Stroke and the Autonomic Nervous System

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Max J. Hilz has nothing to disclose

Learning objective:

This lecture will give you an introduction to

- interactions between the central autonomic network and the cardiovacular system
- autonomic, primarily cardiovascular changes after stroke
- the risk of cardiovascular complications and fatalities after stroke
- associations between stroke location and cardiac risk
- associations between stroke severity and autonomic dysfunction.

After this lecture, you should

- have increased awareness for cardiovascular risk and complications after stroke
- better understand why autonomic dysfunction increases the risk of complications and fatalities after stroke

A Case Report

presented at the

EFAS Summer School

Lisbon 2010

Emergency Room:

69- year old man

onset of motor weakness

7 - 8 hours ago

left brachiofacial hemiparesis

left hemihypesthesia

Babinski sign positive

Emergency Room

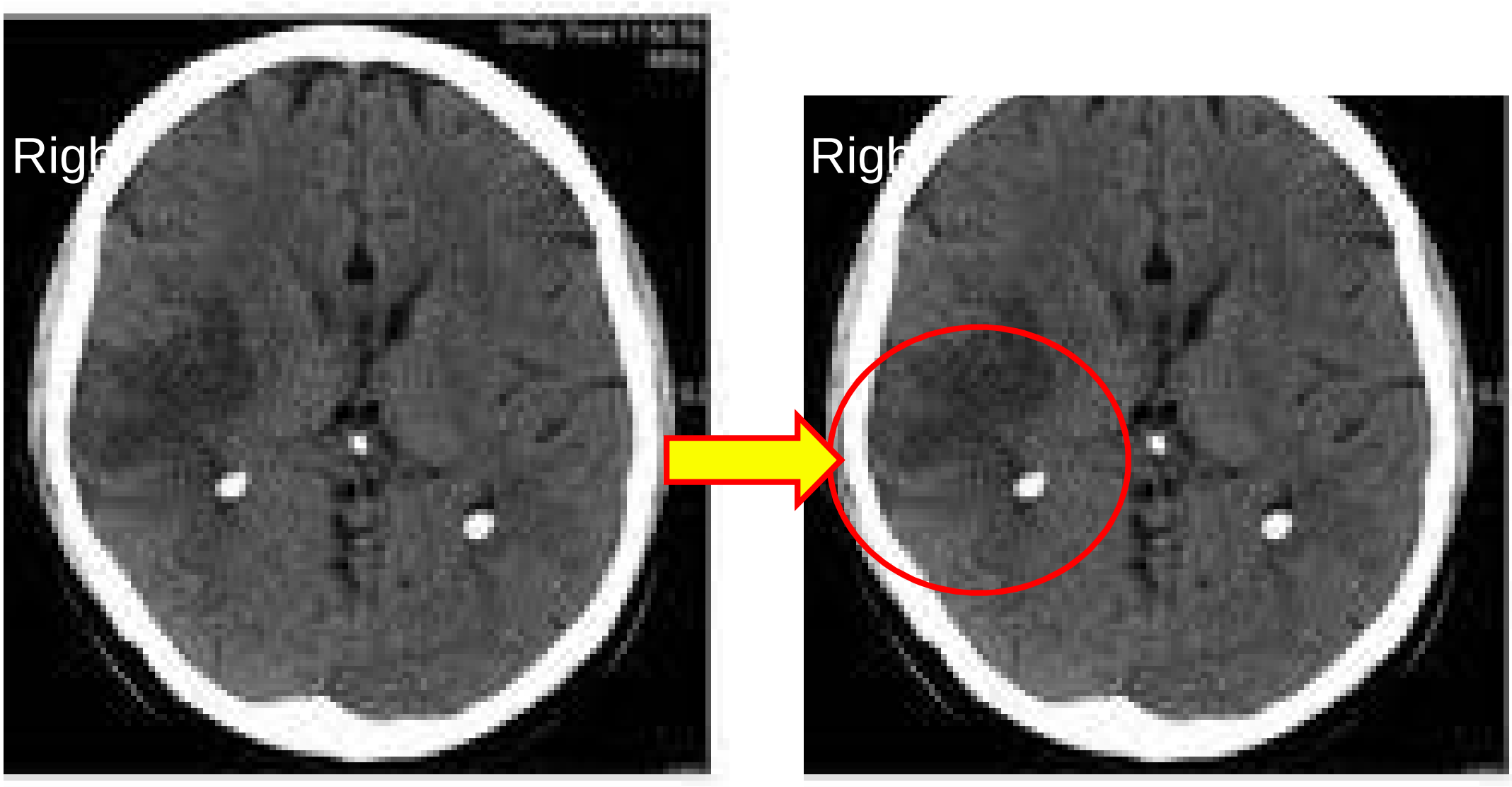
Medical History:

- **diabetes mellitus Type II**
- **arterial hypertension**
- **heavy smoker**
- **hypercholesterolemia**

probable cause:

STROKE !!

- blood pressure: 160/100
- heart rate: 90 bpm regular
- temperature: 37,4 °C
- respiratory rate: 14
- O2-saturation: 92%



CT: hypodense area in right parietal lobe.

è **large middle cerebral artery ischemic stroke**

Stroke Unit:

after two days,

patient complains

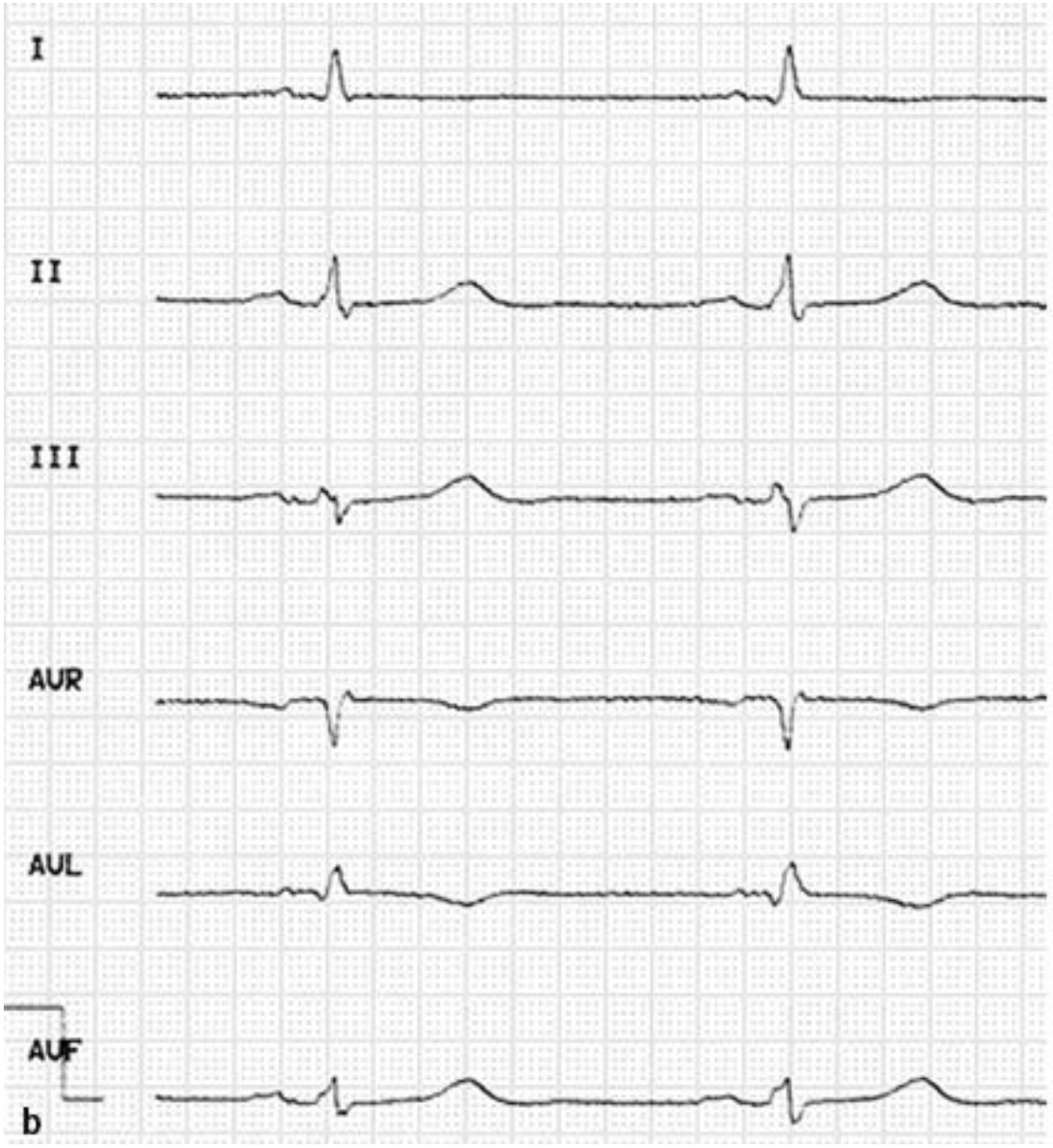
about chest pain

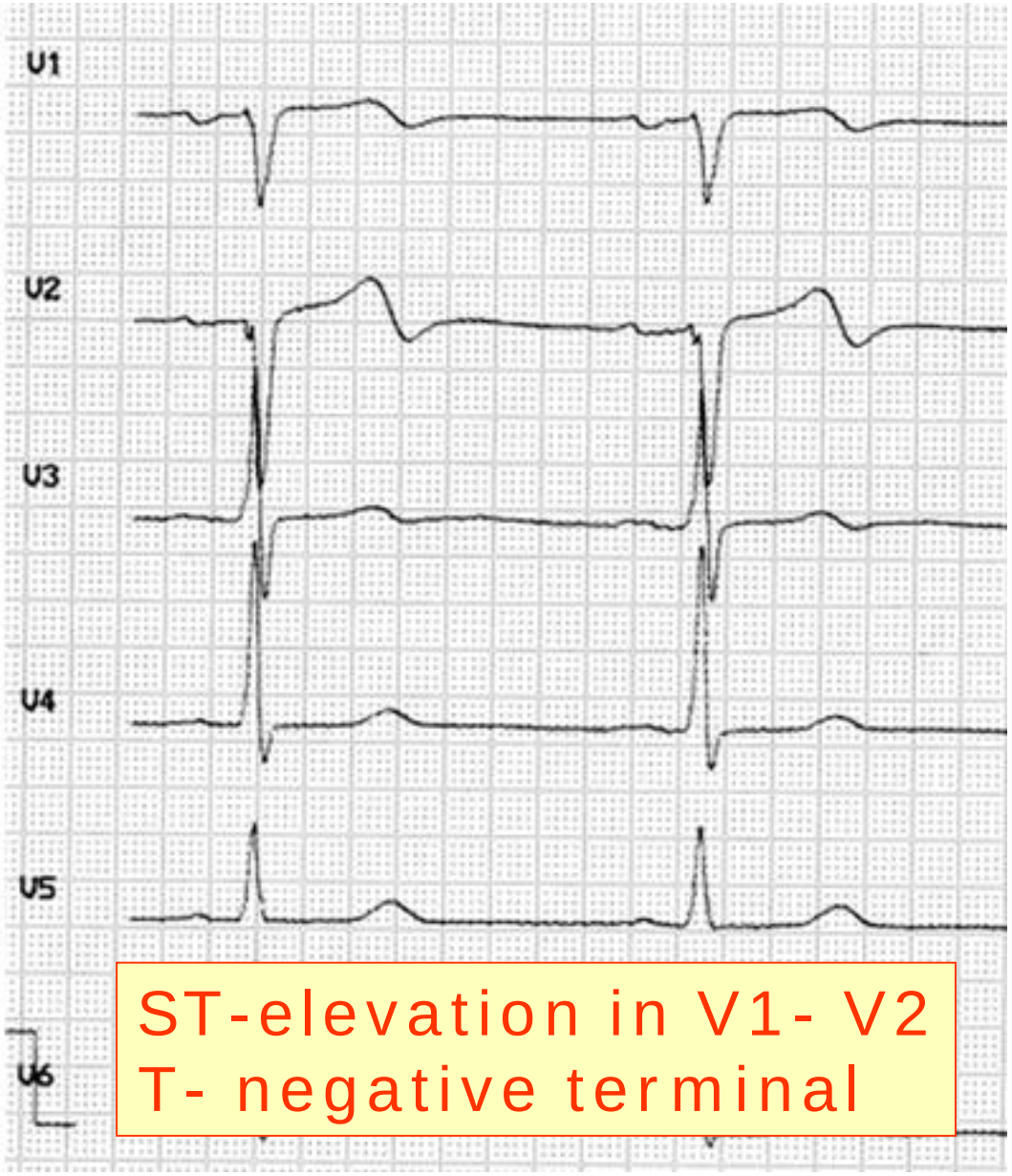
and dyspnea

Myocardial infarction ?

Control of Lab and ECG:

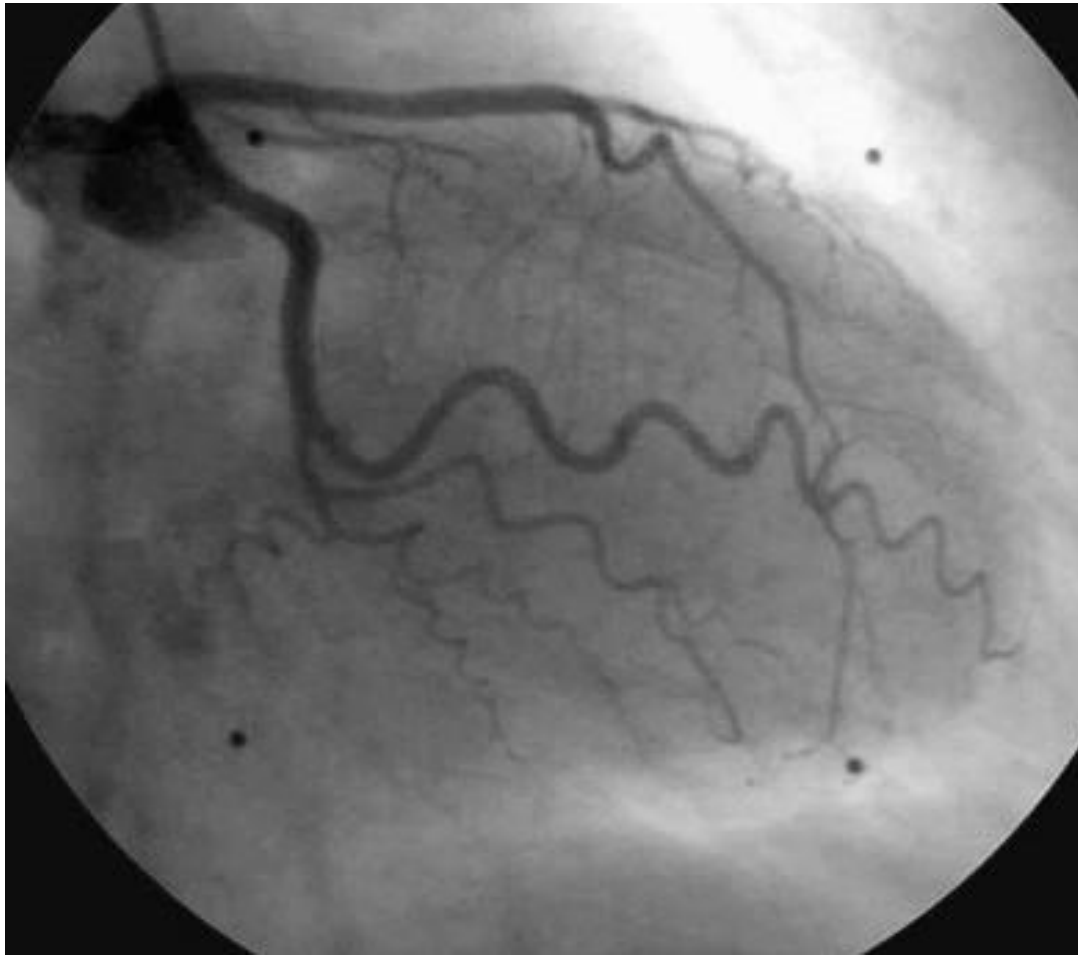
normal: blood count, electrolytes, glucose,





ST-elevation in V1- V2
T- negative terminal

ngiography



Normal !!

Why does he have a myocardial infarction after the stroke ?

Vascular high risk patient

with generalized atherosclerosis ?

Just a coincidence ?

Stress because he realizes his handicap ?

Autonomic dysfunction is common after Stroke

- **Thermoregulation**
  - Assymmetric sweating
  - Cold hemiplegic limbs
- **Urogenital regulation**
  - Urinary incontinence and retention
  - Impotence and orgasmic disability
- **Gastrointestinal regulation**
  - Gastroparesis
  - Stress ulcers

Common but poorly understood clinical significance & prognostic value

Autonomic nervous system disorders in stroke, Korpelainen et al. 1999

Variety of Disturbances

Cardiovascular regulation

- Myocardial infarction
- Cardiac arrhythmias
- ECG- abnormalities
- Hypo- and hypertension
- Decreased HR- and BP- variability

well investigated

Autonomic nervous system disorders in stroke, Korpelainen et al 1999

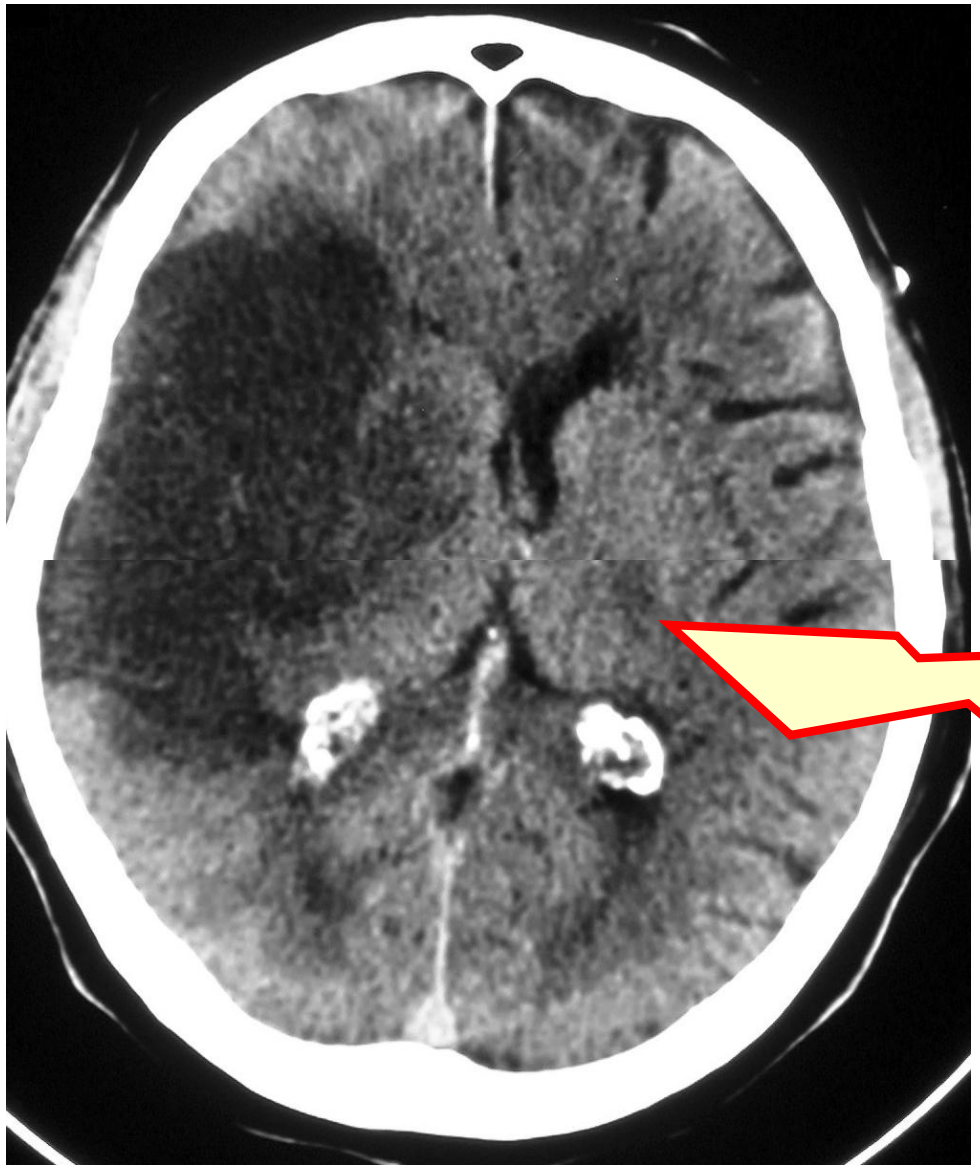
Cardiovascular dysregulation

ECG Abnormalities

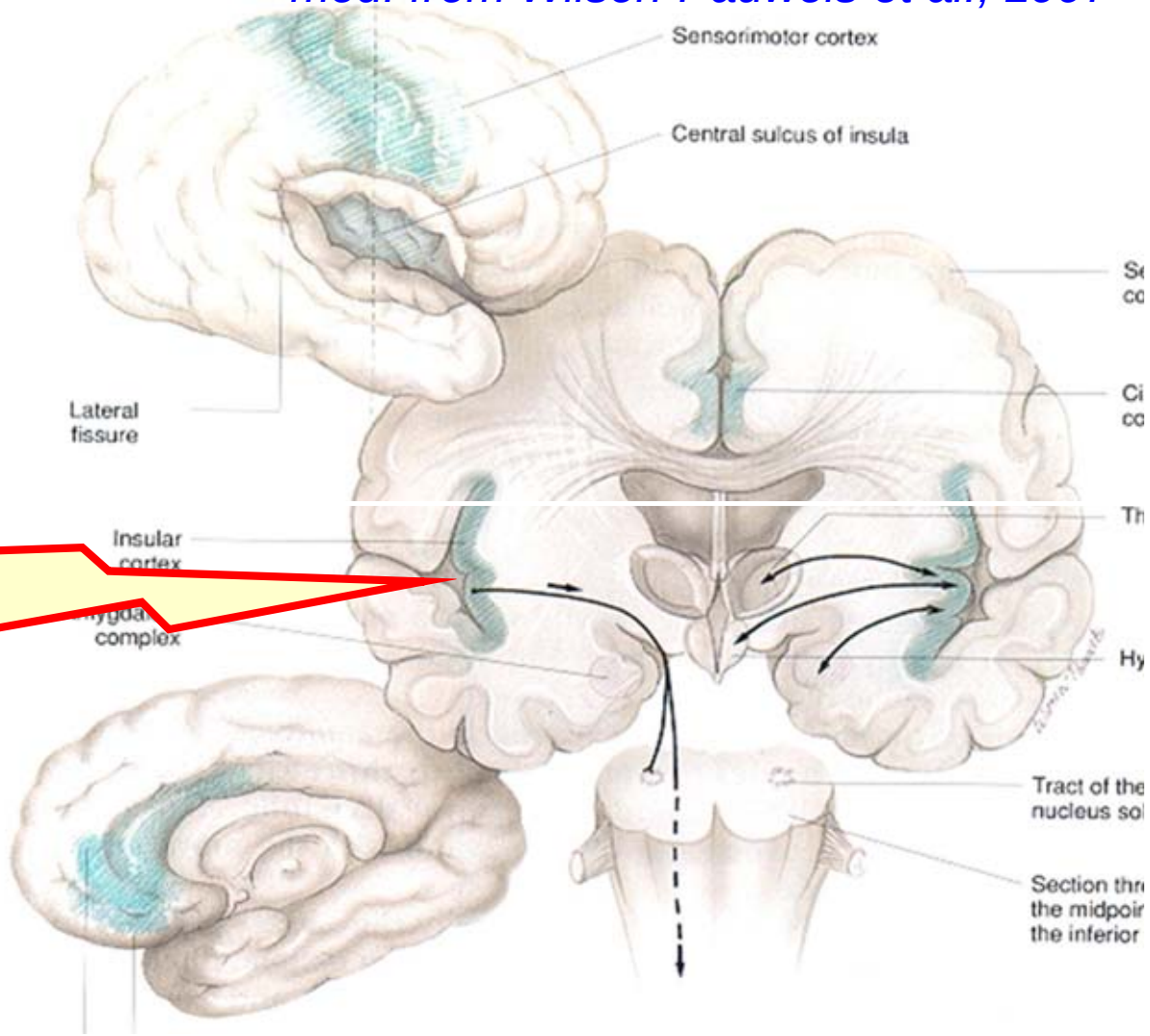
- Atrial fibrillation
- Atrial tachycardia
- Supraventricular extrasystoles
- ST- changes
- QT –prolongation
- T pathologies
- Pathological U Waves
- Sinus tachycardia
- Sinus bradycardia
- Left bundle branch block
- Right bundle branch block
- AV-Block

15-40%

Oppenheimer et al,
Korpelainen et al,
Hachinski et al,



mod. from Wilson-Pauwels et al., 1997



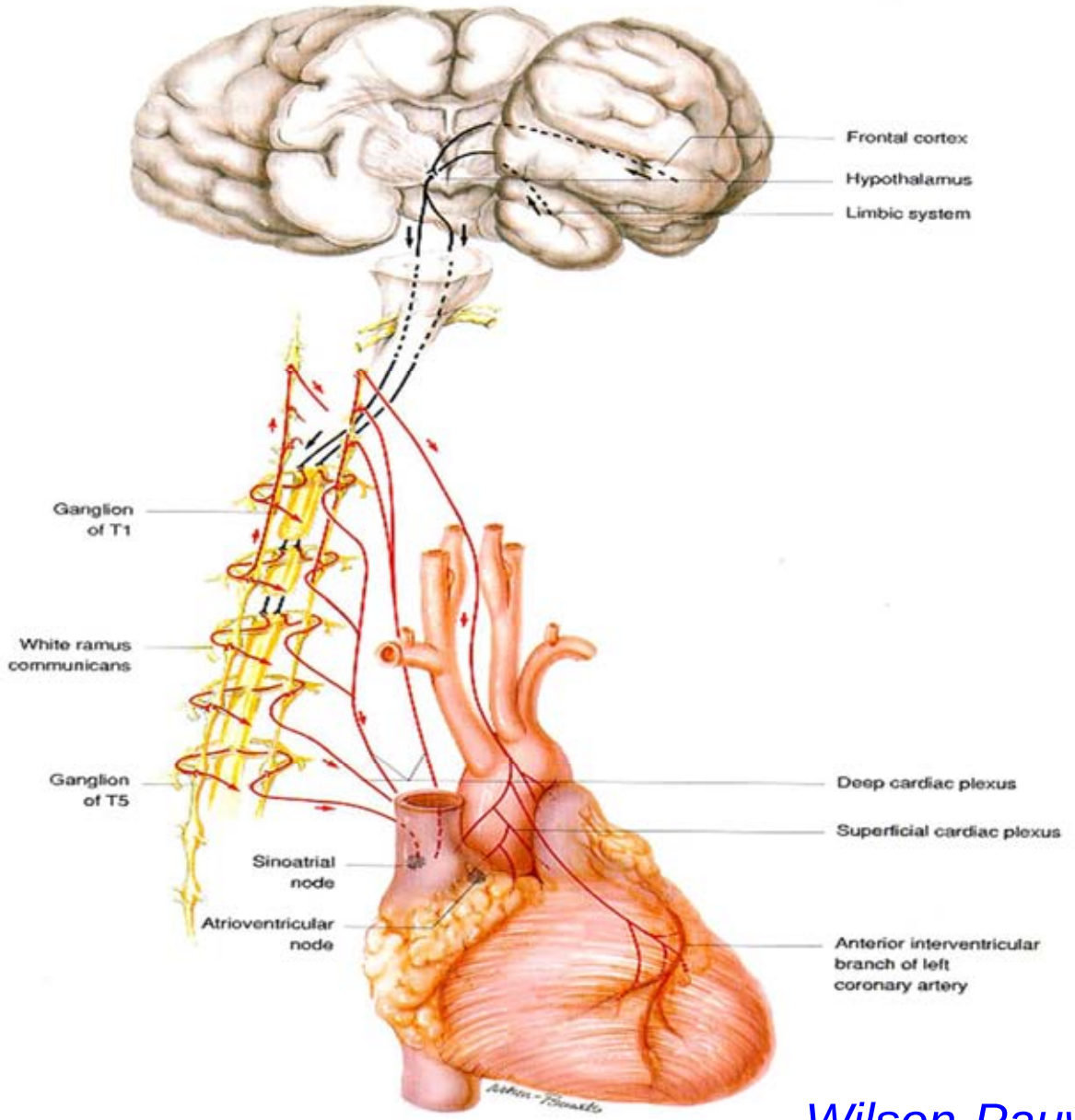
Ischemic lesions

in middle cerebral artery territory

Central autonomic network dysfunction

Impaired autonomic cardiovascular control

……based on brain - heart connection



Wilson-Pauwels et al. 1997

Northern Manhattan Stroke study (NOMAS)

outcome after 5-year follow-up

(Rincon et al., Stroke 2008):

655 patients (age 69.7 ±12.7 years; 44.6% male)

44 patients (6.7%) fatal cardiac events

(38.6% fatal MIs, 18.2% fatal congestive heart failure,
43.2% sudden death)

Predictors of post-stroke mortality ?

Northern Manhattan Stroke study (NOMAS)

outcome after 5-year follow-up (655 stroke pats.)

(Rincon et al., Stroke 2008):

Predictors of **post-stroke mortality rates,**
non-fatal myocardial infarctions,
sudden unexpected death

age,
male gender,
National Institutes of Health Stroke Scale (NIHSS),
history of coronary artery disease

infarct location in frontal,
parietal,
temporal lobe
insula

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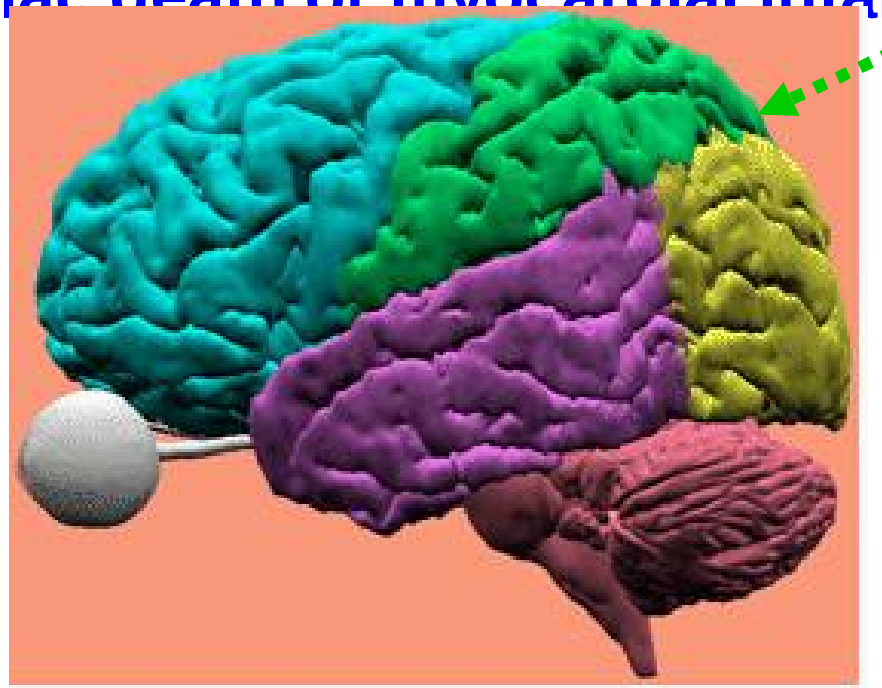
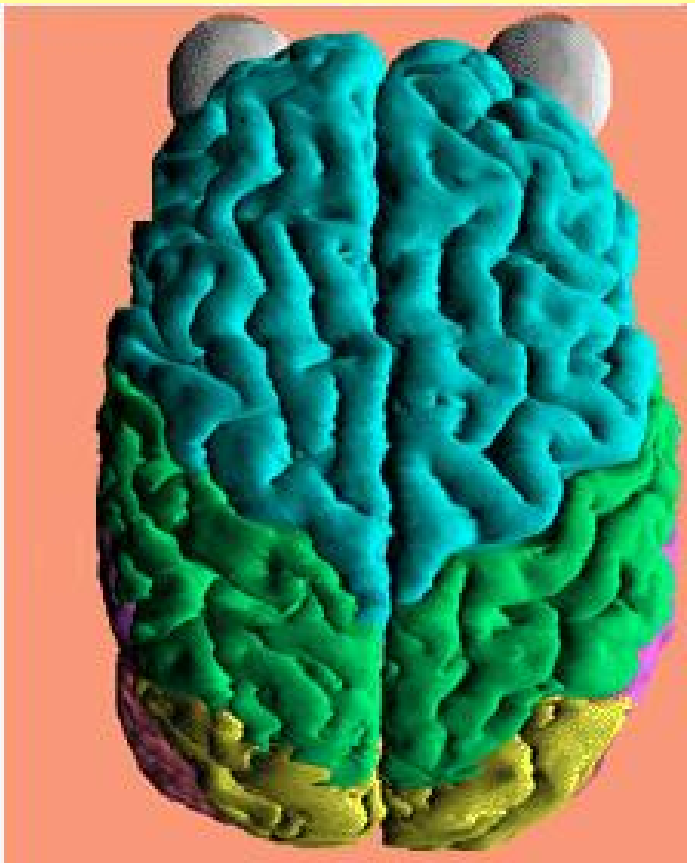
insula

Northern Manhattan Stroke study (NOMAS)
outcome after 5-year follow-up (655 stroke pats.)
(Rincon et al., Stroke 2008):

left & right parietal lobe infarctions associa

cardiac death or myocardial infarction





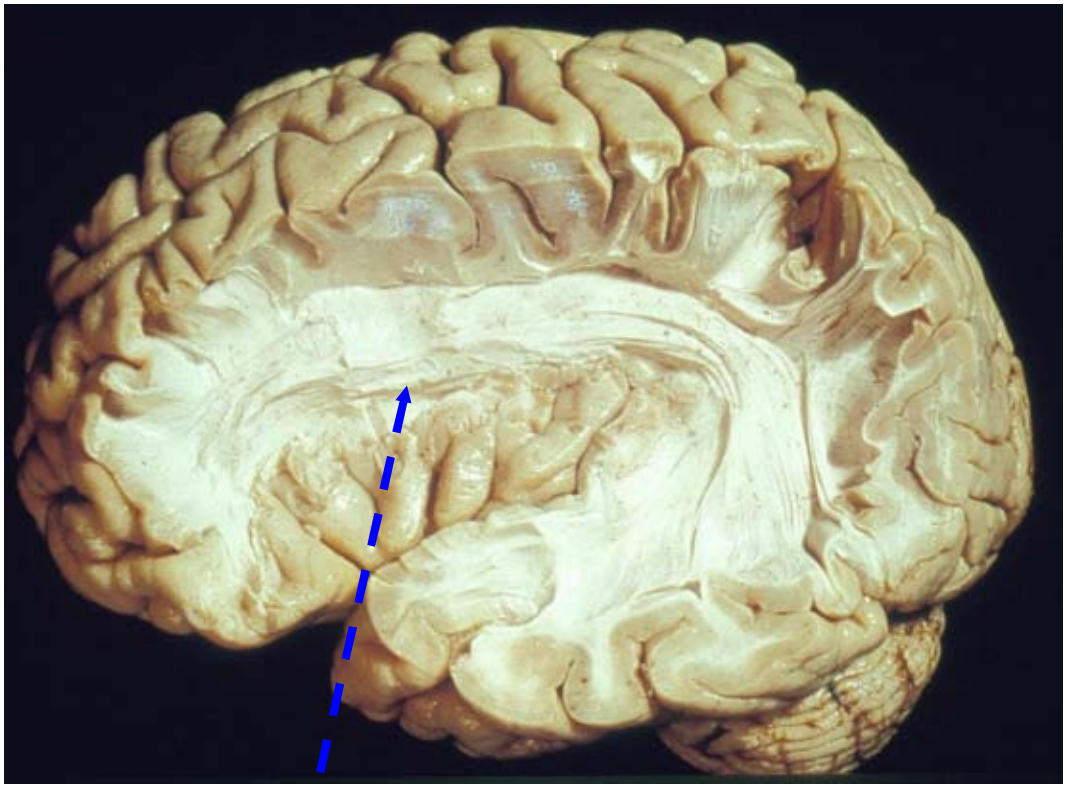
left **parietal lobe** infarction associated with

cardiac death (hazard ratio 3.37; 95% CI, 1.26 -8.97)

Insular cortex

Organotopic viscero-sensory representation

influence on
- blood pressure
- heart rate
- respiration
- gastrointestinal motility
- secretion
- saliva production
- piloerection
- pupillary dilatation



insular cortex

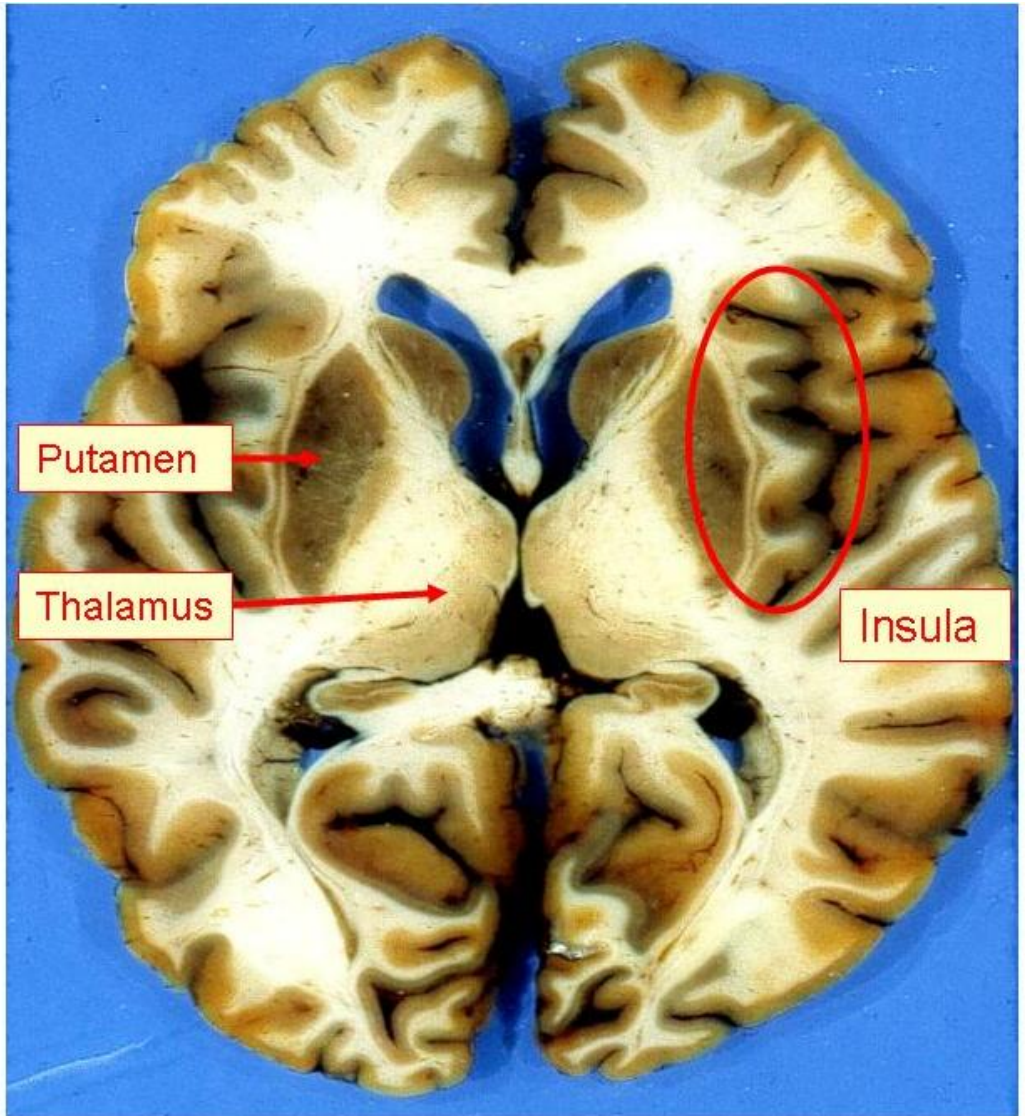
(Bennaroch 2004, Hilz 1999, Saper 2002, Verberne & Owens 1998)

Oppenheimer et al.: Insular cortex pathology contributes to sudden death.

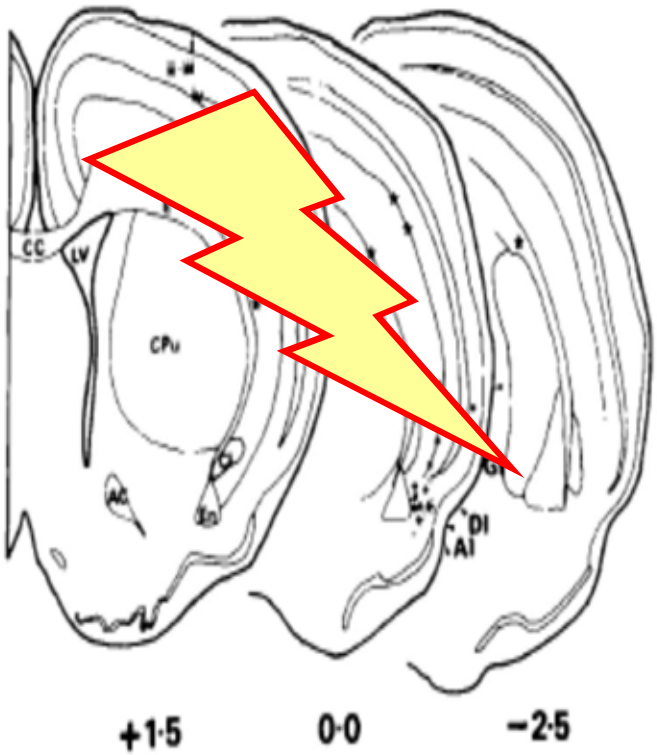
Insular cortex è **organotopic viscero-sensory representation**

influence on
- blood pressure
- heart rate
- respiration
- gastrointestinal motility
- secretion
- saliva production
- piloerection
- pupillary dilatation

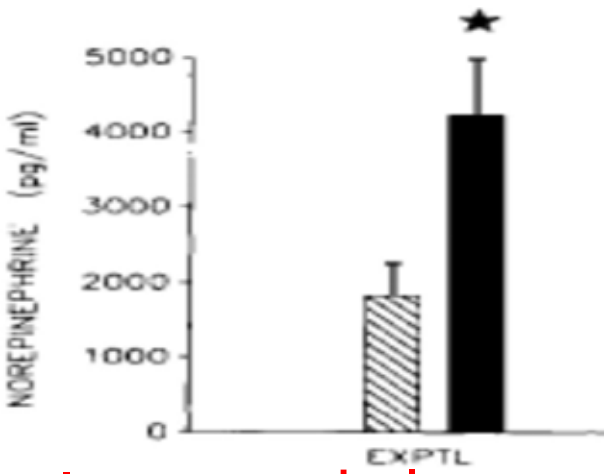
(Bennaroch 2004, Saper 2002, Verberne & Owens 1998)



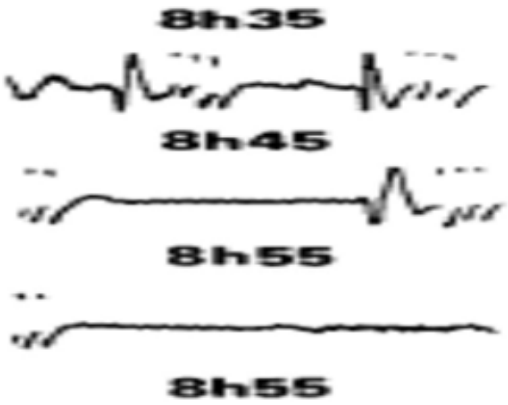
Oppenheimer et al. Insular cortex stimulation produces lethal cardiac arrhythmias - a mechanism of sudden death? *Brain Res 1991; 551:115-21*



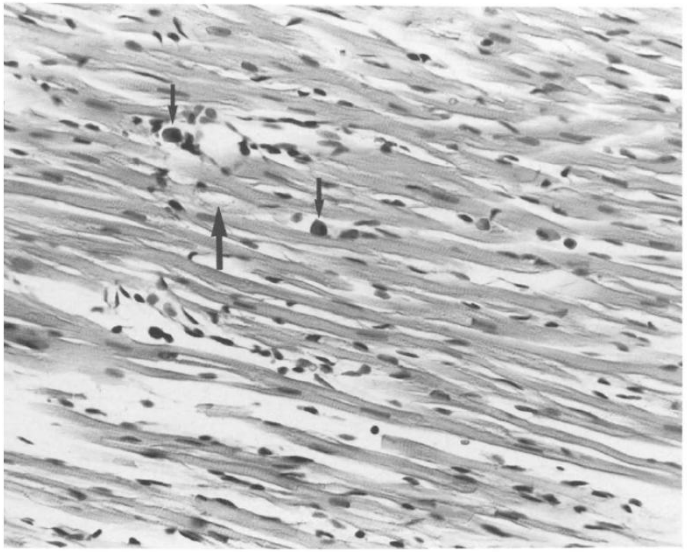
Insular stimulation



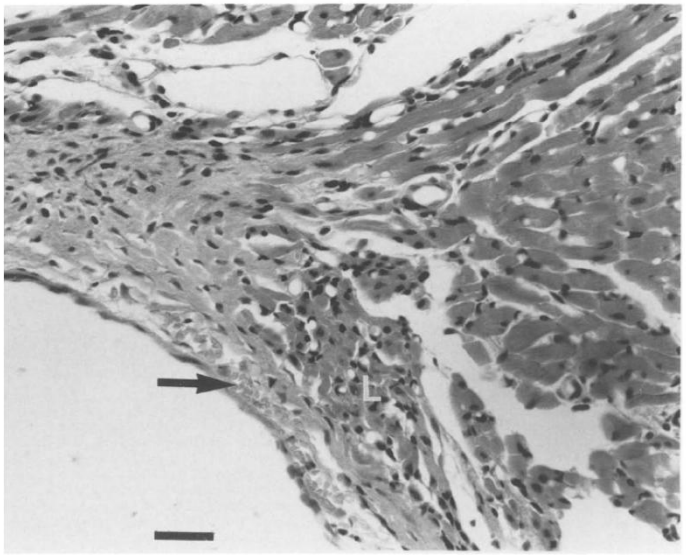
Increased plasma norepinephrine levels



ST segment depression & complete heart block



cardiac myocytolysis



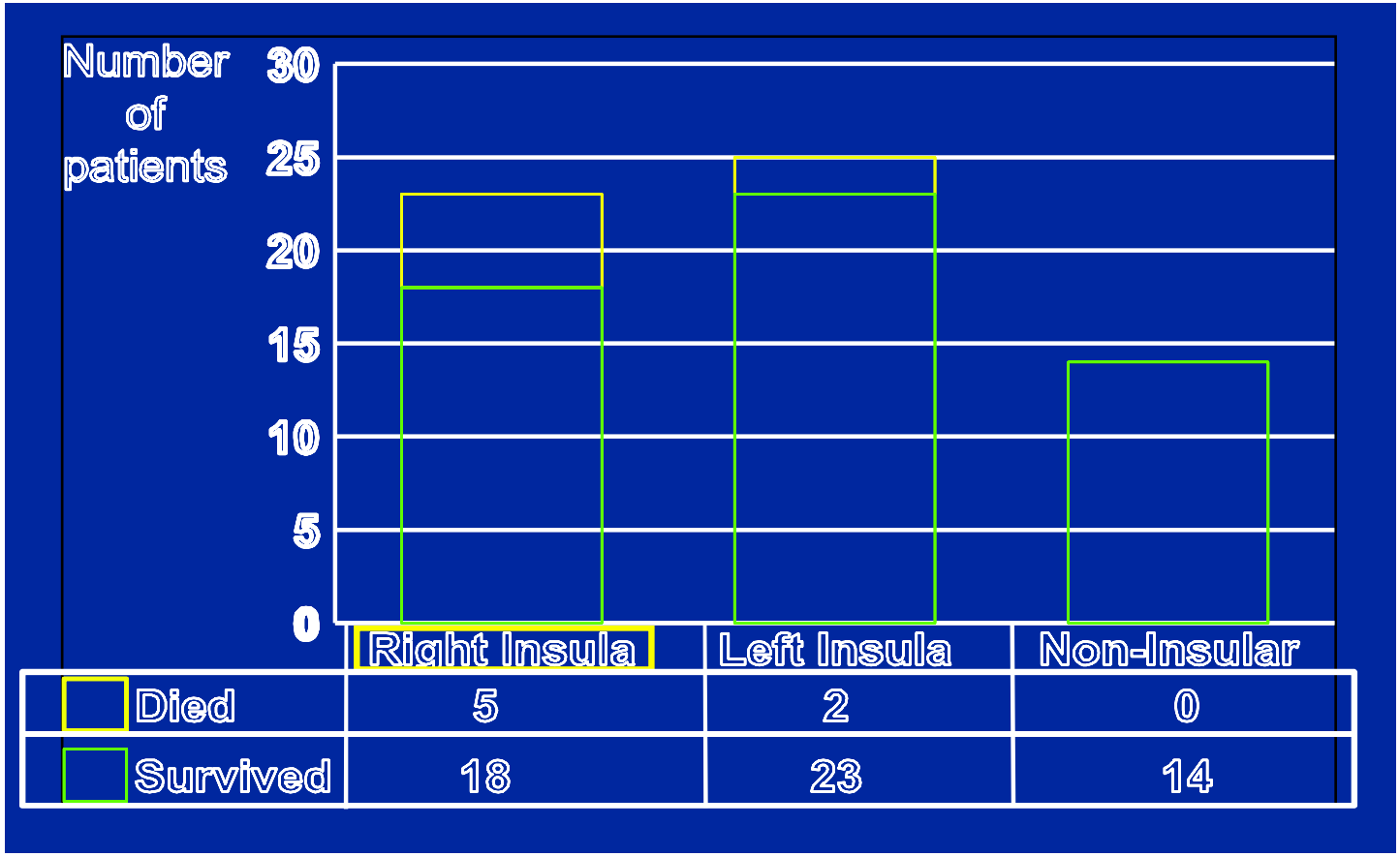
large hemorrhage

Insular Stroke & Sudden Death

Tokgözoglu et al.: Stroke 1999; 30: 1307

62 pats. with acute stroke
in **MCA territory** *(> 3 cm)*

Sudden death in 7 pts
5 right insula,
2 left insula



decreased HRV in all patients **(Right - MCA & insular)**

Stroke in (**right**) insular region è decreased HRV
è increased incidence of sudden death

Neuroanatomic correlates of stroke-related myocardial injury

Ay et al. Neurology, 2006; 66: 1325-1329

elevated serum **cardiac troponin T** (cTnT)

within 3 days of ischemic stroke onset.

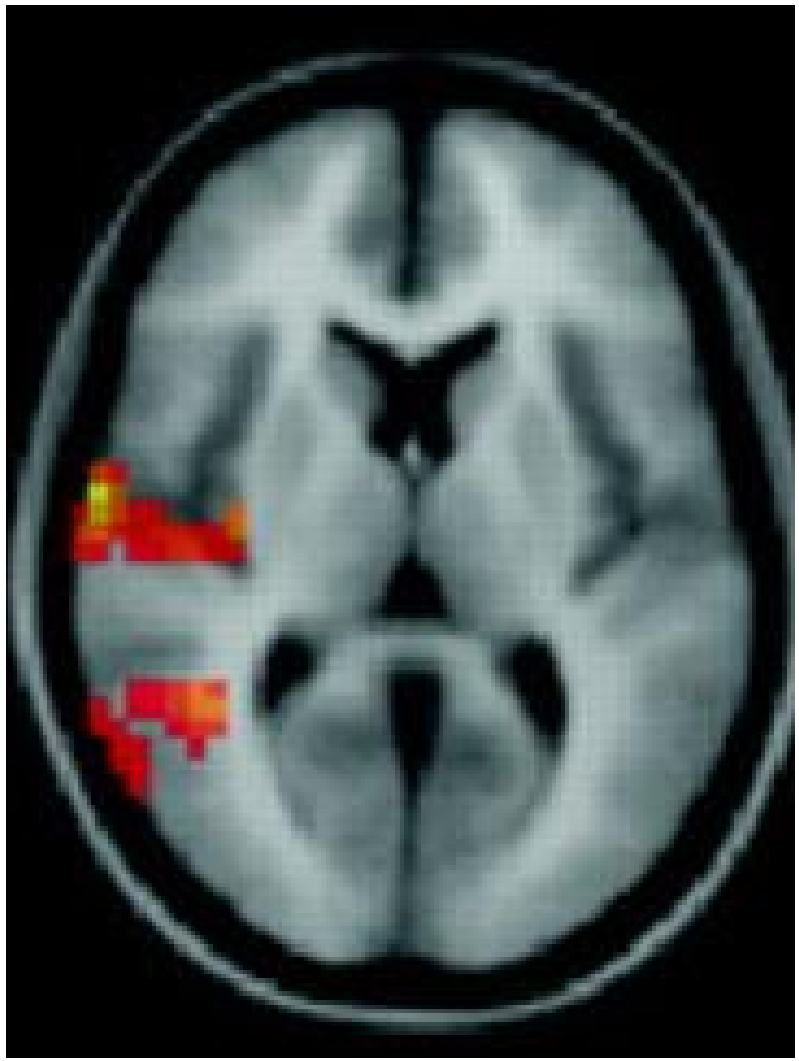
diffusion-weighted MRI

Brain regions associated with cTnT elevation:

right posterior, superior, & medial

INSULA (88%)

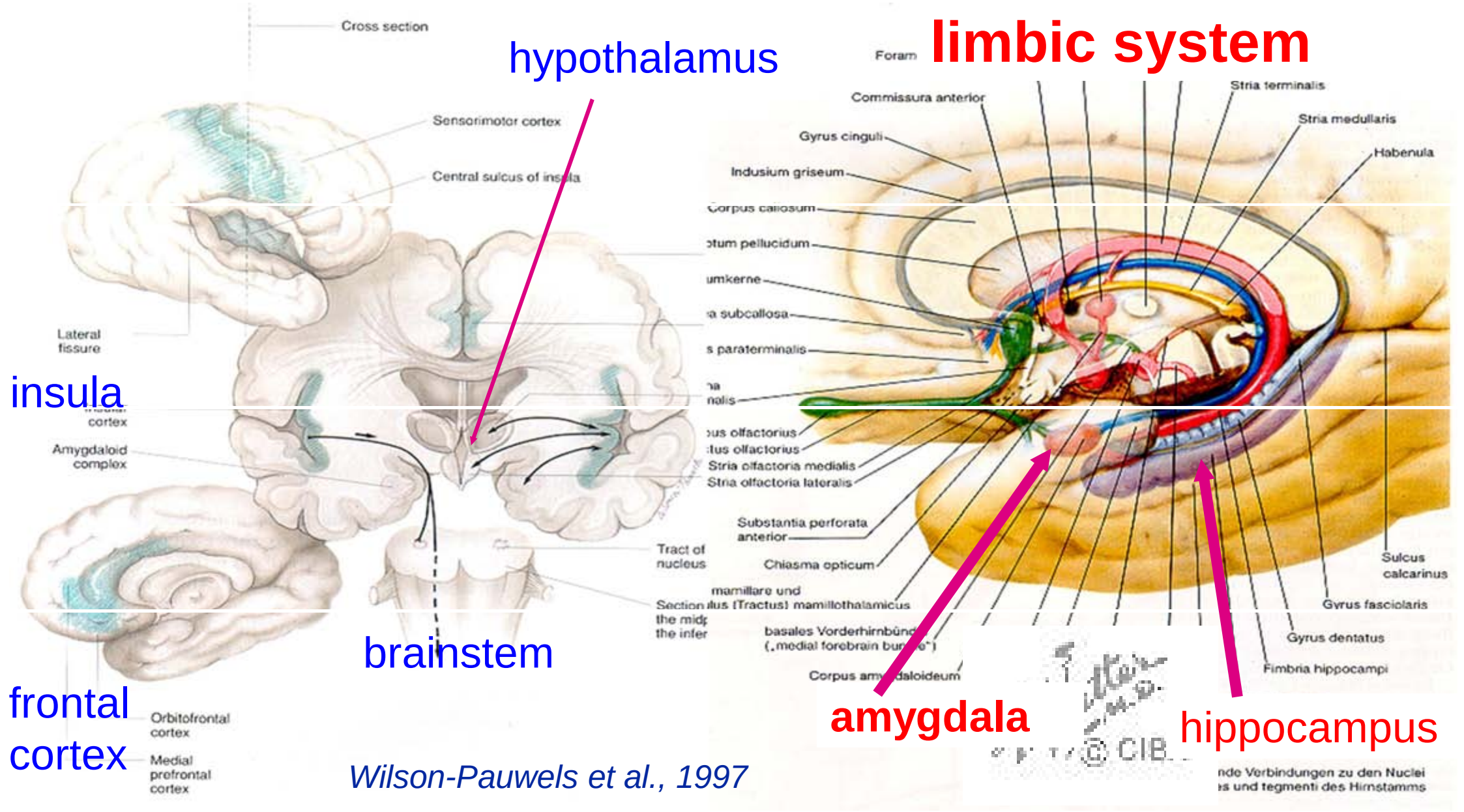
right inferior parietal lobule.



Risk of cardiac complications
and mortality is different
after
left- and right-hemispheric stroke !

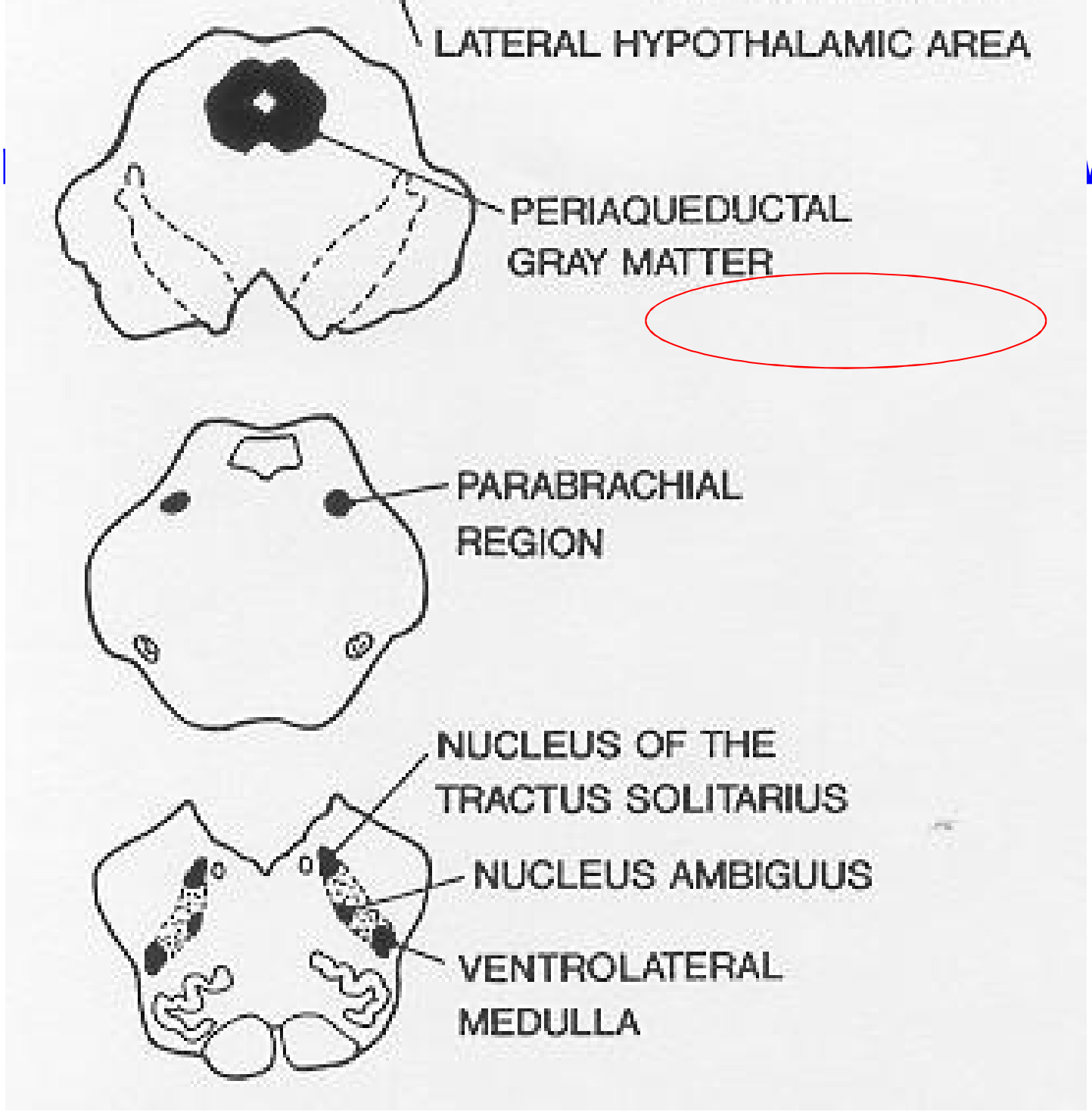
WHY ?

Centers of the central autonomic network



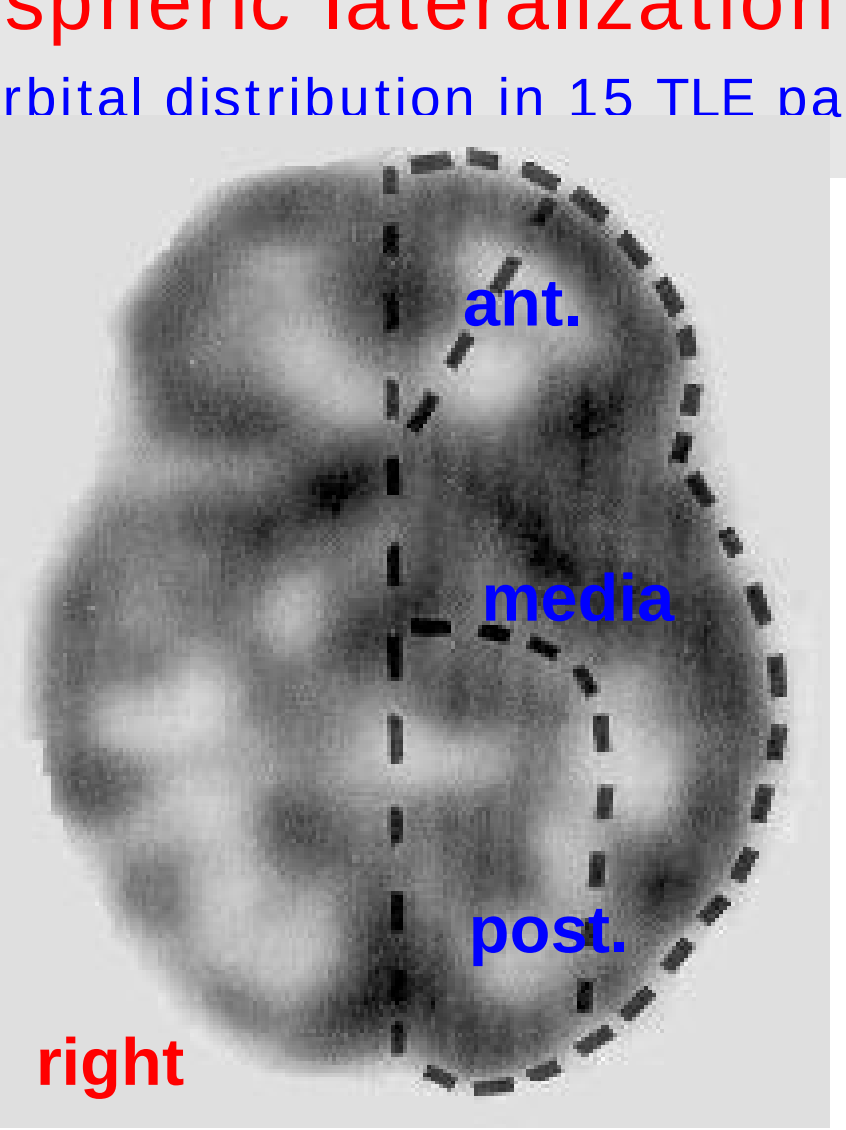
Wilson-Pauwels et al., 1997

Ce work


LATERAL HYPOTHALAMIC AREA
PERIAQUEDUCTAL
GRAY MATTER
PARABRACHIAL
REGION
NUCLEUS OF THE
TRACTUS SOLITARIUS
NUCLEUS AMBIGUUS
VENTROLATERAL
MEDULLA

Hemispheric lateralization of autonomic activity

amobarbital distribution in 15 TLE pats. (Tc-9



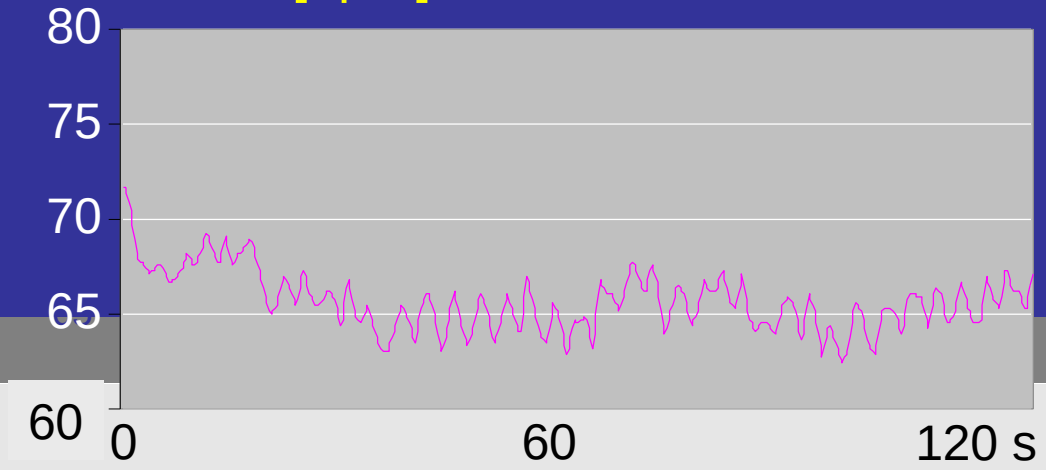
venous injection

selective injection in
left internal carotid artery

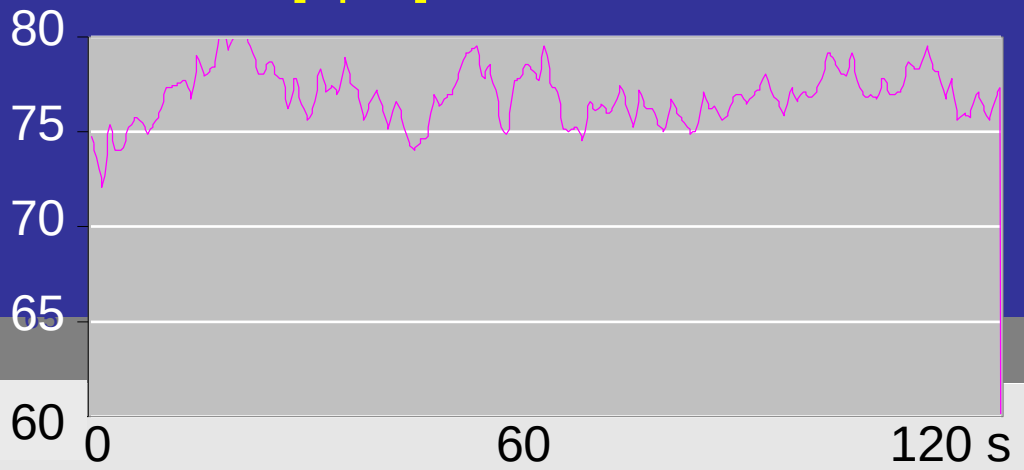
Jeffery et al., Radiology, 1991

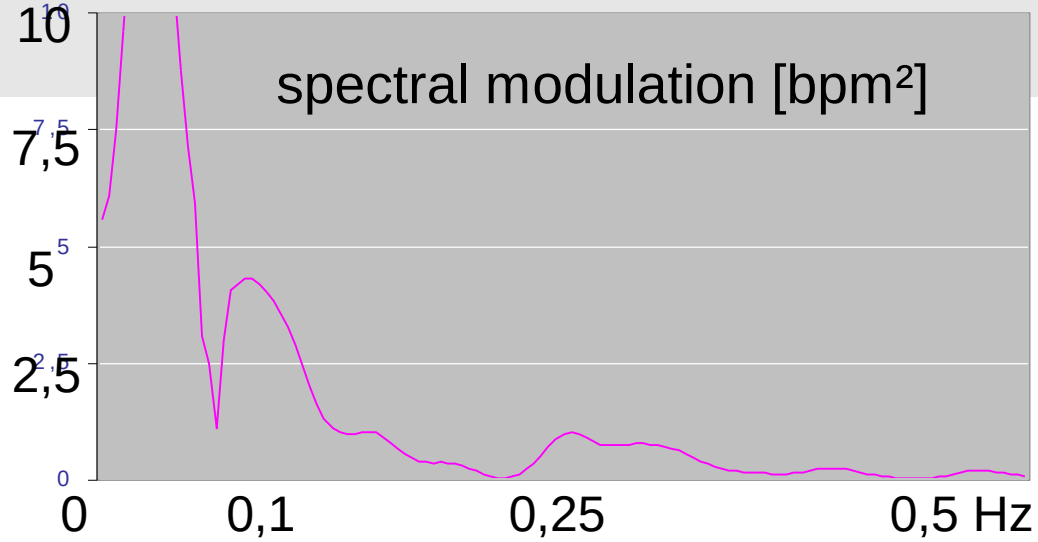
Increase in *sympathetic* modulation of heart rate and blood pressure after **left-**hemispheric **inactivation**

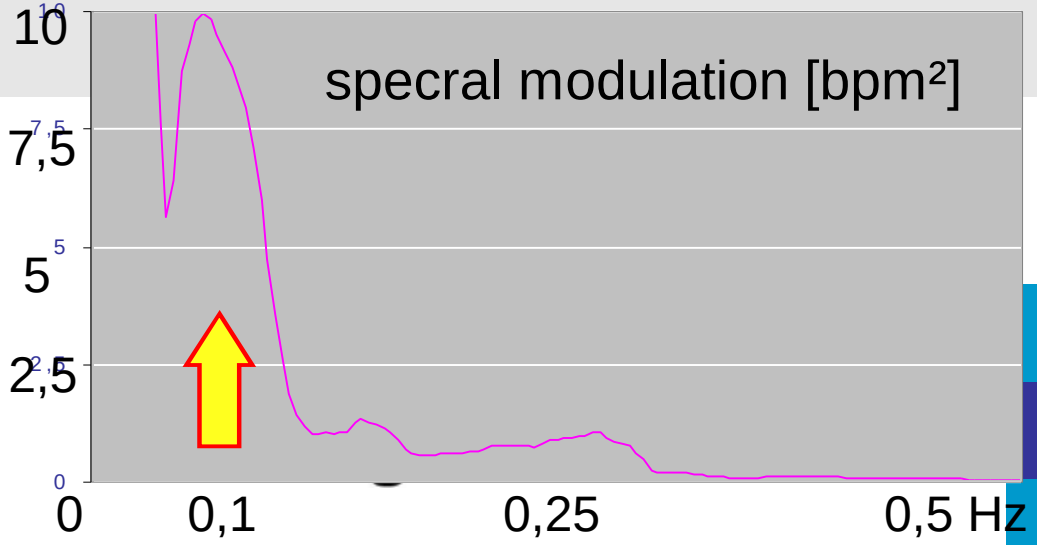
HR [bpm] before left inactivation



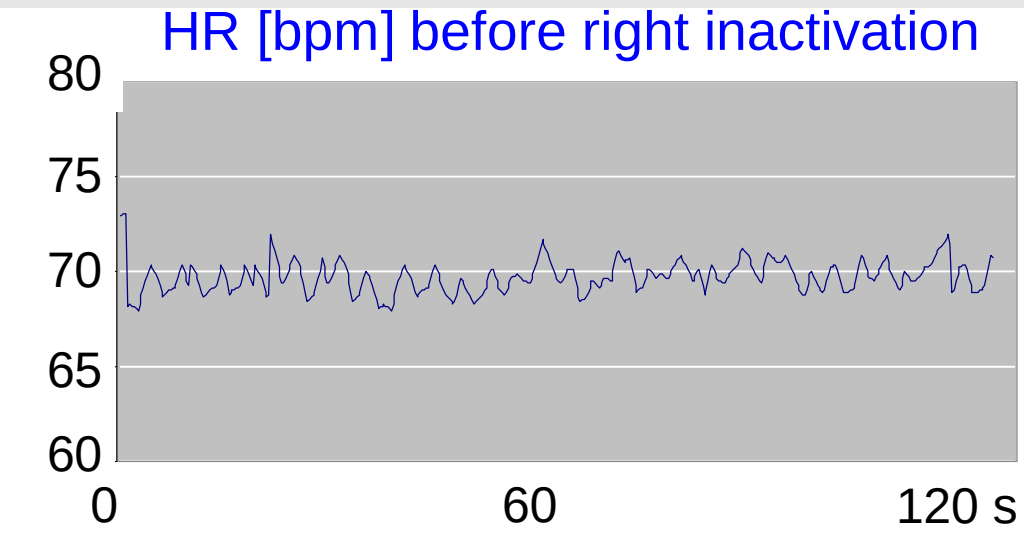
HR [bpm] **after** left inactivation

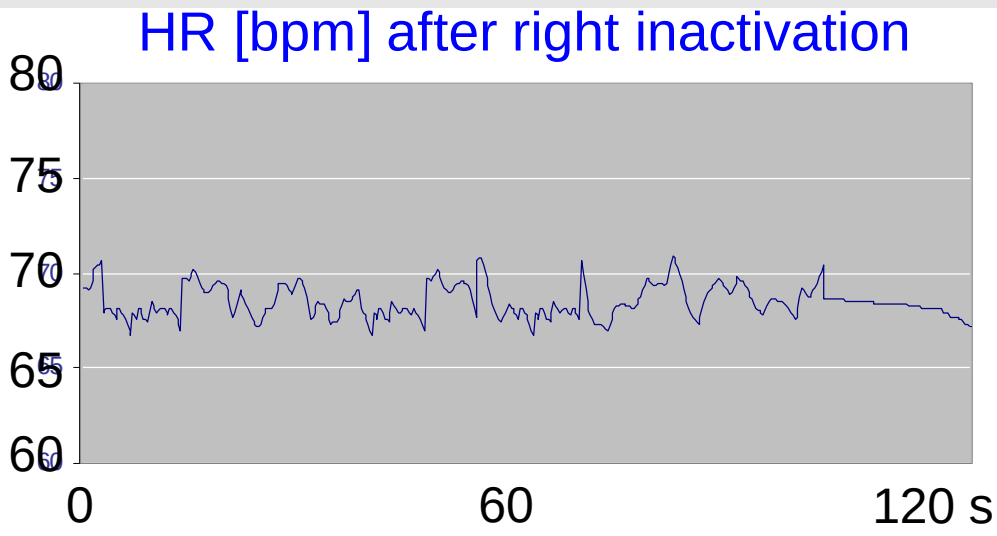


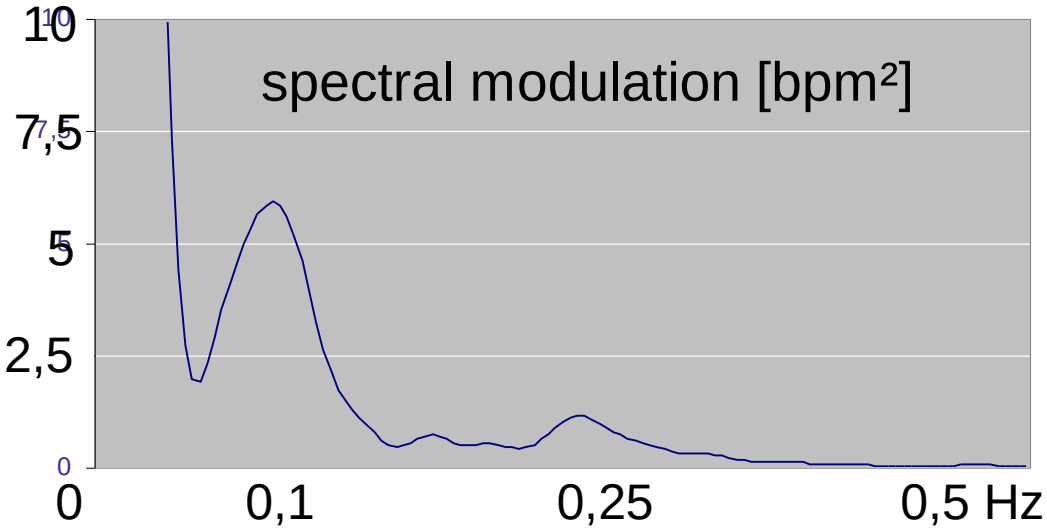


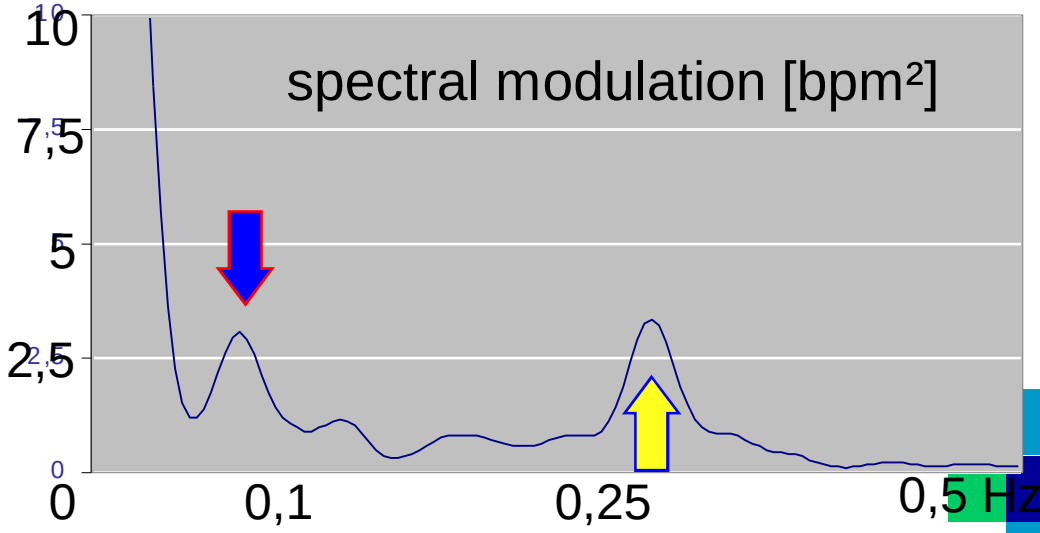


Decrease in sympathetic modulation of heart rate and blood pressure after **right-**hemispheric **inactivation**

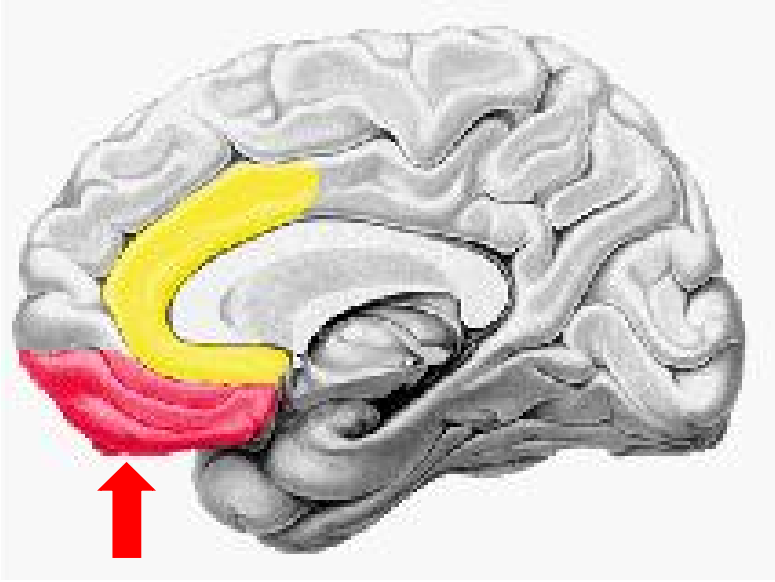






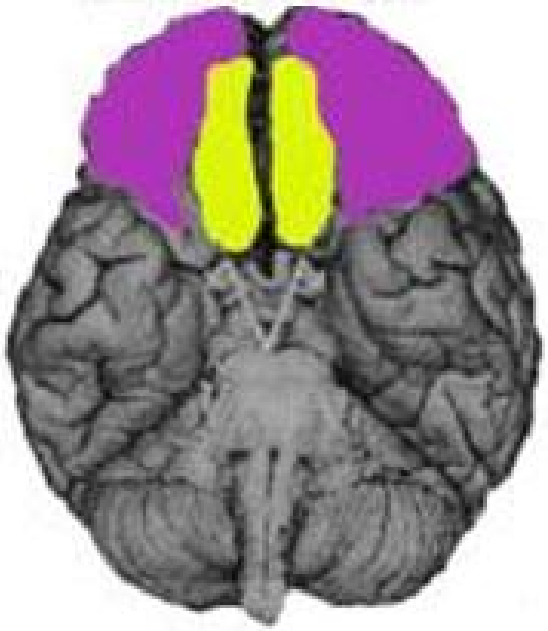


Ventromedial prefrontal cortex (VMPFC)



orbitofrontal & medial prefrontal cortices

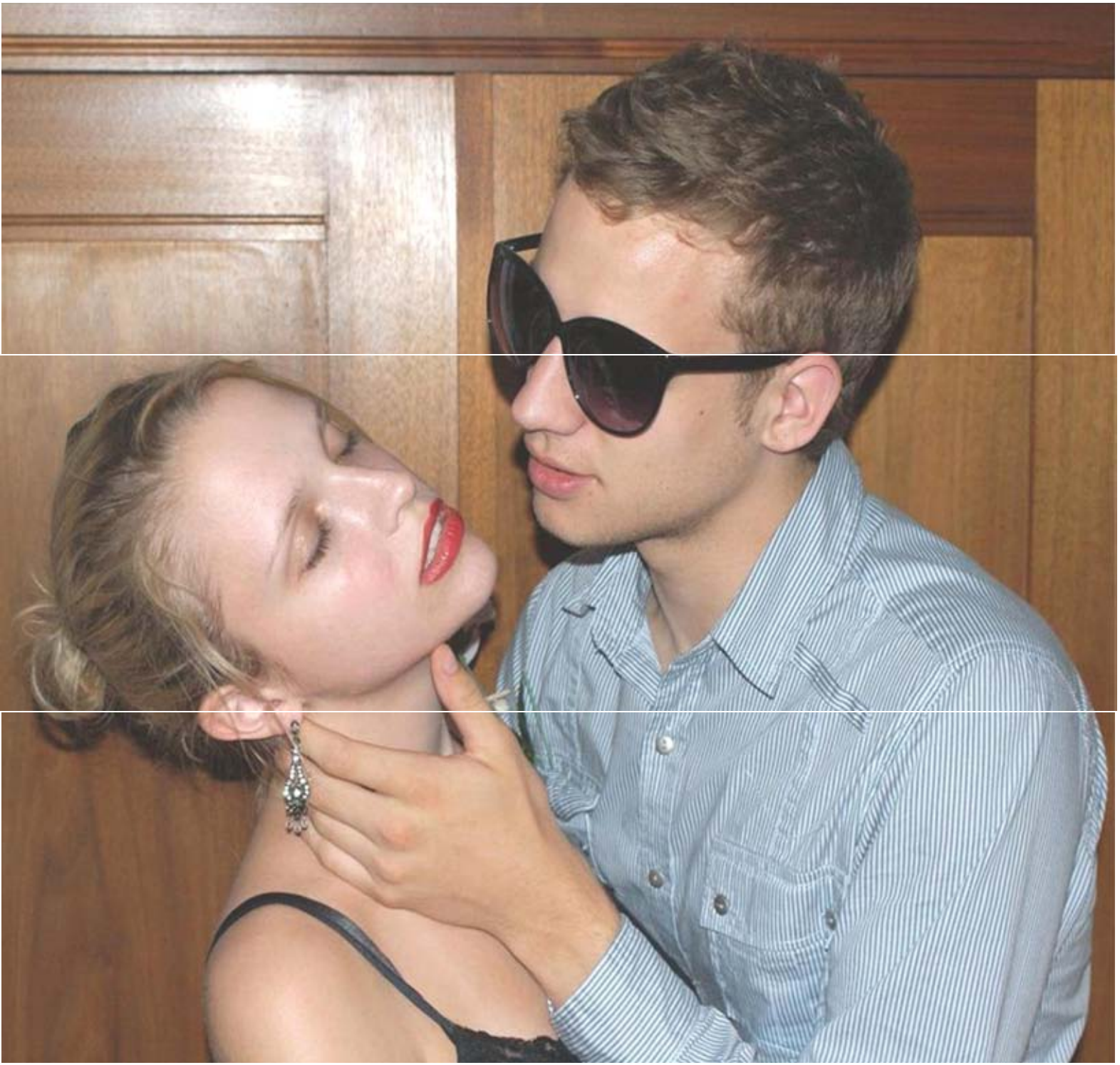
integrate sensory information & emotional stimuli



regulate emotional & cognitive processes

mediate autonomic responses to emotional stimuli,
e.g. changes in skin conductance, heart rate or blood pressure

(Damasio 1994, Phillips et al. 2003; Rolls 2004, Bechara et al. 1994, Critchley et al. 2000)



Emotion
&
Influence
on

sympathetic

&

parasympathetic

innervation
of the heart

Ventromedial prefrontal

altered emotionality

‘acquired sociopathy’

inappropriate affect

poor frustration tolerance

irritability

impaired decision-making

psychosocial dysfunction

(Barrash et al. 2000)

Randomized 20 s presentation of pleasant,
unpleasant, neutral slides
1-min recovery intervals

2 unpleasant slides

quiet room, 24°C ambient temp,

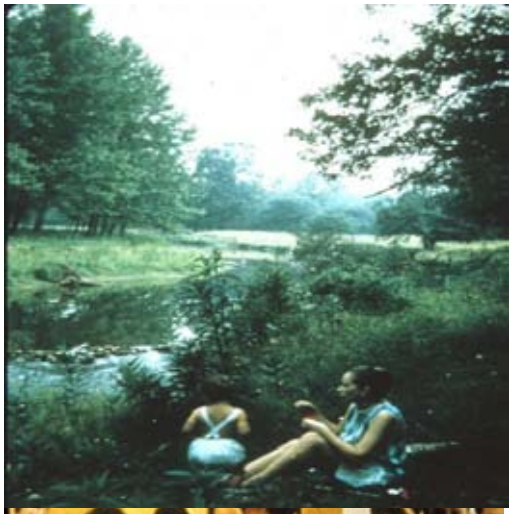
stable humidity, > 40 min rest

monitoring of: R–R-intervals (RRI)

- continuous blood pressure (BP)
- end-tidal CO2 ($ETCO_2$)
- transcutaneous O_2 saturation ($SatO_2$)
- respiratory frequency

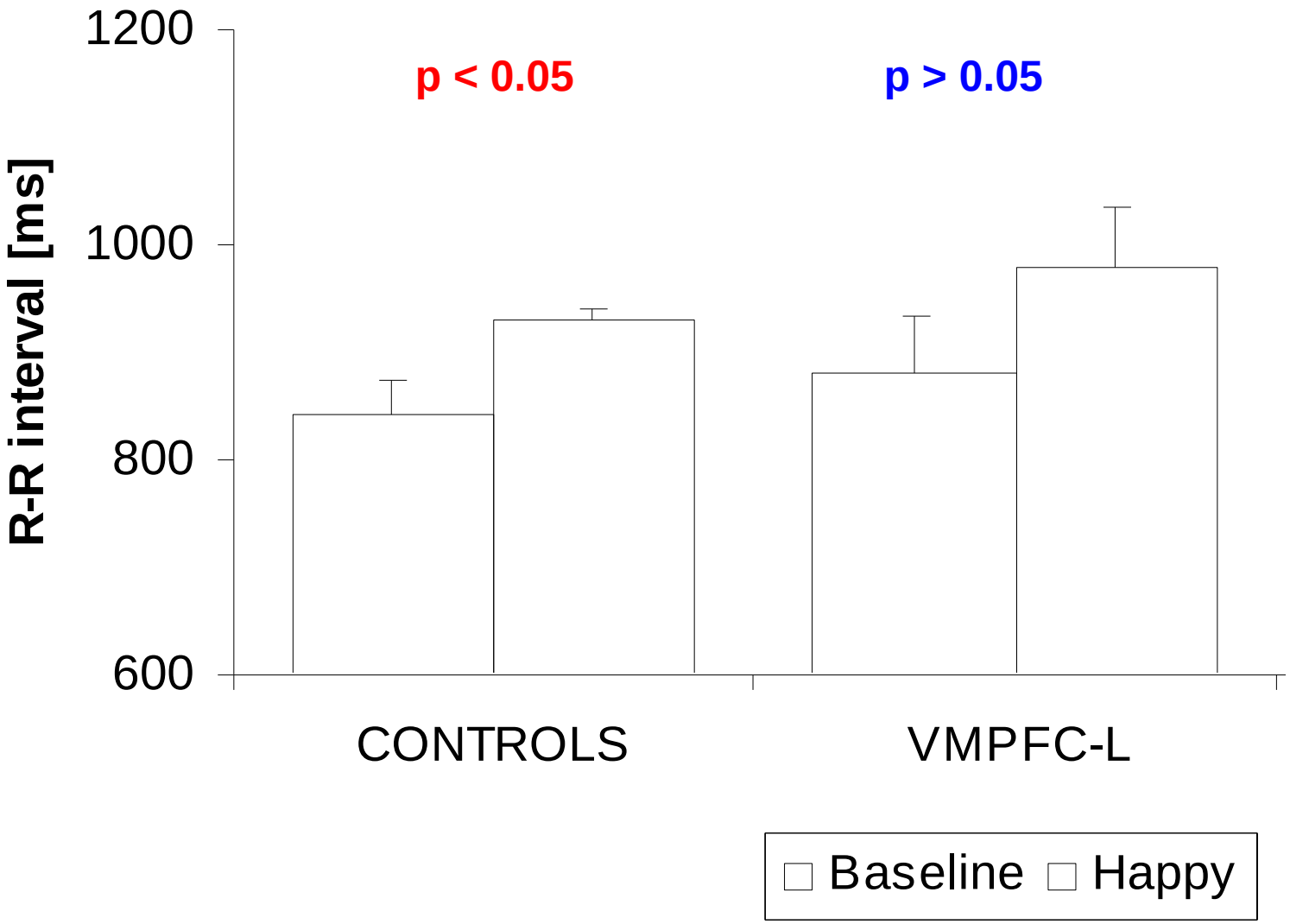
Randomized 20 s presentation of pleasant, *unpleasant*, *neutral* slides *(1-min recovery intervals)*

2 pleasant slides *2 unpleasant slides* *2 neutral slides*



Pleasant emotional stimulation:

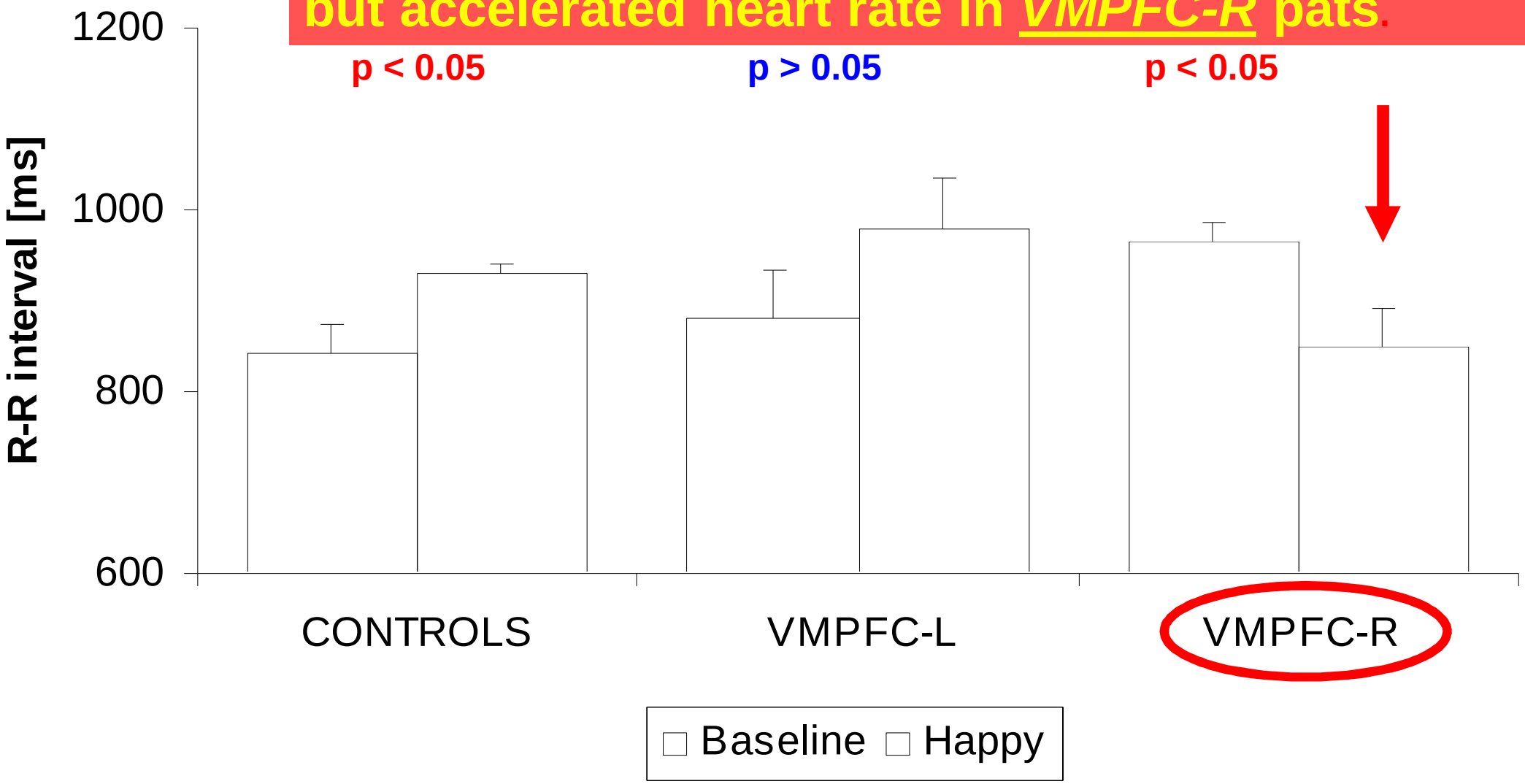
increased RRI in controls & VMPFC-L pats,



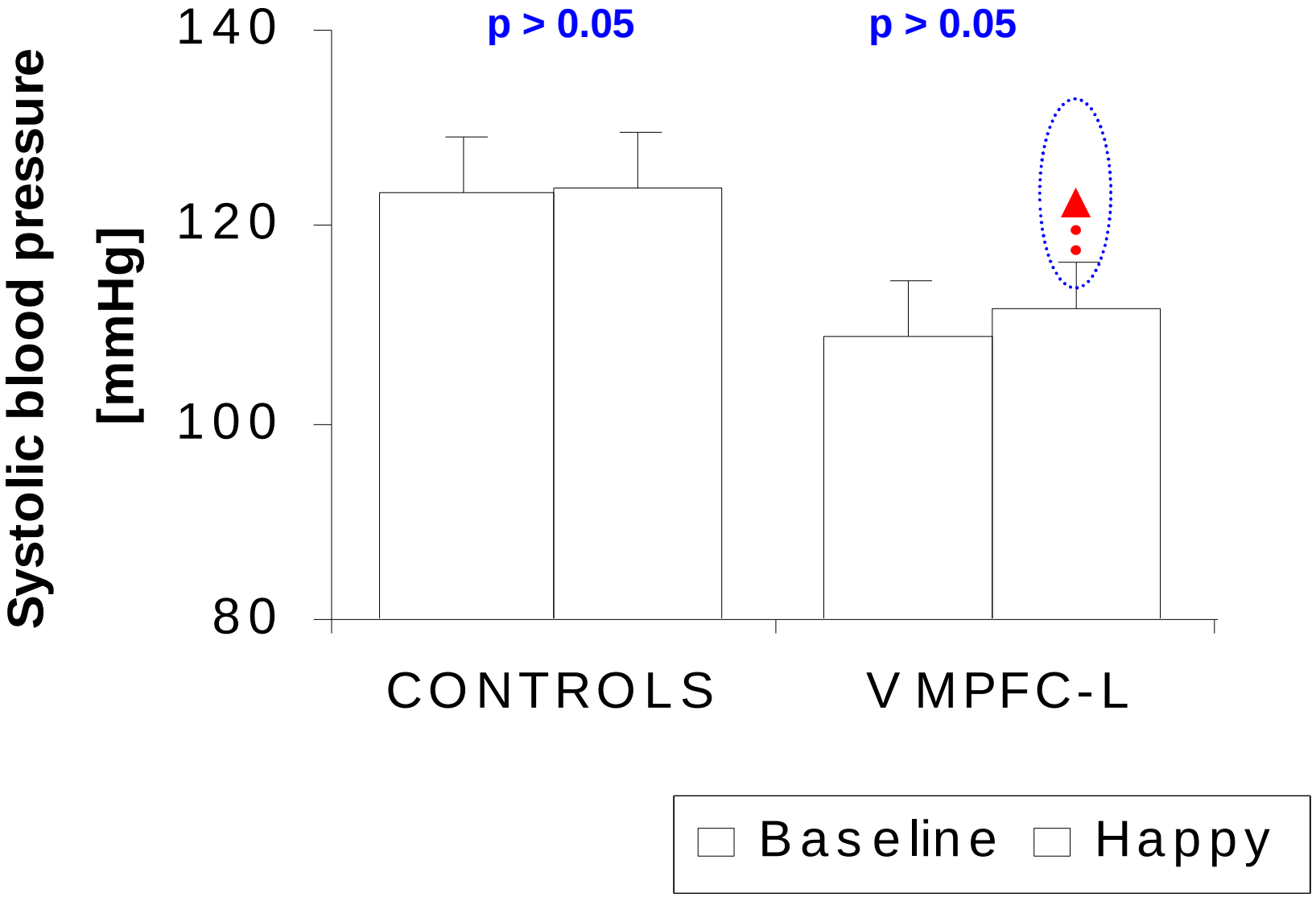
Pleasant emotional stimulation:

increased RRI in controls & VMPFC-L pats,

but accelerated heart rate in *VMPFC-R* pats.

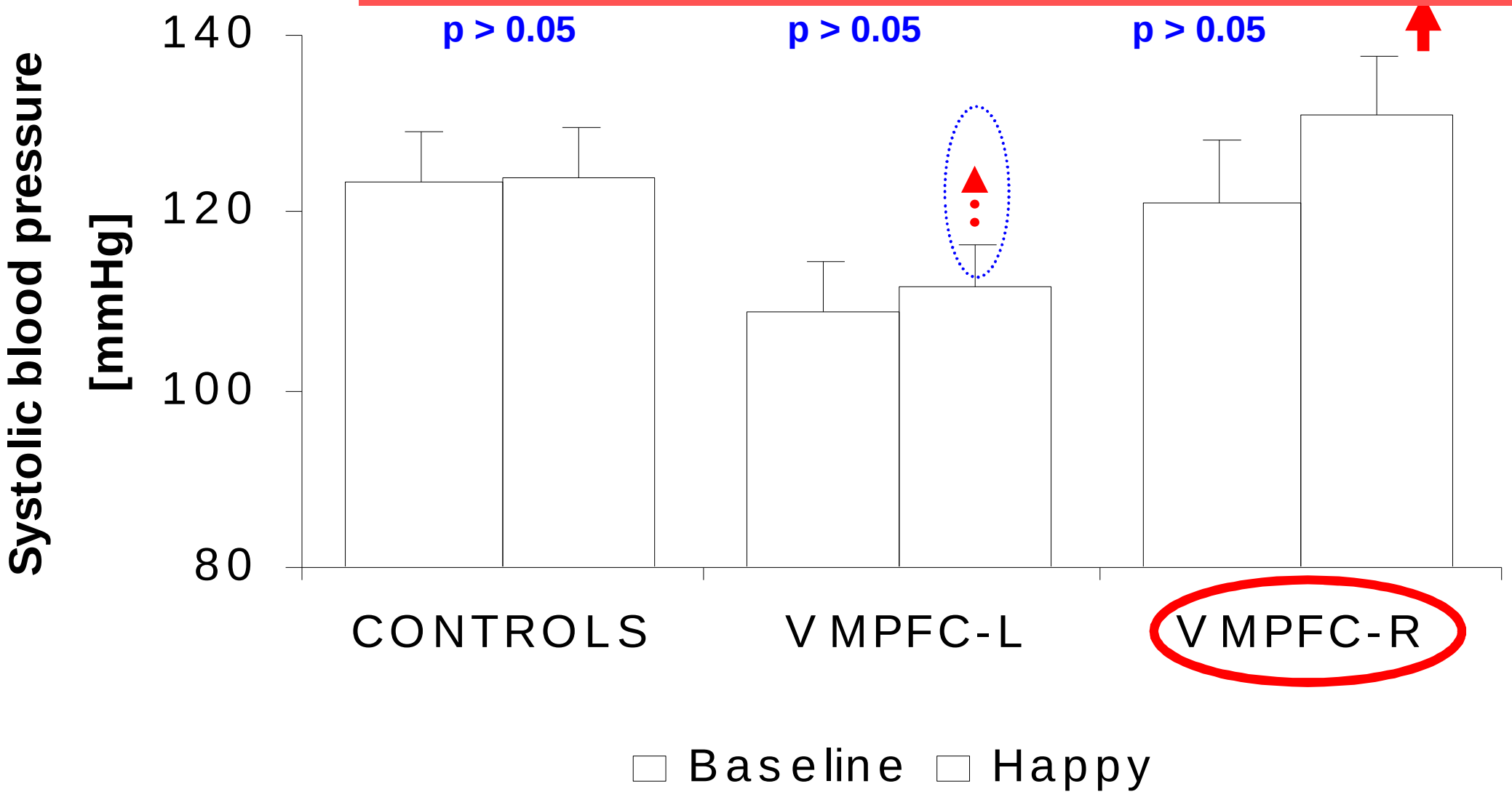


Pleasant emotional stimulation did not change systolic BP in controls, and VMPFC-L patients

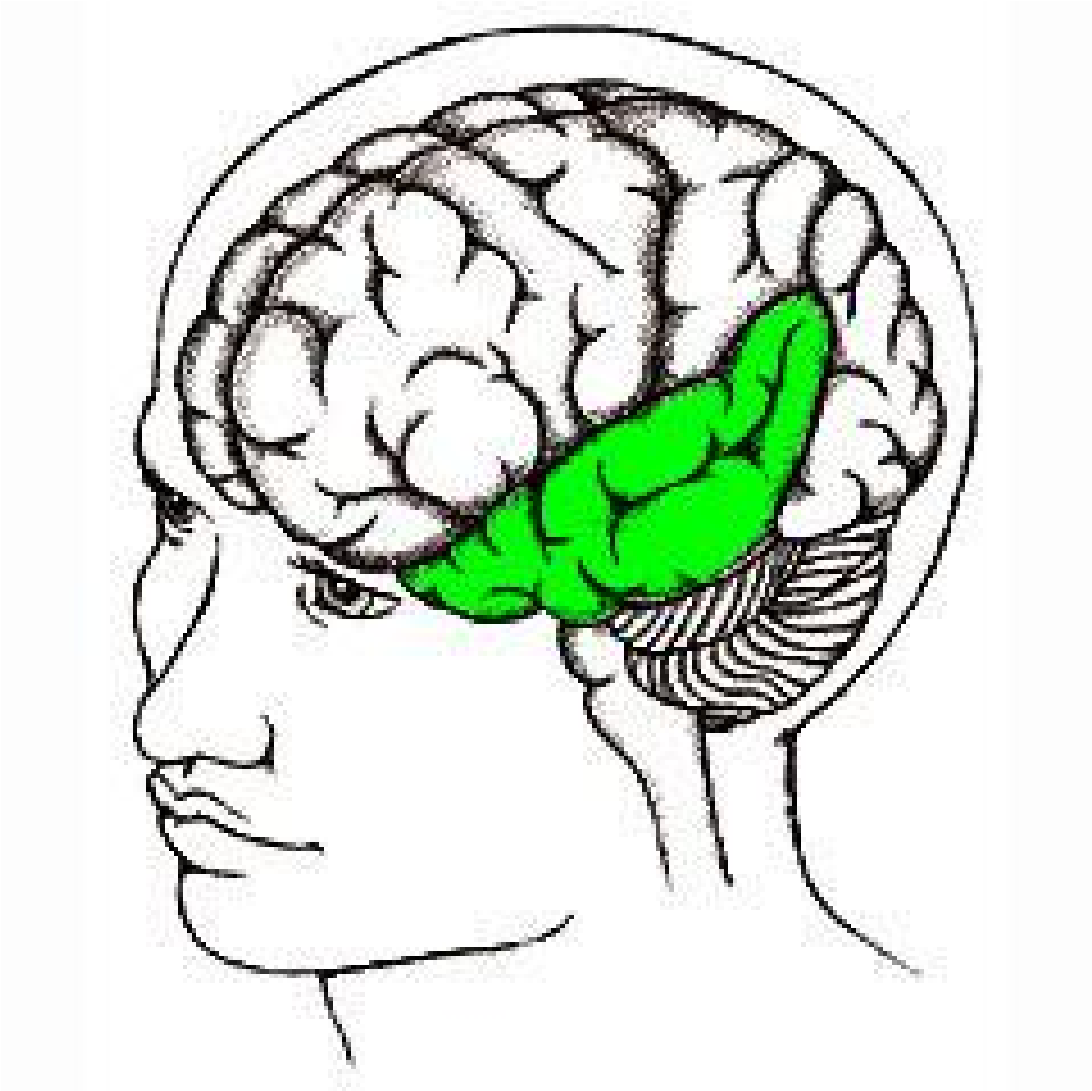


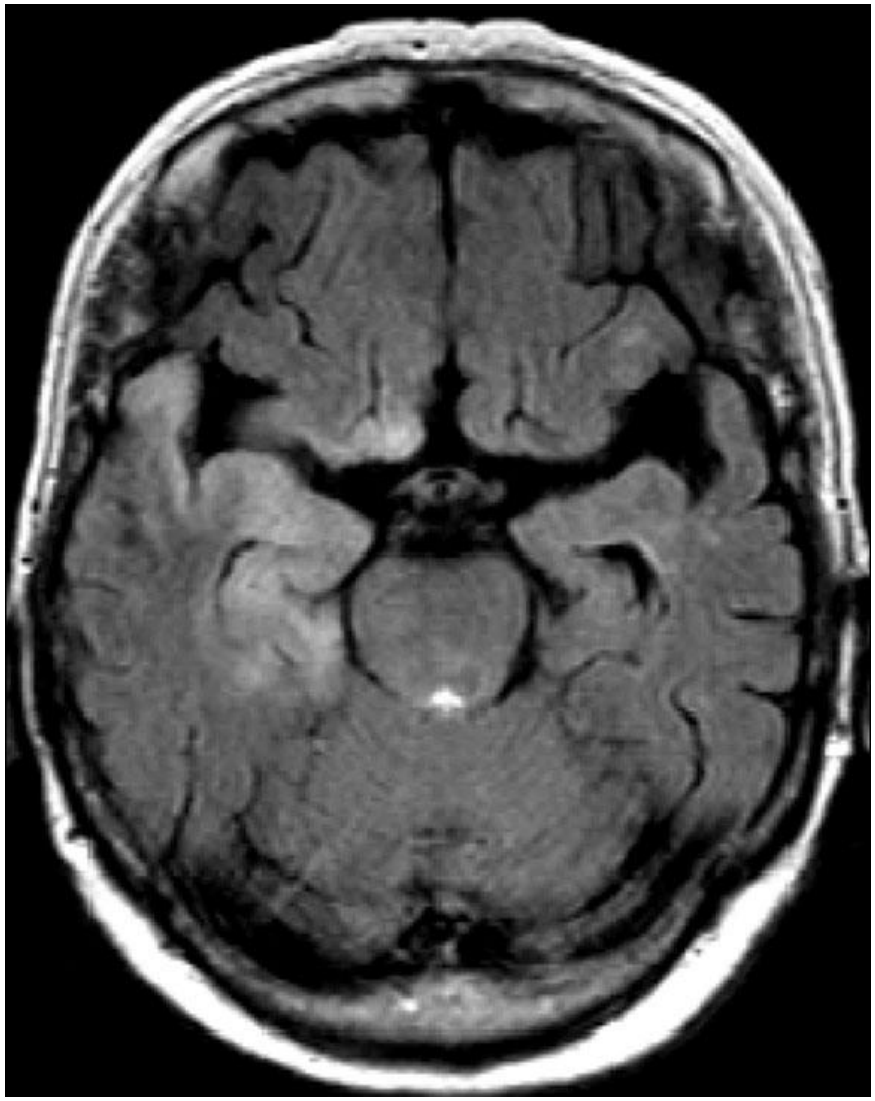
Pleasant emotional stimulation did not change systolic BP in controls, and VMPFC-L patients

but slightly increased BP in *VMPFC-R* pats.

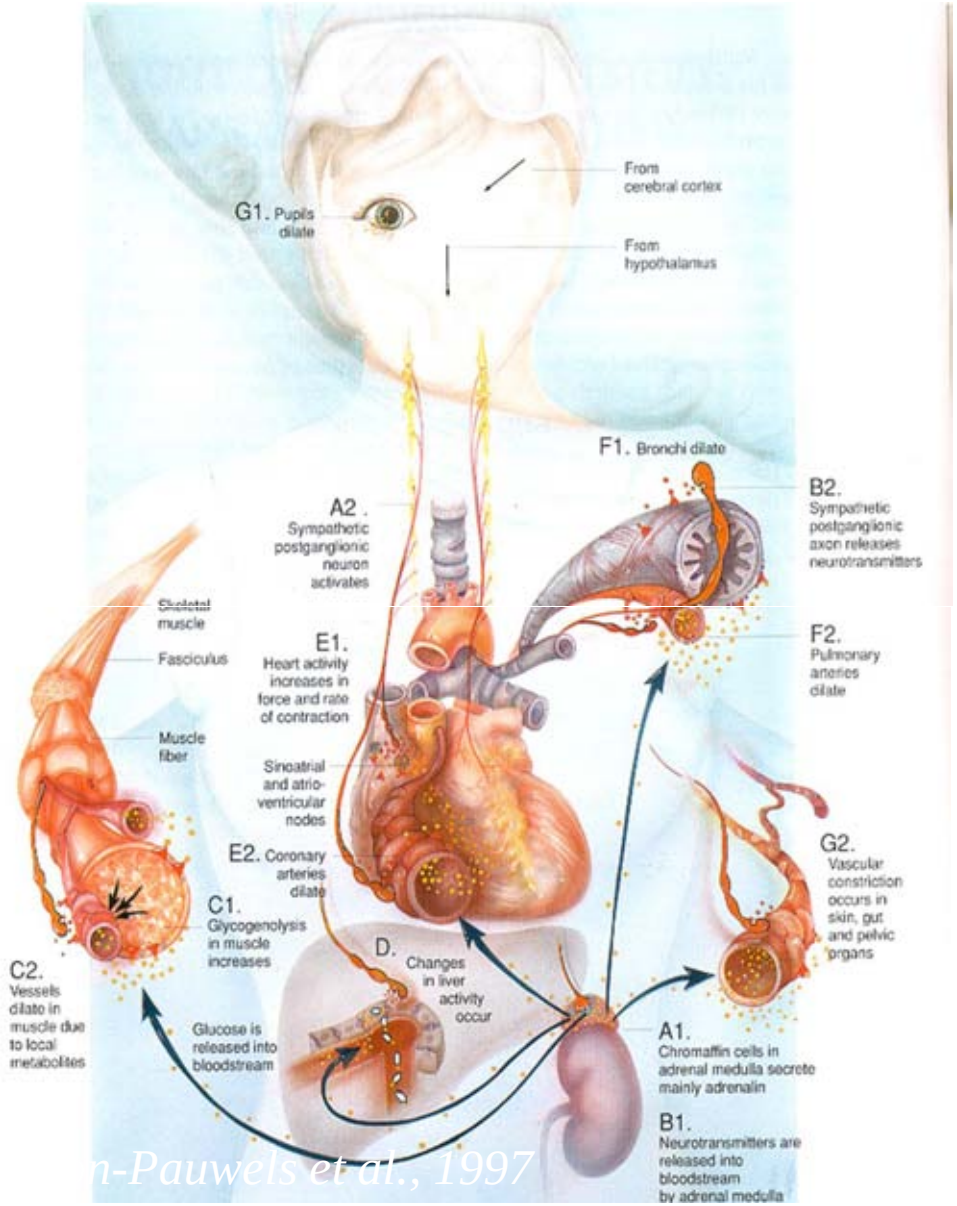


Temporal lobe and central autonomic control





„Fight and flight“ response to acute threat (Walter Cannon, 1932)



n-Pauwels et al., 1997

acute “defense“ response

enhanced energy release,

increased heart rate & cardiac output,

improved perfusion of myocardium,

bronchial dilatation,

improved pulmonary perfusion,

improved oxygenation & CO_2 removal

pupillary dilatation

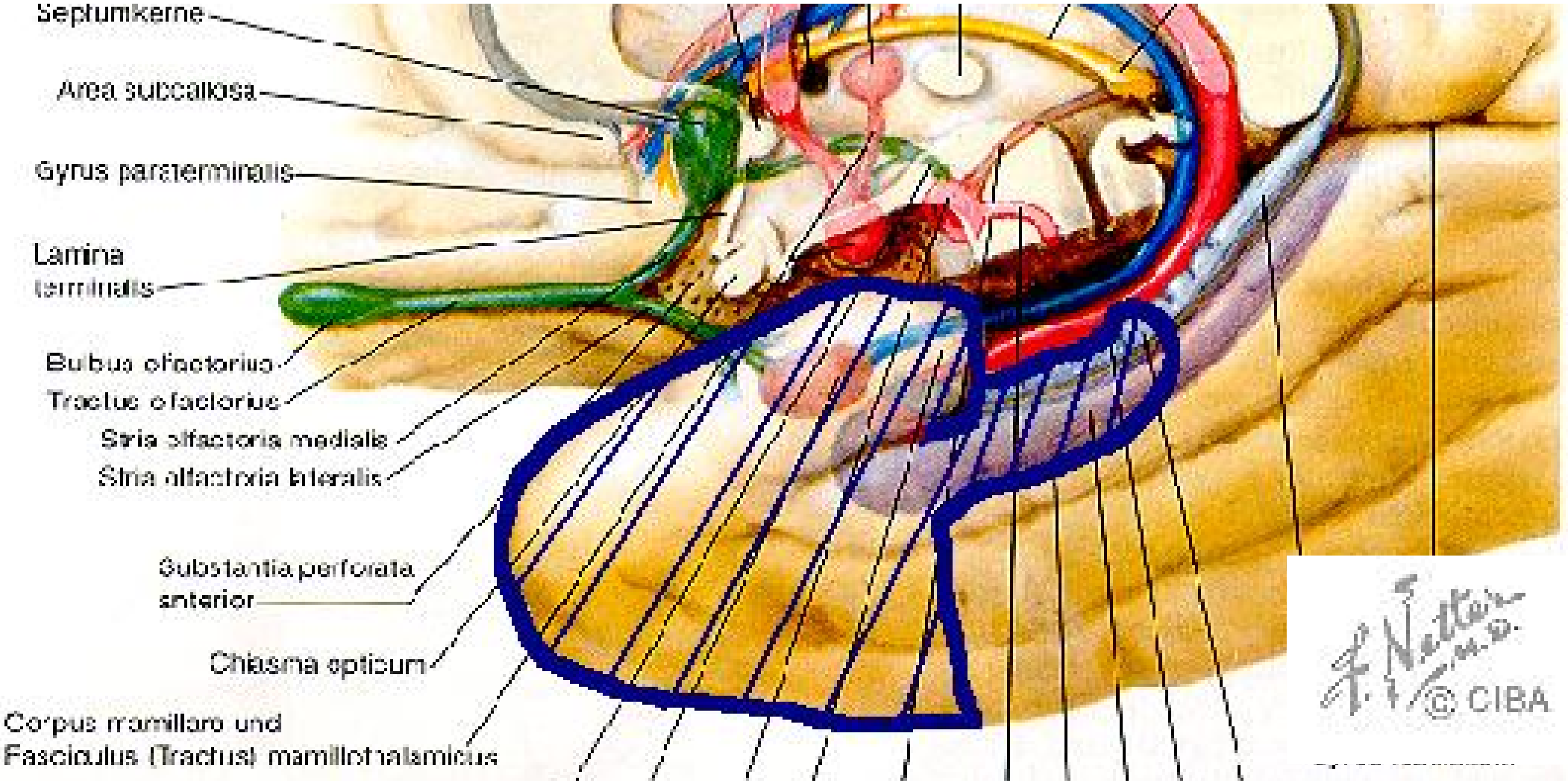
increased muscle perfusion

decreased skin perfusion

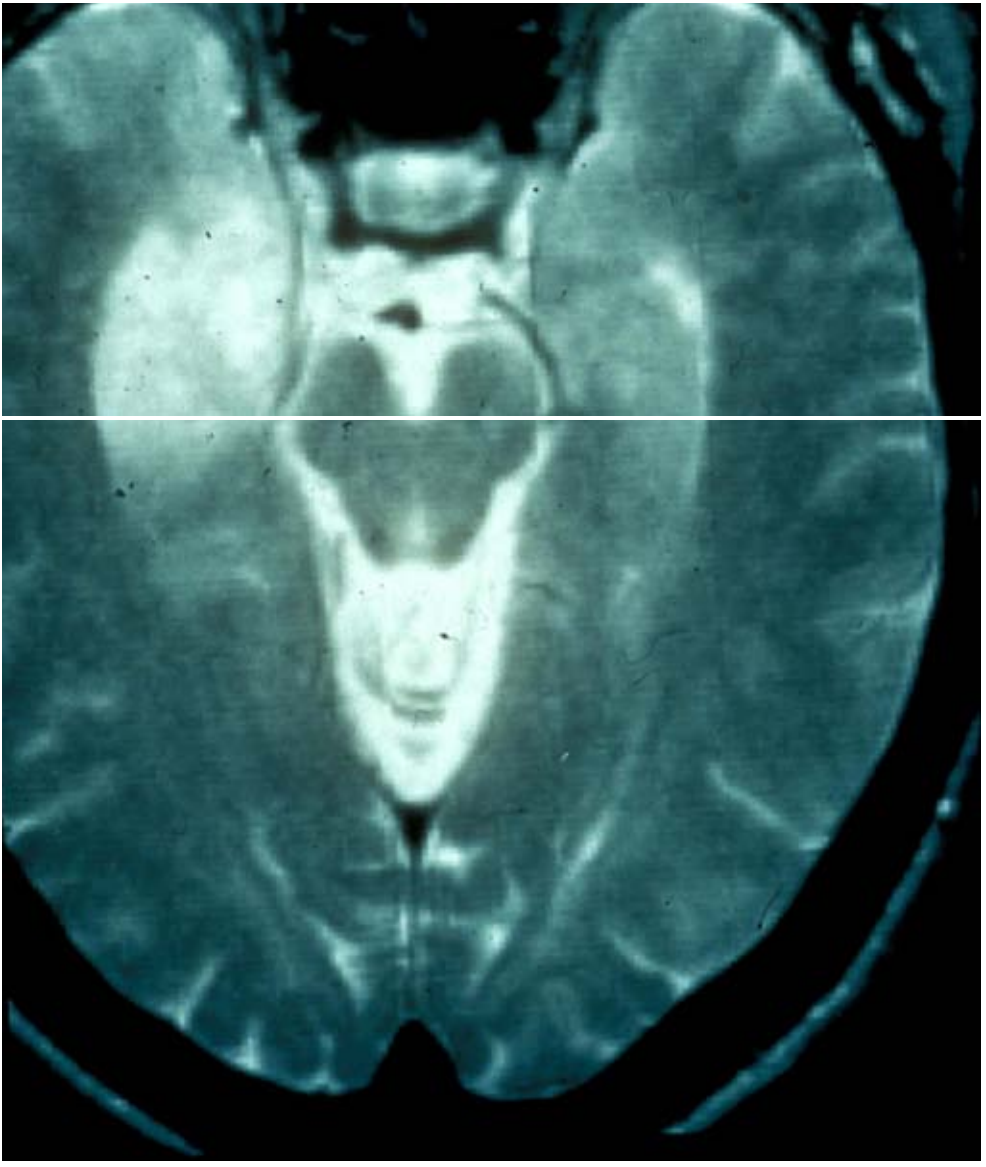
increased sweating *(“**cold sweat**“)*

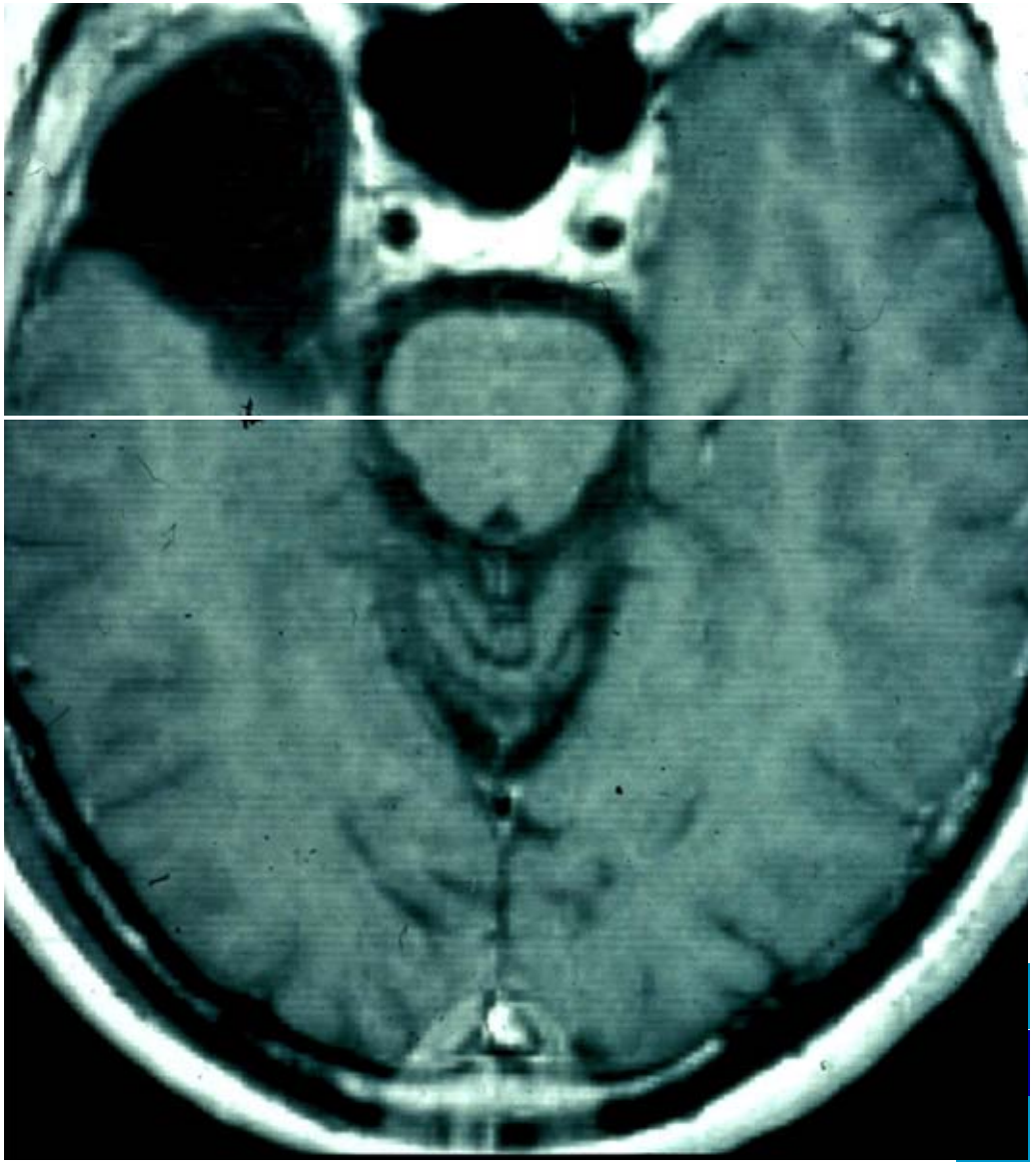
Tailored resection of central ANS areas (amygdala, hippocampus, limbic system)

è decrease in sympathetic modulation

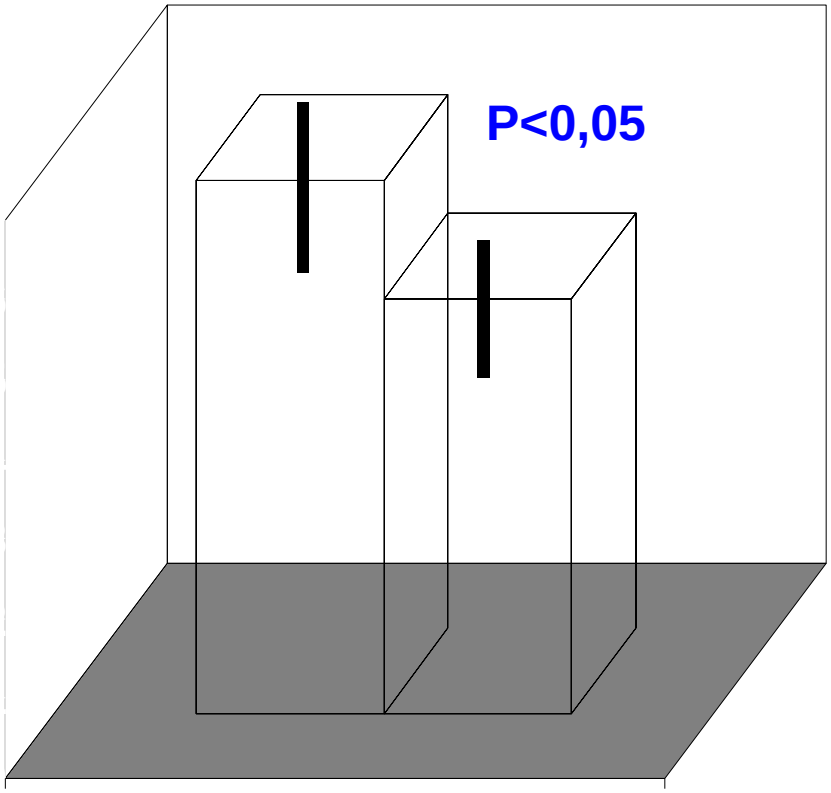


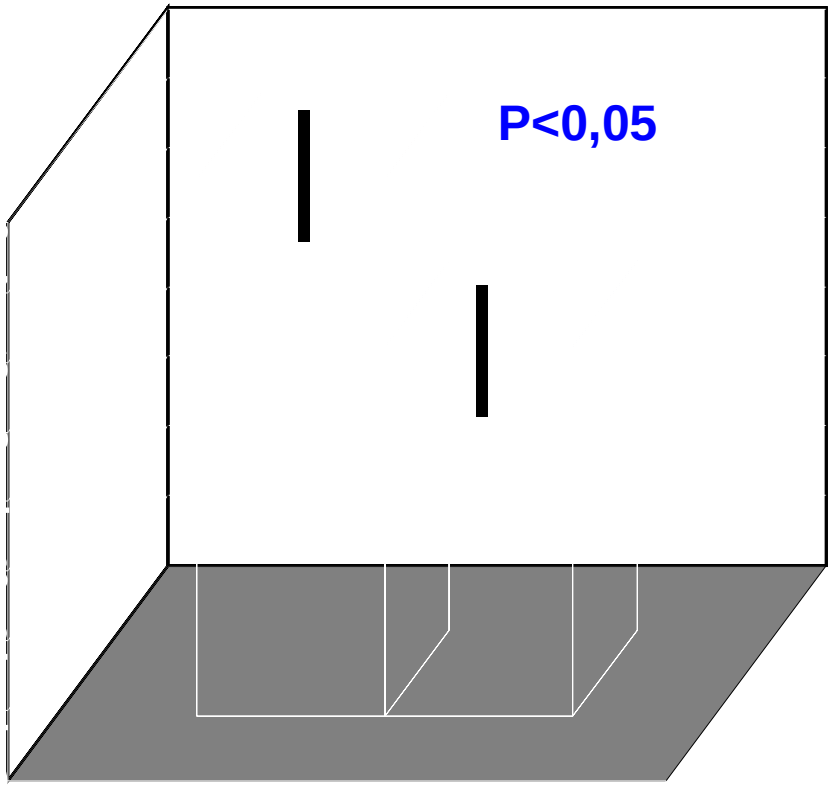
Monitoring of autonomic modulation
before & after temporal lobe tailored resection





Decrease in sympathetic LF-modulation of heart rate and blood pressure after tailored temporal lobe resection





LF - modulation of heart rate

0.67 ± 0.12 **0.52 ± 0.19**

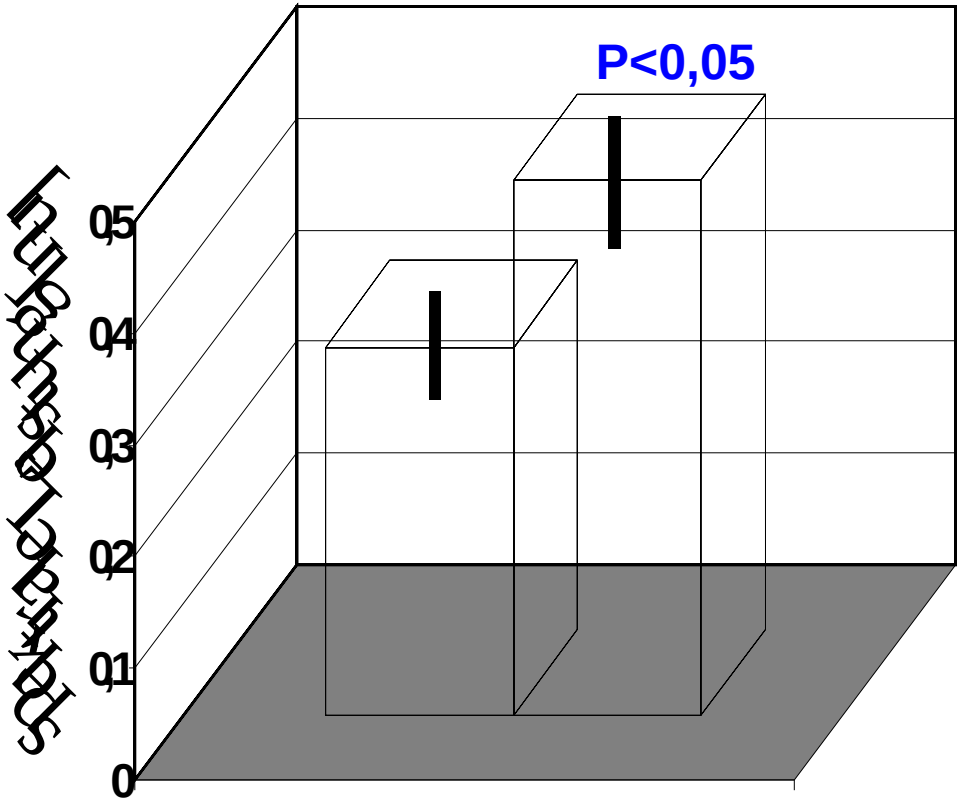
LF-modulation of blood pressure

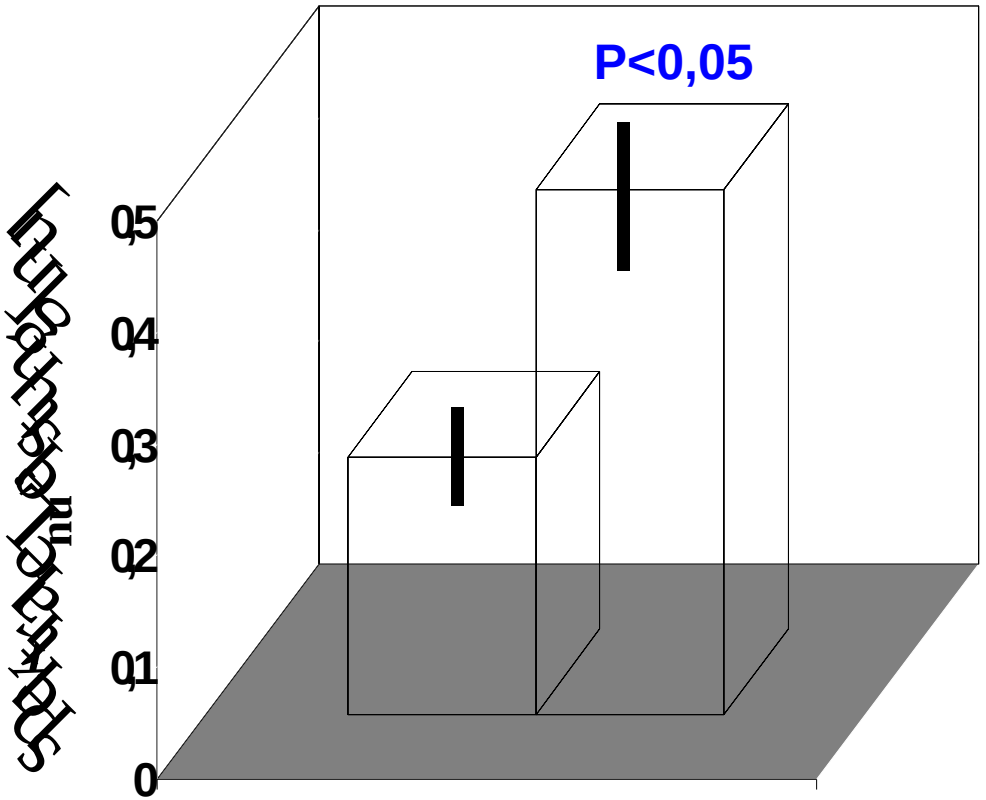
0.77 ± 0.09 **0.53 ± 0.17**

before surgery **er surgery**

Universitätsklinikum Erlangen

Increase in parasympathetic HF-modulation of heart rate & blood pressure after tailored temporal lobe resection





HF-modulation of heart rate

0.33 ± 0.12 **0.48 ± 0.19**

HF-modulation of blood pressure

0.23 ± 0.09 **0.47 ± 0.17**

before surgery **after surgery**

Tailored temporal lobe surgery

sympathetic activity ⇩

parasympathetic activity ⇧

⇨ surgically removed areas

(amygdala, hippocampus, temporal lobe)
enhance sympathetic activity
attenuate parasympathetic activity.

post-surgical reduction of

sympathetic activity

⇨ reduced risk of tachyarrhythmias

Hilz et al., Brain, 2002

High NIHSS values predict significant impairment of cardiovascular autonomic function

Hilz MJ, Moeller S, Akhundova A, Marthol H, Koehn J, DeFina P, Schwab S;
Stroke; 2011; 6: 1528-33

Objective: **To evaluate whether stroke severity correlates with autonomic dysfunction and thus predicts autonomic risk.**

Hilz et al. Stroke; 2011; 6: 1528-33

Methods: 50 pats. with acute ischemic stroke
middle cerebral artery
(25 women, 66±13 years)
32 healthy controls (20 women, 61±8 years)

Assessment of National Institutes of Health Stroke Scale (**NIHSS**) scores
within first 24 hours

monitoring of: **heart rate** (RRI),
blood pressure (BP),
respiration (RESP) for 90-seconds in supine position

Calculation of: RRI-SD: index of sympathetic & parasympathetic modulation
RRI-CV: index of sympathetic & parasympathetic modulation
RMSSD of RRIs: index of parasympathetic modulation

Off-line spectral analysis of underlying RRI- & BP-oscillations: (LF: 0.04 - 0.15 Hz; HF: 0.15 - 0.5 Hz)

RRI-LF-powers	è	sensitive to vagal & sympathetic influences
RRI-HF-powers	è	sensitive to vagal influences only
RRI-LF/HF ratio	è	reflecting sympathico-vagal balance
BP-LF-powers	è	index of sympathetic modulation
BP-HF-powers	è	mechanical effect (changing cardiac output)
BRS	è	gain between RRI- & syst BP-oscillations *(coherence >0.7)*

Correlation between cardiovascular parameters & NIHSS

(Spearman rank correlation tests)

Hilz et al. Stroke; 2011; 6: 1528-33

Results: NIHSS: 1-21 (median: 5; 25th percentile: 3; 75th percentile: 11)

Significant correlation between NIHSS scores

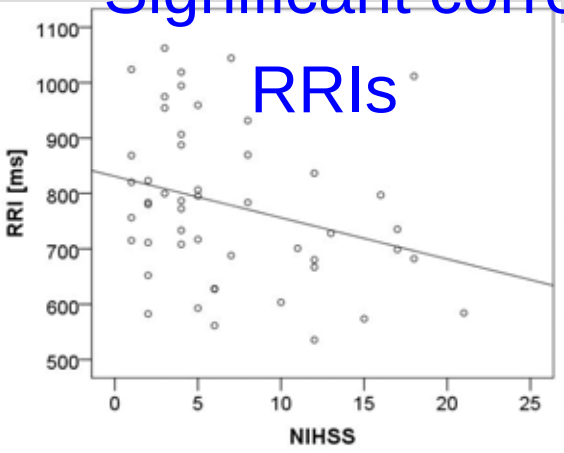
&	RRI-LFnu-powers:	Spearman Rho=0.345, p=0.014
	RRI-LF/HF-ratios:	Spearman Rho=0.345, p=0.014

Significant **inverse** correlation between NIHSS scores

&	RRI:	Spearman Rho=-0.310, p=0.028
	RRI-SD:	Spearman Rho=-0.289, p=0.042
	RMSSD:	Spearman Rho=-0.421, p=0.002
	RRI-HFnu-powers:	Spearman Rho=-0.345, p=0.014
	RRI-total powers:	Spearman Rho=-0.292, p=0.039
	BRS:	Spearman Rho=-0.317, p=0.025

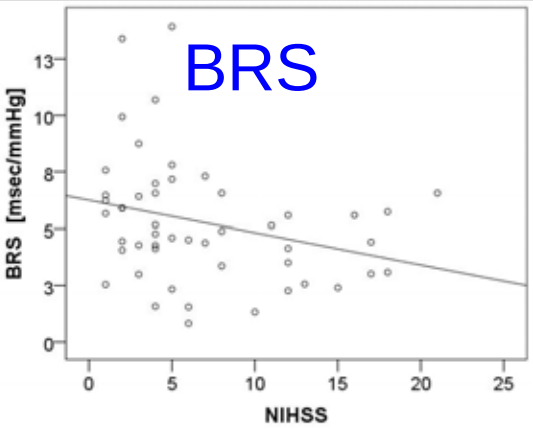
Significant correlation of NIHSS scores with

RRIs



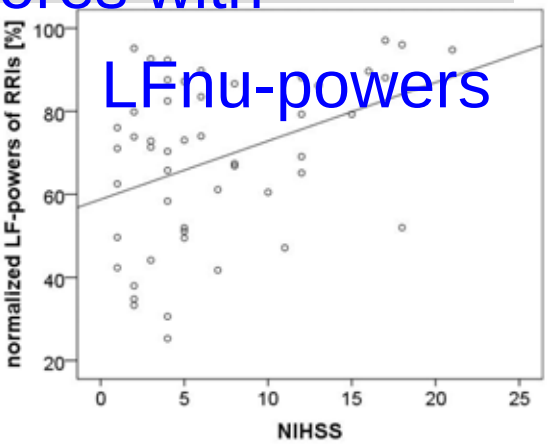
Rho = - 0.310

BRS



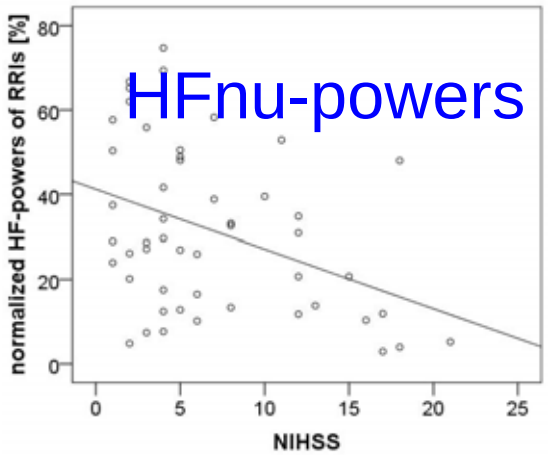
Rho = - 0.317

LFnu-powers



Rho = 0.345

HFnu-powers



Rho=-0.345

Conclusions:

Increasing stroke severity was associated with progressive

- è **loss of autonomic modulation**,
- è **decline in parasympathetic tone & BRS**,
- è **and shift towards sympathetic predominance.**

Higher NIHSS scores predict higher risk of autonomic failure.

All autonomic changes put patients with more severe stroke at **increasing risk of cardiovascular complications & poor outcome.**

Hilz et al. Stroke; 2011; 6: 1528-33

Increased sympathetic cardiac stimulation

è (necrosis) of subendocardial heart muscle cells

not related to arteriosclerosis of coronary arteries

close to sympathetic nerve terminals & cardiac conducting system

è **risk of arrhythmias**

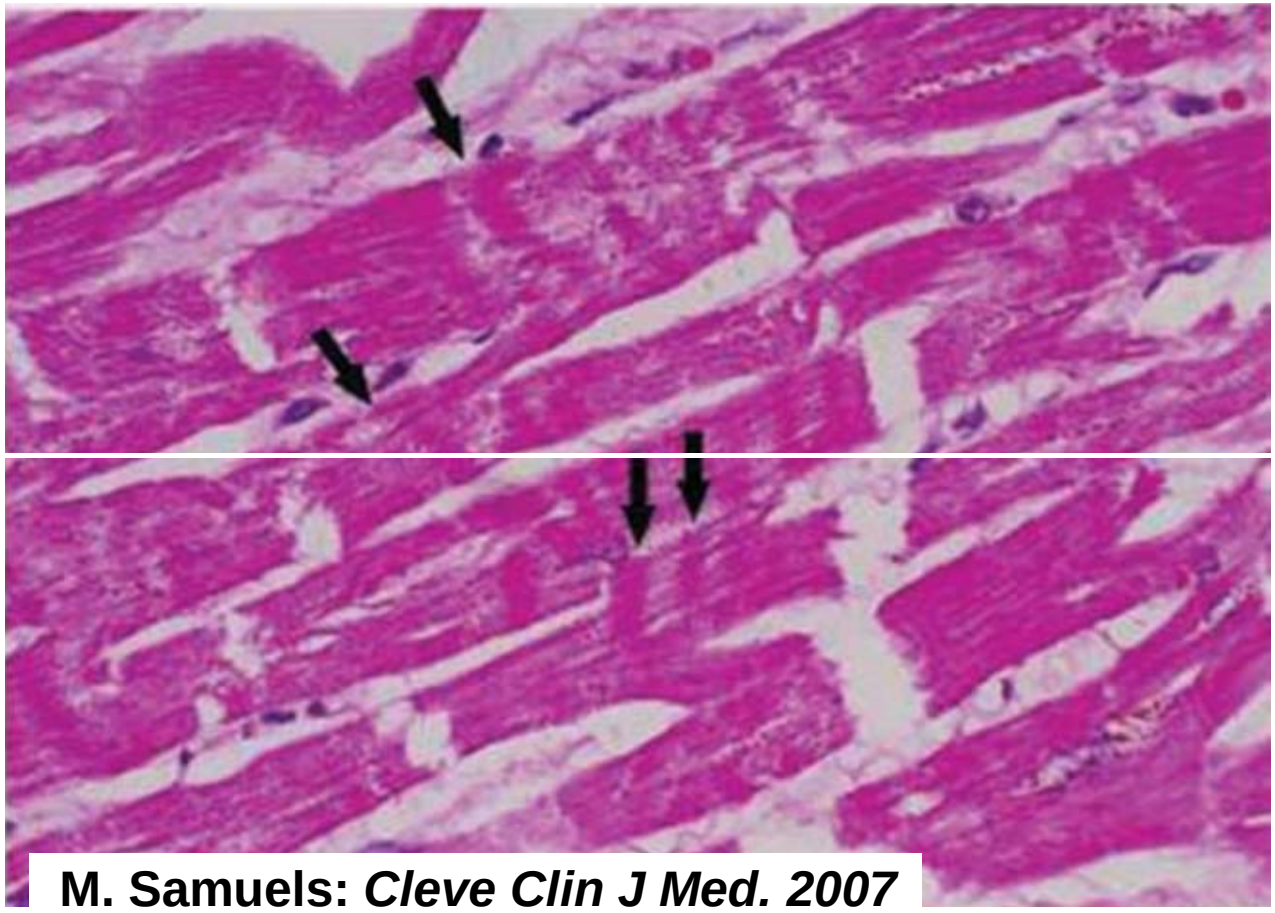
Neurocardiac lesion:

contraction band necrosis

(arrows),

myofibrillar degeneration

coagulative myocytolysis



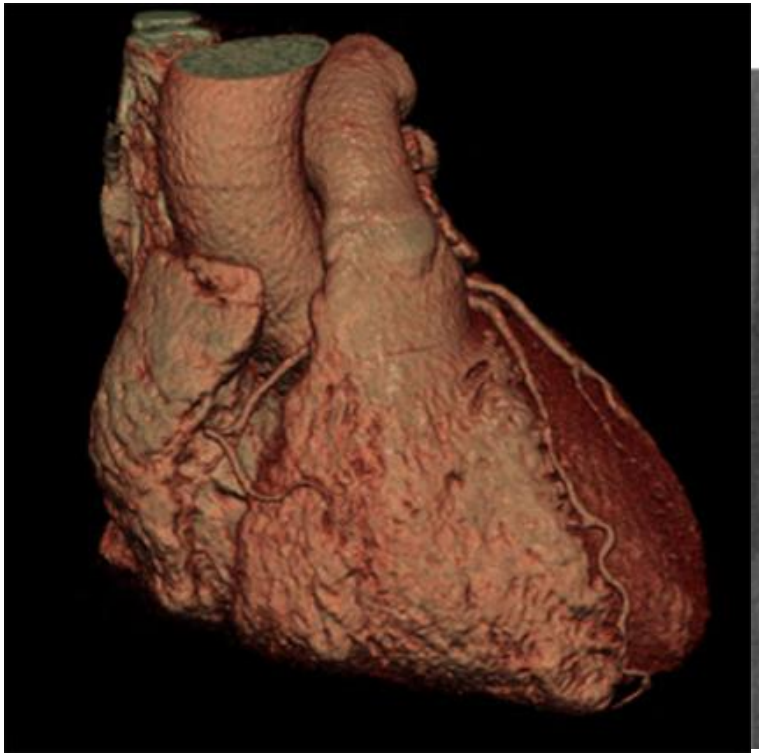
M. Samuels: *Cleve Clin J Med. 2007*

Takotsubo Syndrome - broken heart syndrome

stress cardiomyopathy - transient myocardial stunning

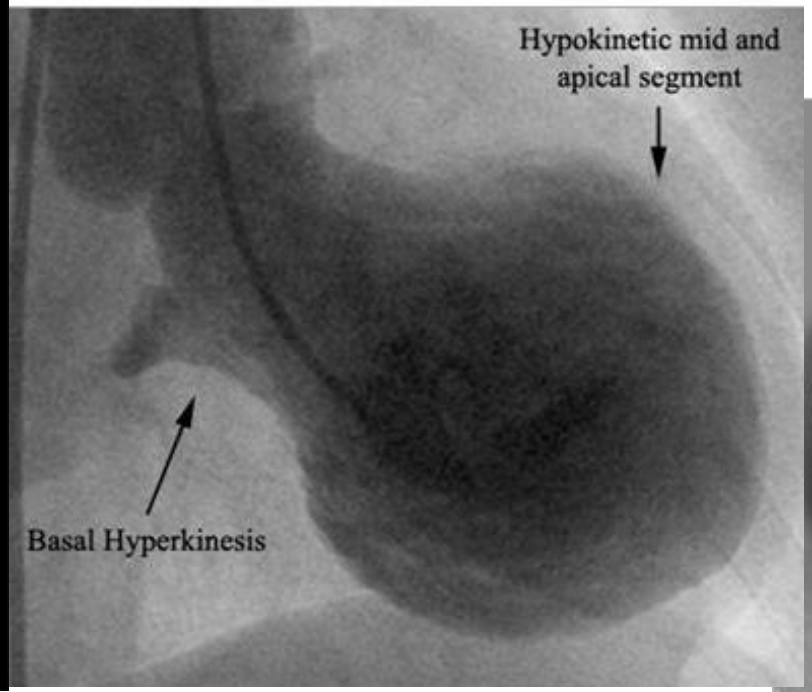
ballooning of heart apex & narrow base,

similar to Japanese octopus trapping pot (takotsubo)



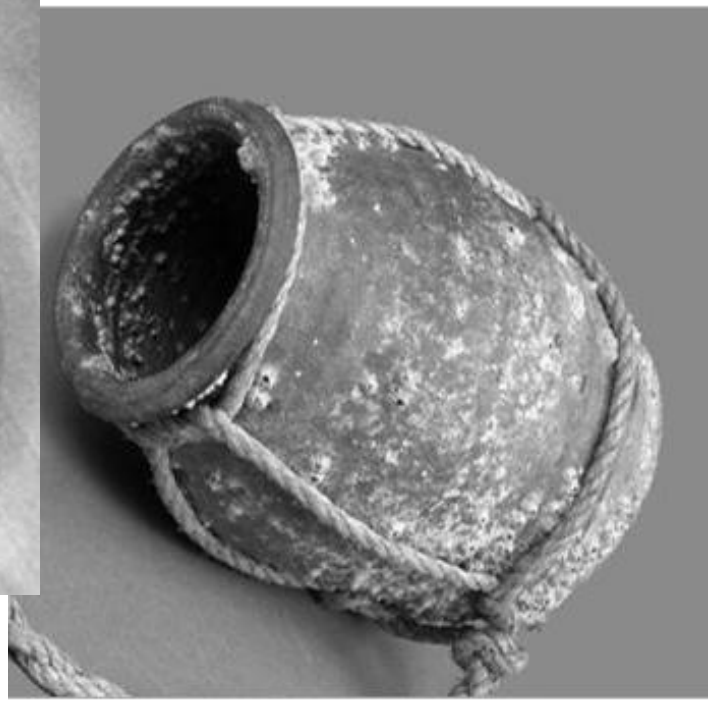
normal heart

(NYU, cardiac CT Angio)



stressed heart

(Shahid et al, 2009)



Japanese octopus trapping pot

C owly

Edvard Munch: The Freeze of Life

References:

1. Naver HK, Blomstrand C, Wallin BG. Reduced heart rate variability after right-sided stroke. *Stroke*. 1996;27:247-251
2. Klingelhofer J, Sander D. Cardiovascular consequences of clinical stroke. *Baillieres Clin Neurol*. 1997;6:309-335
3. Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllya VV. Abnormal heart rate variability as a manifestation of autonomic dysfunction in hemispheric brain infarction. *Stroke*. 1996;27:2059-2063
4. Tokgozoglu SL, Batur MK, Top uoglu MA, Saribas O, Kes S, Oto A. Effects of stroke localization on cardiac autonomic balance and sudden death. *Stroke*. 1999;30:1307-1311
5. Dutsch M, Burger M, Dorfler C, Schwab S, Hilz MJ. Cardiovascular autonomic function in poststroke patients. *Neurology*. 2007;69:2249-2255
6. Korpelainen JT, Sotaniemi KA, Myllyla VV. Autonomic nervous system disorders in stroke. *Clin Auton Res*. 1999;9:325-333
7. Ay H, Koroshetz WJ, Benner T, Vangel MG, Melinosky C, Arsava EM, Ayata C, Zhu M, Schwamm LH, Sorensen AG. Neuroanatomic correlates of stroke-related myocardial injury. *Neurology*. 2006;66:1325-1329
8. Oppenheimer S. Cerebrogenic cardiac arrhythmias: Cortical lateralization and clinical significance. *Clin Auton Res*. 2006;16:6-11
9. Rincon F, Dhamoon M, Moon Y, Paik MC, Boden-Albala B, Homma S, Di Tullio MR, Sacco RL, Elkind MS. Stroke location and association with fatal cardiac outcomes: Northern manhattan study (nomas). *Stroke*. 2008;39:2425-2431
10. Hilz MJ, Schwab S. Stroke-induced sudden-autonomic death: Areas of fatality beyond the insula. *Stroke*. 2008;39:2421-2422
11. Makikallio AM, Makikallio TH, Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllyla VV. Heart rate dynamics predict poststroke mortality. *Neurology*. 2004;62:1822-1826
12. Kuriyama N, Mizuno T, Niwa F, Watanabe Y, Nakagawa M. Autonomic nervous dysfunction during acute cerebral infarction. *Neurol Res*. 2009
13. Ay H, Arsava EM, Koroshetz WJ, Sorensen AG. Middle cerebral artery infarcts encompassing the insula are more prone to growth. *Stroke*. 2008;39:373-378
14. Benarroch EE. *Central autonomic network: Functional organization and clinical correlations*.
15. Armonk, NY: Futura Publishing Company, Inc.; 1997.
16. Oppenheimer SM, Kedem G, Martin WM. Left-insular cortex lesions perturb cardiac autonomic tone in humans.
17. *Clin Auton Res*. 1996;6:131-140
18. Sörös P, Hachinski V. Cardiovascular and neurological causes of sudden death after ischaemic stroke. Lancet Neurol. 2012; 11:179-88.