

Pathologic Mechanisms in the Sudden Infant Death Syndrome

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In determining the causes underlying the Sudden Infant Death Syndrome, we should perhaps consider the possibility of multiple causes, and focus on why common compensatory mechanisms fail.

Sudden Infant Death Syndrome (SIDS)- Characteristics of Victims

- Modified respiratory influences on heart rate
- Periods of tachycardia prior to death
- Profuse sweating
- Possible bradycardia and blood pressure loss during fatal event
- Fewer movements during sleep, fewer arousals during early morning hours

The first four issues suggest aberrant sympathetic and parasympathetic outflow. Some differences present as early as the first week of life.

The fatal event in SIDS can be associated with bradycardia and an absence of breathing influences on heart rate

SIDS victims show tachycardia 3 days before the fatal event; during the fatal event, bradycardia and hypotension occur.

The sequence is similar to what is seen in the two stages of shock- an initial sympathoexcitation, followed by a sympathoinhibition and parasympathetic excitation (bradycardia).

Shock: Two Stages

Deep Pain
Blood Volume Loss
Infection



I. Compensatory

Sympathoexcitation
Profuse Sweating
Tachycardia
Increased Blood Pressure



II. Decompensatory

Sympathoinhibition
Loss of Blood Pressure
Profound Bradycardia



Loss of Perfusion and Death

What Pathology Underlies the Prone Position-Dependent Risk in SIDS?

Possibilities:

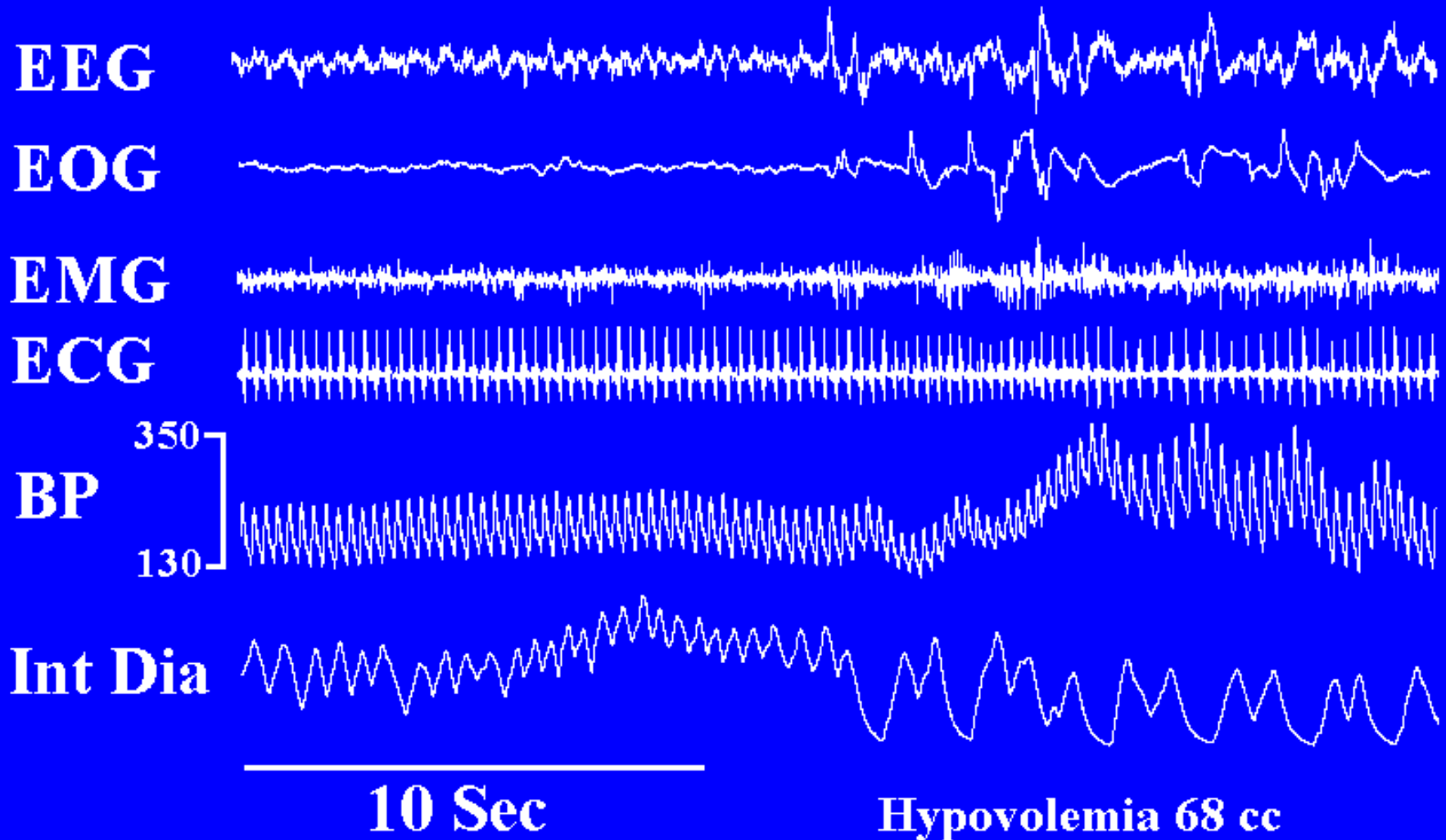
- Entrapped CO₂ near infant's face
- Failure of facial heat dissipation
- Trigeminal somatosensory stimulation effects on breathing
- Vestibular effects on blood pressure

Since blood pressure elevation suppresses breathing, and lowering will enhance breathing rate, (and, conversely, breathing efforts affect blood pressure), the issue of fatal mechanism in SIDS is not either a “respiratory” death or a “cardiovascular” death- the two systems interact.

What normally happens during blood pressure loss?

The cerebellum plays its “error correction” role, and attempts to restore blood pressure with movement; that “movement” includes enhanced breathing efforts.

Strategy: Tachypnea, then switch to repetitive enhanced inspiratory efforts



How does body position
influence blood pressure?

The vestibular system exerts
substantial influence on blood
pressure!

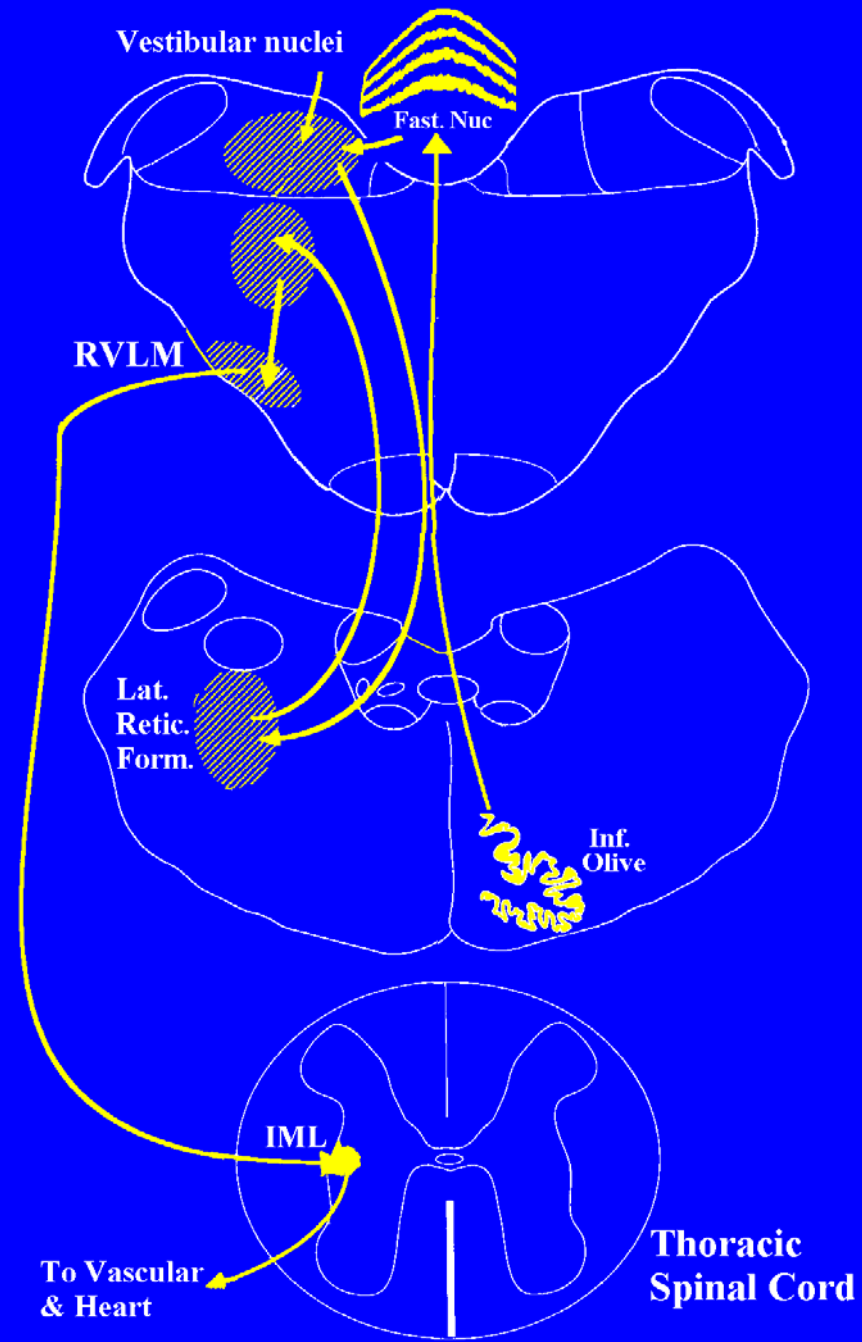
That's why body tilt induces marked blood pressure change.

Infants at risk for SIDS exhibit deficient blood pressure responses to tilt

Harrington et al., 2002; Fifer et al. 2002

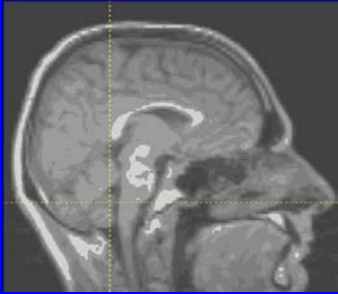
What other brain structures mediate recovery from blood pressure loss?

- Ventral medullary surface
- Caudal Raphe
- Inferior olive
- Fastigial nucleus of cerebellum



Pathways:
 vestibular and
 inferior olive
 mediation
 of blood
 pressure.

T1 Anatomical Scans

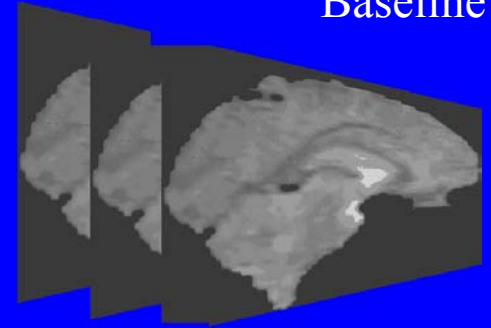


G.E. 1.5 T
Bold Imaging
Echo Planar
TR= 6 sec, TE = 60 msec
30 cm FOV
20 Axial slices
5 mm slice thickness
No interslice gap

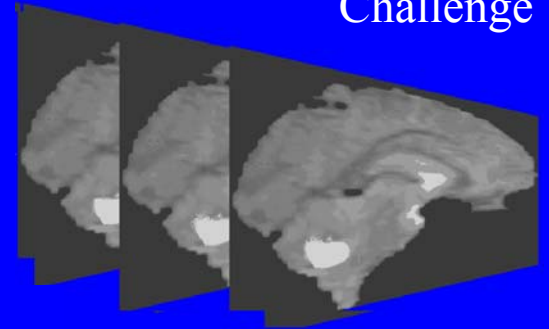


Functional Scans

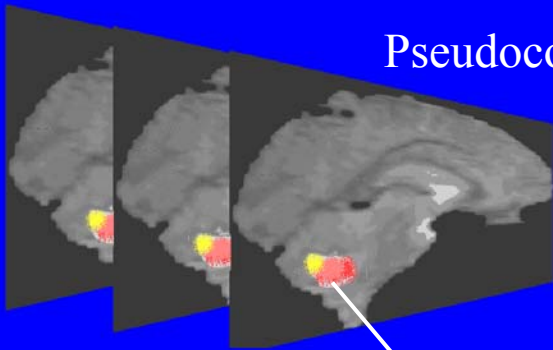
Baseline



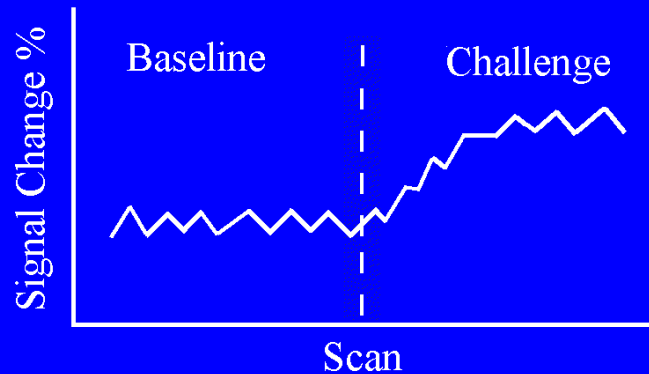
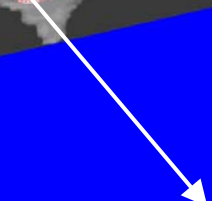
Challenge



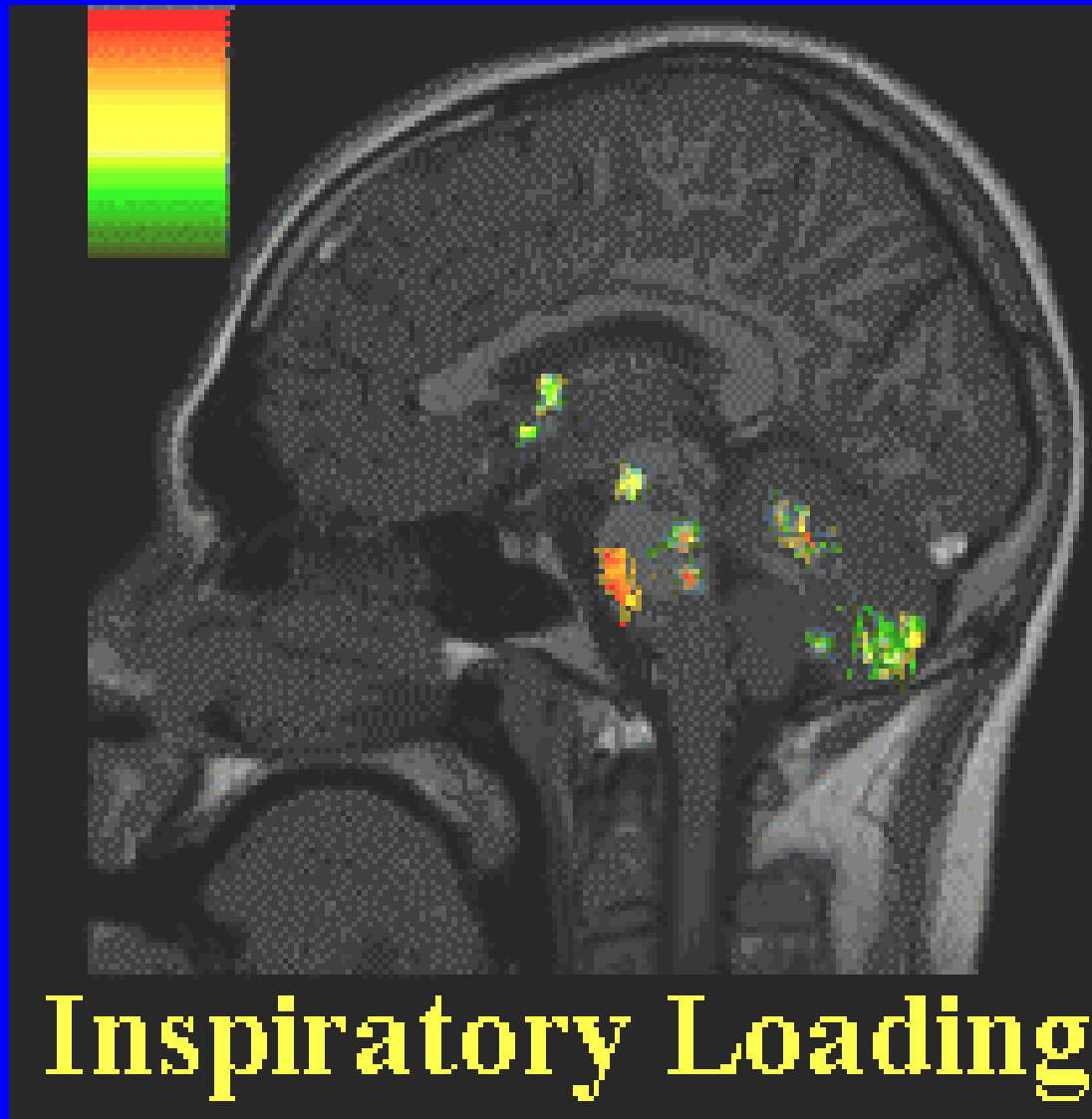
Pseudocolor



ROI Trend

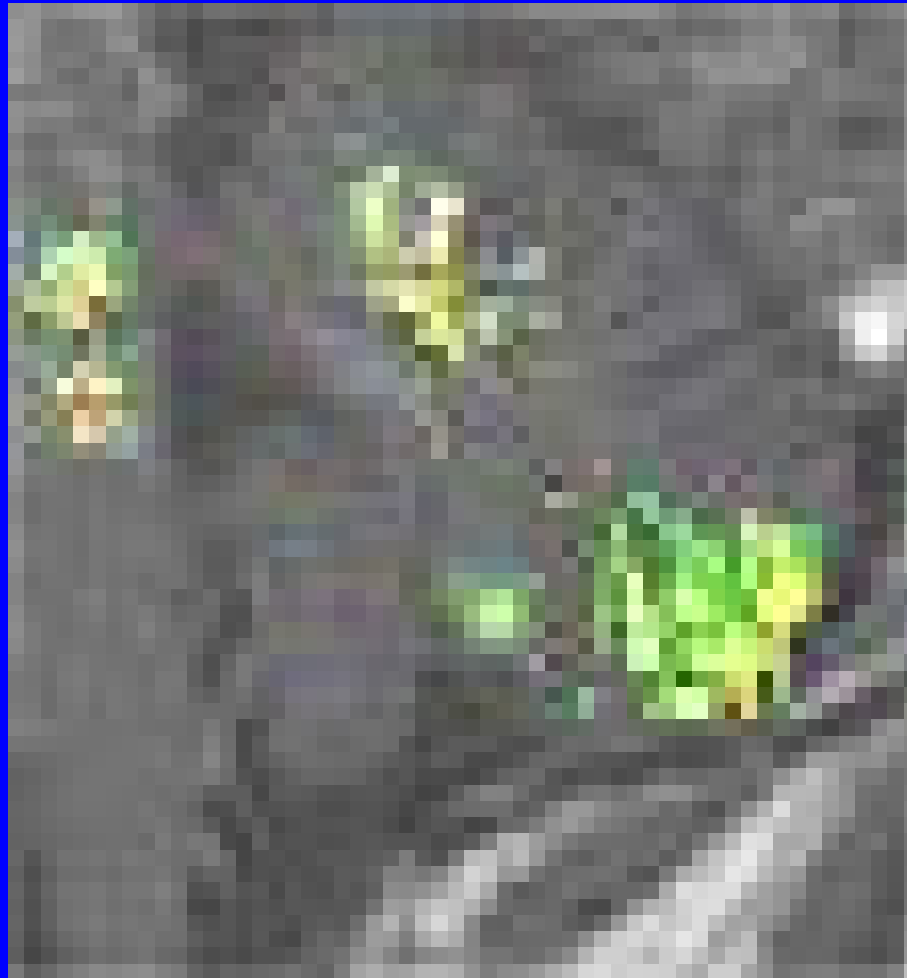


Brain areas activated to inspiration against resistance

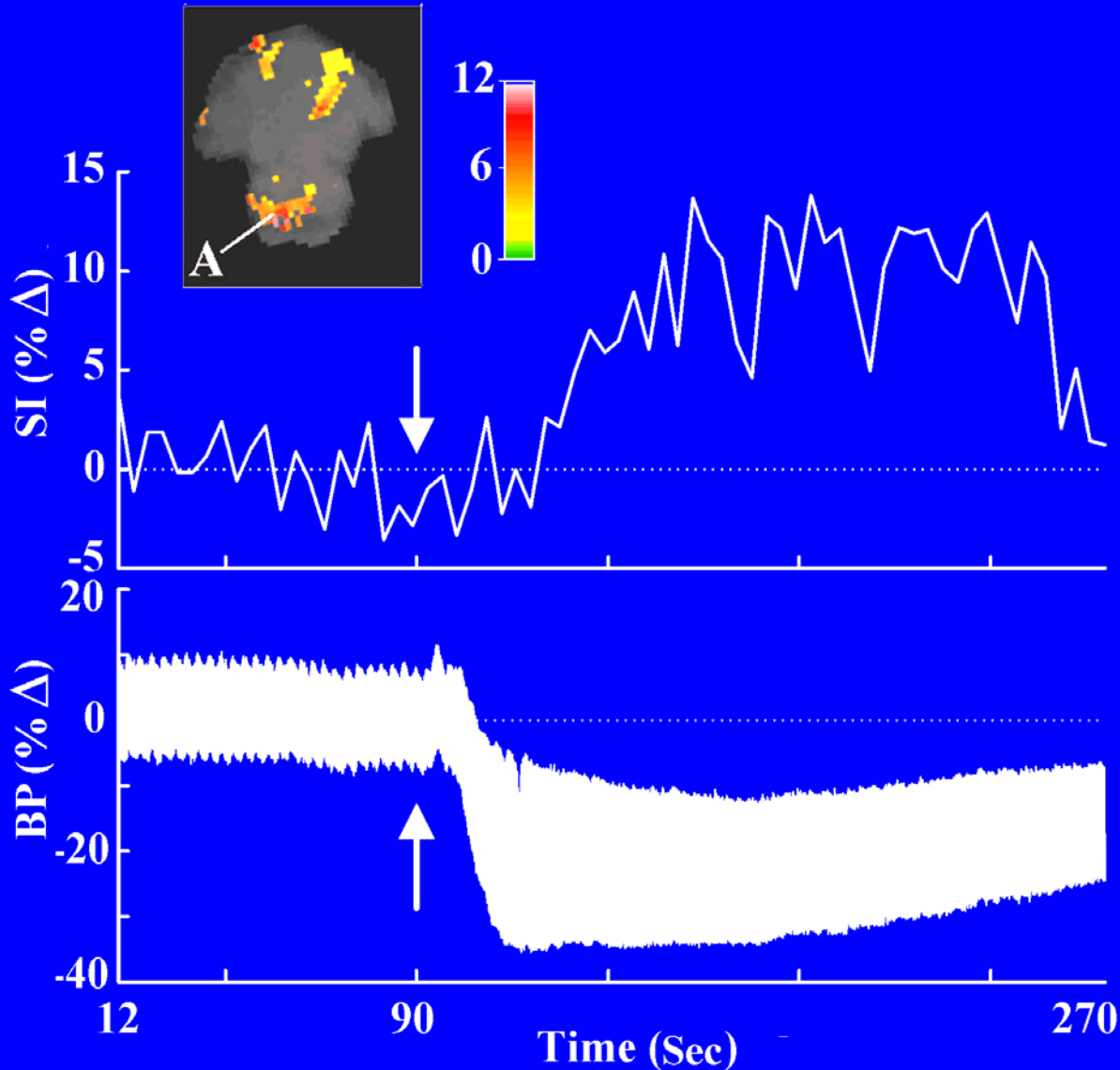


Gozal et al., *PNAS*, 92 (14):6607-6611, 1995

BP elevation by inspiratory loading activates cerebellar regions



The Inferior Olive Activates to a Marked Blood Pressure Decline



What disorders show blood pressure/breathing dysfunction?

- Congenital Central Hypoventilation Syndrome (Ondine's Curse)
- Obstructive Sleep Apnea (OSA)
- Heart Failure with Disordered Breathing

Congenital Central Hypoventilation Syndrome (CCHS)

Characteristics

Loss of drive to breathe during sleep

Loss of ventilatory response to CO₂

Loss of affective components to breathing (e.g., dyspnea).

Deficient cardiovascular and autonomic responses:

Inadequate responses to blood pressure challenges:

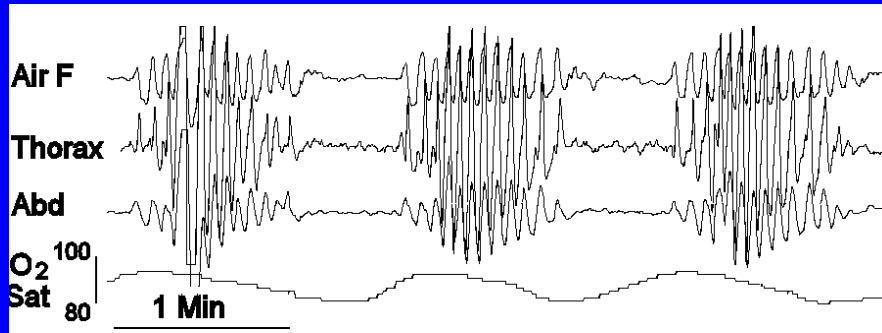
Syncope to elevated blood pressure

Profuse sweating

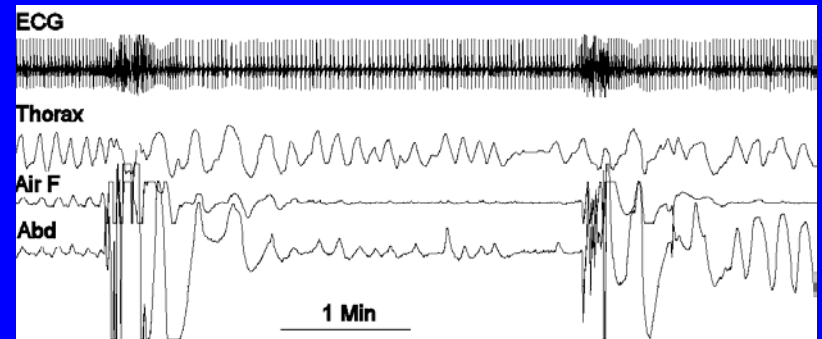
Loss of blood pressure influences on breathing

Cheyne-Stokes Breathing and Obstructive Sleep Apnea

Cheyne-Stokes Breathing



Obstructive Sleep Apnea



Purkinje cells are preferentially damaged following ischemic events.

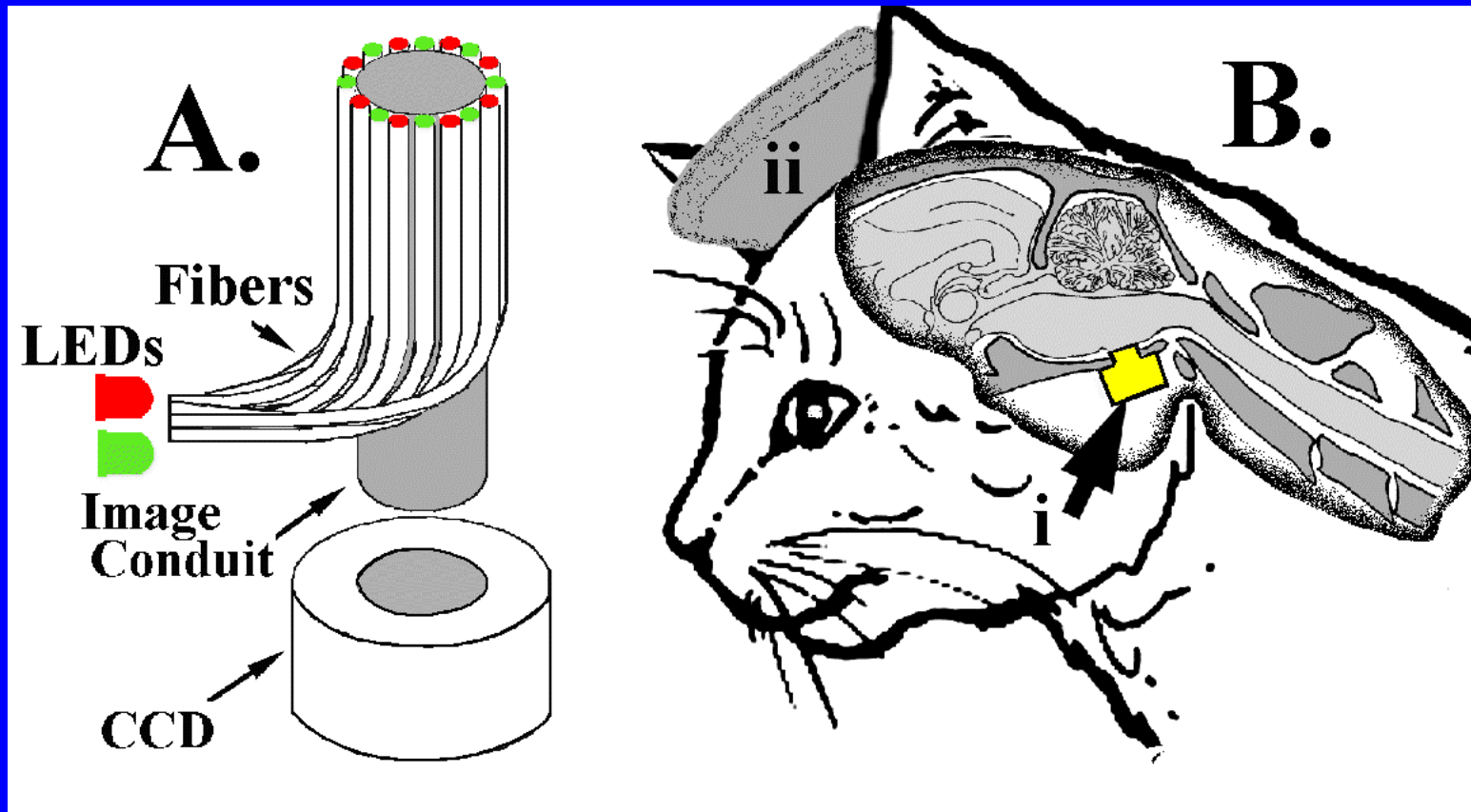
Unilateral destruction of fibers from inferior olive prevents cell death.

Welsh et al., *Adv. Neurol.*, 89:331-359, 2002

It's not just the cerebellum that's a problem; the cerebellum outputs through ventral medullary to the sympathetic column and also influences rostral brain sites through deep nuclei.

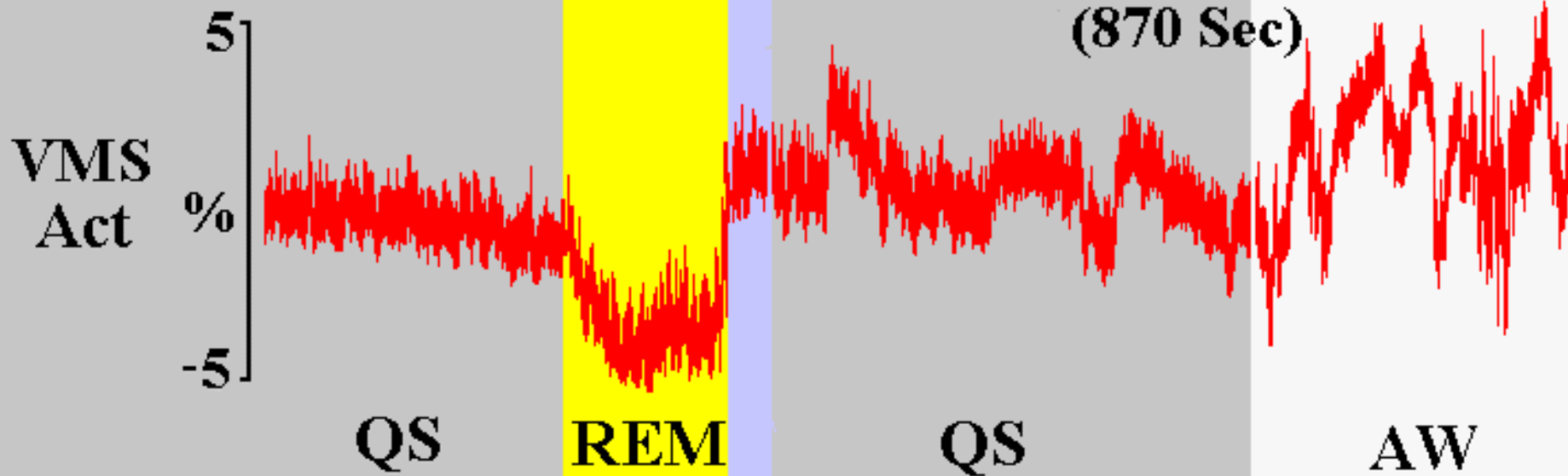
These nuclei include the insula and cingulate gyrus, which modulate sympathetic and parasympathetic outflow, and show deficient responses in CCHS and OSA patients

Optical Imaging of Ventral Medullary Surface (VMS)



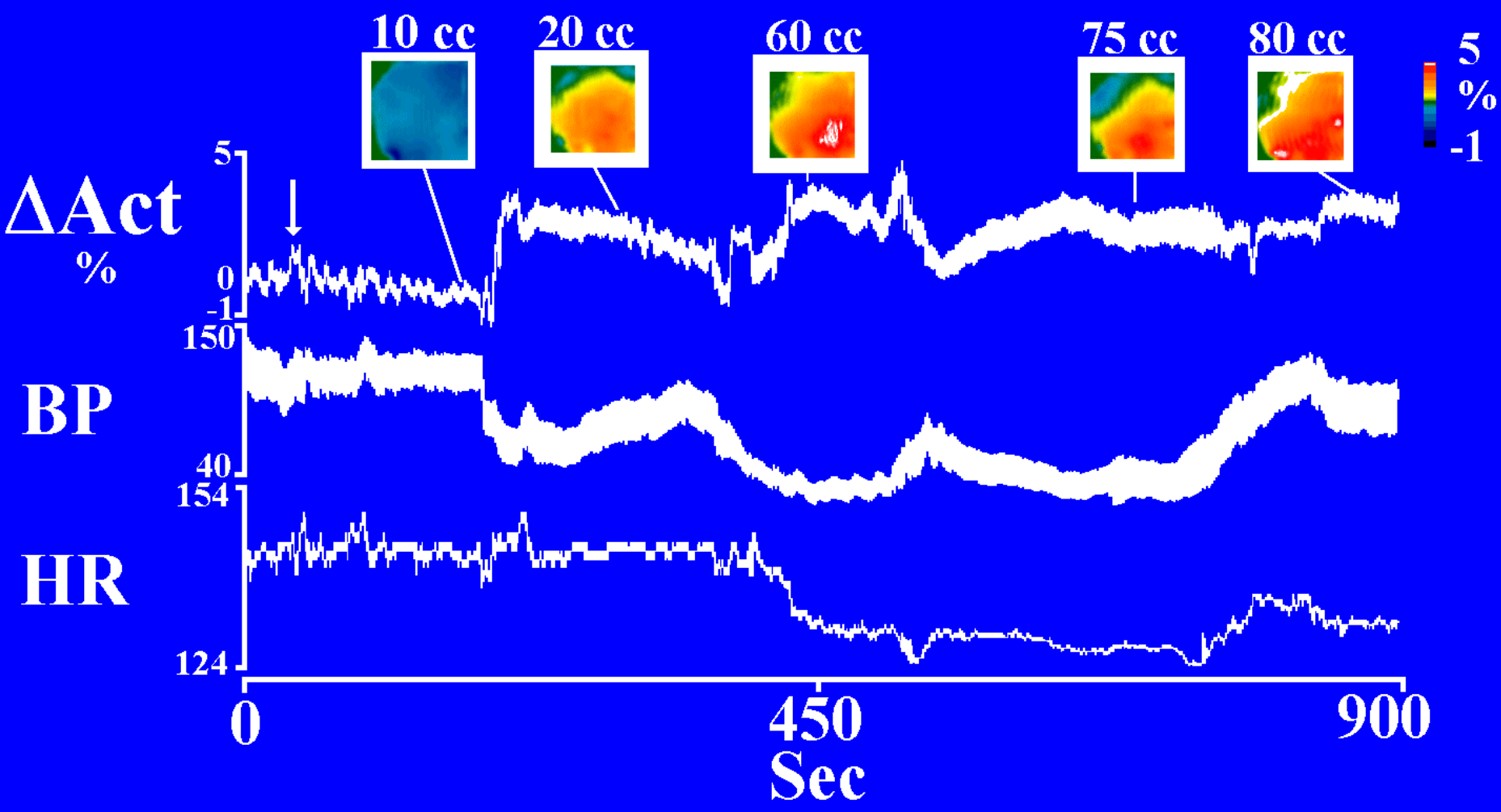
Rector et al., *Am. J. Physiol.*, 278:R1090-R1098, 2000

Decline in Ventral Medullary Surface Activity During REM Sleep

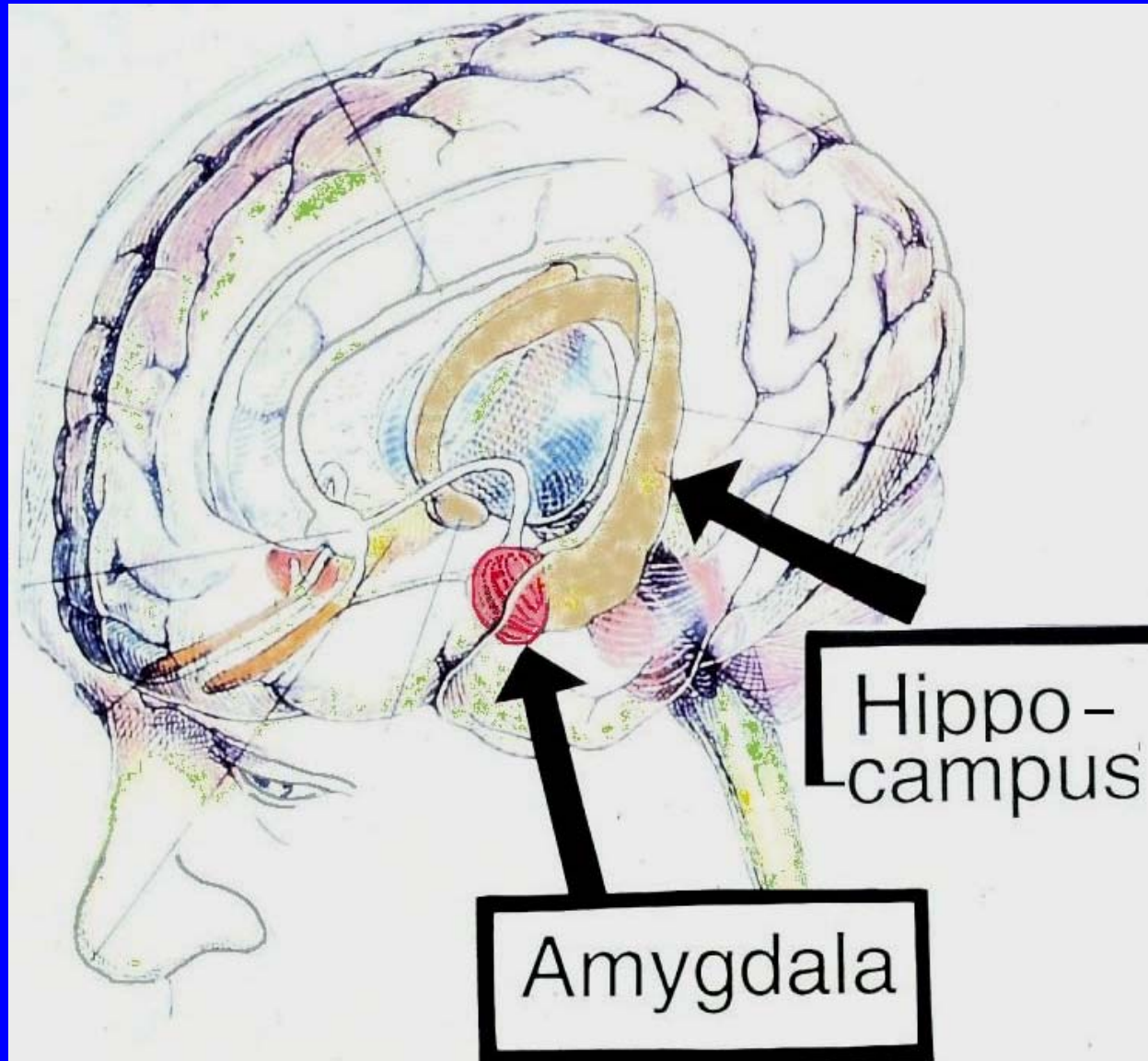


From: Richard et al., *Am. J. Physiol.*, 277:R1239-R1245, 1999

Ventral Medullary Surface Activation to Shock



Limbic structures, such as the amygdala, play significant roles in arousal and breathing



Conclusions

- The prone position results in different vestibular input to cerebellar blood pressure control areas, potentially modifying blood pressure responses to challenges
- Cerebellar damage occurs in several syndromes of sleep disordered breathing and cardiovascular control; structures that modulate cerebellar/blood pressure interactions, e.g. ventral medullary surface, inferior olive, are often altered in SIDS
- Cerebellar structures are very sensitive to ischemic or toxic insults
- We speculate that SIDS results from an uncompensated blood pressure fall as a consequence of cerebellar or cerebellar-related structural damage, and failure of that system to restore perfusion and to maintain autonomic tone.
- Damage in more-rostral sites, e.g., insula, may contribute to failure by establishing abnormal levels of autonomic tone.