

# Cardiac-Respiratory-Locomotor coup

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# Objectives

- Coupled systems
- Pathophysiology of Cardiac- Respiratory and Locomotor interactions
- Gait and balance
- Clinical Implications

# Entrainment phenomena



# Entrainment phenomena

Biological rhythms generated in oscillating networks exhibit entrainment phenomena that can be triggered internally or in response to external periodic inputs.

- Central autonomic and locomotor networks exhibit oscillatory patterns at different time-scales. True oscillators e.g. cardiac and respiratory networks interact “on demand” with locomotor central pattern generators and sensory inputs.
- Coupling entrainment or “ synchronization” by chance?

# Rhythm generation

- Patterns of neuronal responses
- Rhythm generation by endogenous rhythmic bursts in pacemaker cells coupled with “follower” cells

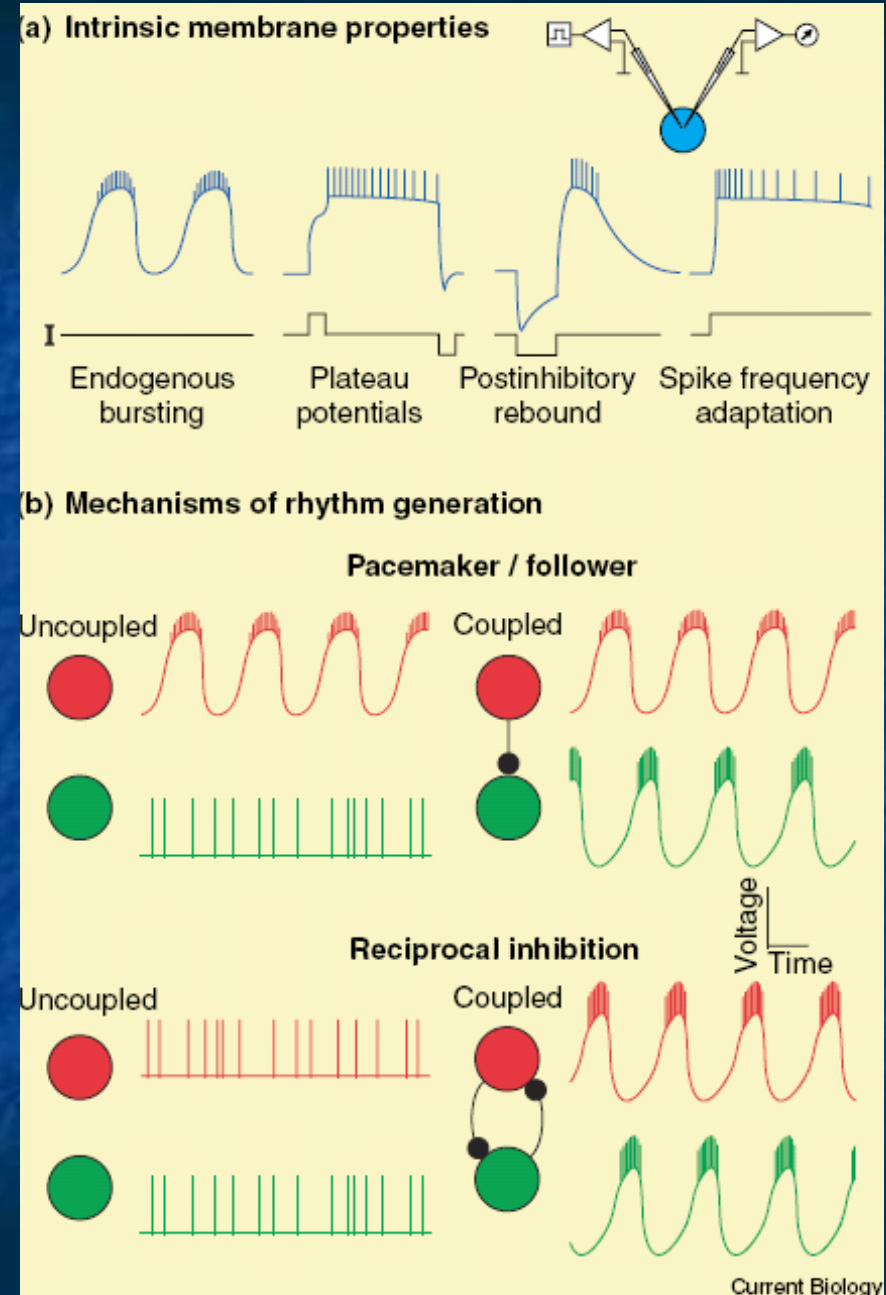
Activation vs. inhibition coupling

Synaptic coupling- Reciprocal inhibition

Network oscillator of 2 neurons that fire independently when uncoupled

but fire in alternating bursts when **coupled**

Marder E. Current Biology  
2001,11:R986-R996

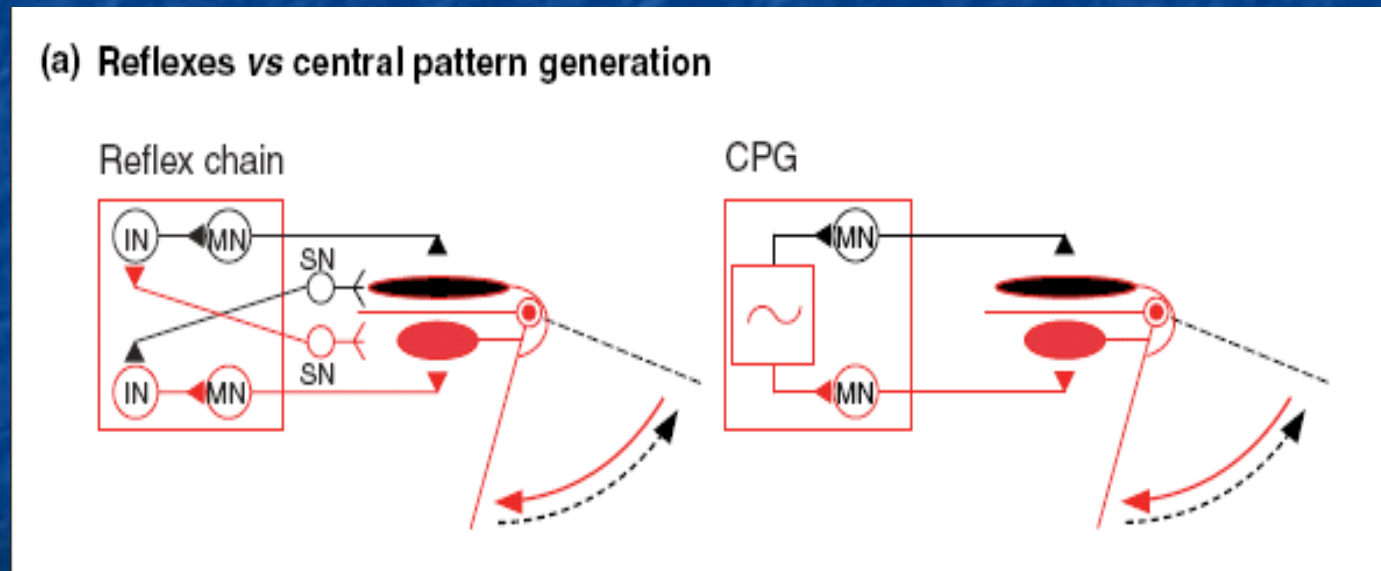


# Central pattern generators

- a. Reflex chain model – alteration of activation and inhibition (left)
- b. Central pattern generator (right)

Pattern generated by both models may appear similar

Coupling vs. Chance?





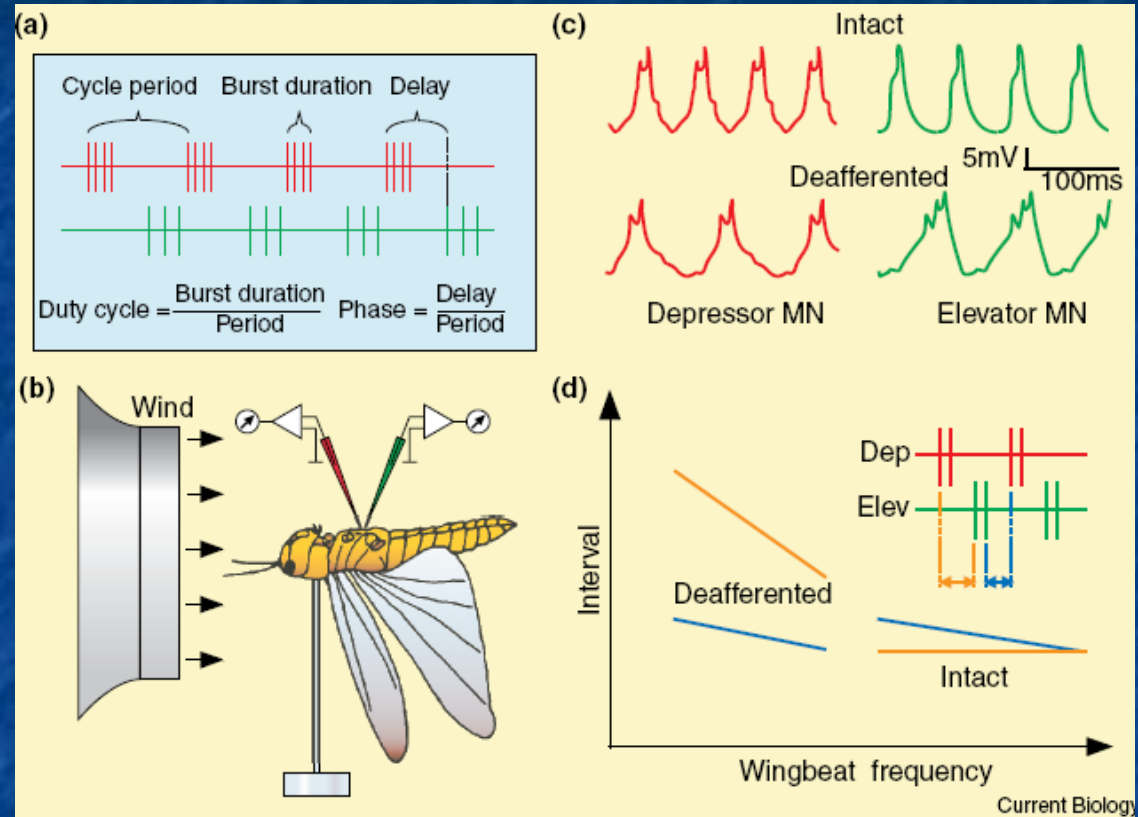
# Interaction between central pattern generator and sensory inputs

a. Rhythmic pattern – the cycle period, burst duration, duty cycle, firing phase

b. Measurement set up of locust wing movements in wind

c. Intact recordings from depressor and elevator motor neuron-phase shift

d. De-afferented recording show de-phasing



# Cardio-Respiratory coupling

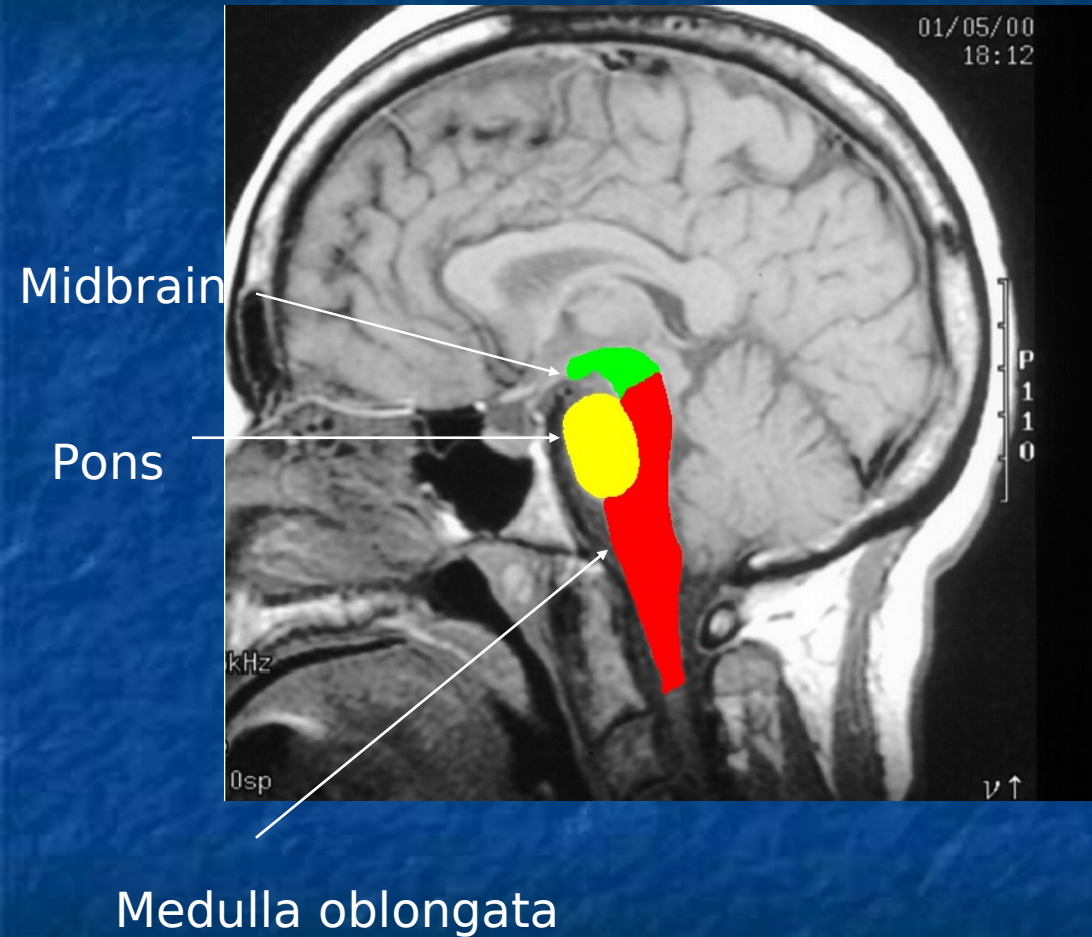




# Cardio-Respiratory coupling

- RSA- respiratory modulation of heart beat and sympathetic outflow (Lyon 1862, Traube-Hering 1865)
- Central cardio-respiratory networks (Langhorst, Koechen 1981)
- Feedback- central & peripheral connections
- Baroreflexes and chemoreflexes
- Respiratory muscles and lung movements

# Brain stem



- Brain stem-the oldest part of the brain that connects it the spinal cord.

- Respiratory, vasomotor and cardiac centers, as well as many mechanisms for controlling reflex activities such as coughing, gagging, swallowing and vomiting.

- Vital neurological functions necessary for survival (breathing, digestion, heart rate, blood pressure) and for arousal (being awake and alert).

# Brain Stem cont'd

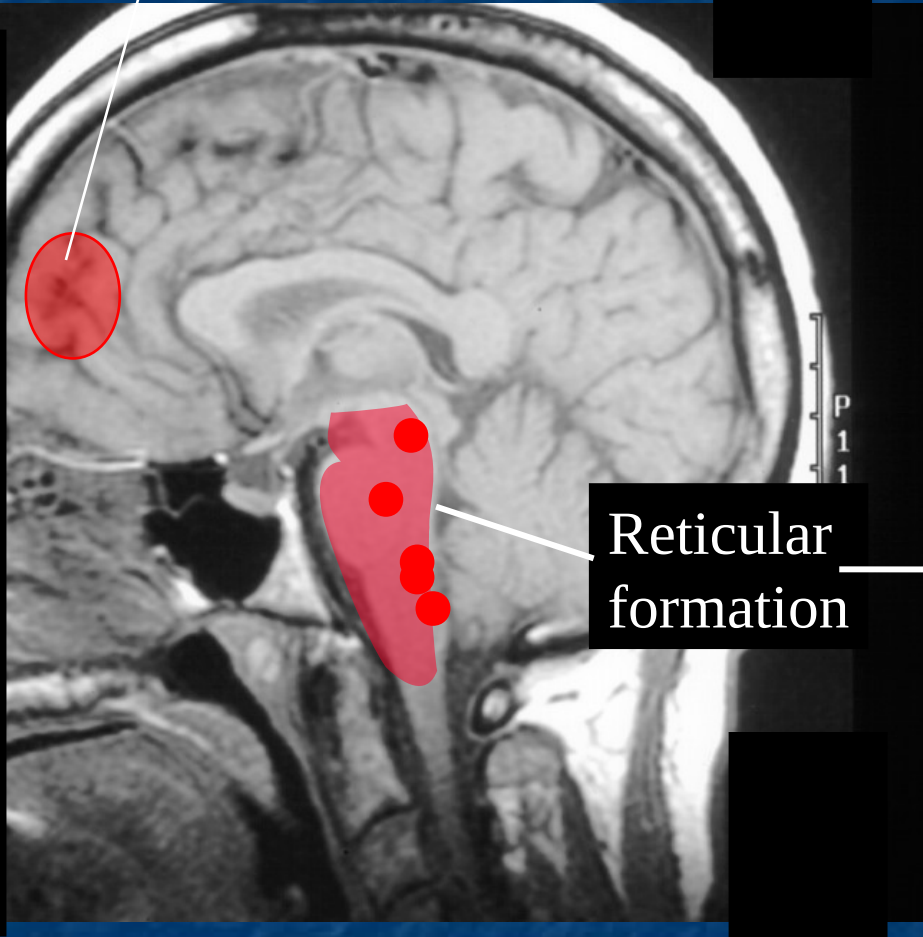
- **Midbrain** - The midbrain serves as the nerve pathway of the cerebral hemispheres and contains auditory and visual reflex centers.
- **Pons** - is a bridge-like structure which links different parts of the brain and serves as a relay station from the medulla to the higher cortical structures of the brain. It contains the respiratory centers, cardiac vagal and motor centers.
- **Medulla Oblongata** - primarily as a relay station for the crossing of motor and sensory tracts between the periphery, spinal cord and the brain, all ascending and descending pathways.

**Respiratory centers** - set the automatic breathing patterns of inspiration, expiration and pause

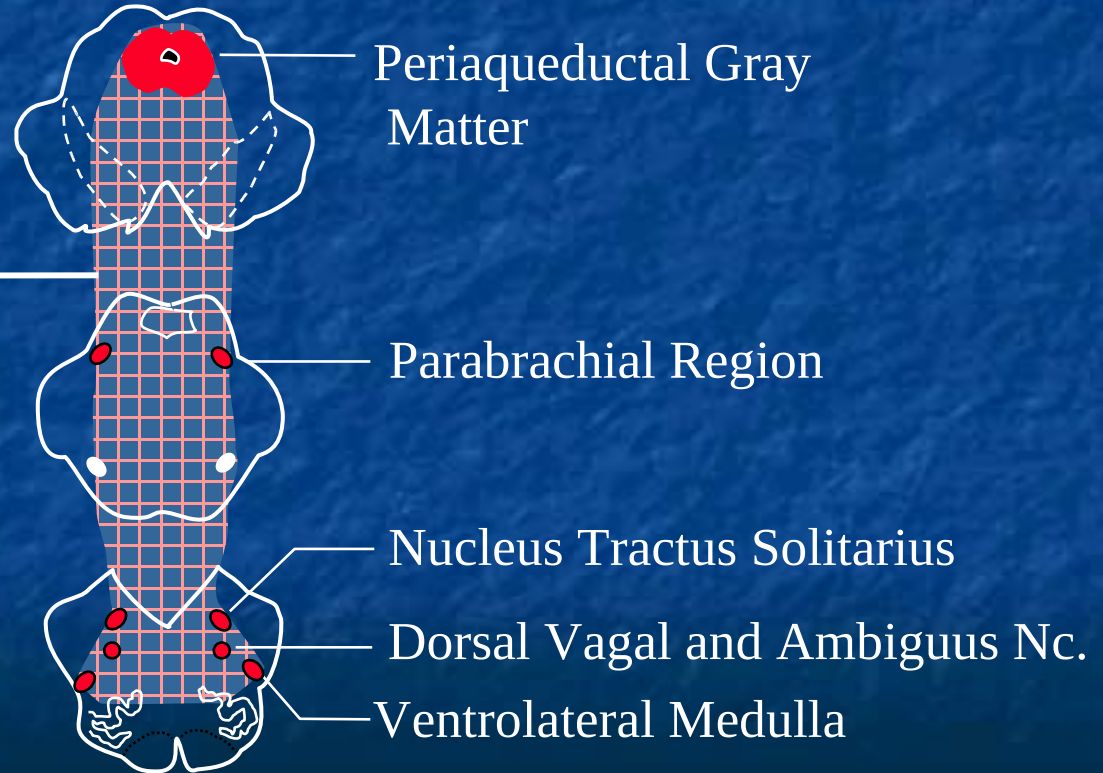
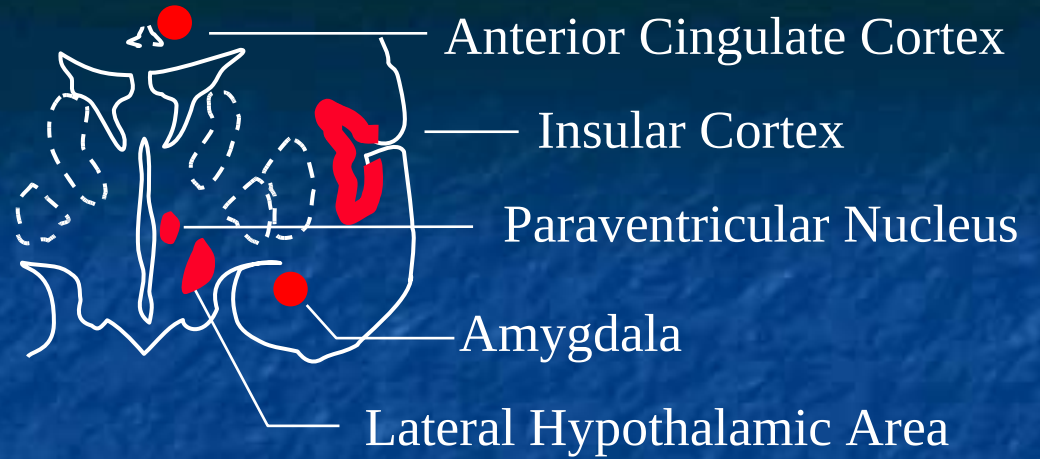
- Connect with autonomic centers (nc. X vagus) and nc. VI (ambiguus), other cranial nerves, sympathetic centers in medulla and central autonomic network and locomotor networks and many cortical areas

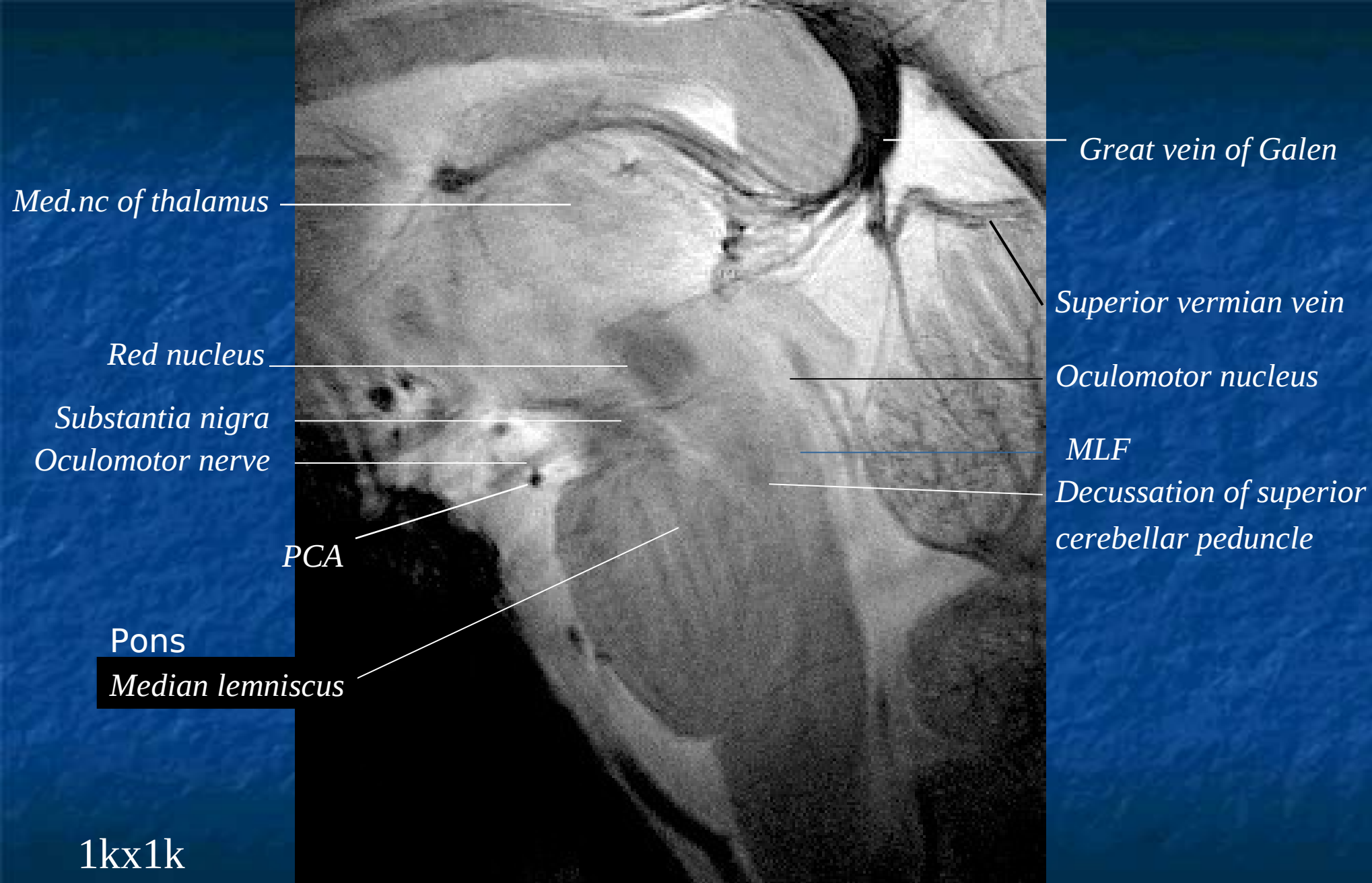


Ventromedial Prefrontal Cortex



Reticular formation





*Great vein of Galen*

*Med.nc of thalamus*

*Superior vermian vein*

*Red nucleus*

*Oculomotor nucleus*

*Substantia nigra*

*MLF*

*Oculomotor nerve*

*Decussation of superior  
cerebellar peduncle*

*PCA*

*Pons*

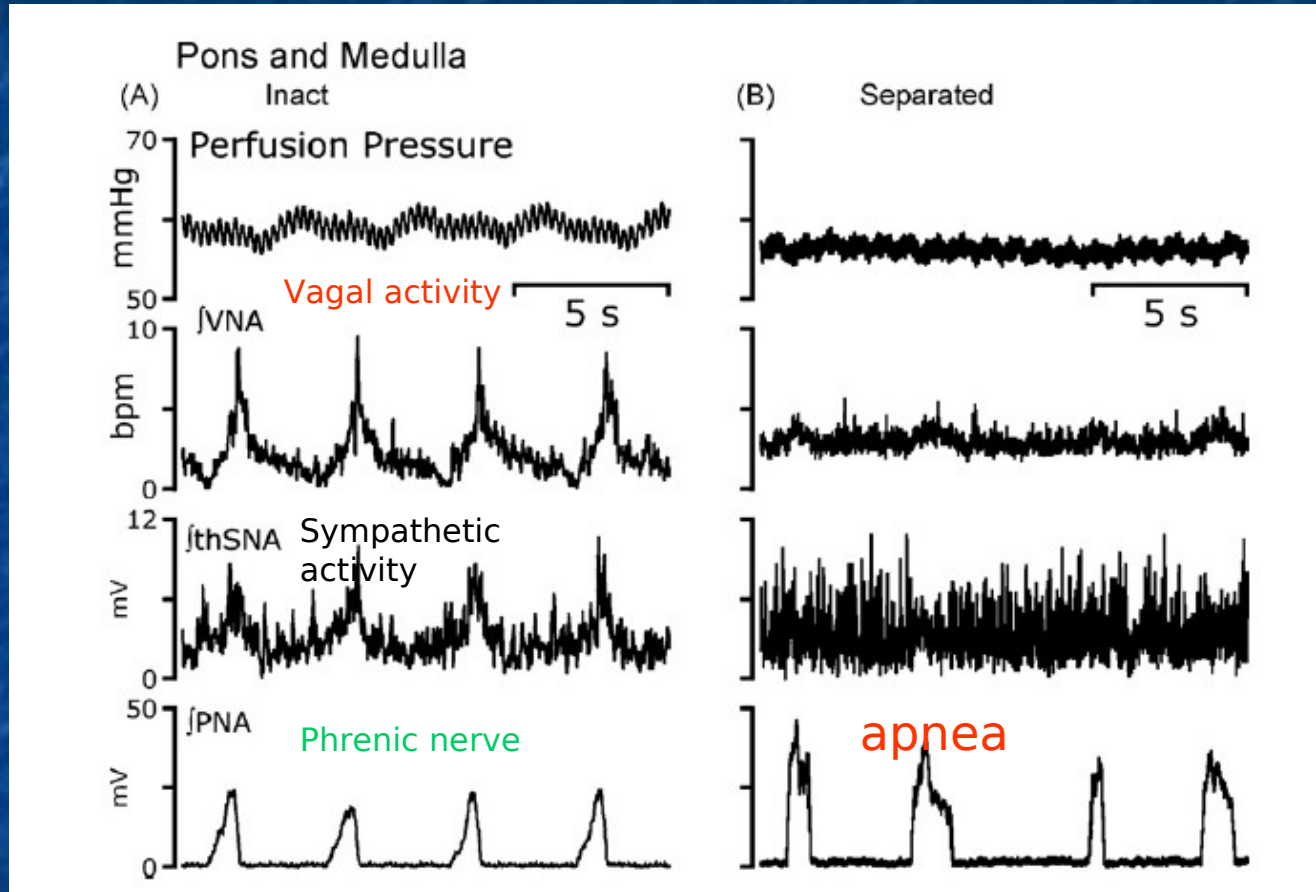
*Median lemniscus*

**1kx1k**

**Resolution 200 microns**

# Ponto-medullary transection

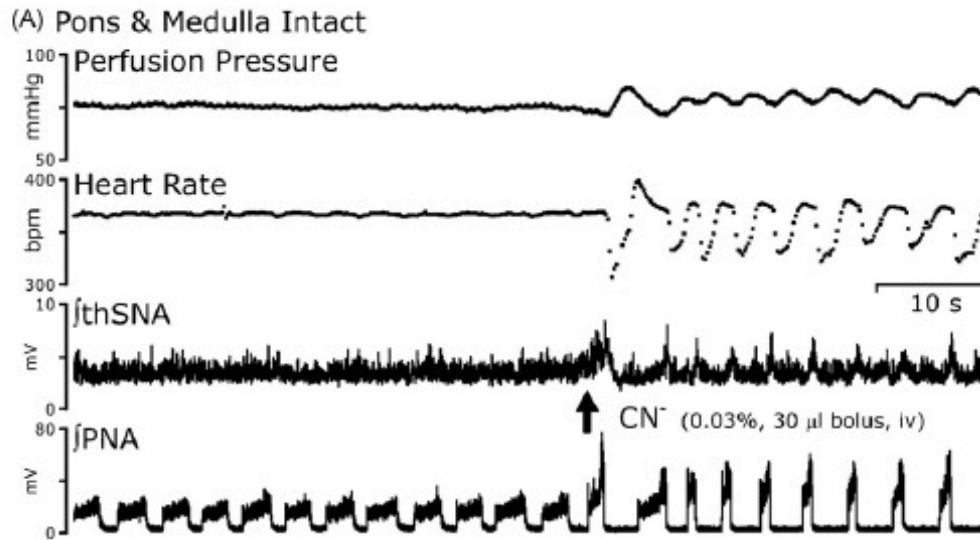
- Eliminates respiratory modulation of cardiac rhythm and sympathetic effectors
- Creates a breathing pattern with apnea (breath holds)
- Small amplitude BP modulation present





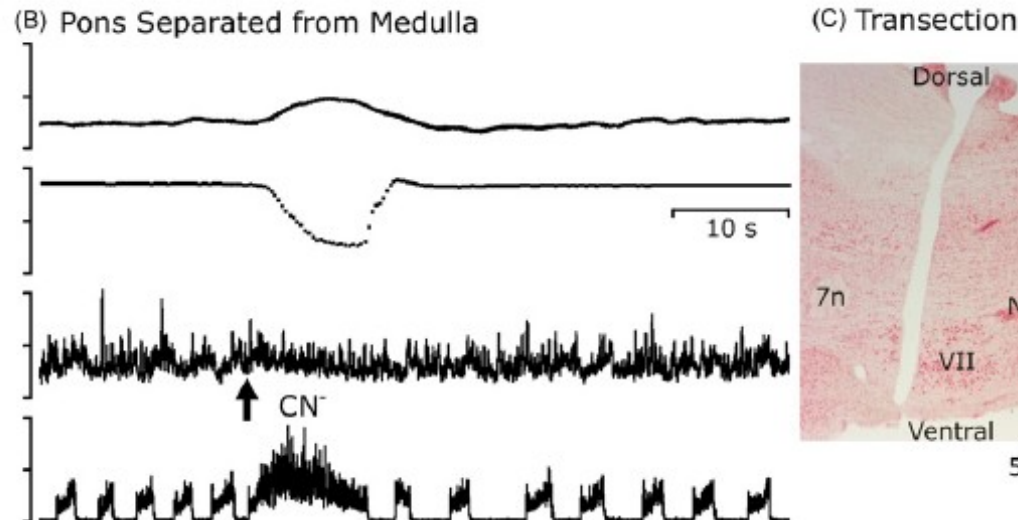
# Ponto-medullary transection

Intact Pons  
and Medulla

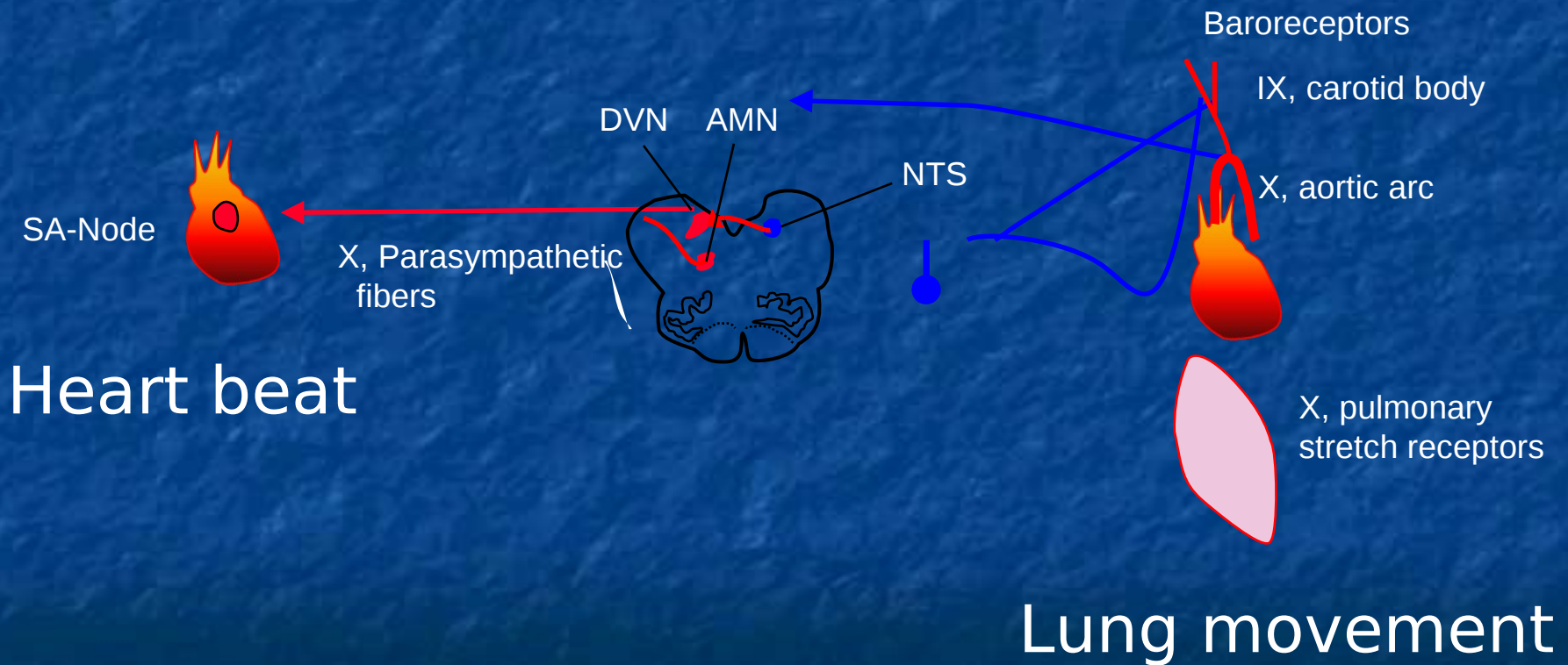


Increased perfusion  
pressure, cyanide  
injection

Pons  
separated  
from  
Medulla



# Deep breathing circuit



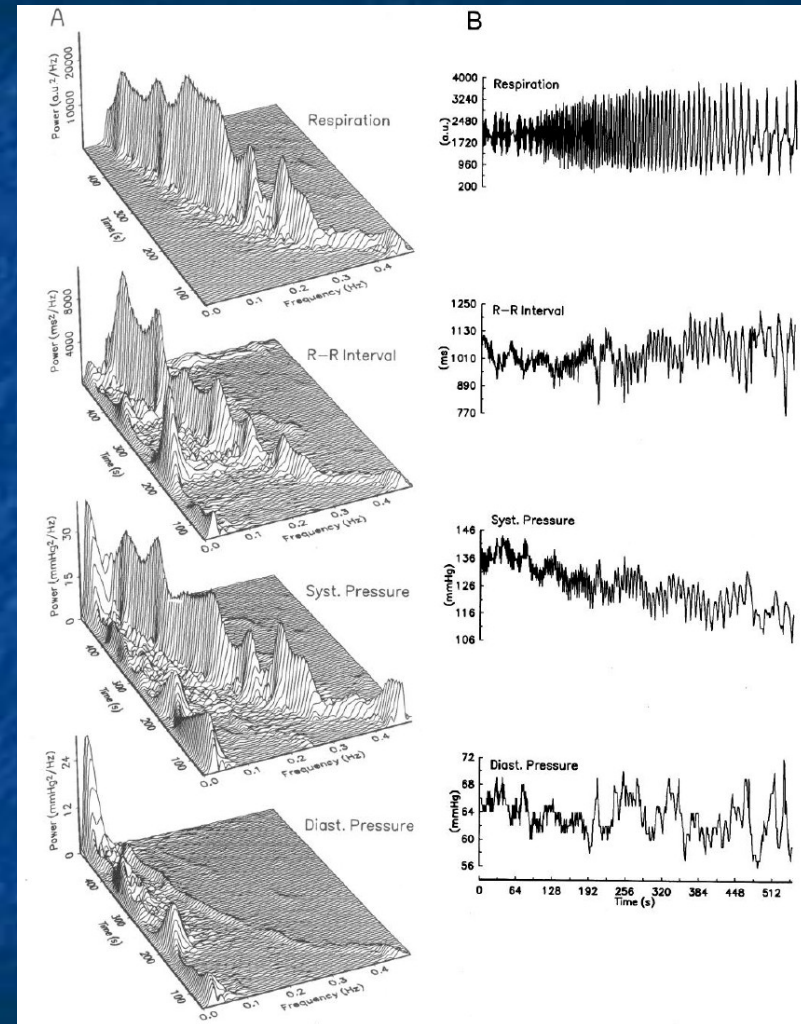
# Cardio-Respiratory Coupling

- Respiration modulates heart beat over a wide range of frequencies from 0.01- 2 Hz

The effects of RSP on R-R internals increases exponentially at slower breathing frequencies

- increased RSP volume
- increased vagal modulation
- increased CO<sub>2</sub>

- Beat-to-beat SBP/DBP are also modulated by respiration
- Amplitude of respiration, R-R intervals, blood pressure also modulated by very slow rhythms < 0.01 Hz



Novak V et al. J. Appl. Phys. 1993; 74: 617-26.

Eckberg et. Al. J. Appl. Phys. 1993;74:

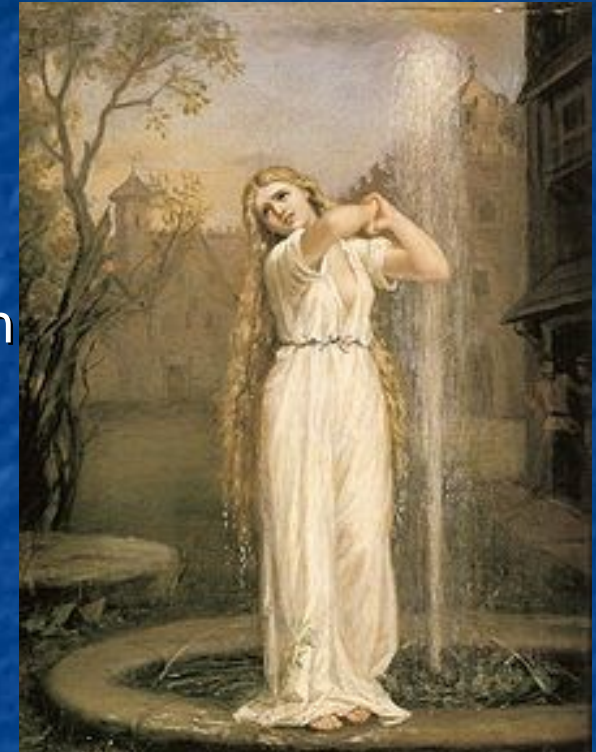


# Brain stem lesions

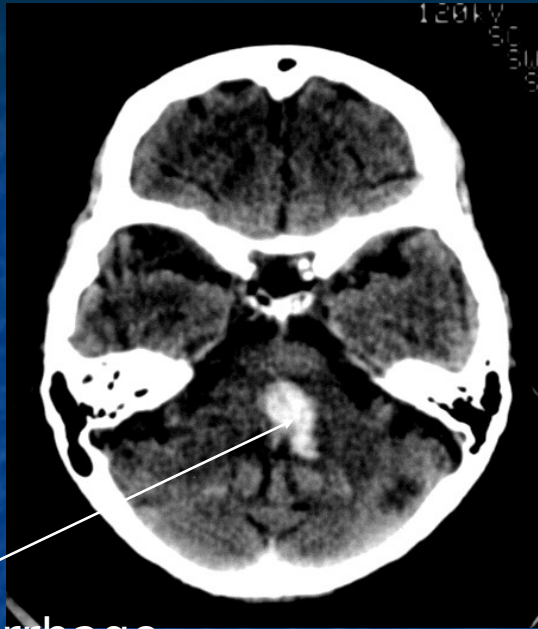
- Death
- “Lock in “ syndrome
- Dysautonomia-hypertension/hypotension
- “Ondine’s curse”

## “Ondine’s Curse” Congenital Central Hypoventilation Syndrome

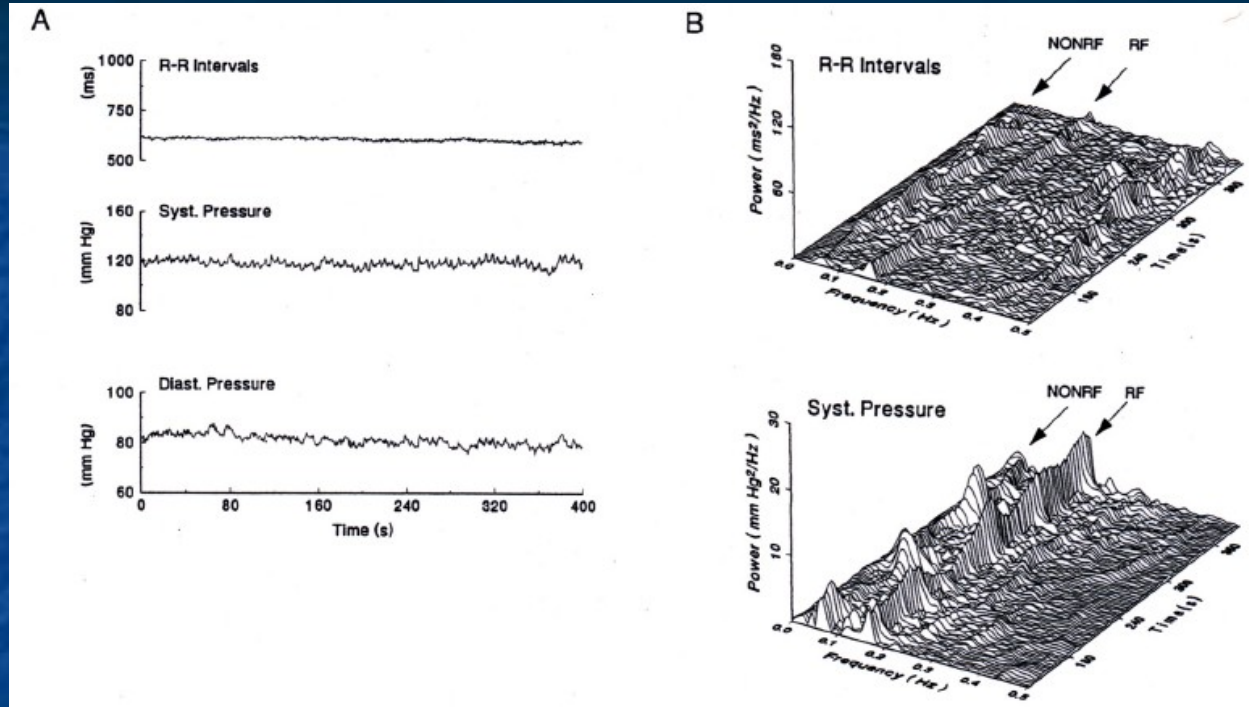
CCHS causes patients to lose autonomic control of breathing, resulting in the need to consciously initiate every breath. If untreated, patients with CCHS will die--like Ondine's unfaithful spouse--if they fall asleep and can therefore no longer consciously breathe.



# Pontine hemorrhage- Brain Stem death



hemorrhage



- 81yr old F with pontine hemorrhage, unconscious
- Artificially ventilated at 0.15 Hz
- R-R oscillations abolished (only minimal amplitude)
- Systolic BP oscillations both respiratory and slow oscillations (Mayer waves) present



# Cardiac-Locomotor Coupling



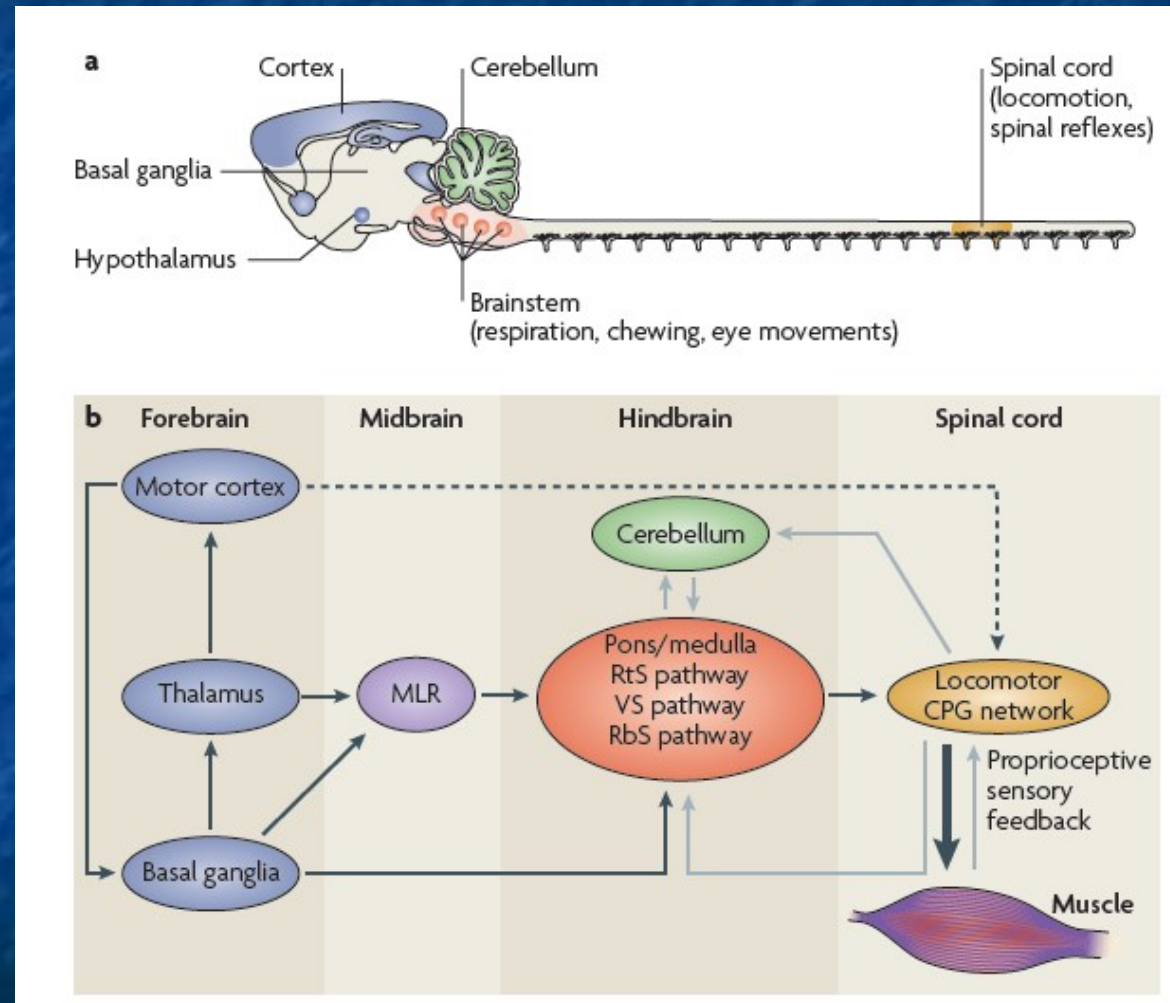


# Cardio-locomotor coupling (CLC)

- Coupling between locomotor, respiratory and cardiac rhythms has been reported in humans during walking and running, cycling, in response to periodical thigh pressure and finger tapping, (Kirby 1989, Niizeki 1993, Nomura 2001, Niizeki 2005).
- Respiratory-locomotor coupling- wheelchair propulsion (Lou, 2003) and in animals.
- Cardio-locomotor coupling was enhanced during periods when cardio-respiratory coupling (RSA) decreased.
- Coupling is short lasting and typically occurred during walking or running at faster speeds.
- Kirby (1989) - heart and step rate within 1% of closest

# Locomotor circuits

- Voluntary control
- Central pattern generator circuit-basal ganglia- sensory-motor cortex
- Sensory inputs
- Spinal reflexes
- Feedback



# CLC-Central Theory

- Central coupling between locomotor activity and heart rate was demonstrated by stimulation of the locomotor mesencephalic area in decerebrated vagotomized cats (Kawahara, 1993).
- “ Fictive gait” – coherences an entrainment between EMG discharges in gastrocnemius m., phrenic nerve activity and ECG.
- Locomotor circuits generating patterns and timing of the gait cycle interact with cardiac and respiratory centers in the brainstem and upper medulla (Guadagnoli, 2000).
- A hierarchical model of central command was proposed, based on temporary synchronization from locomotor to respiratory to cardiac rhythms.



# Central CLC

Central command



Locomotor  
circuits



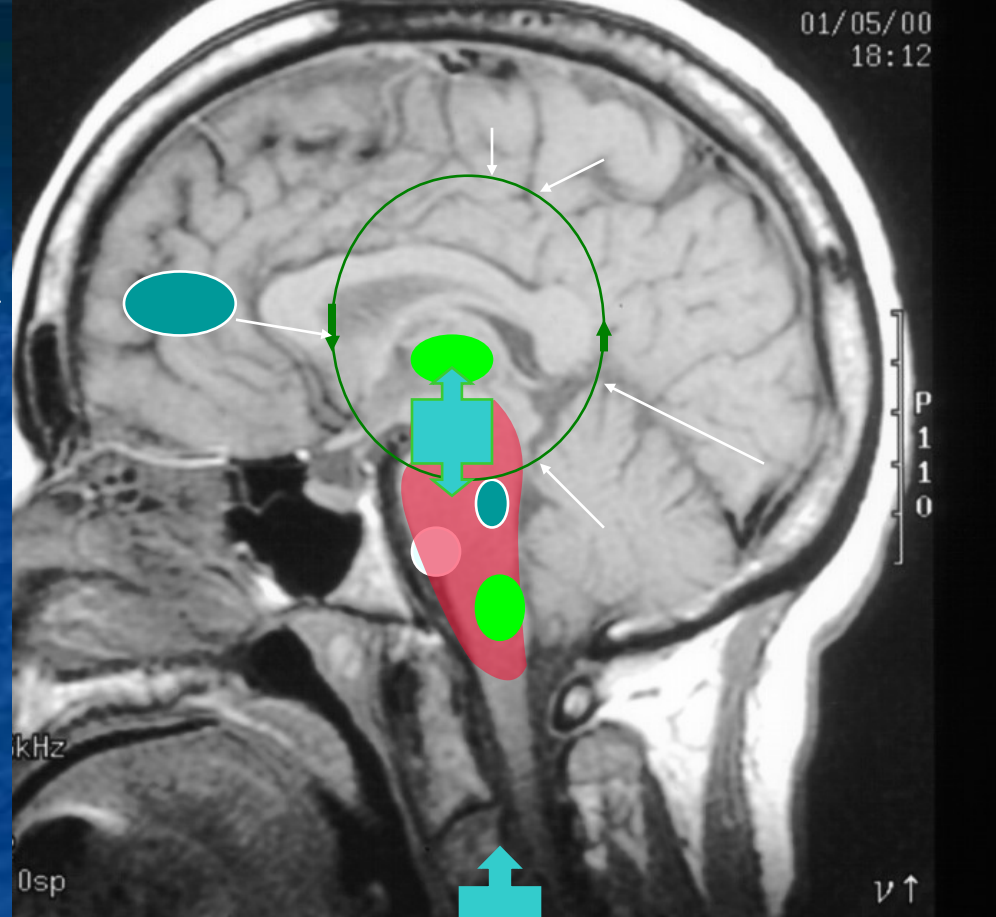
Cardiac

Respiratory

Motor



Walking



Visual Cortex

Cerebellum

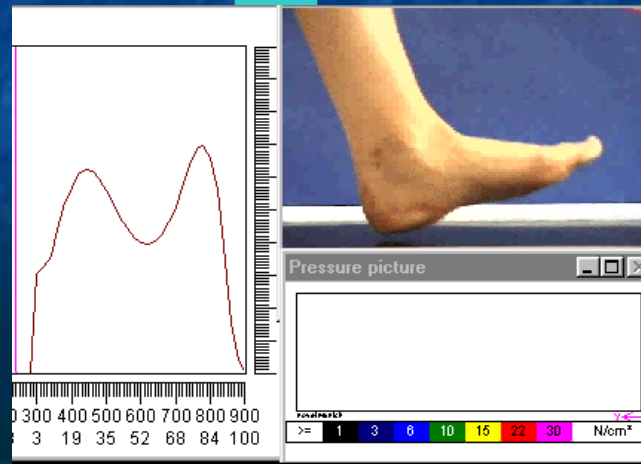
Vestibular  
system

Prefrontal  
cortex

Sensory  
Cortex

Motor Cortex

Autonomic  
networkV



# CLC- Peripheral theory

- Changes in intramuscular pressure, muscle tone and blood flow in exercising muscle provide periodical inputs to cardiovascular system.
- The peripheral concept of cardiac-locomotor coupling was based on phase dependency between active muscle contraction and cardiac cycle (Nomura 2003, Niizeki 1999)
- CLC occurs because the afferent signal from active muscle by via sensory group III afferent activity to parasympathetic cardiac centers.
- Positive slope between EMG and RRI in the first  $\frac{1}{4}$  of cardiac cycle and negative slope for remaining  $\frac{3}{4}$  of cardiac cycle (Niizeki and Miamoto 1999)



# ■ Walking speed

a marker of an overall functional state,  
hallmarks frailty in the elderly

- Central command
- Rhythmic pattern
- Muscle strenght
- Sensory inputs
- Cardiovascular response

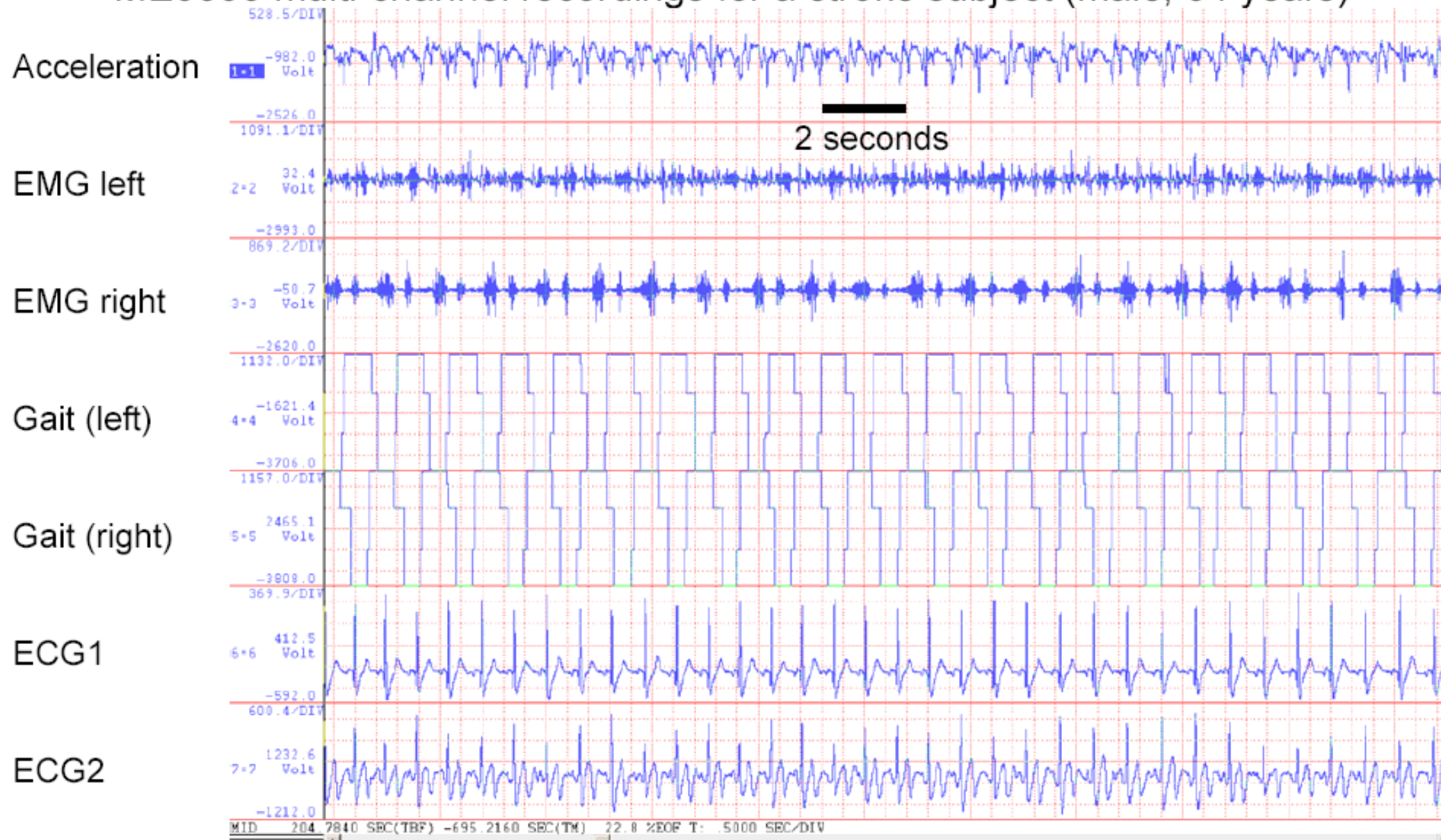




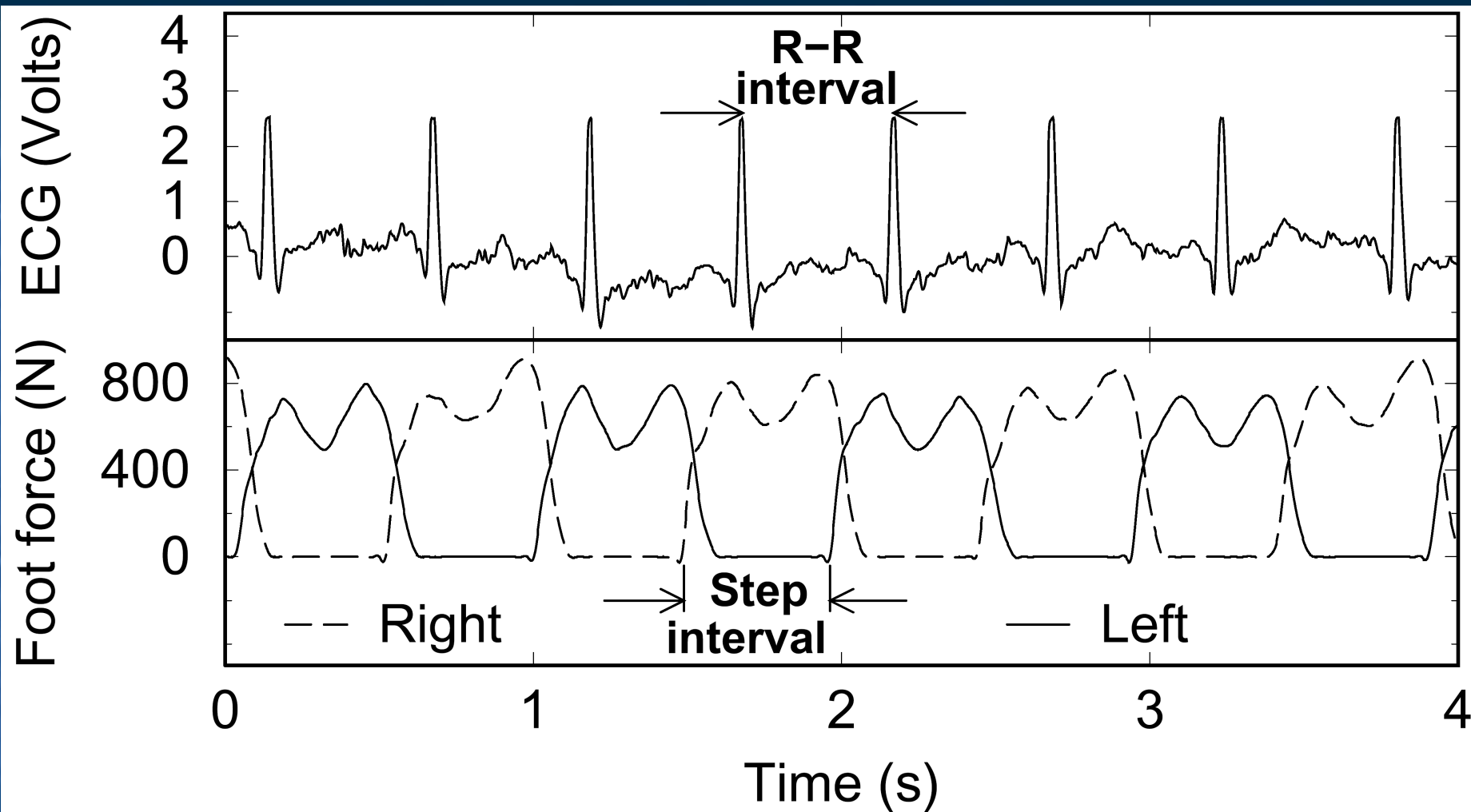
# Walking in Aging

- Walking is a complex act that requires the coordination among locomotor, cardiovascular and autonomic systems. Aging may affect each of these systems and alters physiological mechanisms regulating interactions between them.
- The processing speed and sensitivity of end-organs to central and peripheral stimuli decline with age.
- Degradation of feedback mechanisms contributes to diminished responses to stress.
- Gait abnormalities - slow speed, unsteady patterns and falls predict development of vascular dementia and adverse outcomes in elderly people (Verghese, NEJM

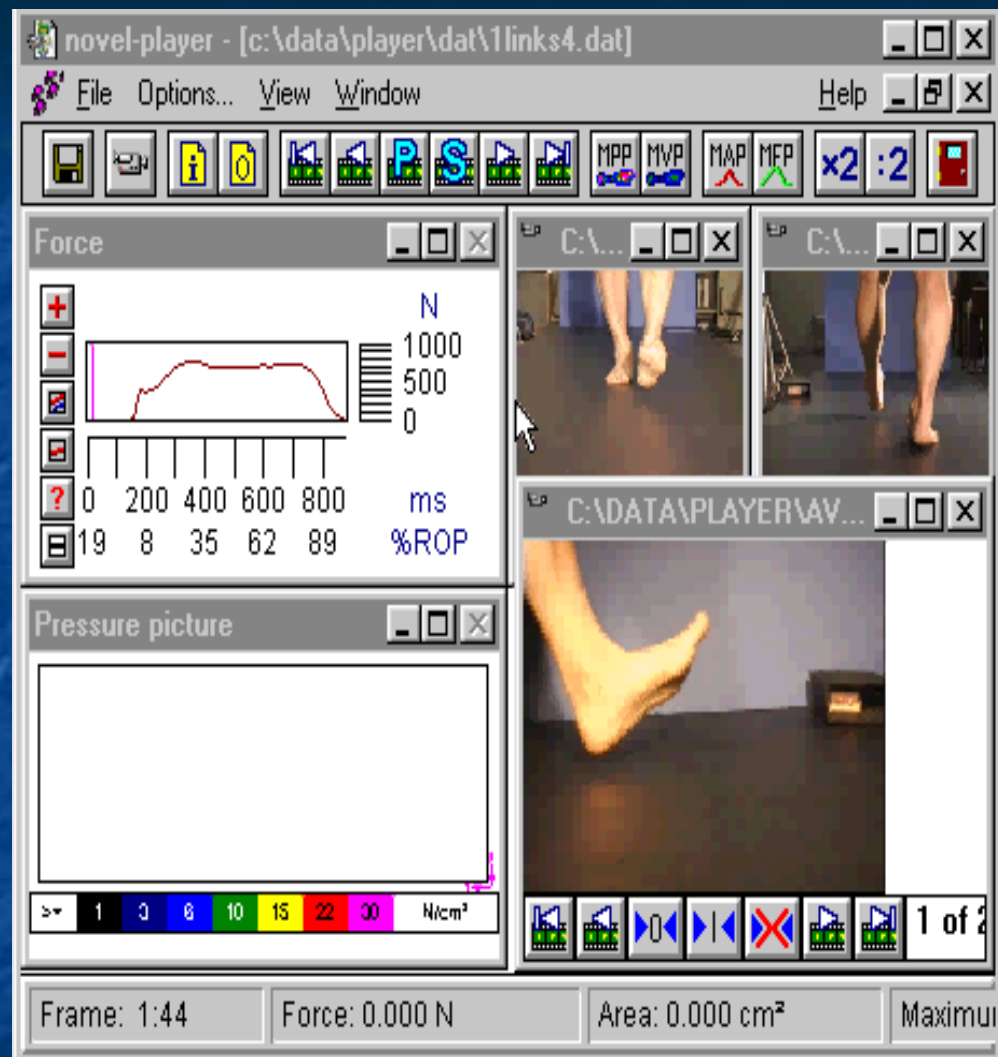
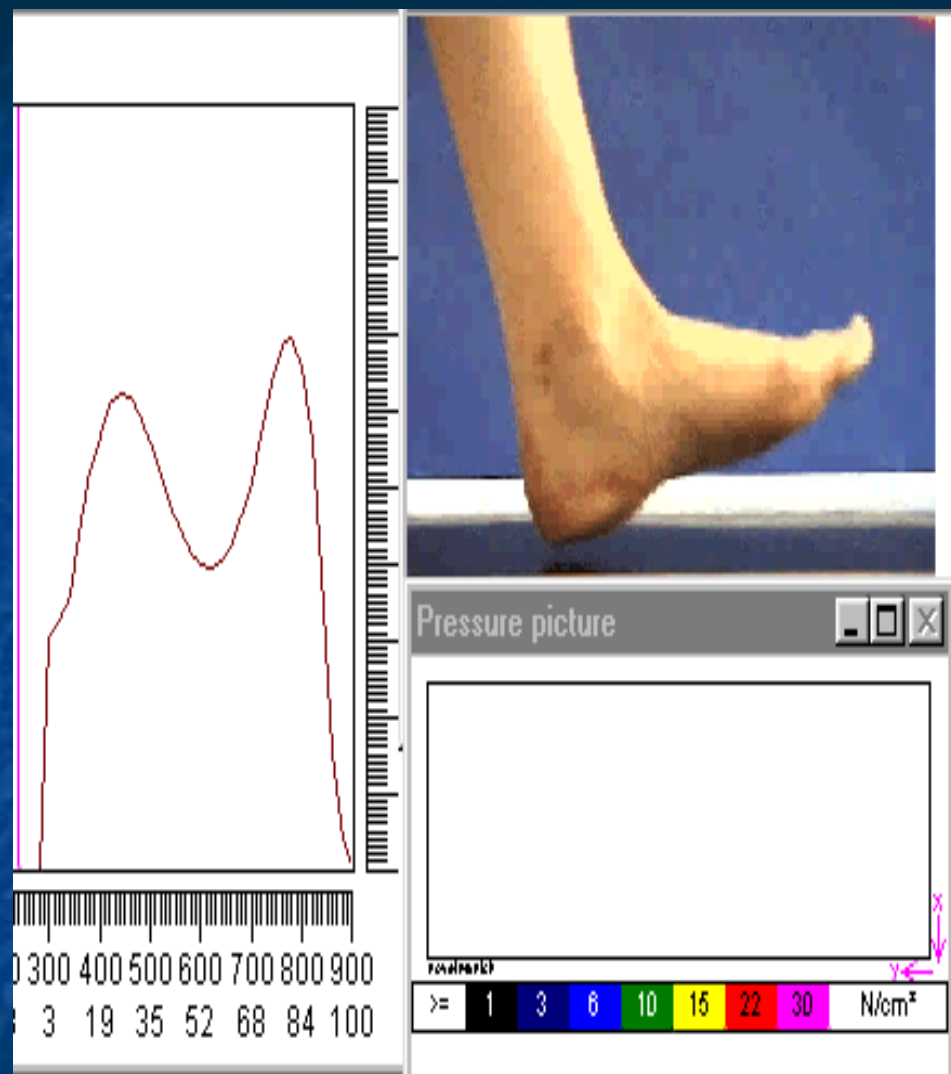
# ME6000 multi-channel recordings for a stroke subject (male, 64 years)

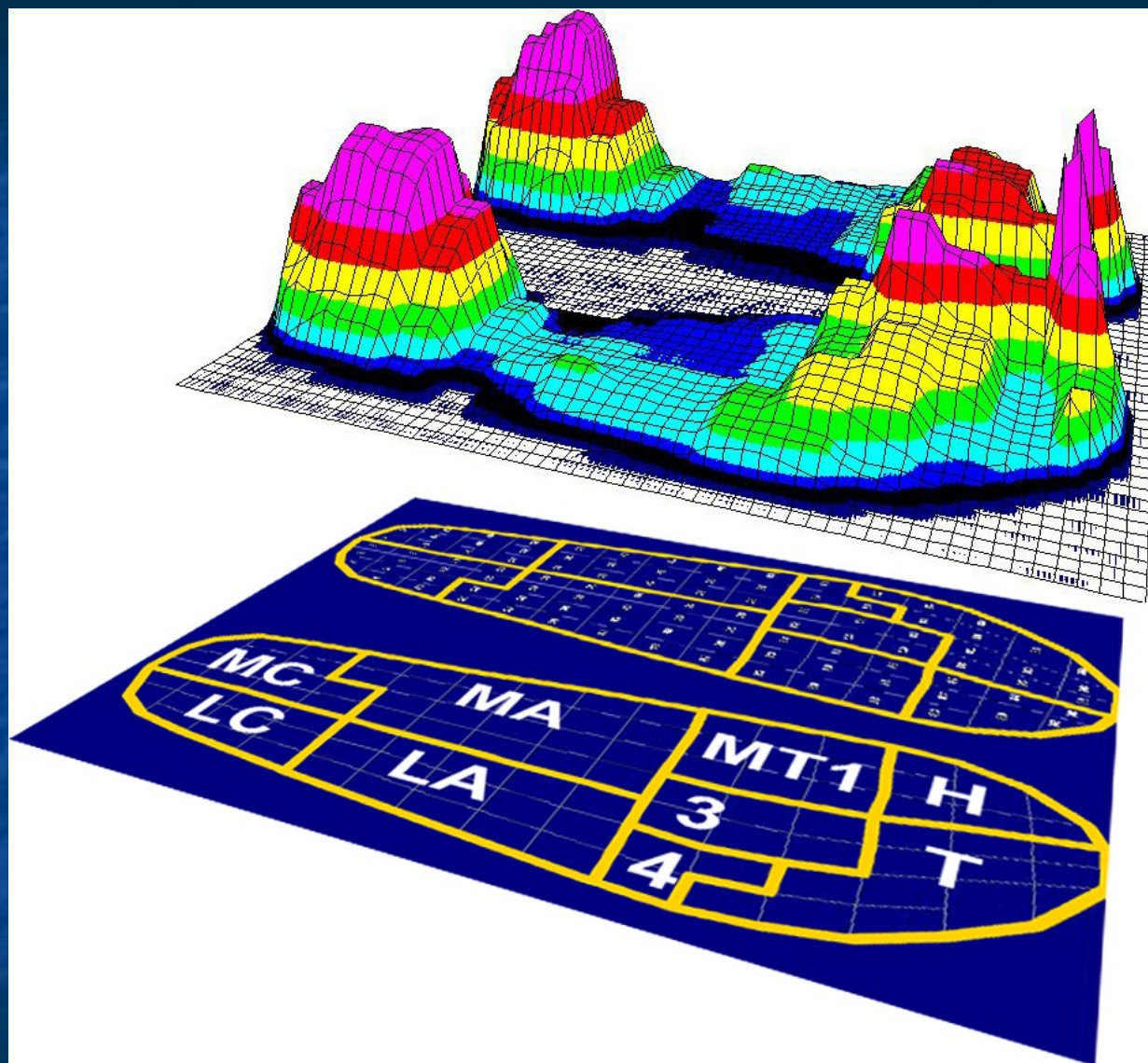


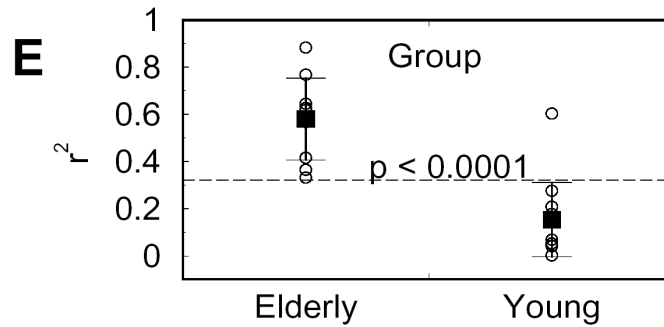
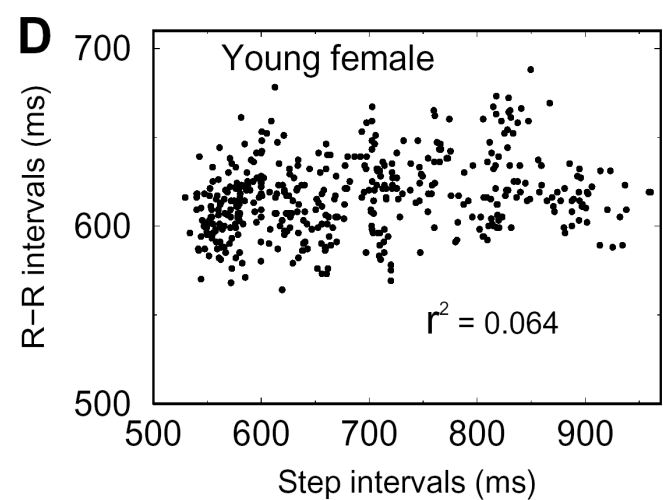
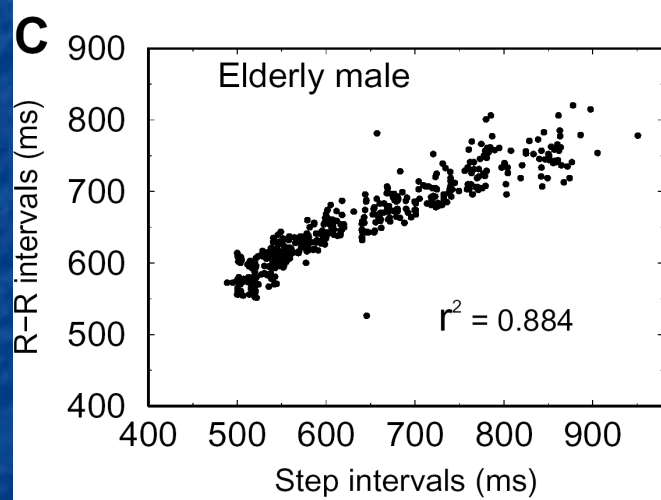
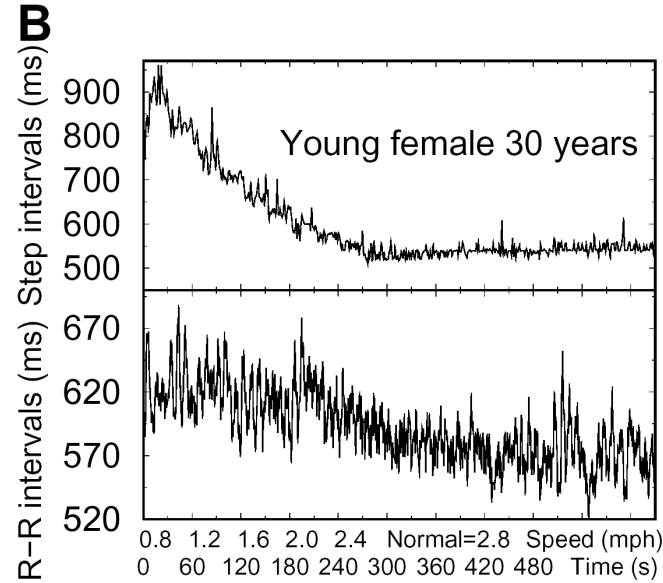
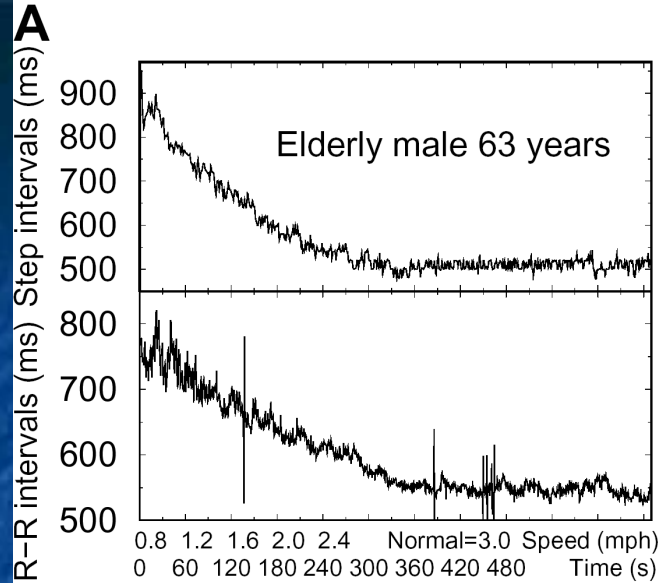
Hallway walking







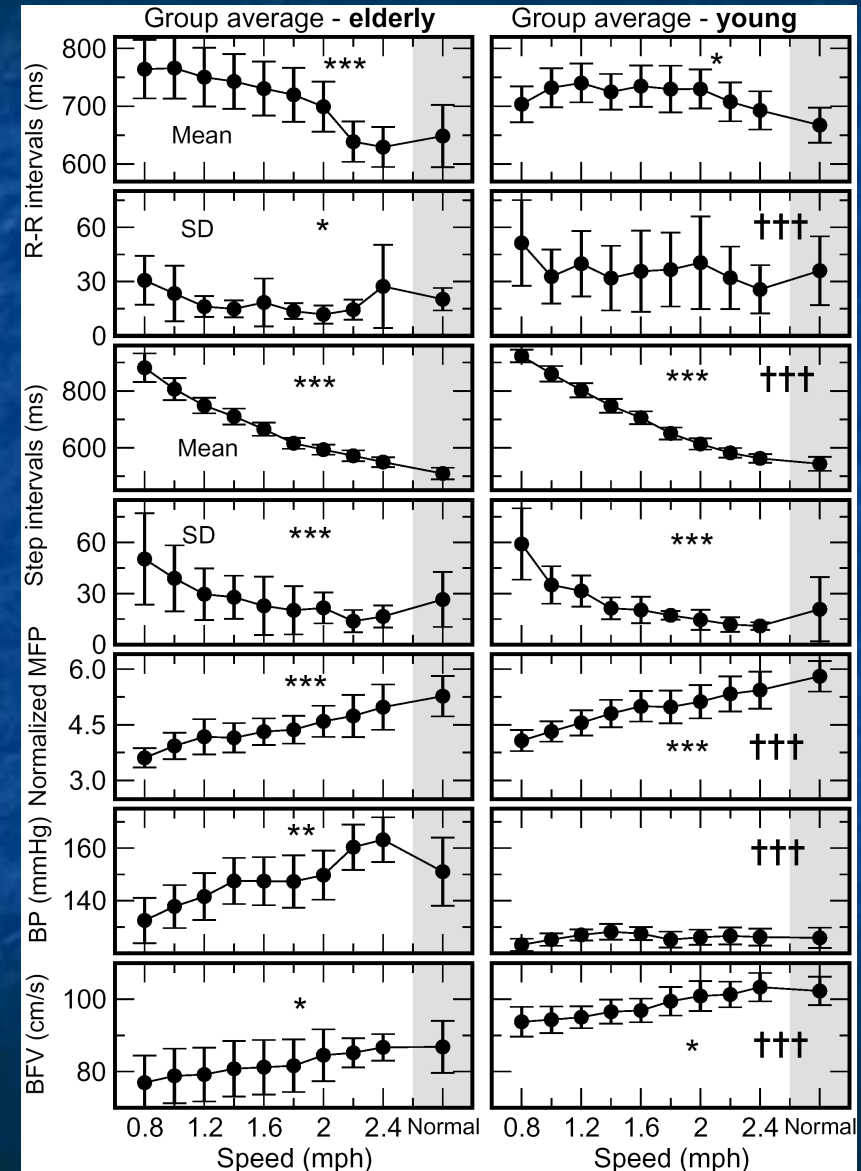






# CLC in Aging

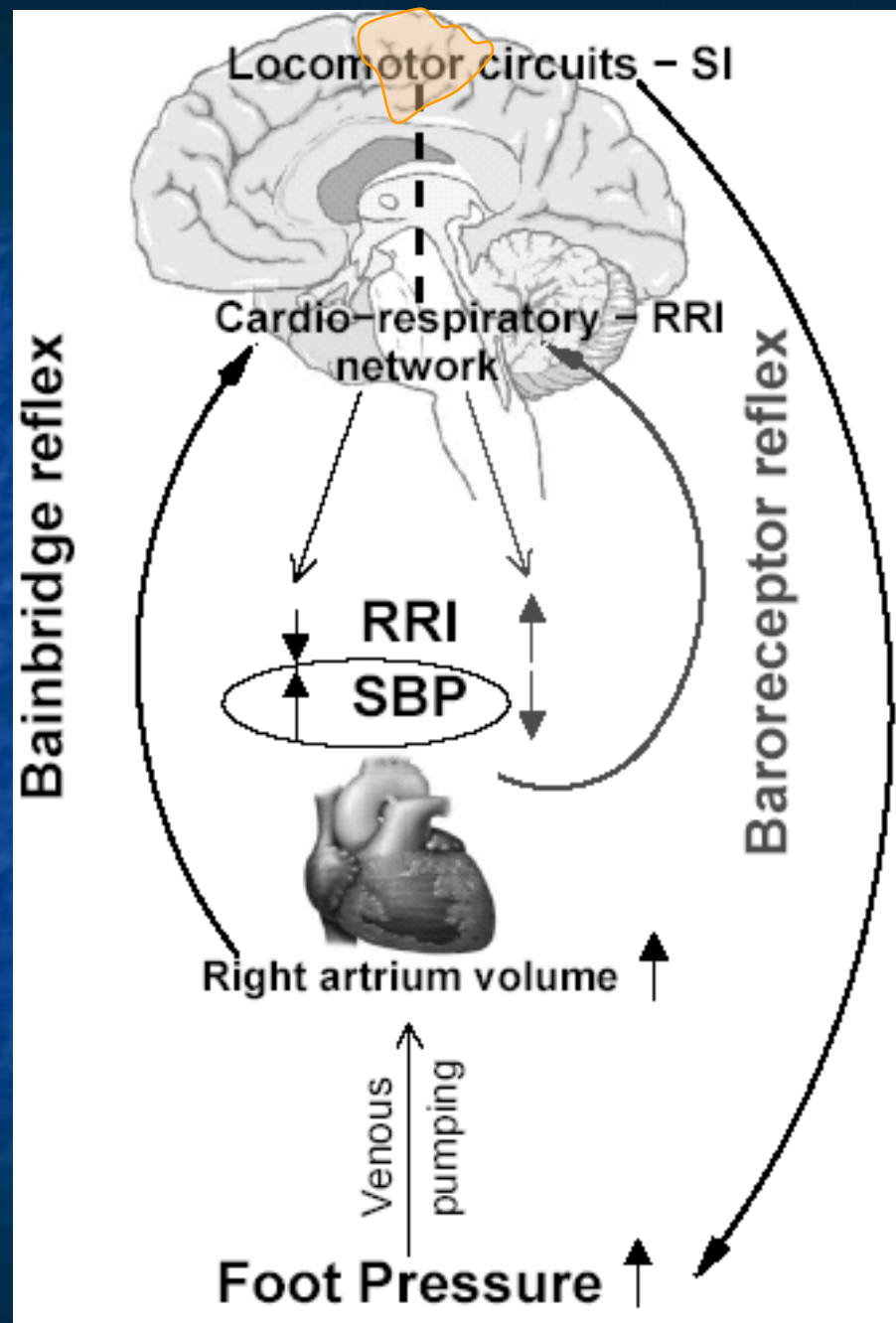
- For similar walking speed and heart rate, old adults showed lower HR and step interval variability, lower force, greater blood pressure and lower blood flow velocity.
- In young subjects, beat-to-beat increases in systolic BP are dampened by the baroreflexes, leading to R-R interval prolongation and increased R-R interval variability, stable BP and cerebral blood flow.
- Cardio-locomotor coupling and periodic increases of blood pressure may improve adaptation to exertion and may have positive effects on brain perfusion in old people.



Central  
Command  
↓  
Regional  
perfusion  
autoregulation

Locomotor  
Respiratory

Cardiac



# Cardio-locomotor coupling

- Cardio-locomotor coupling that becomes manifest with aging may optimize cardiovascular adaptation to walking. In elderly people, forces generated during the gait cycle may be transmitted to arterial pressure and thus synchronize the central cardiovascular network with the stepping rhythm.



# Postural-Respiratory Coupling



86 yr old kiteboarder

<http://www.youtube.com/watch?v=4ufqy9p8c94>







# Postural Control

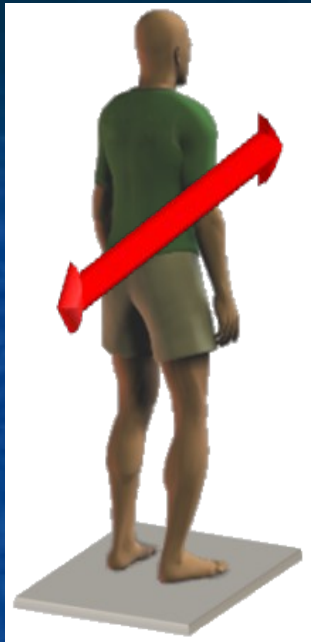
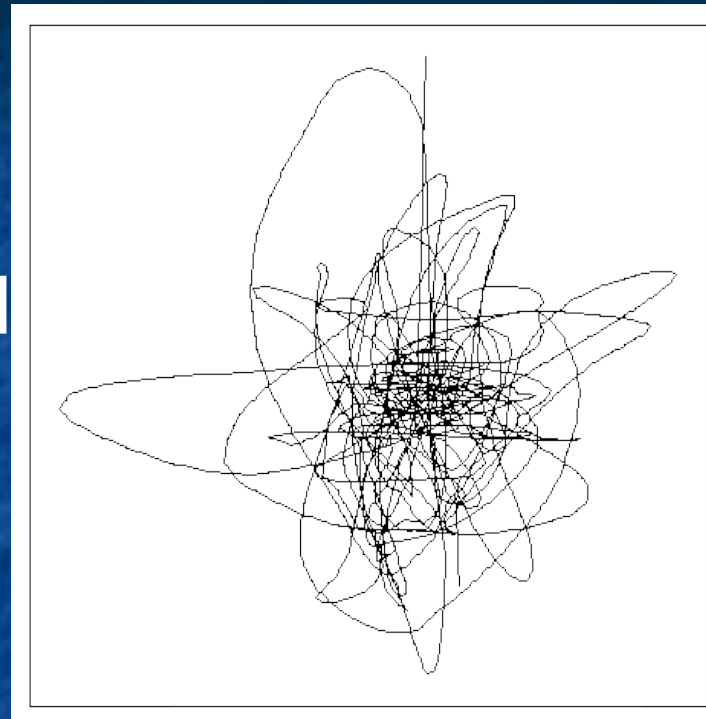
Postural control is regulated by a complex system comprised of somatosensory, visual and vestibular sensory elements, ascending and descending neural pathways, numerous brain regions, and the musculo-skeletal system.

- Voluntary-central command
- Body position-vestibulo-sympathetic reflex
- Motor response
- Proprioceptive inputs (sensory, joints, tendons etc..)
- Cardiovascular response- blood pressure, HR
- Brain Perfusion
- Feedback



# Posturo-Respiratory Coupling

- The dominant oscillatory mode of respiration and the corresponding oscillatory mode of anteroposterior center-of-pressure dynamics were extracted from each signal using empirical mode decomposition (Huang et al 1998).
- Instantaneous phase shifts between the two extracted oscillatory signals were calculated over the entire trial using Hilbert transform, and were used to obtain the degree of posturo-respiratory coupling using an entropy-based synchronization analysis.

**A****Force Platform****B****Anterior****Medial****Lateral****Posterior**

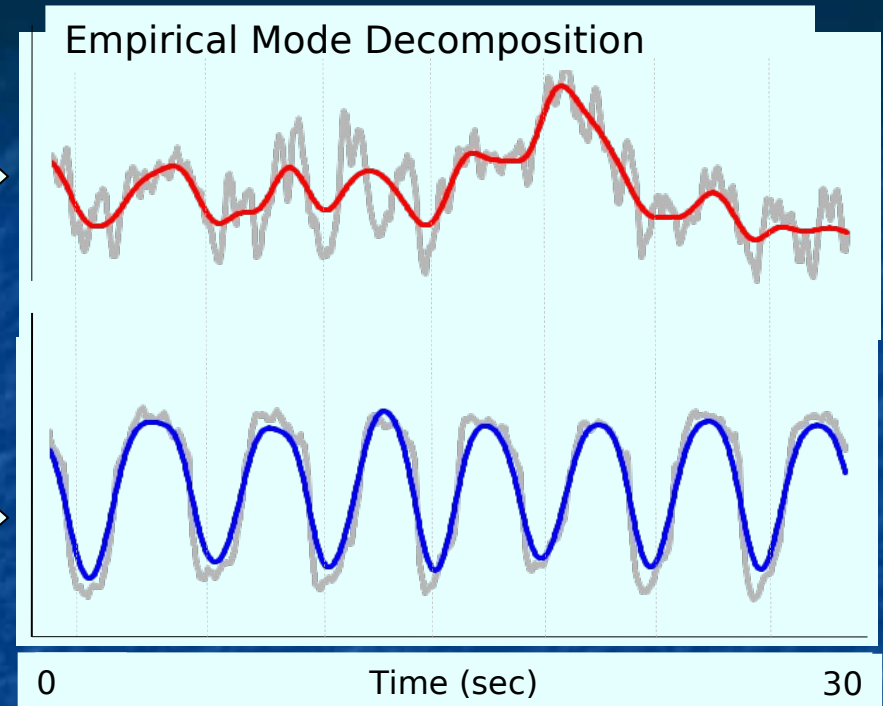
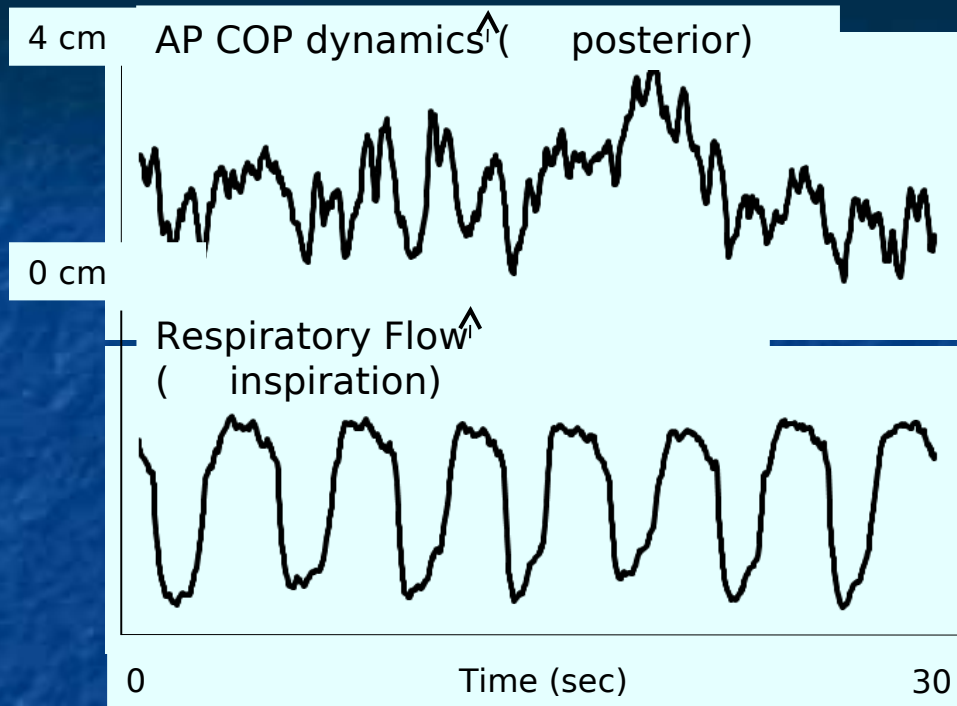
■ Respiration continuously perturbs the body's center-of-mass (red arrow) (A). The postural control system compensates for these perturbations, thereby minimizing their effect on center-of-pressure movement (B) beneath the feet.

■ Spontaneous respiration perturbs the body's center of mass during quiet standing (Schmid et al 2004), thereby contributing to complex, non-linear center-of-pressure dynamics beneath the feet.

# Postural-Respiratory coupling

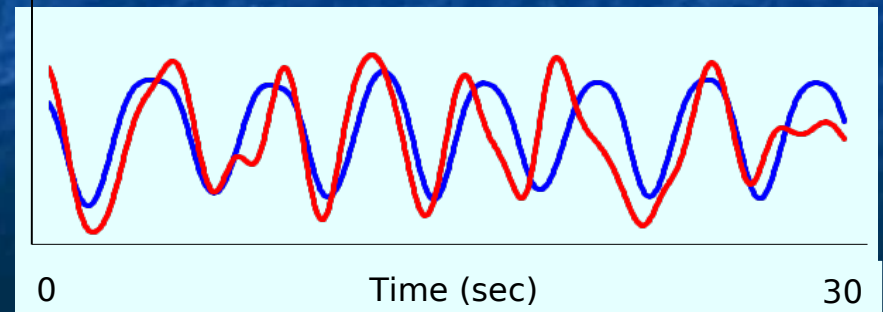
- Degradation of the control system, as might occur in aging and neurological diseases, may reduce compensatory control and lead to increased “posturo-respiratory coupling.”
- We hypothesized that both aging and stroke are associated with increased posturo-respiratory coupling during upright stance.



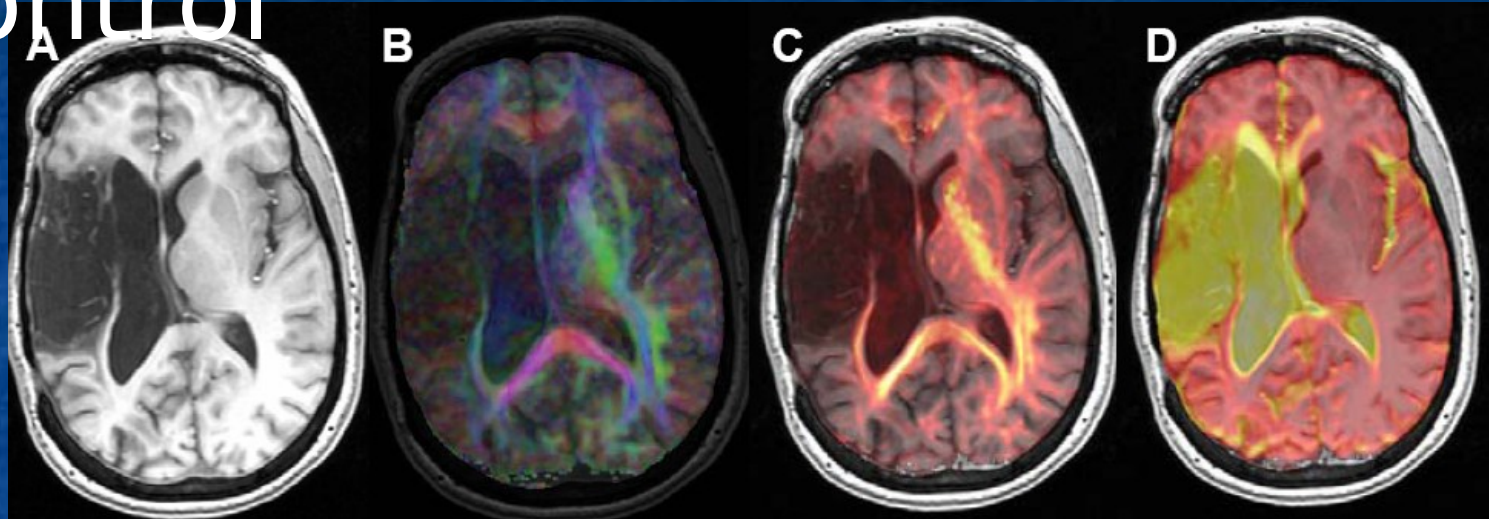


Determination and comparison of corresponding oscillatory modes of simultaneously recorded antero-posterior center-of-pressure and respiratory flow dynamics.

### Comparison of oscillatory modes



# Stroke-disrupts postural control



## Subjects

25 with chronic cerebral infarctions (15 females, aged 51-79yrs, height =  $1.68 \pm 0.10\text{cm}$ , body mass =  $76 \pm 14\text{kg}$ )

35 age-matched controls (22 females, aged 50-80yrs, height =  $1.67 \pm 0.11\text{cm}$ , body mass =  $71 \pm 13\text{kg}$ )

## Protocol

Subjects stood on a force platform with eyes-open and eyes-closed for 3-min each.

Center-of-pressure fluctuations and respiratory flow volumes were simultaneously recorded.

# Stroke effects on

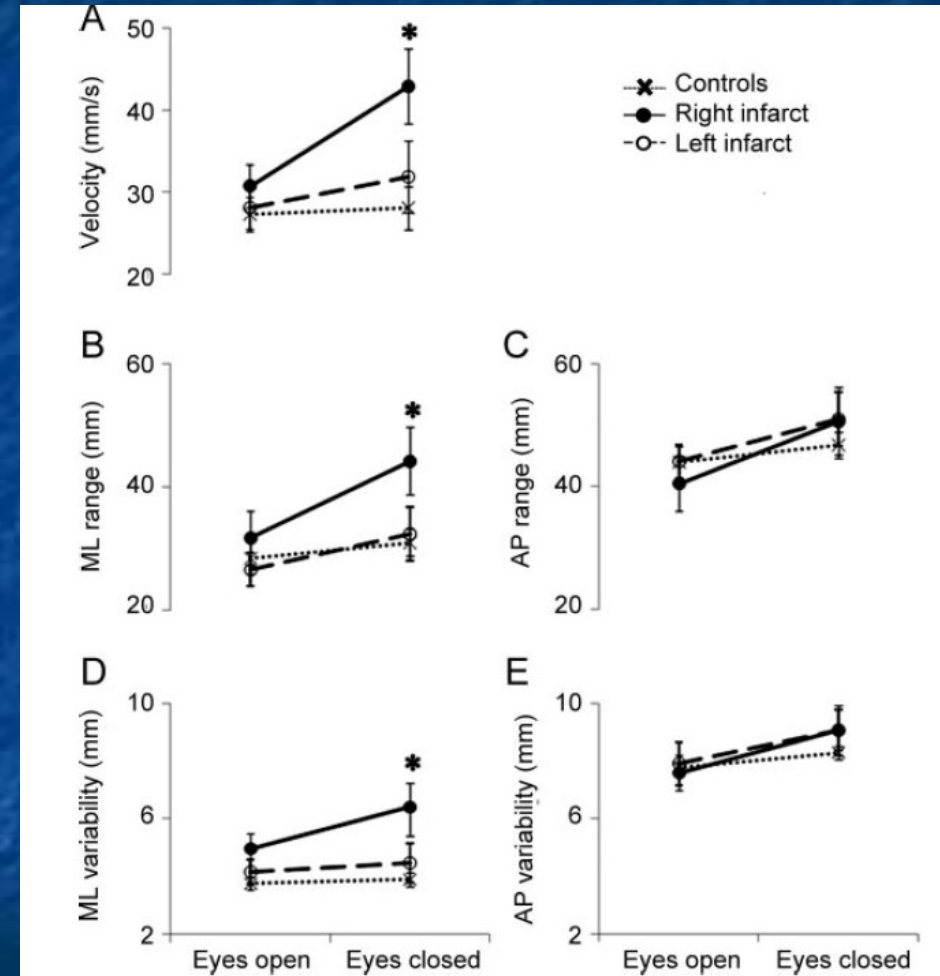
## Balance

- a. Sway velocity
- b. Mediolateral range
- c. Anteroposterior range
- d. Mediolateral variability
- e. Anteroposterior variability

Stroke patients had worse balance with

Only right-sided infarctions

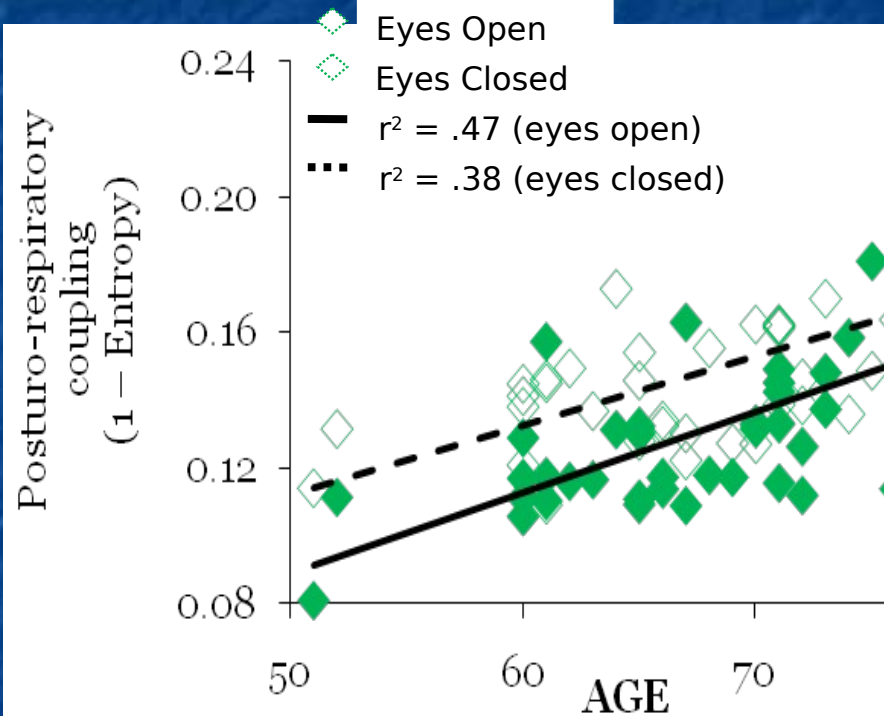
Only with eyes closed



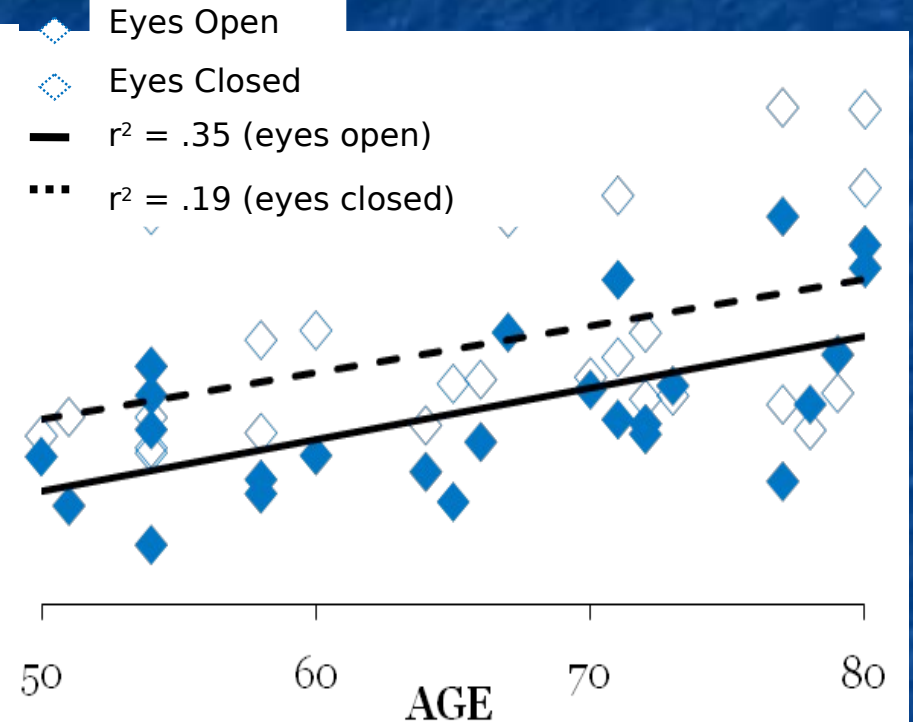


# Balance-Respiratory coupling

**A Older Adult Controls**

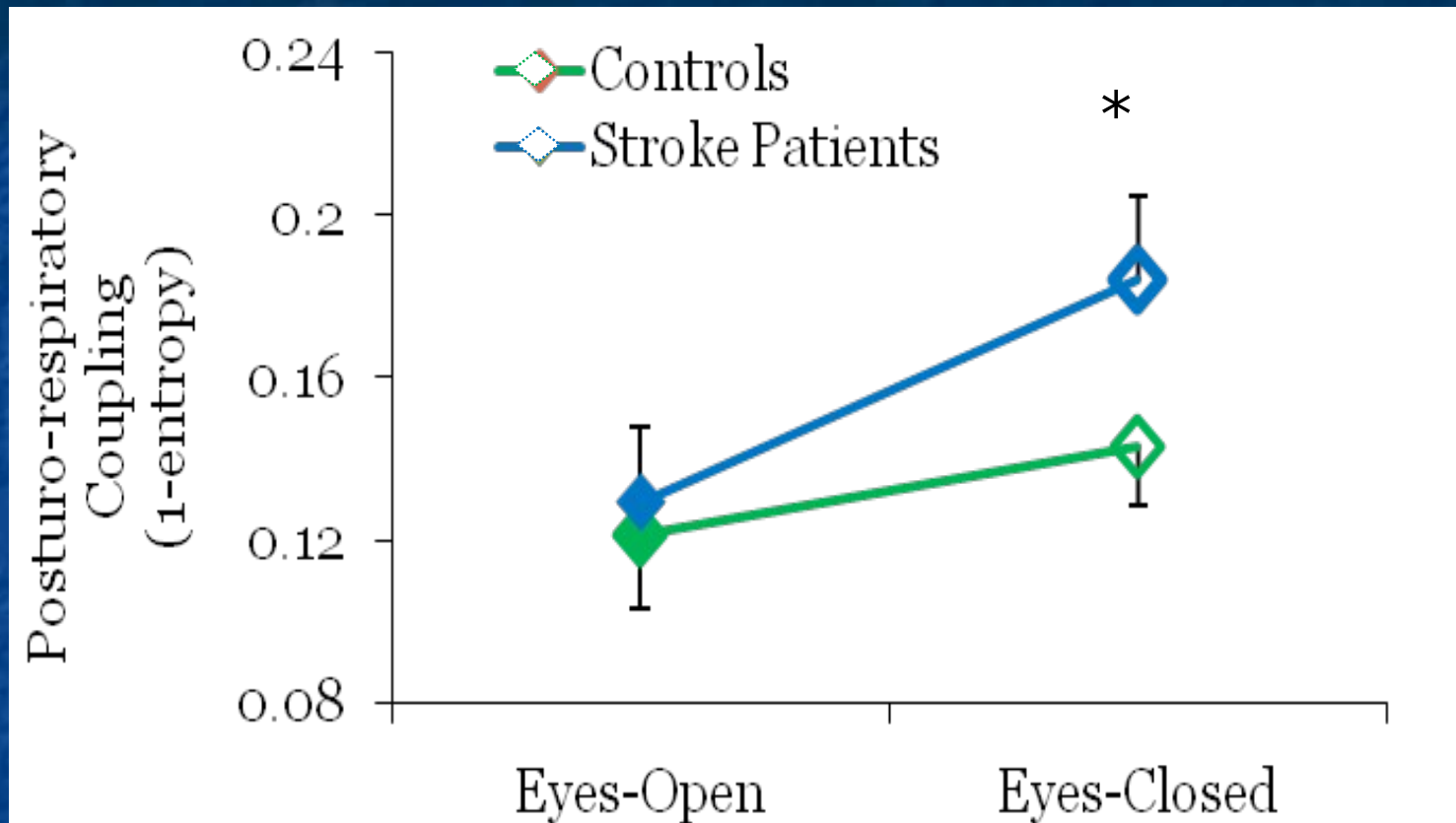


**B Chronic MCA Infarct patients**



Posturo-respiratory coupling is stronger with increasing age in controls (A) and stroke patients (B) during standing with eyes open and eyes closed.

# Balance-Respiratory coupling



Stroke patients demonstrated an exaggerated increase in coupling when asked to stand with eyes closed when compared to controls. \* indicates a group X condition interaction ( $p = 0.03$ ).

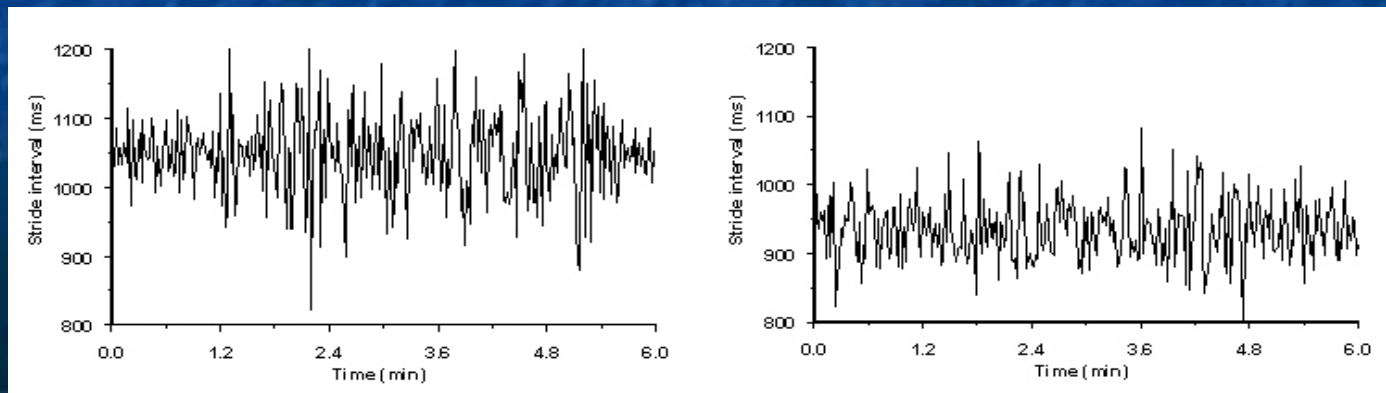
# Posturo-respiratory coupling

- Evidenced by increased posturo-respiratory coupling, the control system responsible for dissipation of respiratory perturbations is dependent upon vision and degrades with advancing age and stroke.
- Future studies outlining the central and/or peripheral pathways involved in this control system are therefore warranted.



# Posturo-respiratory coupling & improved balance

- Enhancement of sensory feedback
- Vibration stimulation of the soles improves gait and balance in Parkinson's Disease
- Posturographic training
- Tai-chi- combines deep breathing with postural control – improves balance









# Cardiac-Postural Coupling



Credit: U.S. Army Golden Knights





# Clinical implications of cardiovascular control failure

- Falls
- Syncope
- OH
- Strokes



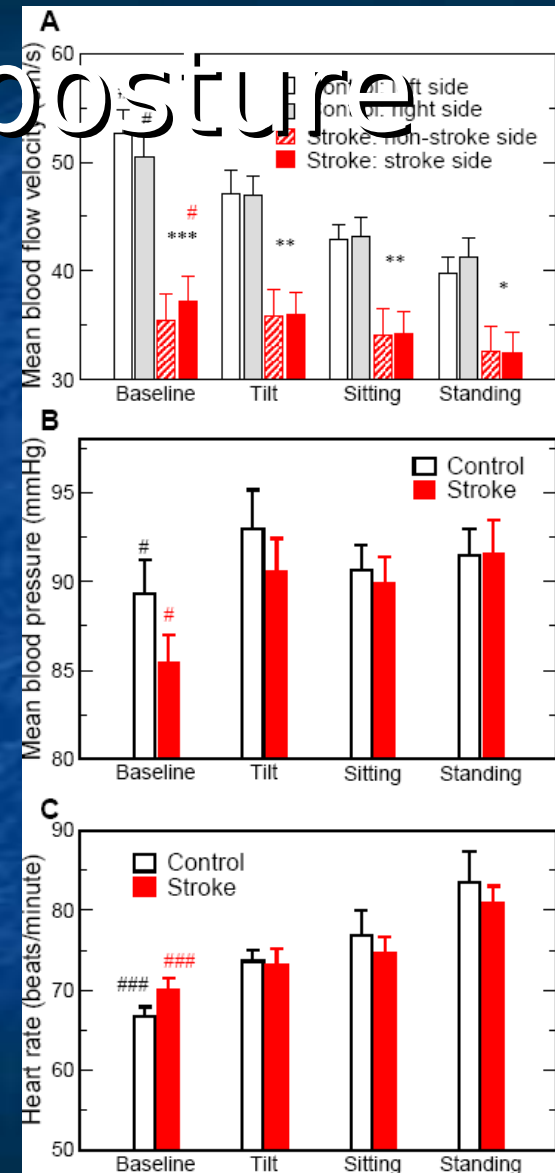


**Jerk Chicken**



# Cerebro- cardiovascular responses to upright posture

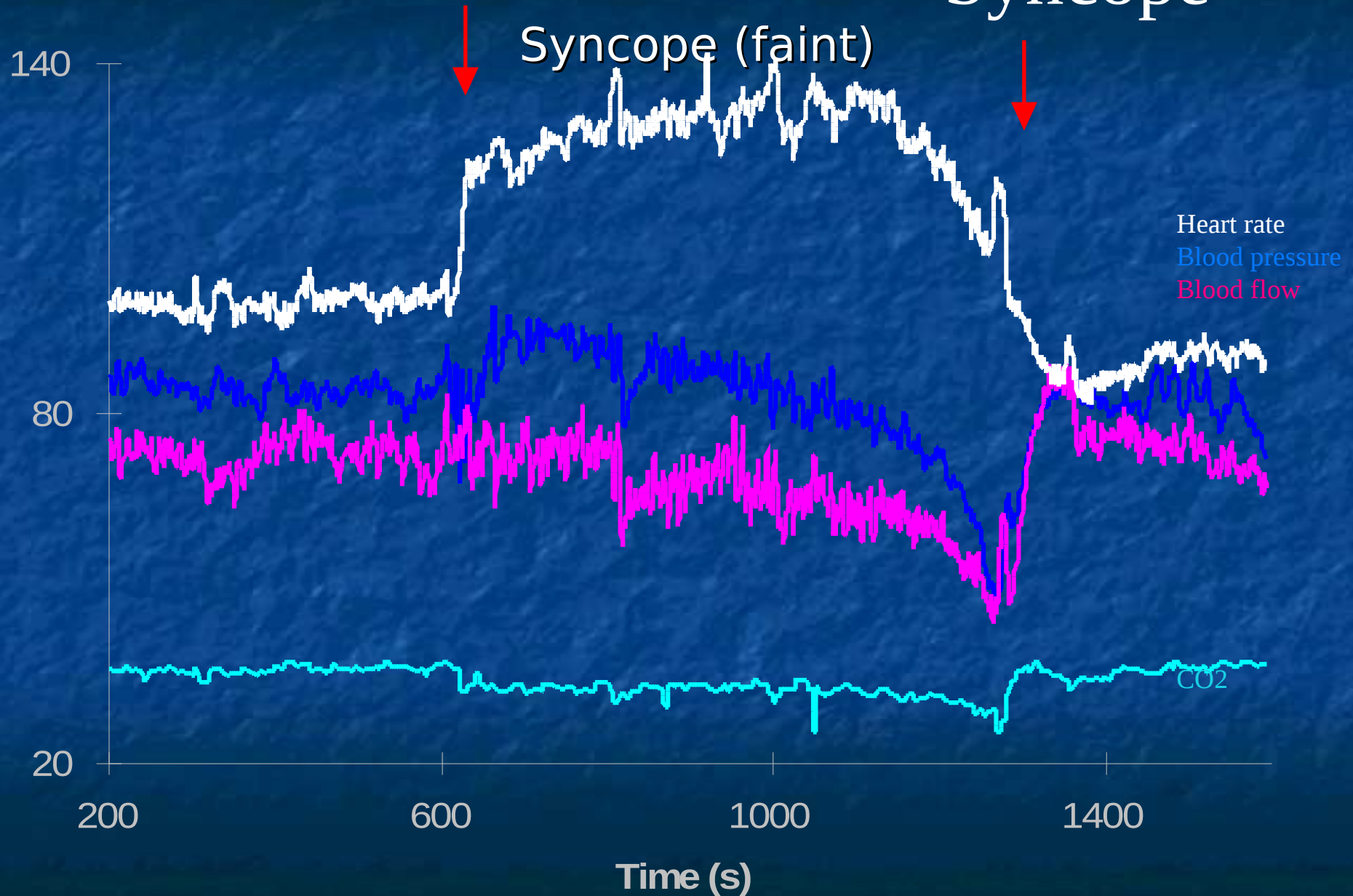
- Heart rate and blood pressure increases in responses to sitting, standing and tilt
- Cerebral blood flow velocities, decline in upright posture in older adults
- Decline in blood flow velocities is more prominent after a stroke
- Flow velocities post-stroke become dependent on perfusion pressure





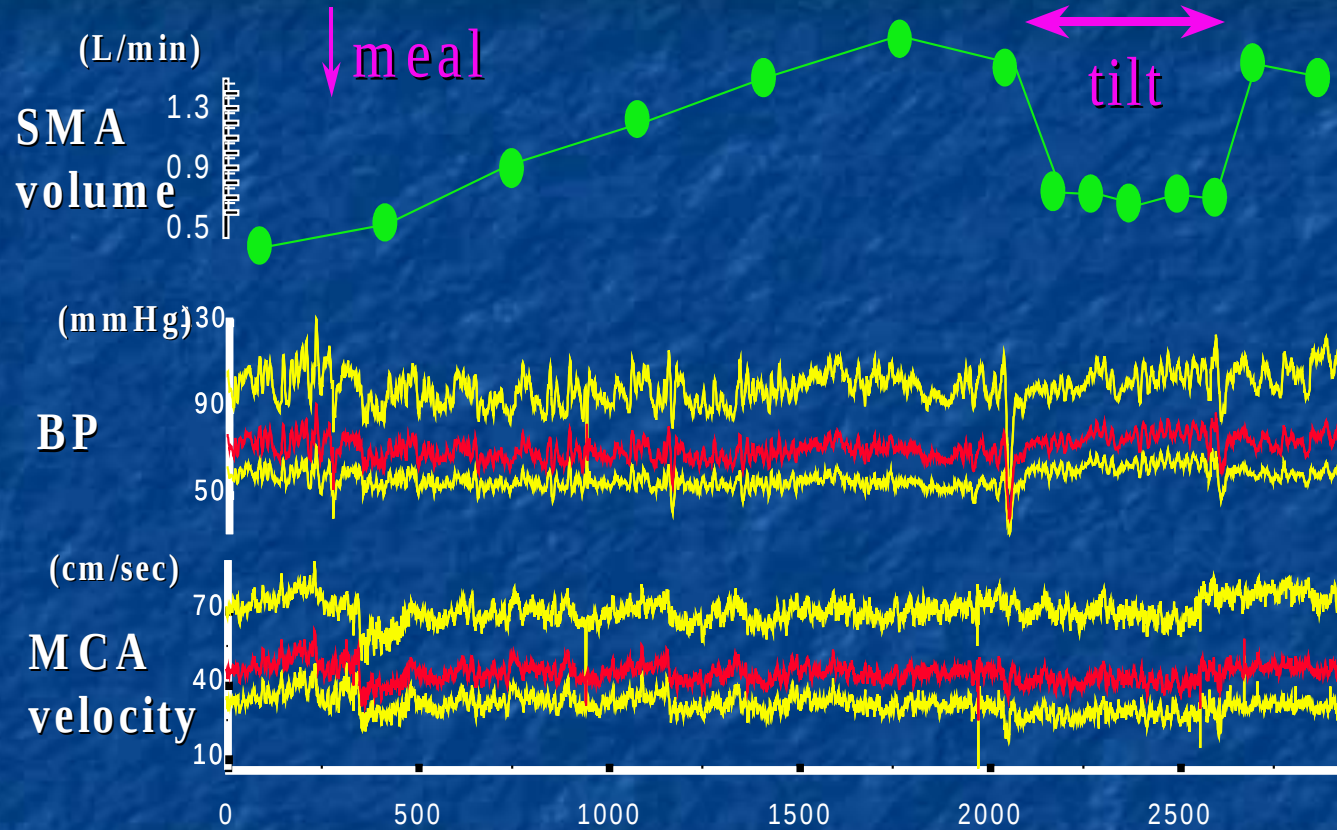
# Head-up tilt

# Syncope



# Hypotension after a Meal

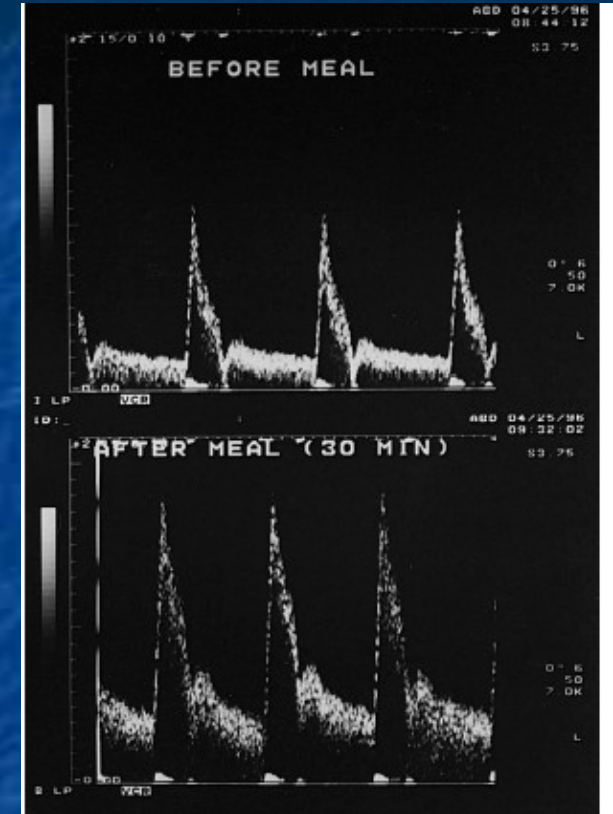
Tilt after meal - Control



Increased abdominal blood flow

Normal blood pressure

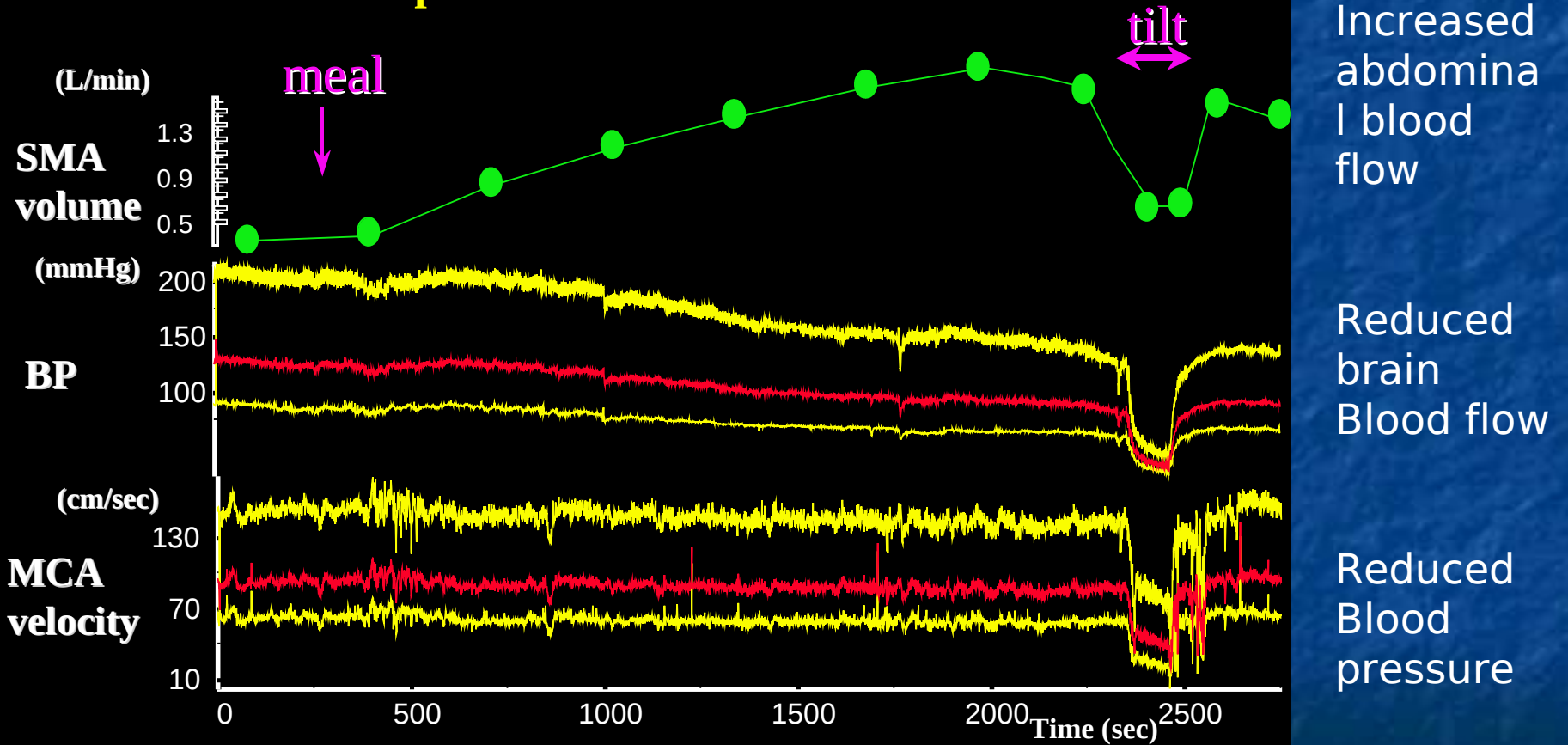
Normal blood flow in the brain



Increased abdominal blood flow

# Faint

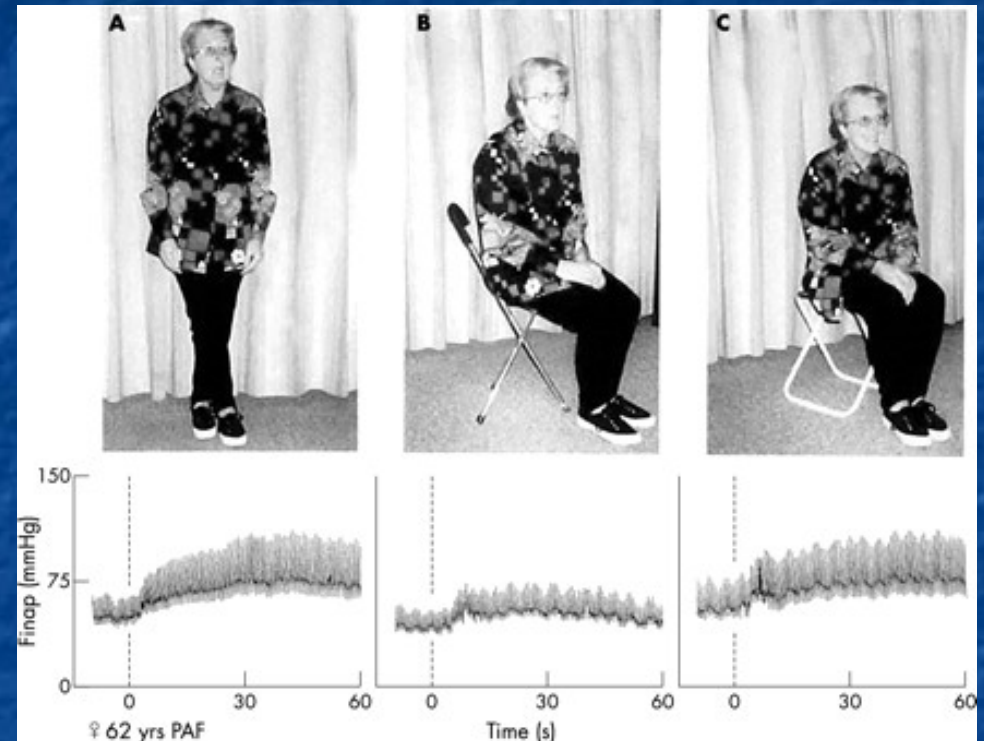
## Tilt after meal - OH patient





# Falls/hypotension prevention

- Engaging muscle pump can improve cardiovascular response to upright posture.
- Cardiac-locomotor coupling thus may be beneficial to maintain/improve cardiovascular adaptation to walking and standing up.

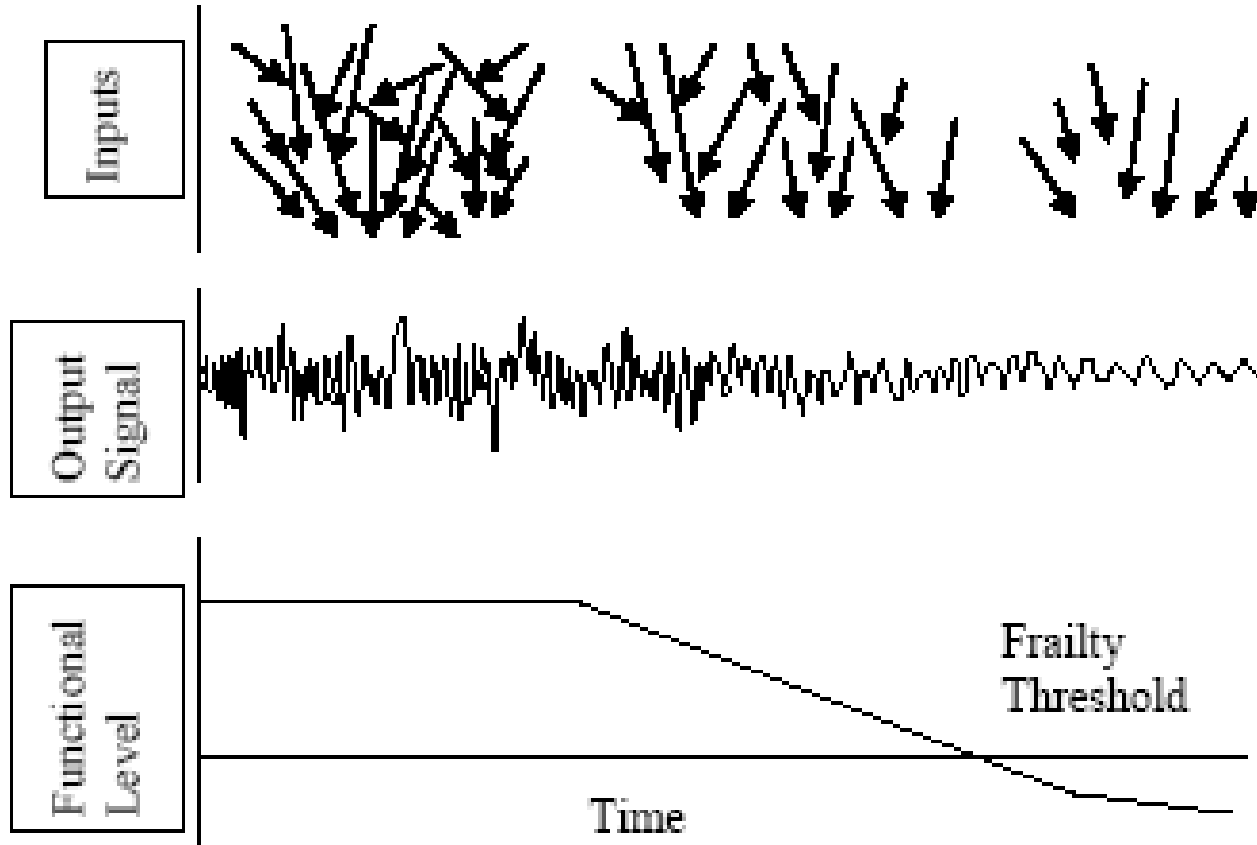


↑  
Muscle  
pump

↑  
Deep  
breathing  
alone

↑  
Squatting  
+DB

# Complex Coupling and Aging



*Figure 2: Loss of Complexity: The Physiologic Basis of Frailty*





# Conclusions

- Coupling and entrainment phenomena represent signaling among multiple organ systems.
- As signaling and processing speed declines with aging, coupling among other systems may be enhanced.
- Cardiac-respiratory and postural coupling may enhance performance during adaptation to daily living in older adults.





■ Ageing is inevitable for humans. But if you have goals in life, you should go through the physical and mental training, forget about age and embark on the challenges,” said Yuichiro Miura. Climbed Mount Everest at 76 yrs 340 days old

# SAFE Laboratory- Members. Collaborators

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M. Selim, MD PhD- Vice-Chief Stroke Service  
P. Novak, MD PhD- Dept. of Neurology  
I. Hajjar, MD- Division of Gerontology  
L. Lepicovsky, BS-analysis and photography

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