People & Ideas: CO2 and Chemoreception

CO_2 Chemoreception: **Linking CO_2 to Breathing**

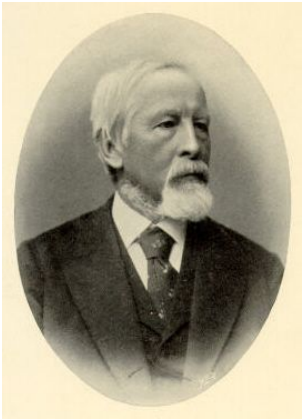
Holding your breath creates a vigorous drive to breathe.

Why is breathing important?

- Gas exchange: acquire O_2 and eliminate CO_2

Back then, this wasn't known.

Why do we breathe? What happens if we stop breathing?



A. Kussmaul

1857

- Blocked brain circulation in anesthetized dogs
- Noticed cerebral vessels acquired vein-like appearance
- Induced hyperventilation and gasping in dogs

The head is important in responding to hypoxia and hypercapnia

CO_2 Chemoreception: **Linking CO_2 to Breathing**

What's more important: an increase in CO_2 or a lack of O_2?

T.B. Rosenthall (and others)

1862

- In animals, induced hyperventilation or gave mixtures of CO_2 to breathe
- Used narcotizing levels of CO_2

Low O_2 is a stronger stimulus for ventilation than high CO_2

But actually...

F. Mieschner

1885

- Human subjects
- Small ↑ in inspired CO_2 = significant ↑ in ventilation
- Larger ↓ in inspired O_2 = non-significant ↑ in ventilation

Normal stimulus to ventilation is CO_2, not O_2

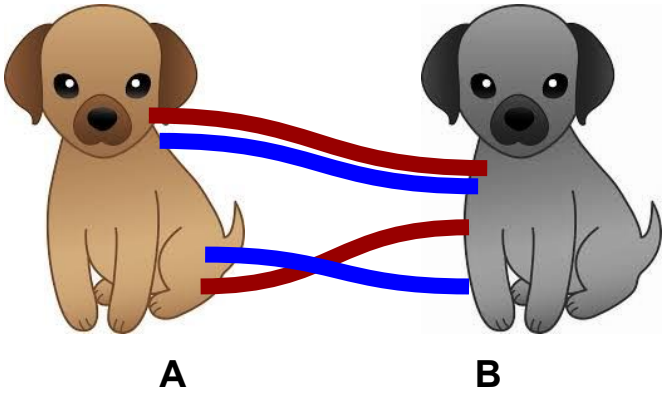
CO_2 Chemoreception: **Linking CO_2 to Breathing**

Similarly...

Léon Fredericq

1980s

- Cross perfusion studies in dogs
- Connected artery and vein of Dog A to Dog B, and vice versa



What happens if we:

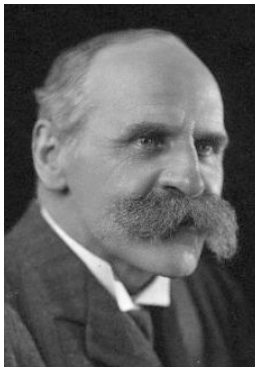
- **Block the trachea of dog A?**
  - Dog B hyperventilates
  - Dog A has apnea
- **Hyperventilate dog A?**
  - Dog B has apnea
- **Give dog A hyperoxic air?**
  - Dog B does not have apnea

Léon Fredericq

Hyperventilation is due to a decrease in CO_2, not an excess in O_2

CO_2 Chemoreception: **Linking CO_2 to Breathing**

More confirmation...



J.S. Haldane

1980s

- Human subjects (including himself and his son)
- Increasing inspired CO_2 by 3% produced ventilation changes
- Inspired O_2 reduced to 14% before same ventilation changes

pCO_2 in the respiratory centers normally regulates ventilation

… and a new observation...

H. Winterstein

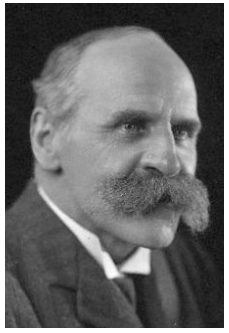
1911

- Injected animals with acid
- Saw an increase in ventilation

Arterial $[H^+]$ stimulates ventilation

CO_2 Chemoreception: **Linking CO_2 to Breathing**

$[H^+]$ or CO_2?



J.S. Haldane et al.

Shortly after

CO_2-induced H^+ produced a much bigger ventilation response than an equal increase in $[H^+]$ from fixed acid injection

H. Winterstein

1915

- Observed hypoxia causes blood to become alkalotic

OK, you're right

CO_2 Chemoreception: **Linking CO_2 to Breathing**

Continued refinement by other figures:

M.H. Jacobs

CO_2 can diffuse into cells and make them acidic, but H^+ of fixed ions cannot penetrate the cell wall easily

H. Winterstein

H^+ locally in the respiratory centers, not the blood, regulate ventilation

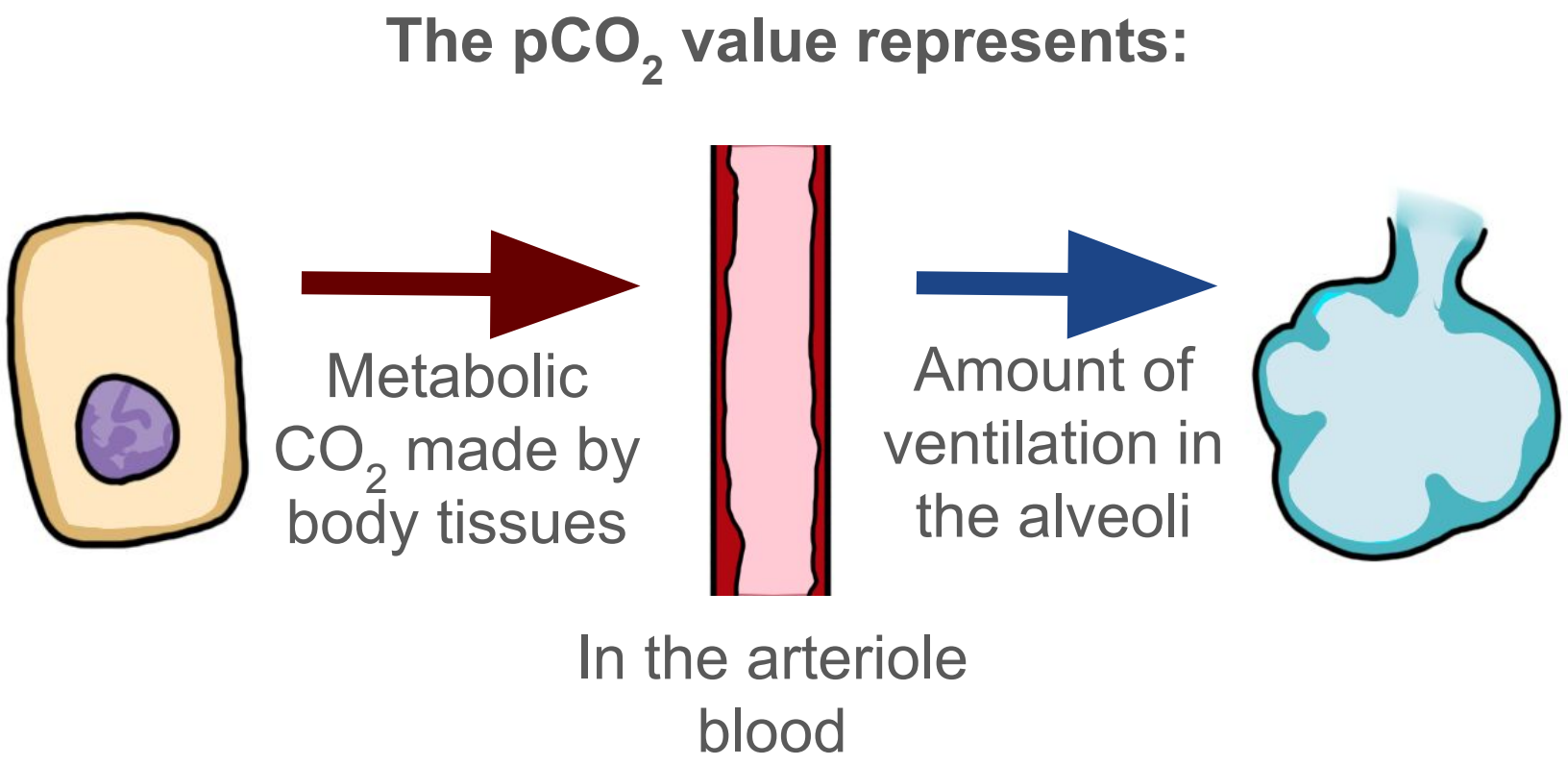
R. Gesell

Intracellular H^+ of cells in the respiratory centers regulate ventilation

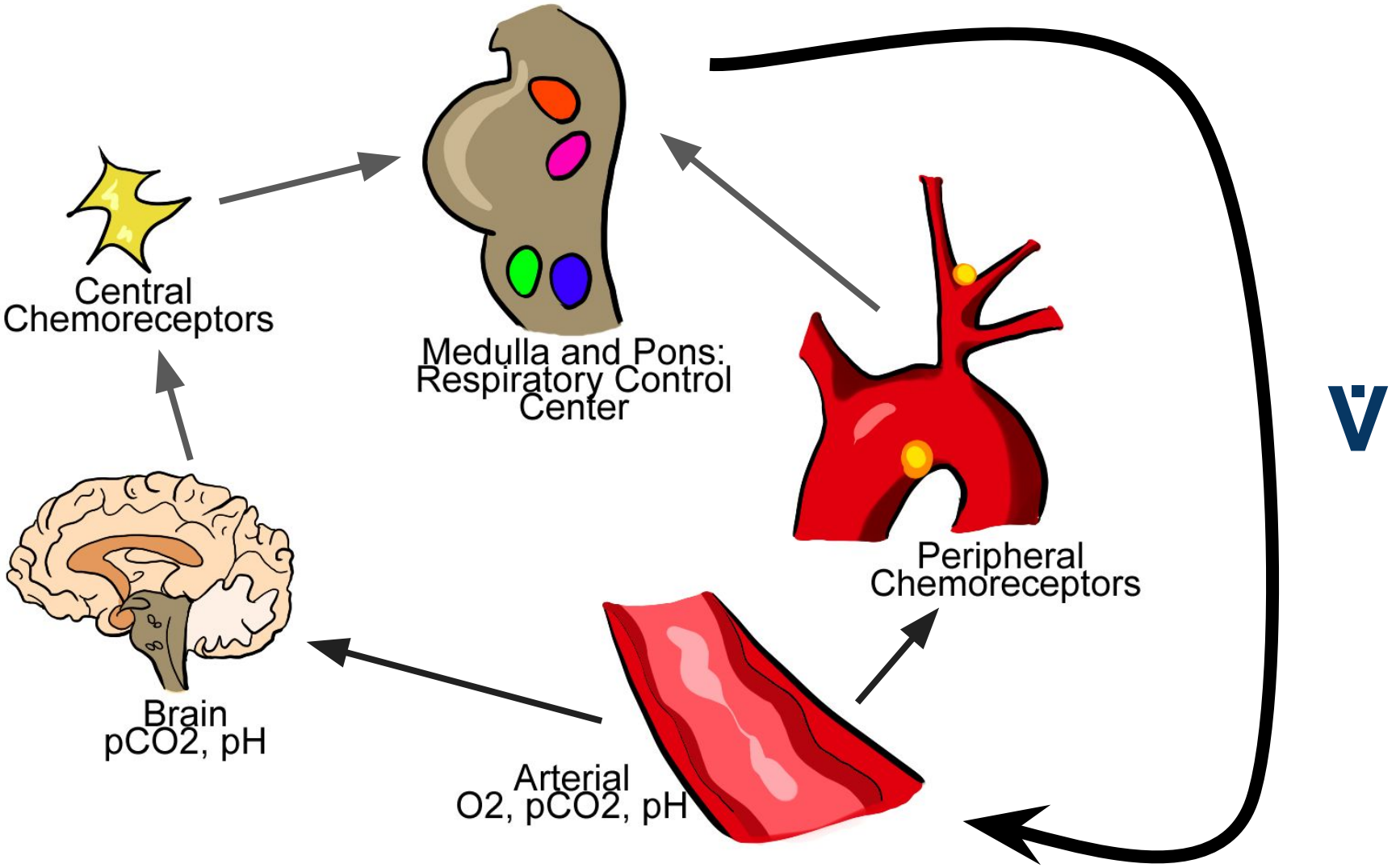
Early 1900's: CO_2 regulates ventilation by changing intracellular $[H^+]$ in respiratory center cells

What do we know now about CO_2 chemoreception and how it impact breathing?

CO2 sensitive chemoreceptors show adequacy of alveolar ventilation relative to metabolism



Chemoreceptors transmit changes in CO_2 to the respiratory control center



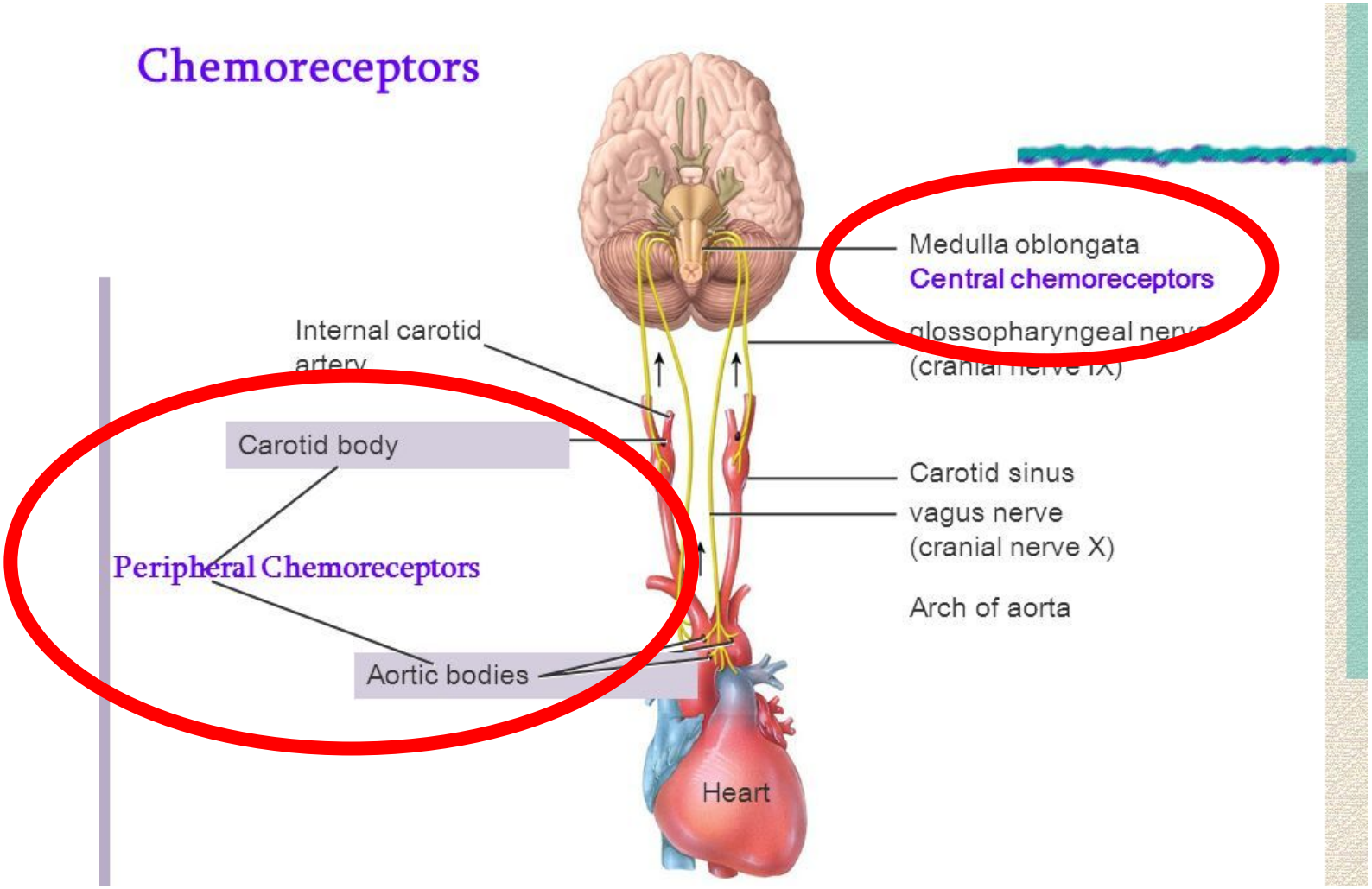
CO_2 levels are detected as changes in pH

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

CO_2 converts to carbonic acid, which dissociates into a proton and bicarbonate

→ In carotid bodies Type I cells have pH sensitive potassium channels, pH sensitive sodium extrusion protein: depolarize upon acidosis

What kinds of chemoreceptors are involved in CO2 sensing?



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Peripheral Chemoreception: **Carotid Bodies**

- Close to bifurcation of carotid artery
- Pathway: carotid sinus nerve (CSN) → glossopharyngial IX cranial nerve → cell body in petrosal ganglion → medulla, nucleus tractus solitarius (NTS)

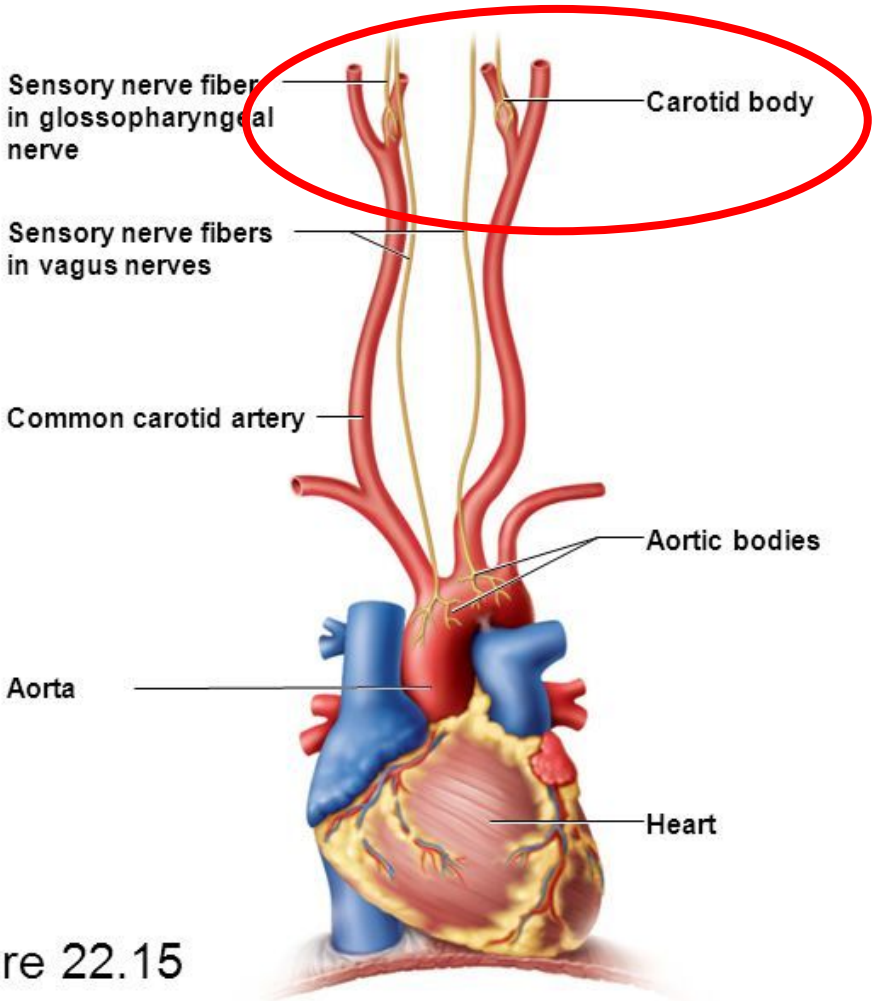

Figure 22.15

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Peripheral Chemoreception: **Carotid Bodies**

- Carotid Chemoreceptors = major determinant of ventilatory CO_2 sensitivity during normal breathing
- Low levels of hypercapnia: carotid > central contribution
- Quick response
- Maintains stable $PaCO_2$ despite decrease in intracranial CO_2-H^+ chemosensitivity via CFN lesion

Peripheral Chemoreception: **Aortic Bodies**

- Between arch of aorta and pulmonary artery
- Joins vagus X cranial nerve → cell body in nodose ganglion → medulla, NTS

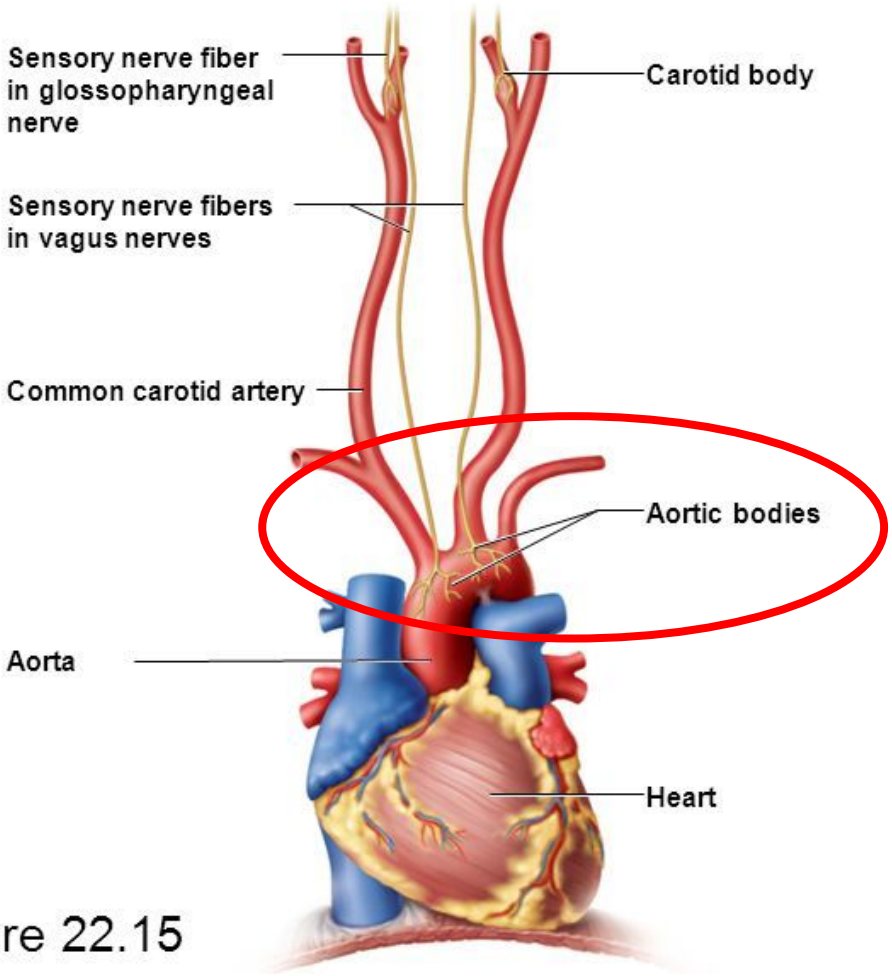

Figure 22.15

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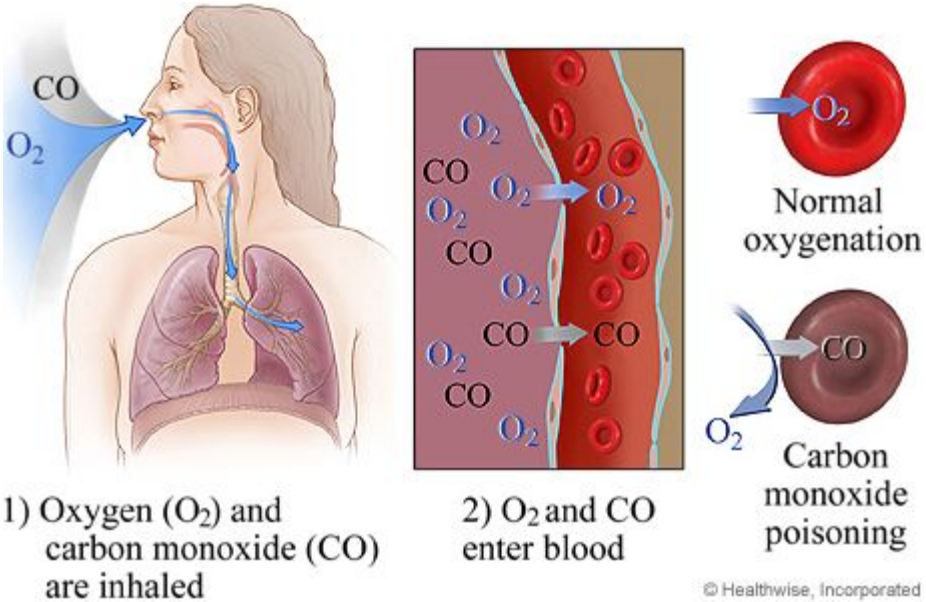
Peripheral Chemoreception: **Aortic Bodies**

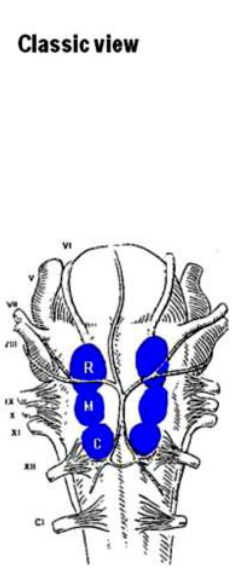
- Sense O2 saturation
  - Carboxyhemoglobinemia (CO + Hb)→ stimulation of aortic bodies before carotid bodies
- Important in the chronic absence of carotid bodies
  - Recovery of hypoxic ventilatory response from sectioning of carotid sinus nerves

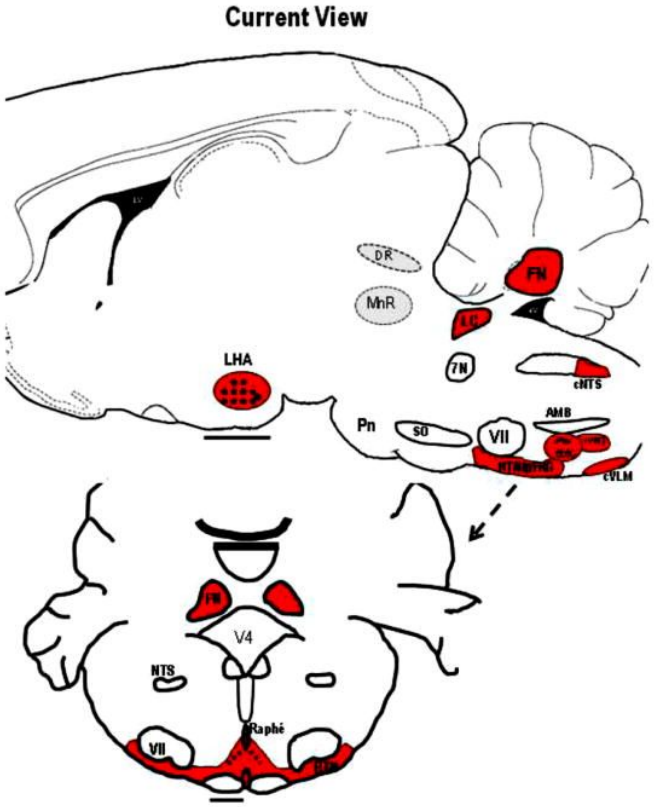


https://myhealth.alberta.ca/Health/_layouts/15/healthwise/media/medical/hw/h9991480_001.jpg

Central Chemoreception: Medullary Receptors

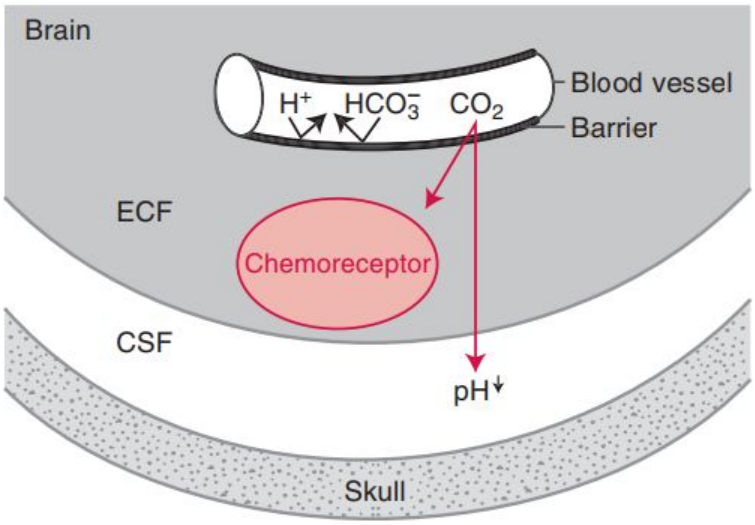
- Location: brainstem, cerebellum, hypothalamus, midbrain
  - Previously: ventral surface of medulla
  - Medullary blood vessel distribution → located more deeply in the medulla?

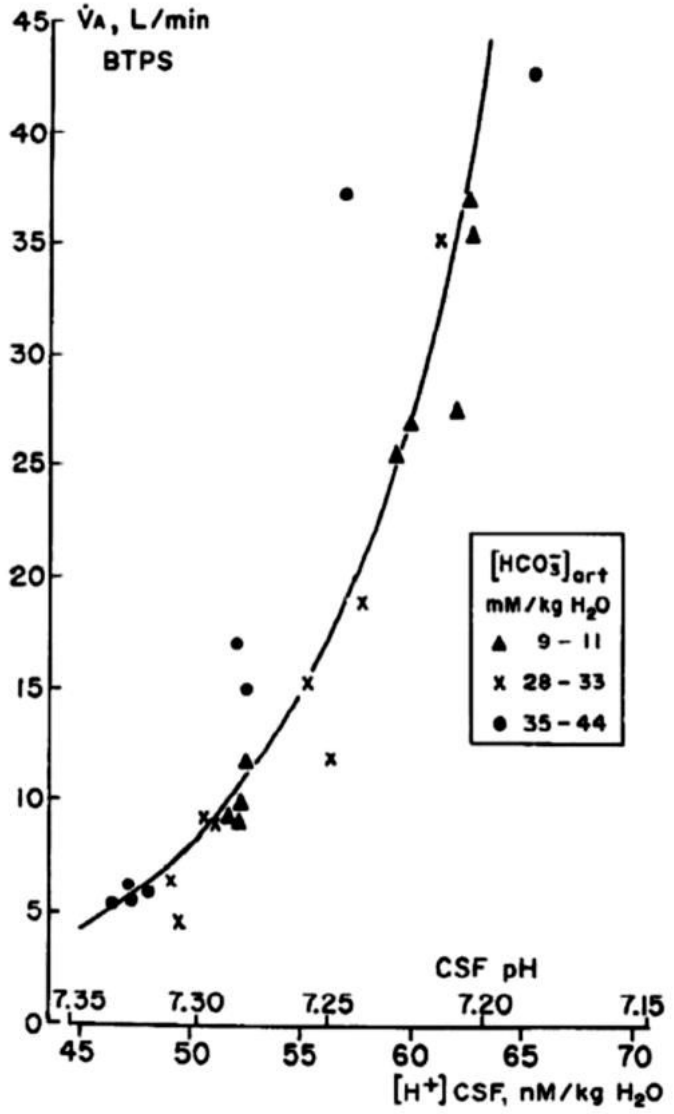




Central Chemoreception: Medullary Receptors

- Detect CSF pH (CO2 levels)
  - CO_2 accessible where there is high perfusion of arterial blood
  - Local acidosis stimulation = increased ventilation





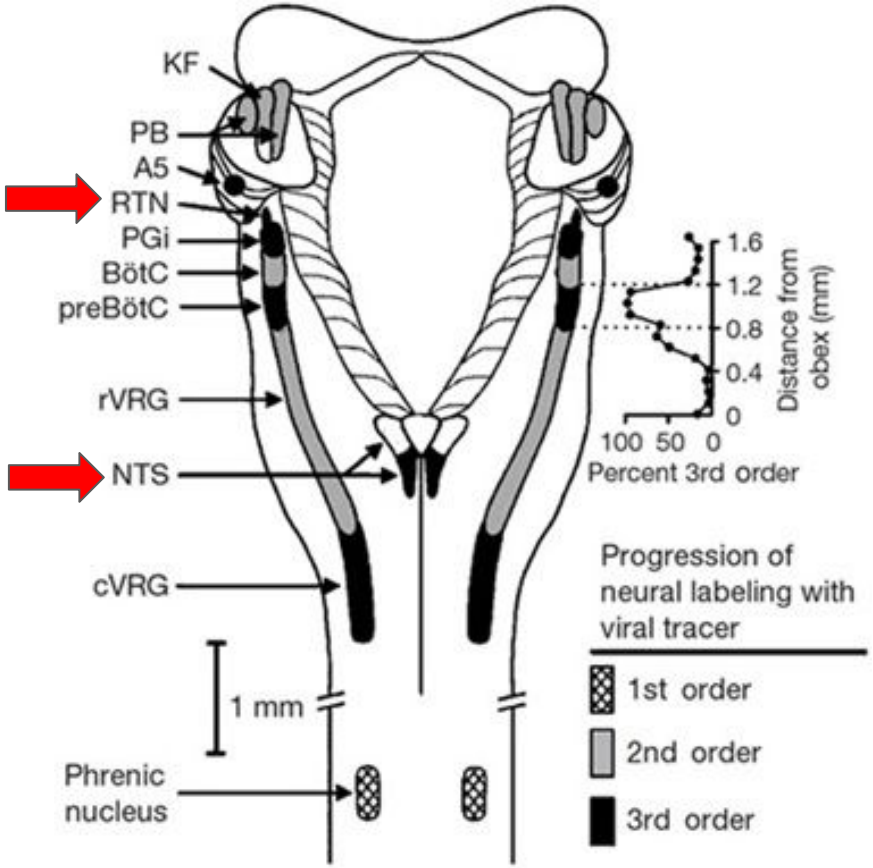
Connections between peripheral and central chemoreceptors?

Interdependence between central and peripheral chemoreceptors

- Anesthesia vs awake states
  - hypocapnia results in apnea
  - ‘Wakefulness drive’ overrides inhibition
  - Balance between both inputs
- Carotid bodies inhibited ⇒ compromised central CO_2 response
  - CB contribute tonic drive to normal breathing
  - Bilateral CB resection: reduced central CO_2 sensitivity & plasticity

Interdependence between central and peripheral chemoreceptors

- Potential pathway:
  - Carotid afferents → synapse at NTS → possibly communicate with retrotrapezoid nucleus (RTN, a central chemoreceptor site)
  - Phox2b transcription factor defect & abnormal CO2 response



http://www.nature.com/gimo/contents/pt1/images/gimo10-f2.jpg

What can go wrong?

1. Sudden Infant Death Syndrome (SIDS)
2. Lesions in brainstem
3. Congenital Central Hypoventilation Syndrome (CCHS)

Sudden Infant Death Syndrome and Hypercapnia

Sudden death of infants under 1 years old during sleep → SIDS
infants show impaired ventilatory response

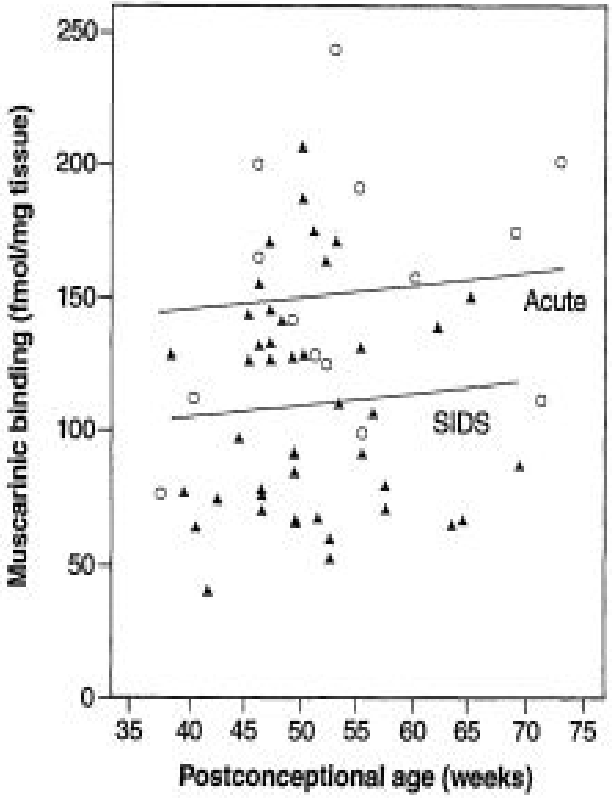
Sleeping face-down → rebreathing exhaled gases → increased inspired CO_2

Hypercapnia is sensed by normal infants, leading to arousal and protective reflexes

SIDS is related to muscarinic receptor binding in the Arcuate Nucleus

Kinney and colleagues considered muscarinic binding in 17 regions of the brainstem between SIDS and acute control groups:

Significant difference found in cell number (↓) and muscarinic binding (↓) of the Arcuate Nucleus (region of rostral ventrolateral medulla RVLM) between the 2 groups



Ventilatory abnormalities observed in individuals with lesions in the RVLM

Morrell and colleagues studied patients with lesions in the RVLM, cerebellum, pons or medial medulla and found:

RVLM group had below normal sensitivity to inhaled CO_2
Non-RVLM group had normal sensitivity to inhaled CO_2
Both groups showed normal breathing during awake state, while RVLM group displayed fragmented sleep and obstructive sleep apnoea.

→ similar to animal models (cat) where RVLM is disrupted

CCHS is characterized by the absence of central chemoreception

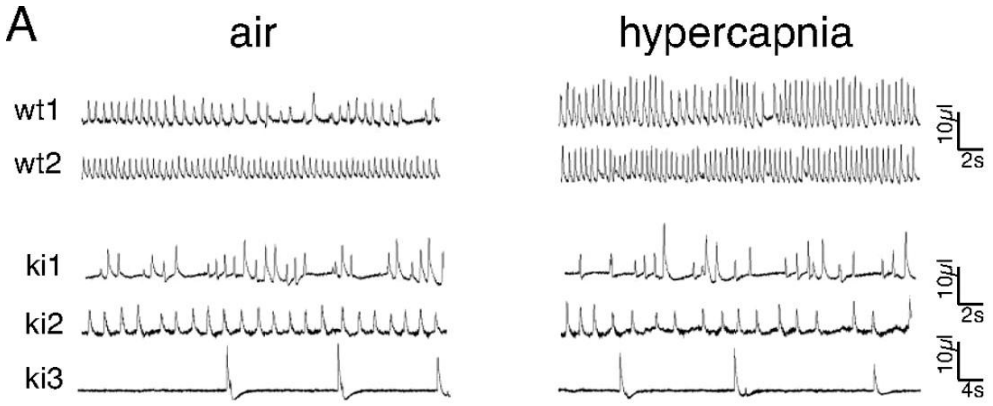
→ increasing the CO_2 levels of inspired air does not increase breathing

→ most dramatic response is seen during sleep: severe hypoventilation during sleep requiring night time ventilatory support for survival

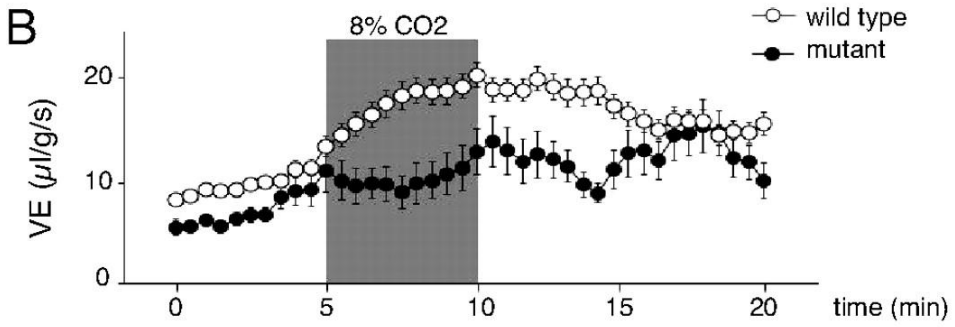
Paired-like homeobox 2B gene (PHOX2B) is disease-defining for CCHS

- Transcription factor involved in the autonomic nervous system reflex
- Individuals with CCHS are heterozygous for PHOX2B mutation
- 90-92 % of mutations: polyalanine repeat expansion mutation
- 8-10 % of mutations: missense, frameshift, nonsense (non-polyalanine repeat expansion)

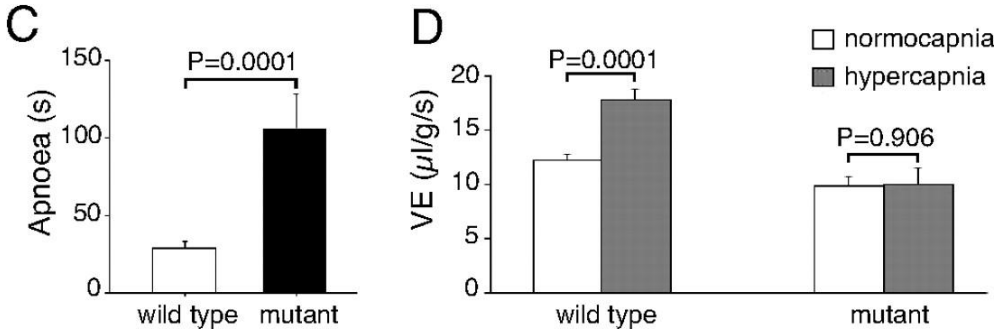
Mouse models of CCHS show irregular breathing patterns and do not respond to an increase in CO_2



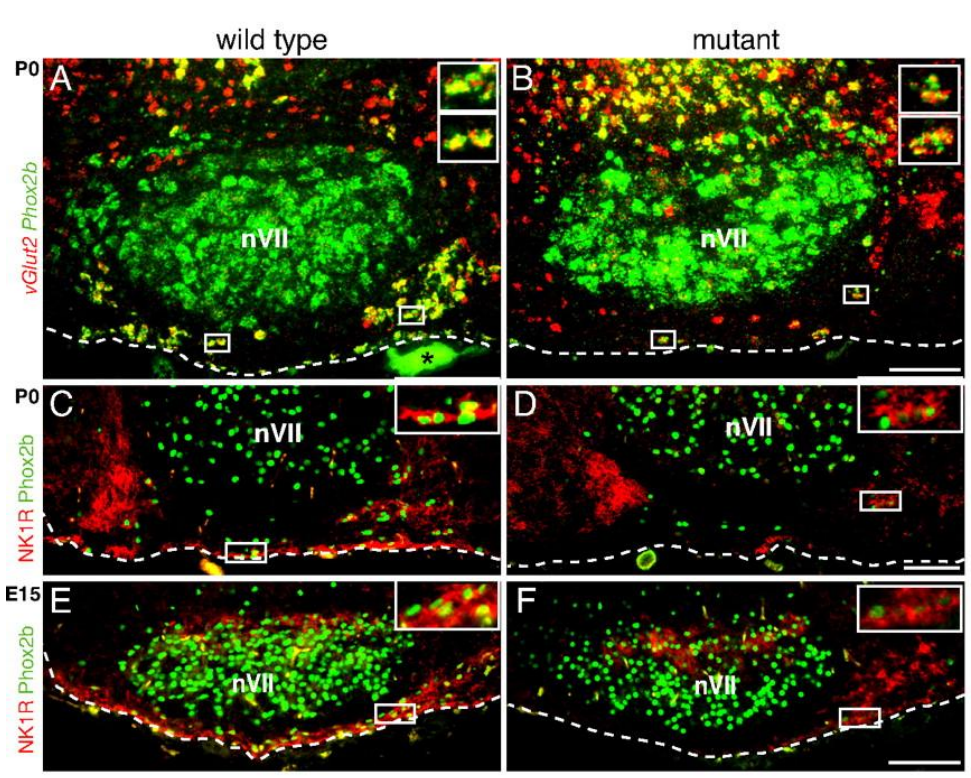
Slower breathing pattern in mutants, showing periods of apnea

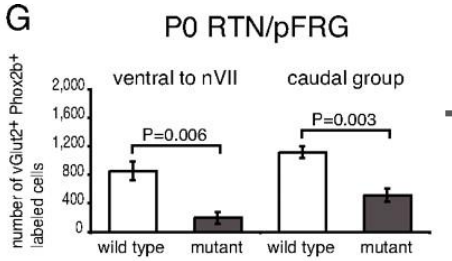


No response to an increase in CO_2 in mutant mice

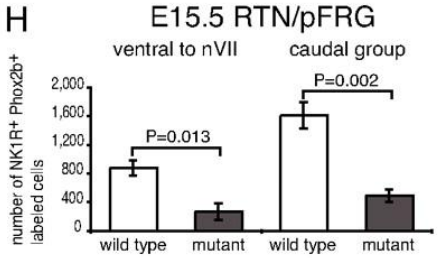


Mouse models of CCHS shows reduction in glutamatergic Phox2b-expressing neurons in parafacial regions (RTN/pFRG)

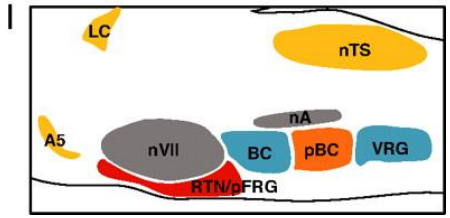




77% & 54% reduction



70% reduction



Thank you for listening!