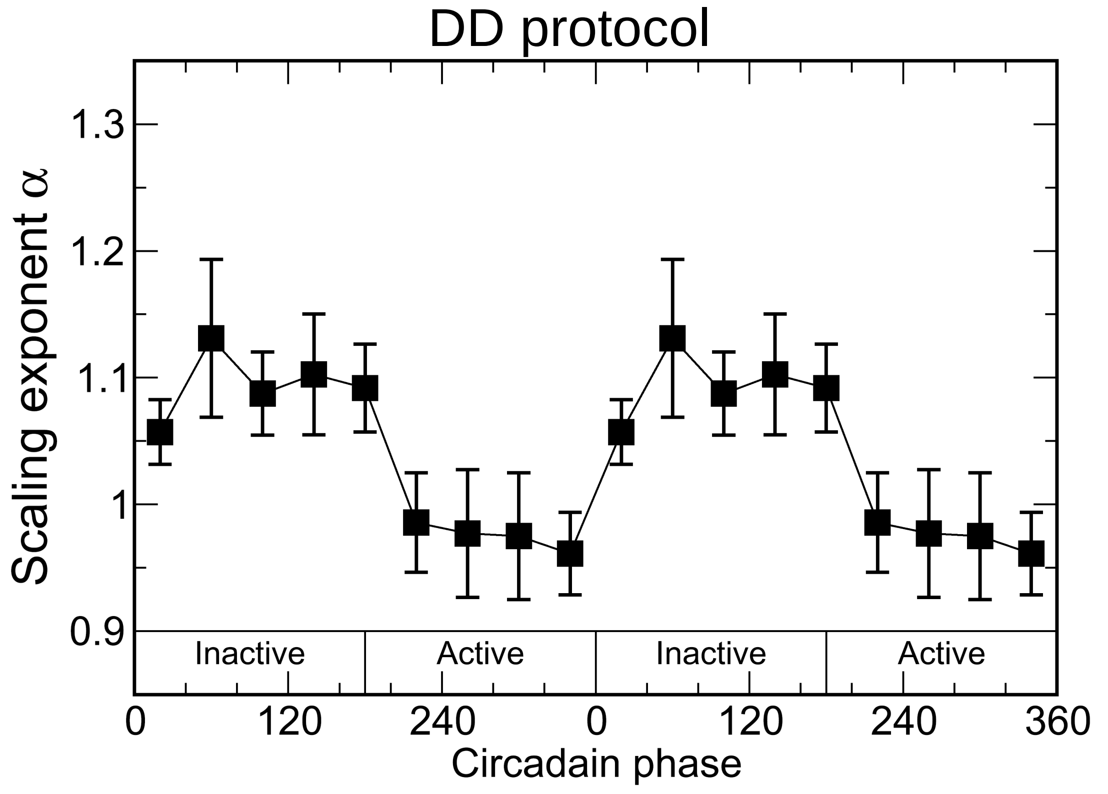
Scheer *et al.*, *Neuroscience* 2005; **132**, 465-477.

Circadian rhythms are abolished by SCN lesion



Hu *et al*., Journal of Biological Rhythms 2008; 23, 265-273

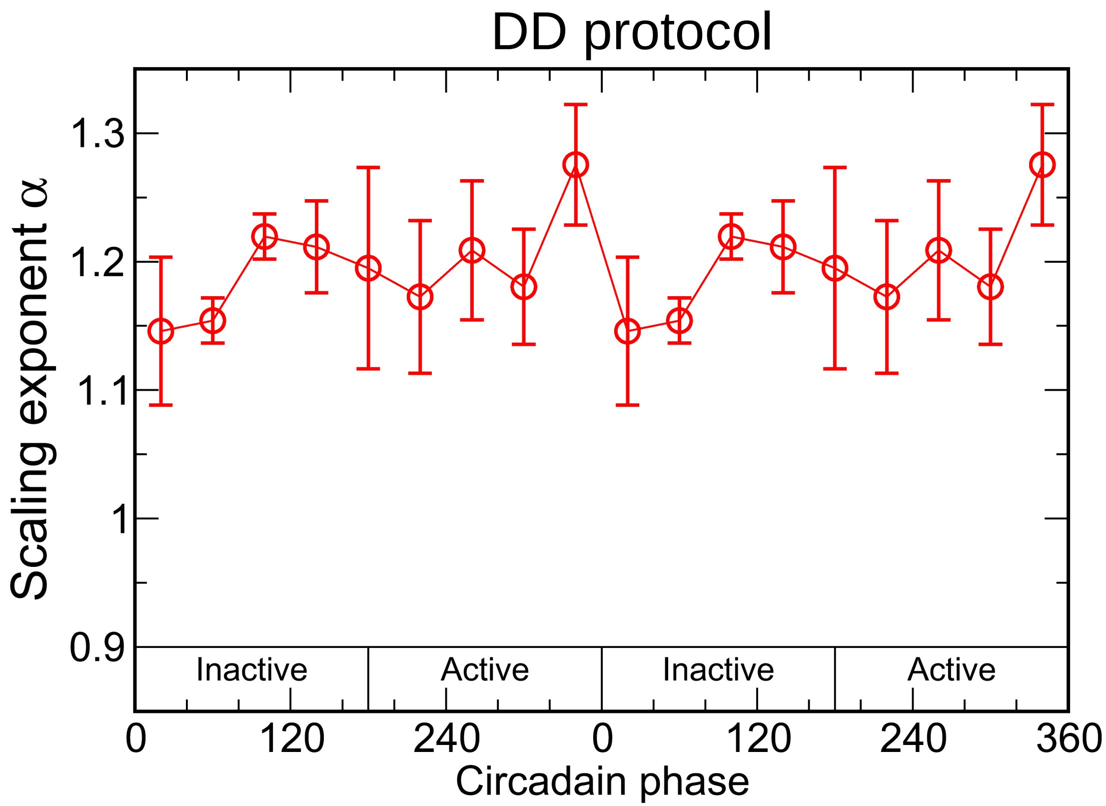
Circadian rhythms in cardiac fractal correlations



In control rats:

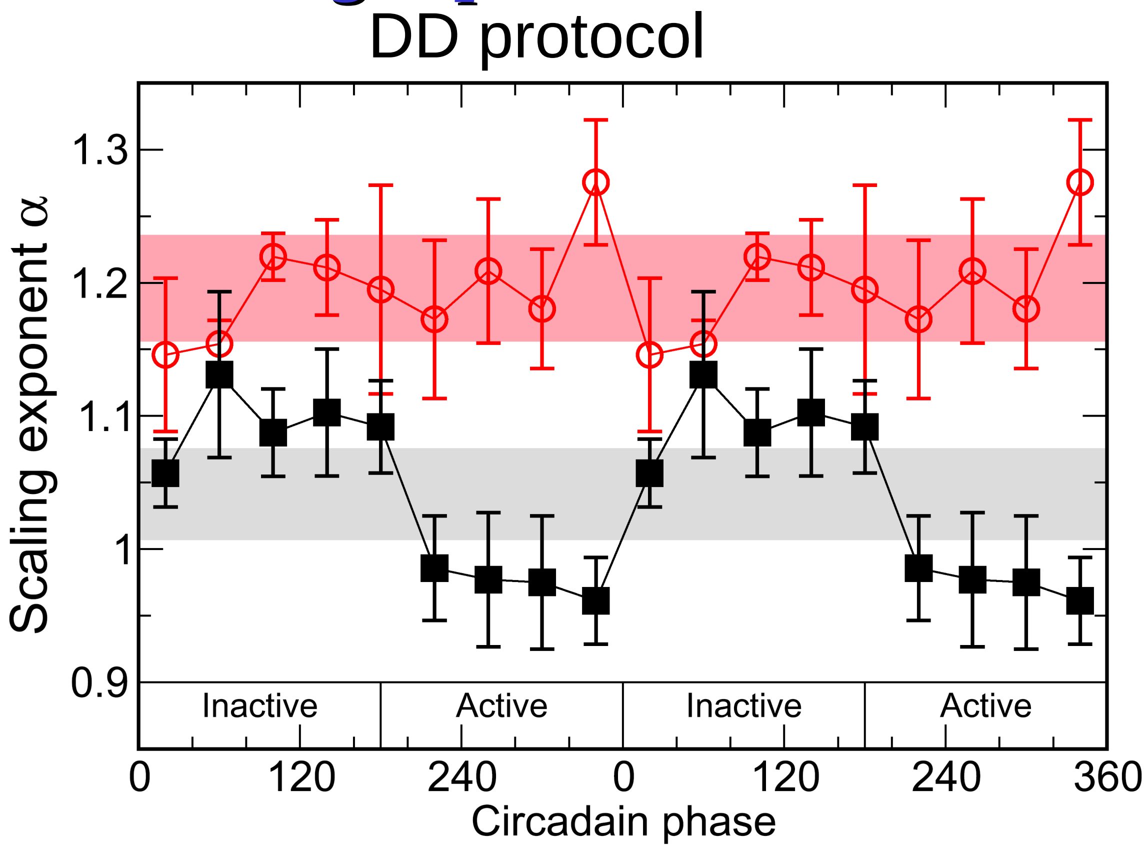
- scale exponent α=1.03±0.04 (Mean ± SE)
- a significant circadian rhythm (p=0.0006)
- peak during the biological day (inactive phase for rats)
- peak to trough amplitude ~18% of the mean.

Effect of SCNx on fractal heart rate fluctuations: abolished circadian rhythm



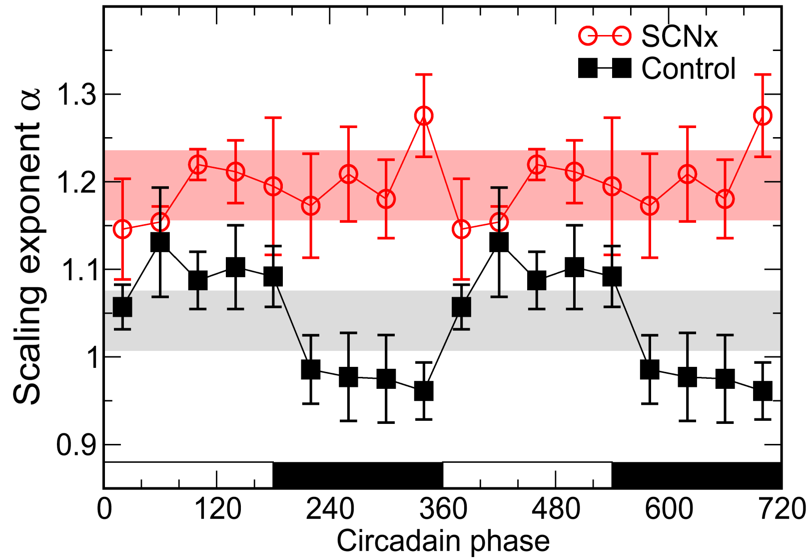
SCNx rats showed no circadian rhythm in cardiac fractal correlations ($p>0.2$).

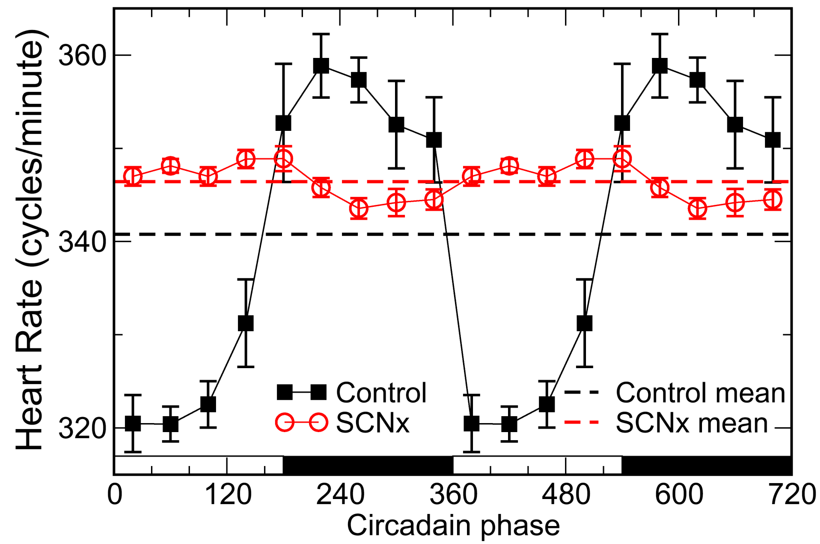
Effect of SCNx on fractal heart rate fluctuations: increased scaling exponent

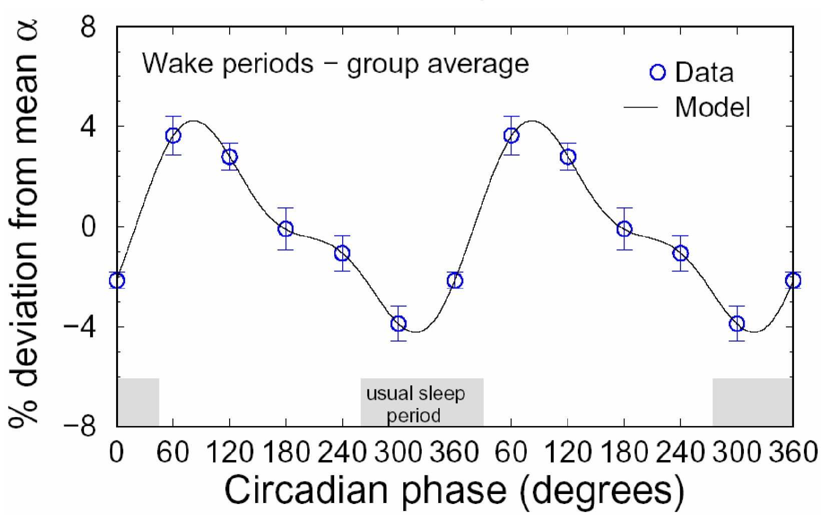


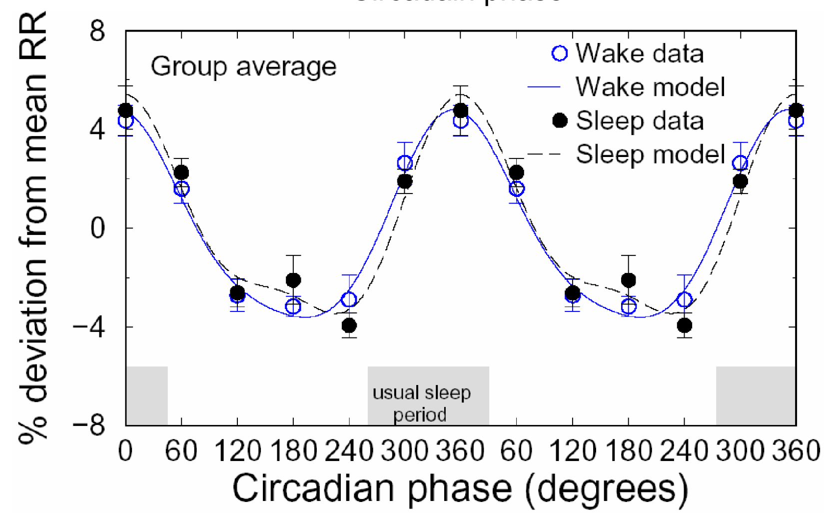
- A significant increases in the scaling exponent in SCNx: $\alpha = 1.2 \pm 0.04$ (Mean ± SE) ($p=0.01$).
- Interaction between group and circadian phase ($p=0.04$)

Fractal patterns of heart rate fluctuations are independent of mean heart rate

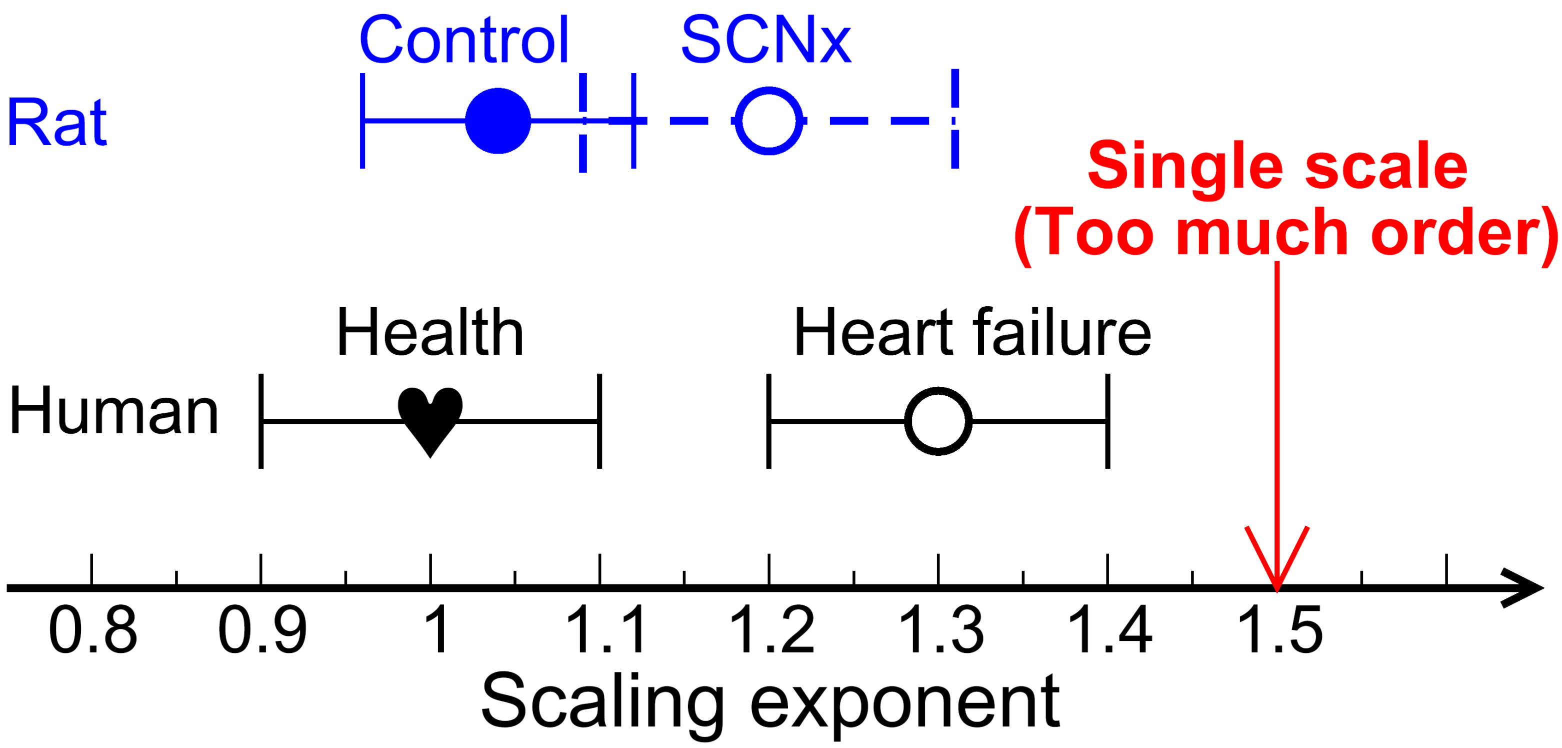








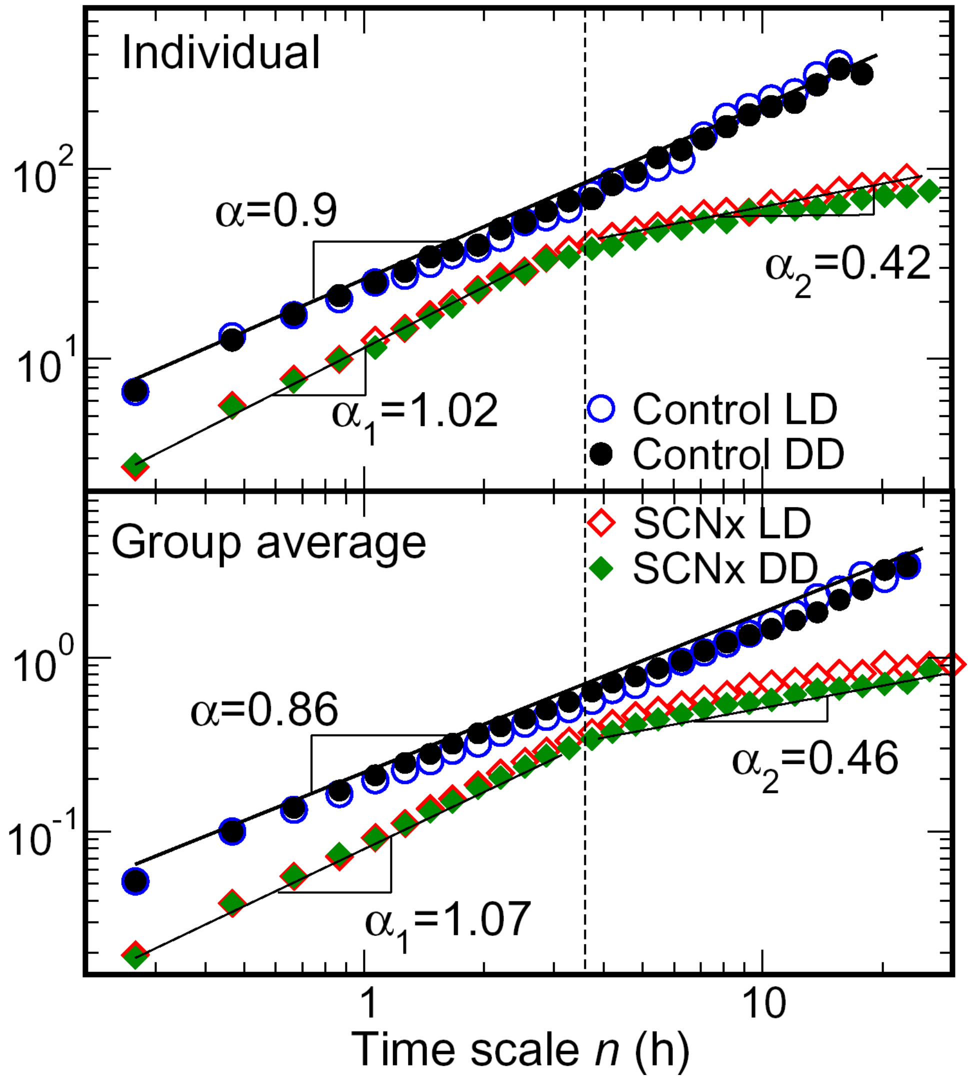
Effect of SCN lesion on fractal heart rate fluctuations



The above results are focused on the time scales < 1 hours

What about fractal patterns at larger time scales?

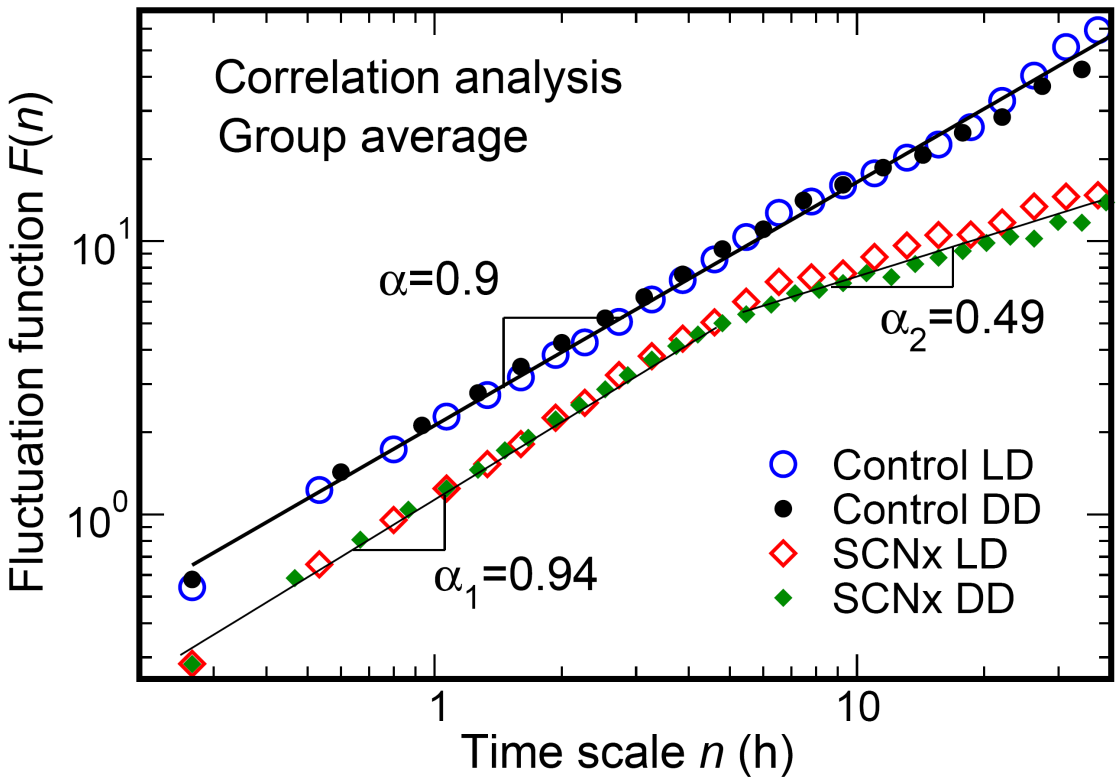
Effect of SCN-lesion on fractal heart rate correlations at a wide range of time scales



- Correlations completely break down at >4 hours
- Correlations persist but with a significant change at < 4 hours
- Independent of light influences

Hu *et al.*, Journal of Biological Rhythms 2008; 23, 265-273

Effect of SCN-lesion on fractal activity correlations at a wide range of time scales

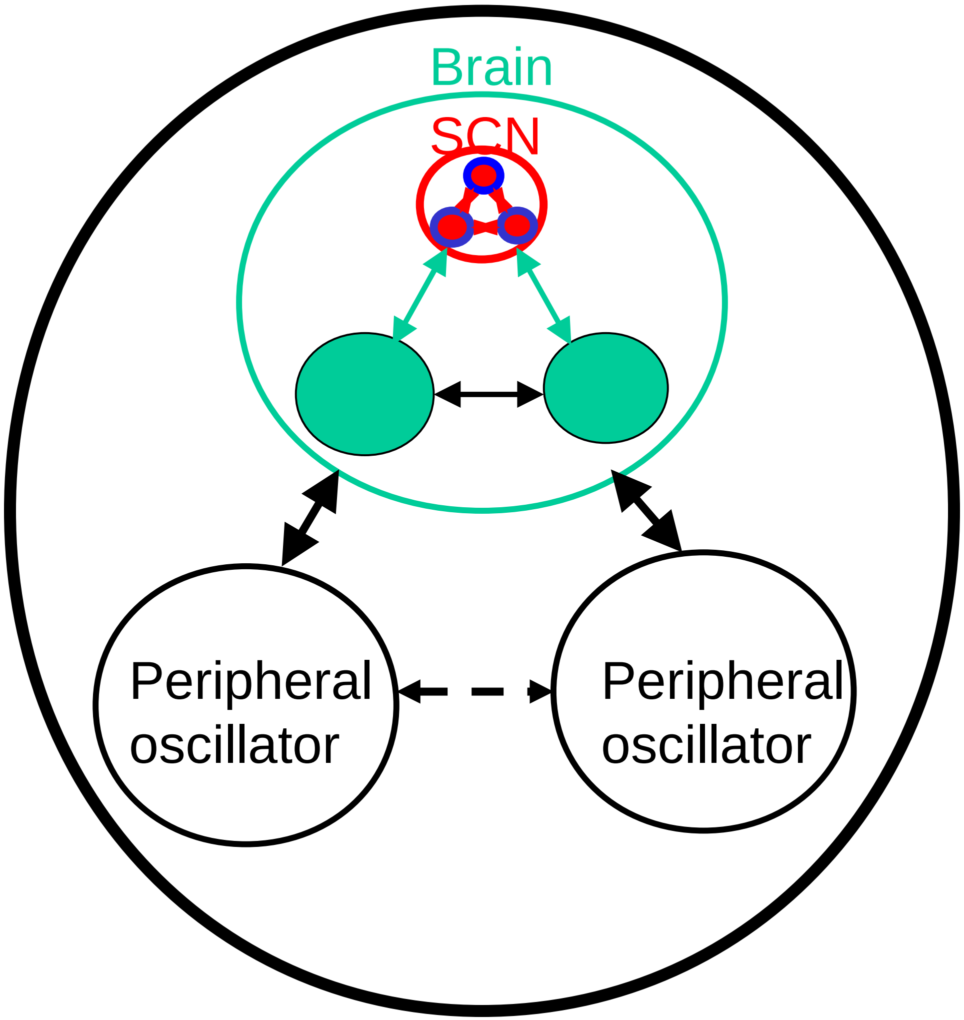


- Scale invariant correlations in control rats from minutes to at least 24 hours
- White-noise behavior at time scales >4 hours in SCN-lesioned rats
- Independent of light influences

K. Hu *et al.*, Neuroscience **149,** 508 (2007).

Control Mechanisms for Scale-invariant Regulation

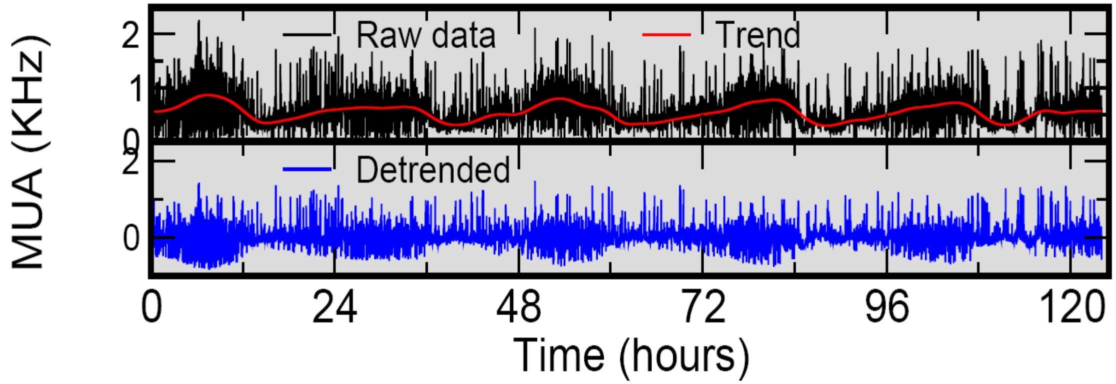
Integrative physiological system



•The SCN is a major node in the network of fractal regulations.

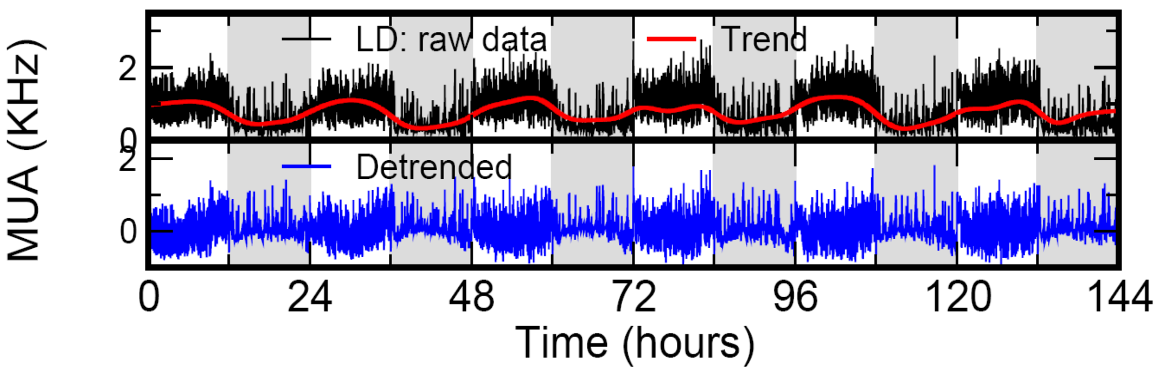
The multi-scale influences of the SCN may be through neuronal interactions
within the SCN; or
between the SCN and other neuronal nodes

Multiunit activity of the SCN



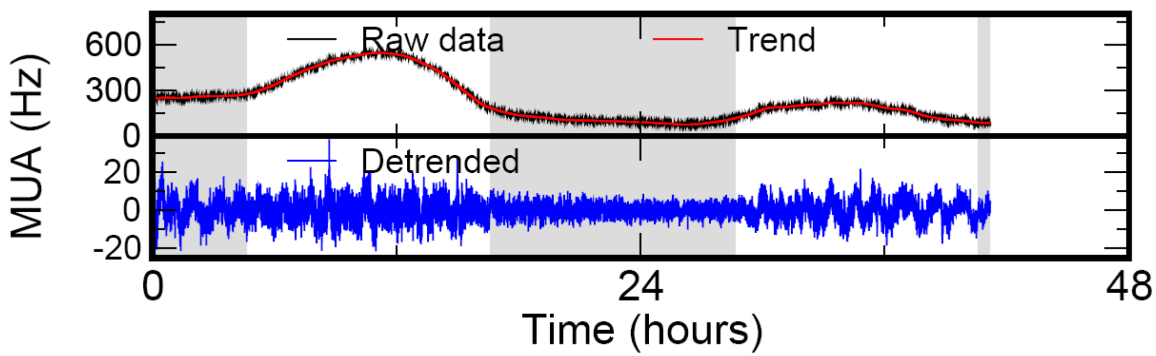
In vivo:

constant dark



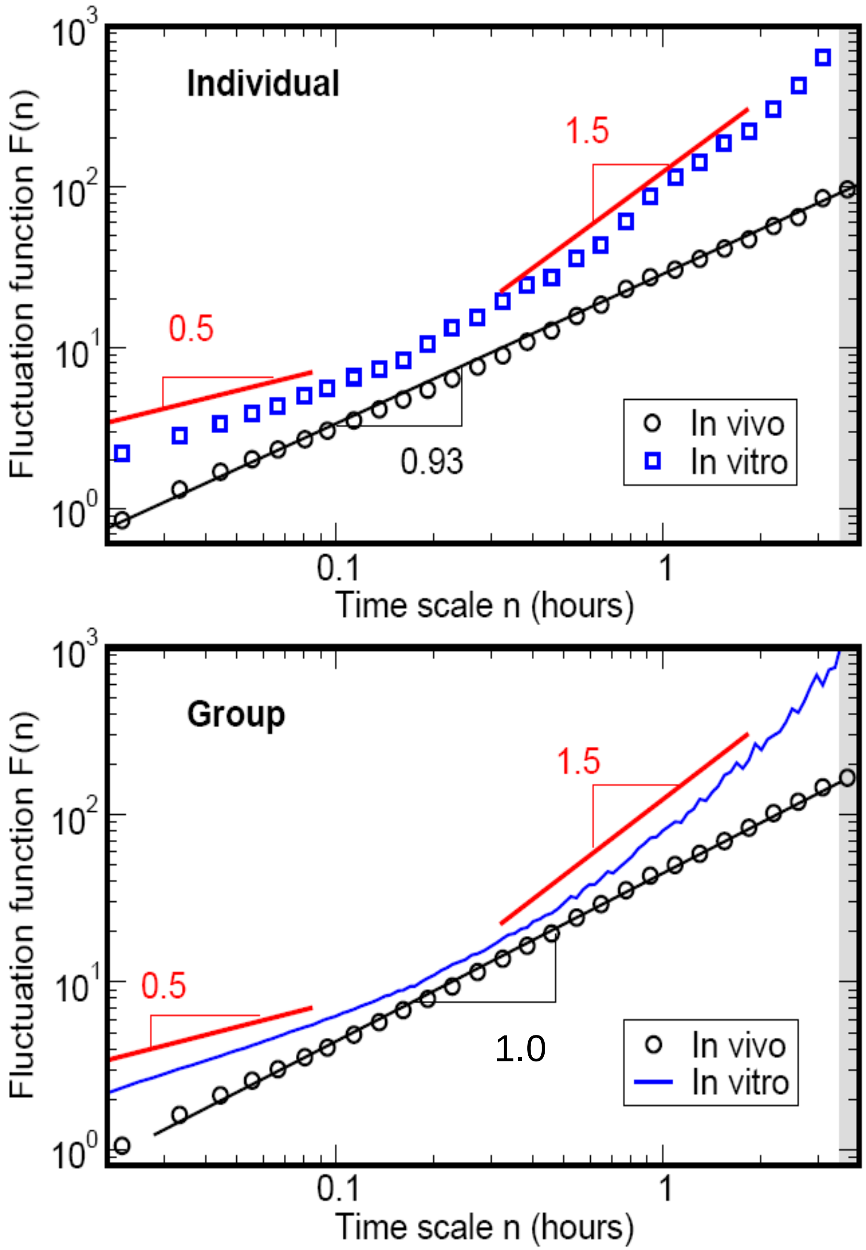
In vivo:

Light-Dark (12h:12h)



In vitro

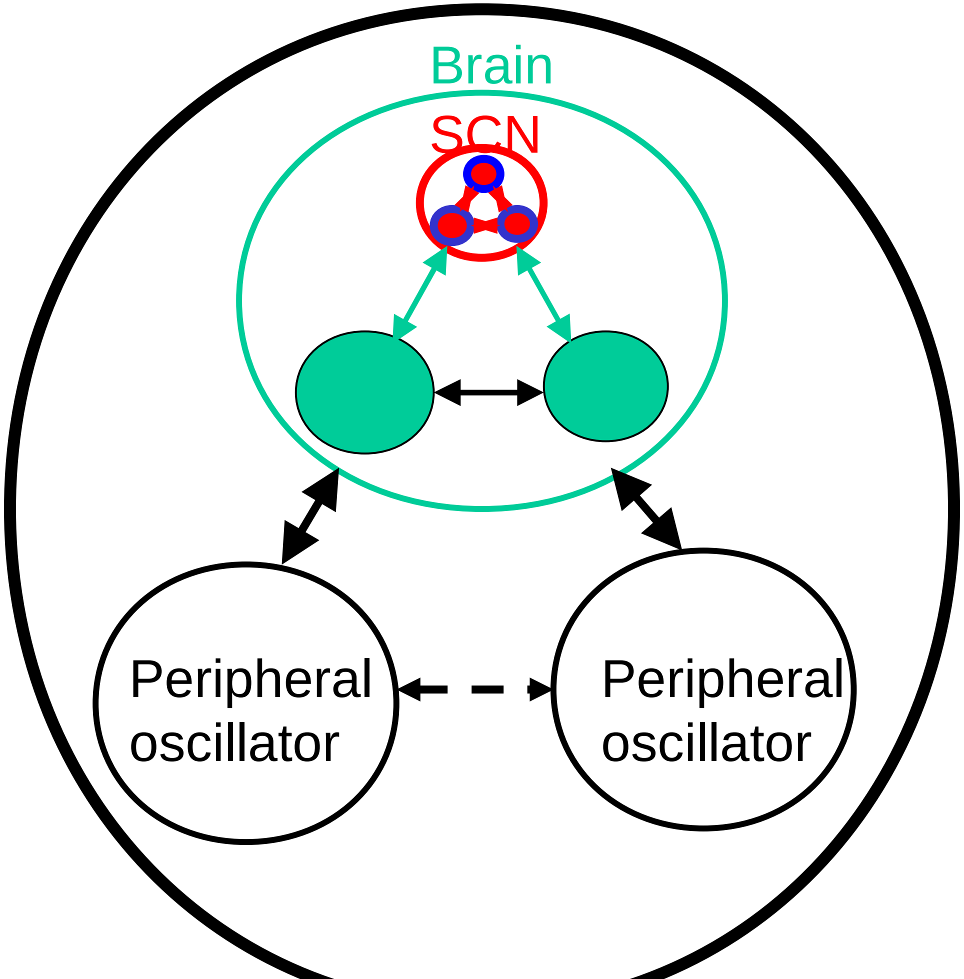
Fractal correlations in SCN MUA



Fractal correlations in vivo at time scales from ~1min to 3h

Abolished fractal patterns in vitro

Control Mechanisms for Scale-invariant Regulation



Summary

- **Healthy cardiac dynamics show fractal regulatory patterns**
- **There is an endogenous circadian rhythm in fractal cardiac control at time scales < ~1 h**
  - Independent of behavioral and environment influences
  - With larger scaling exponent during biological day and smaller scaling exponent during biological night
  - Similar in diurnal and nocturnal mammals
- **Removing the SCN (the master clock) abolishes the fractal cardiac correlations at large time scales (> ~4h)**
  - The SCN functions beyond a simple circadian pacemaker
  - There is a network responsible for the fractal cardiac control and the SCN is one major node in the network
- **The SCN activity also display fractal patterns**
  - Due to the interactions between the SCN and other neuronal nodes

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