SURVIVING THE PAIN AND FEAR OF CHRISTMAS

Bristol Sensory and Motor Systems Group

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University of BRISTOL

PAIN ⟷ **FEAR**

Fear induces changes in Pain perception
Pain (actual or anticipated) can induce Fear

Normally, both pain and fear are vital to survival

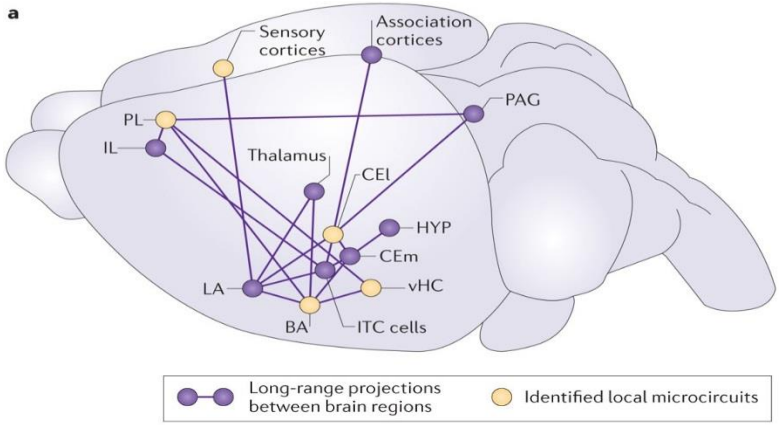
Maladaption/Malfunction
of neural networks leads to debilitating disorders
e.g. chronic pain and emotional disorders (phobias, PTSD)

Co-morbidity of chronic pain and PTSD/anxiety

Neural circuits for fear

Tovote, Fadok Luthi (2015)

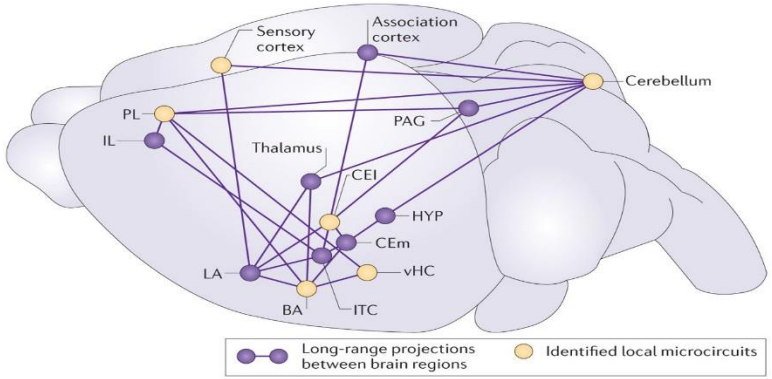
Nature Reviews Neuroscience **16**, 317



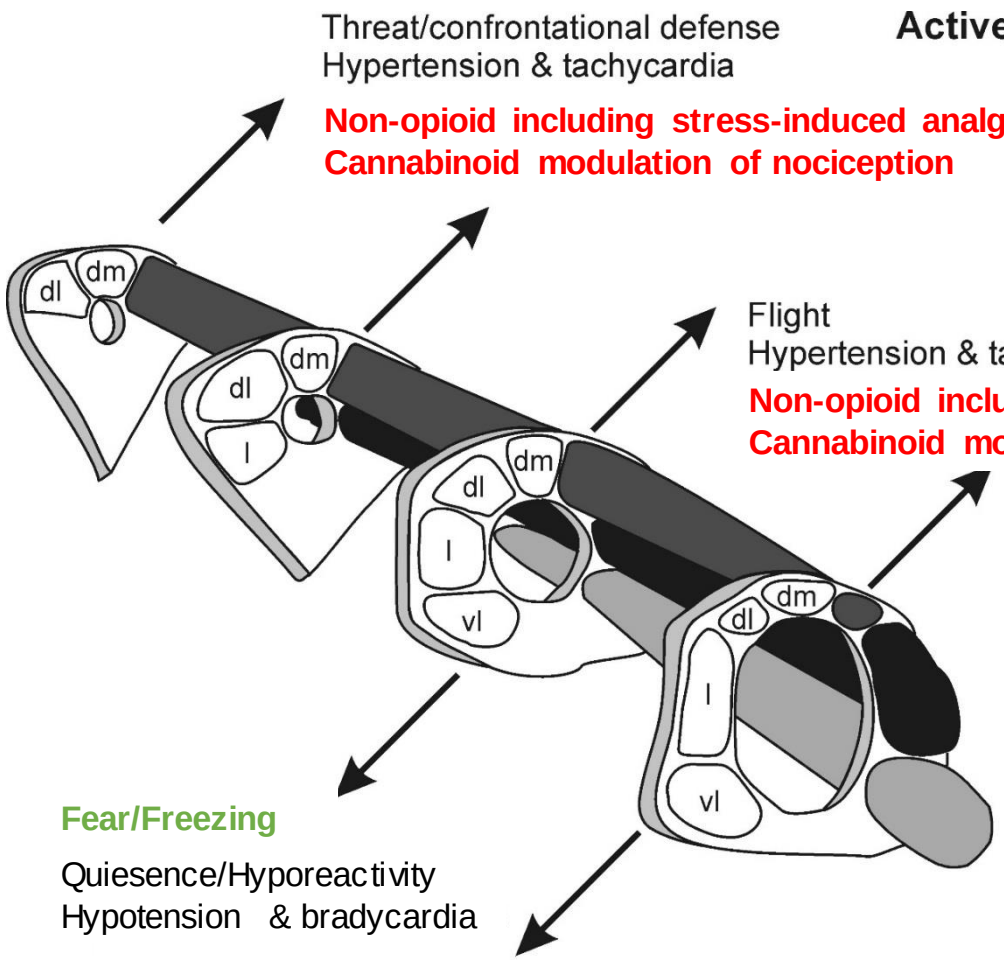
Neural circuits for fear - the missing link

Apps & Strata (2015)

Nature Reviews Neuroscience 16, 642



Functional Organisation of the PAG



Threat/confrontational defense
Hypertension & tachycardia

Active coping

Non-opioid including stress-induced analgesia
Cannabinoid modulation of nociception

Flight
Hypertension & tachycardia

Non-opioid including stress-induced analgesia
Cannabinoid modulation of nociception

Fear/Freezing

Quiesence/Hyporeactivity
Hypotension & bradycardia

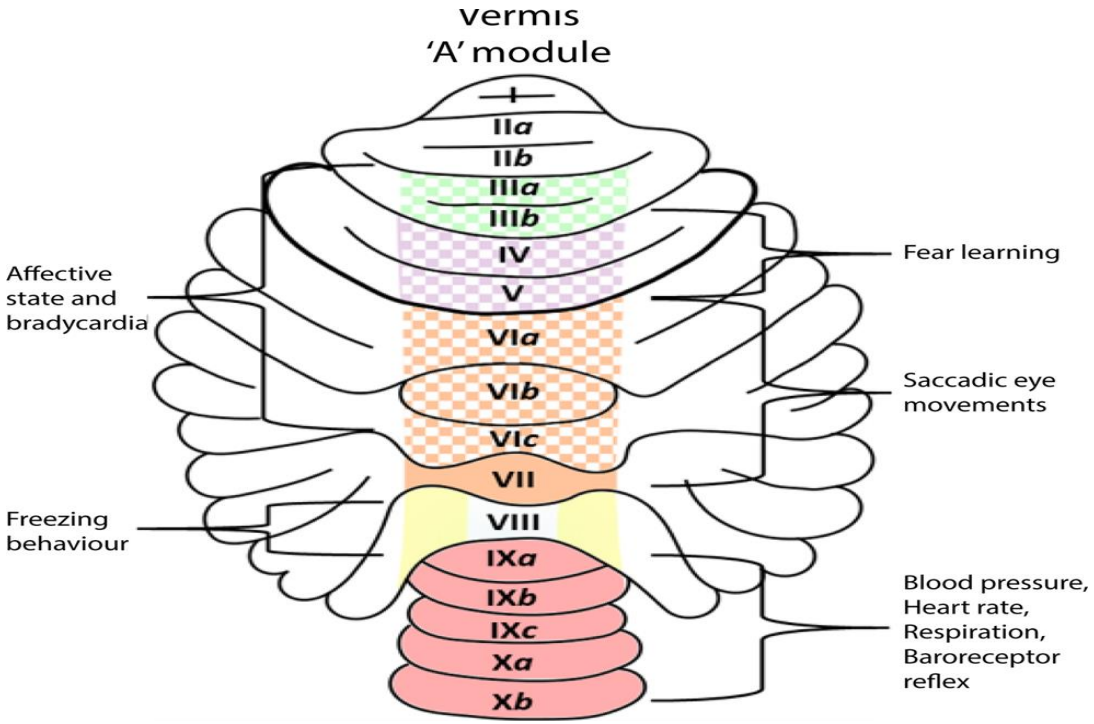
Cannabinoid and vanilloid modulation of nociception
NSAID analgesia
Opioid-mediated analgesia

Passive coping

Bandler & Shipley,1994

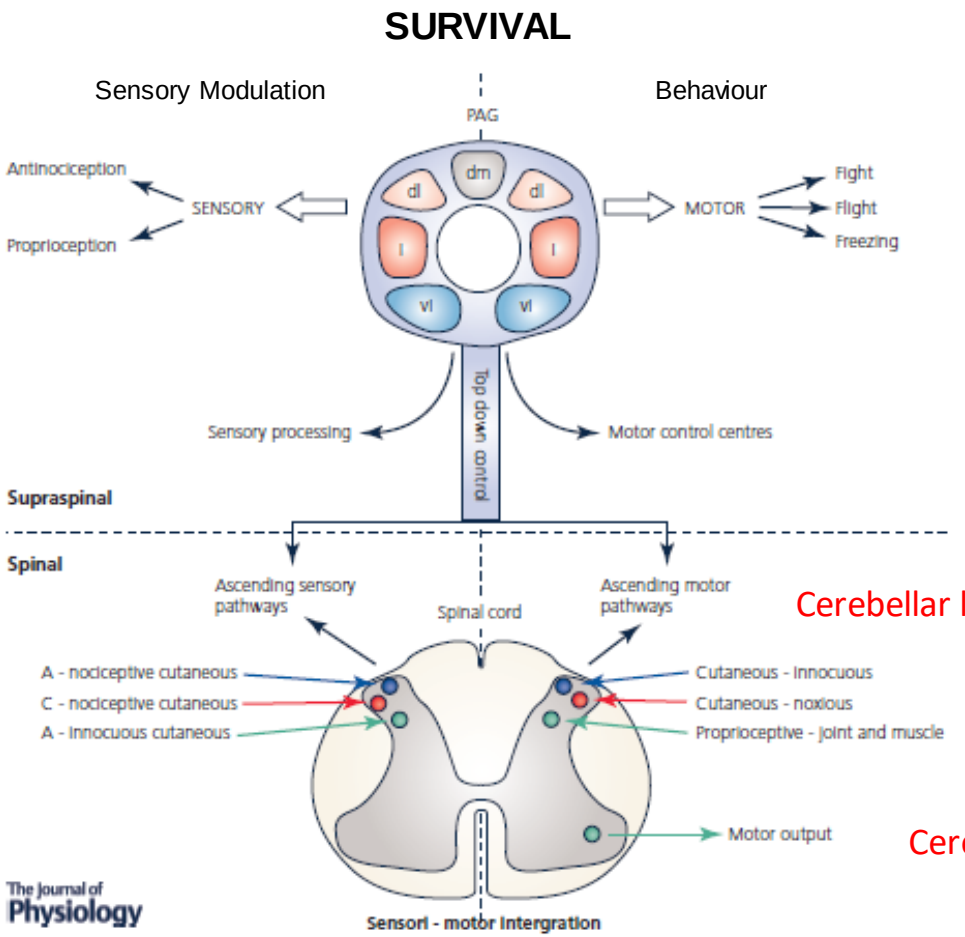
Lumb & Leith, 2008

Do different parts of the Cerebellar A module regulate the motor, autonomic and cognitive aspects of fear-related behaviour?



Lawrenson et al (2018)

Activation in different regions of the A module inhibit or facilitate spinal nociception



Cerebellar link

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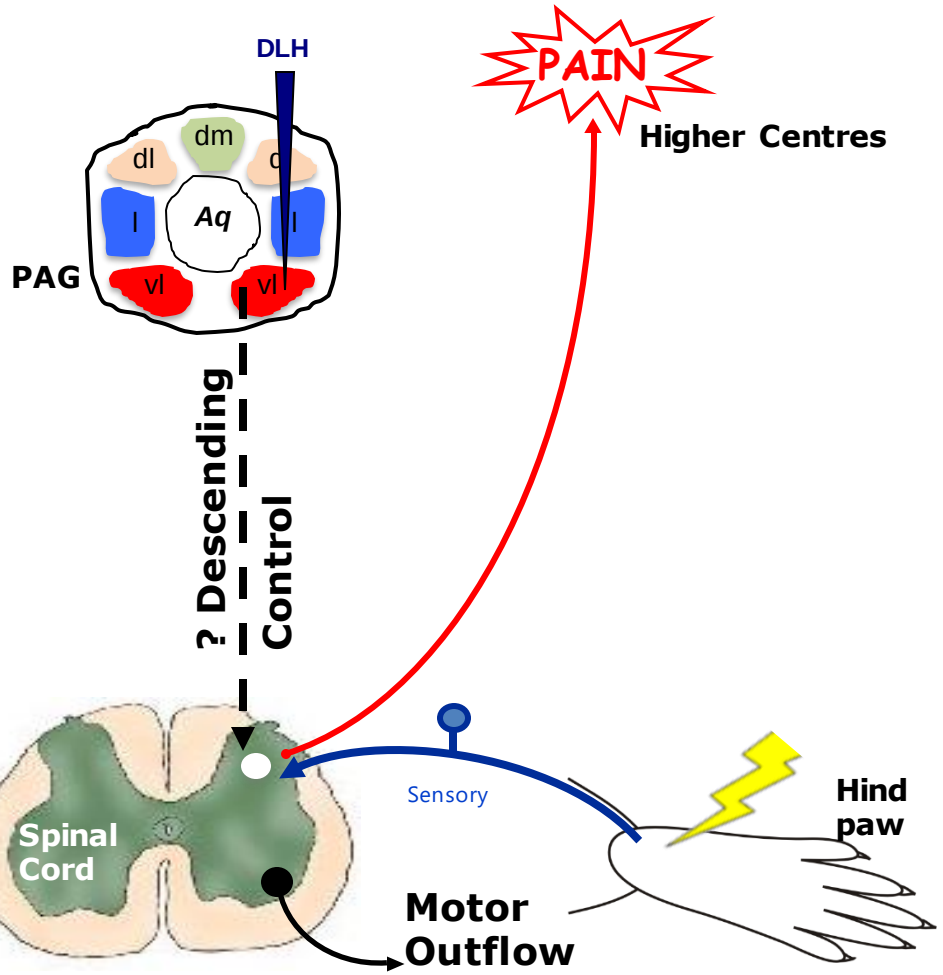
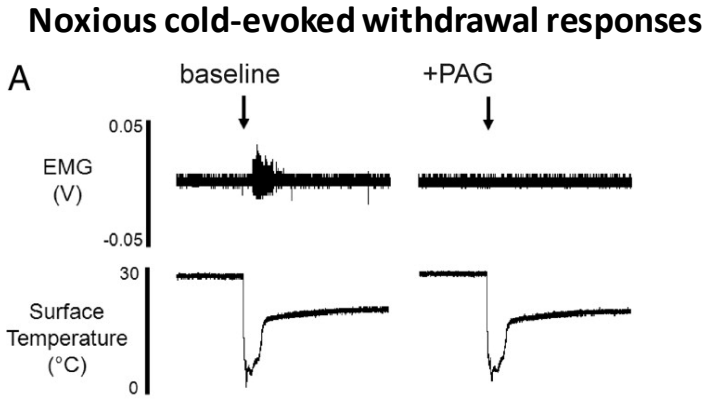
Koutsikou, Apps & Lumb 2017

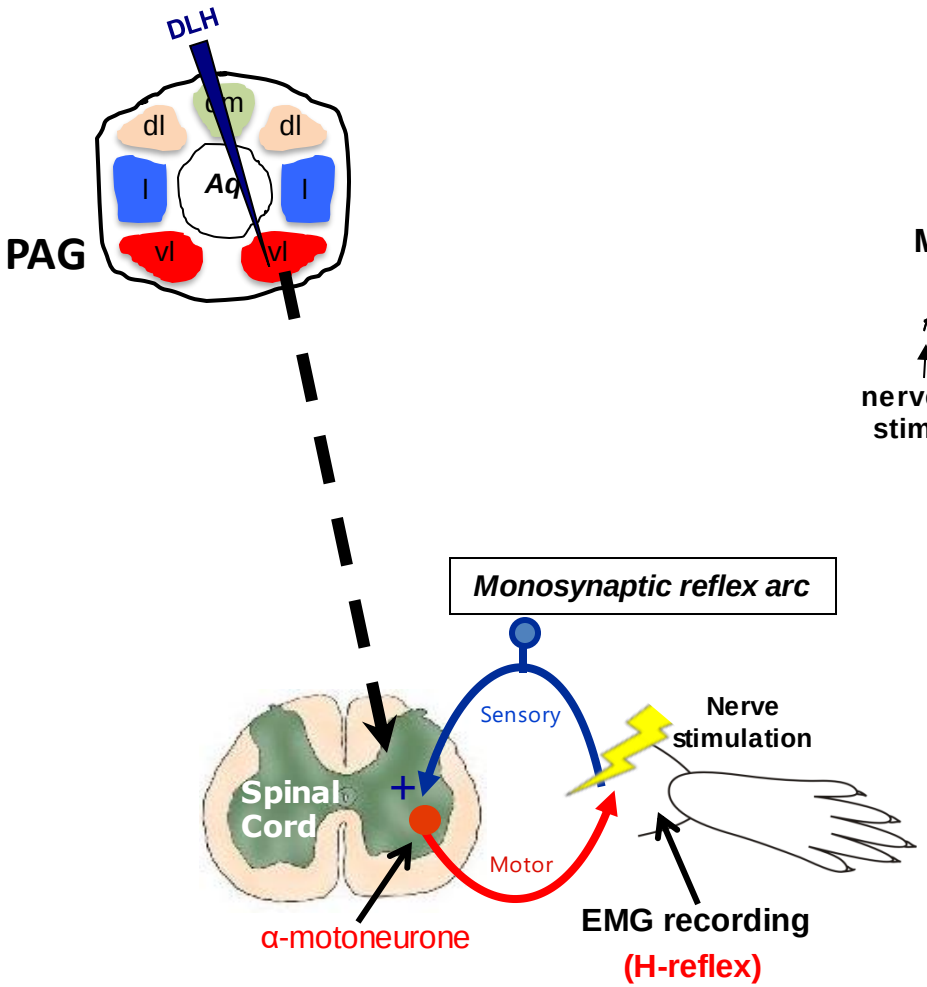
vlPAG descending control of pain processing (*antinociception*)

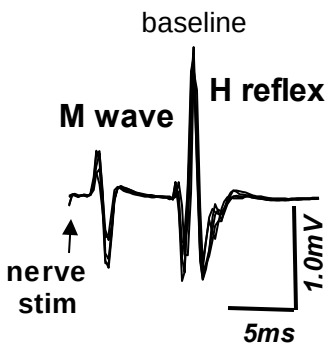


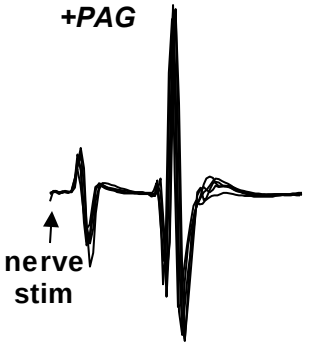


Leith, Koutsikou et al (2010) J Neurosci 30(14):4933-4942
Koutsikou et al (2014) J Physiol 592.10: 2197-2213

vlPAG descending facilitation of monosynaptic spinal reflexes







- **H-reflex**: electrical equivalent of monosynaptic stretch reflex
- **H-reflex:** indicative of α-motoneurone excitability

Leith, Koutsikou et al (2010) J Neurosci 30(14):4933-4942
Koutsikou et al (2014) J Physiol 592.10: 2197-2213

SUMMARY I

- **vlPAG is an important source of descending control at the level of the spinal cord:**
  - Reduces nociceptive information (antinociception)
  - Reduces polysynaptic withdrawal responses
  - Facilitates monosynaptic spinal reflexes (increased muscle tone)

Koutsikou et al (2014) J Physiol 592.10: 2197-2213
Koutsikou et al (2015) J Neurosci 35: 14132-14147

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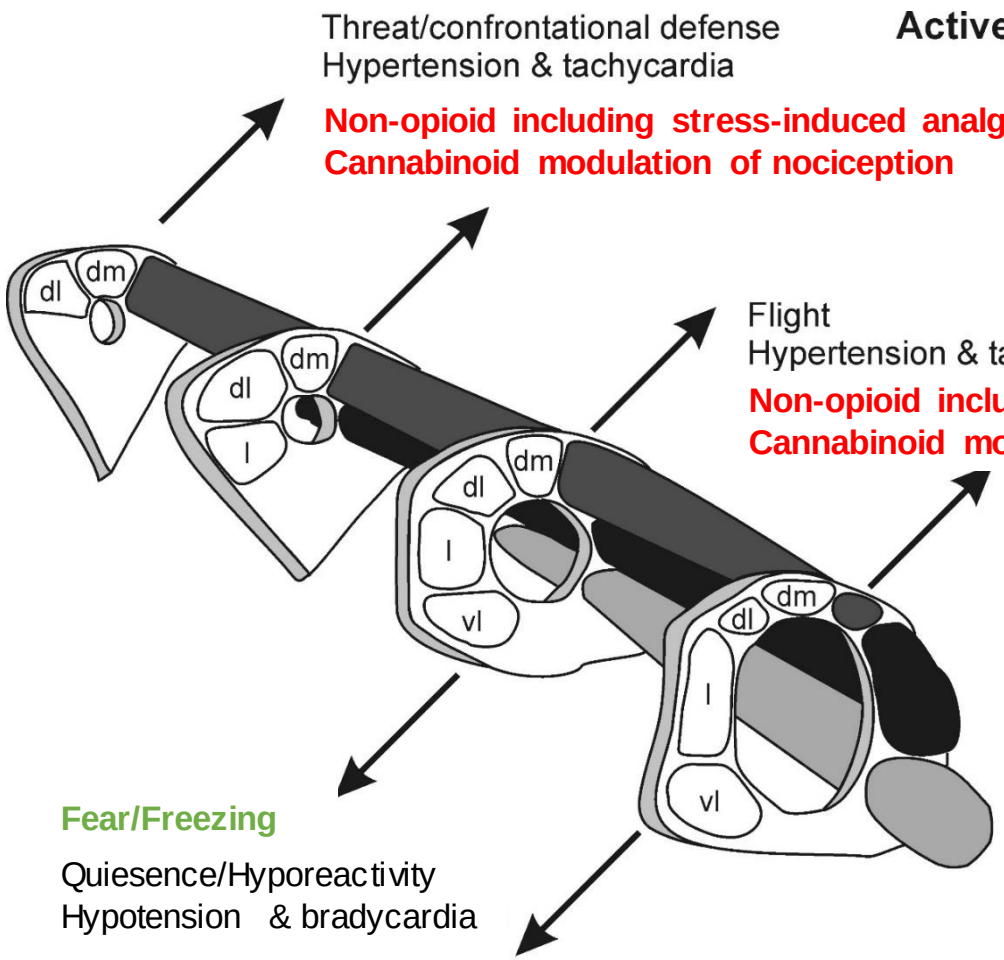

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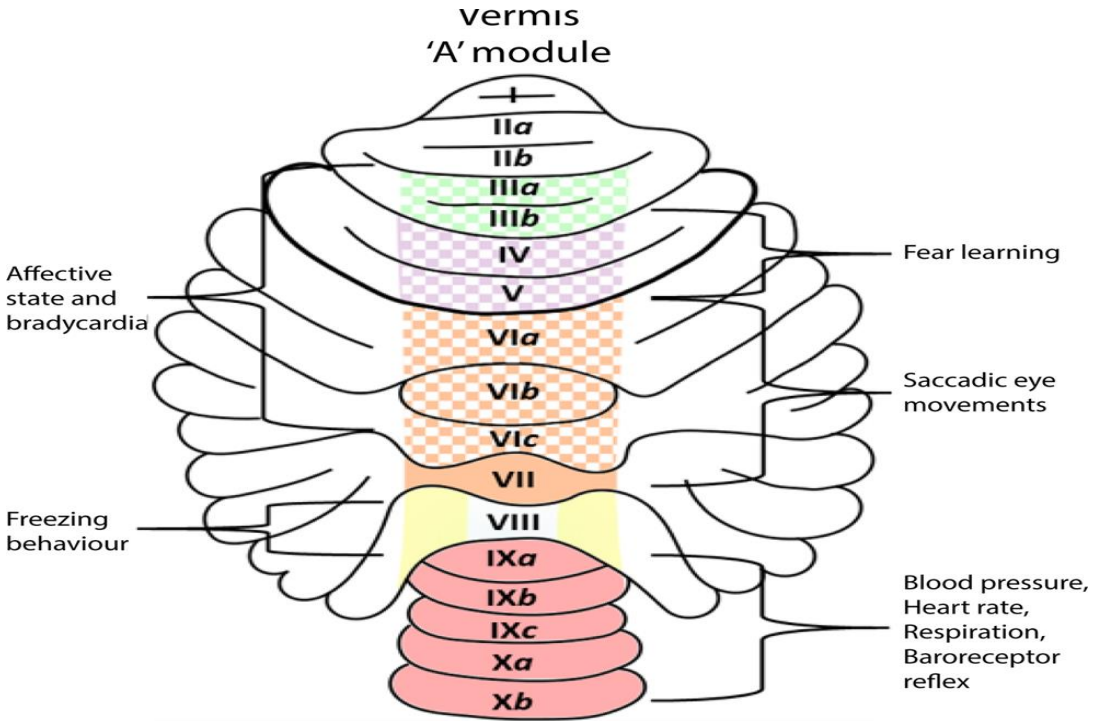

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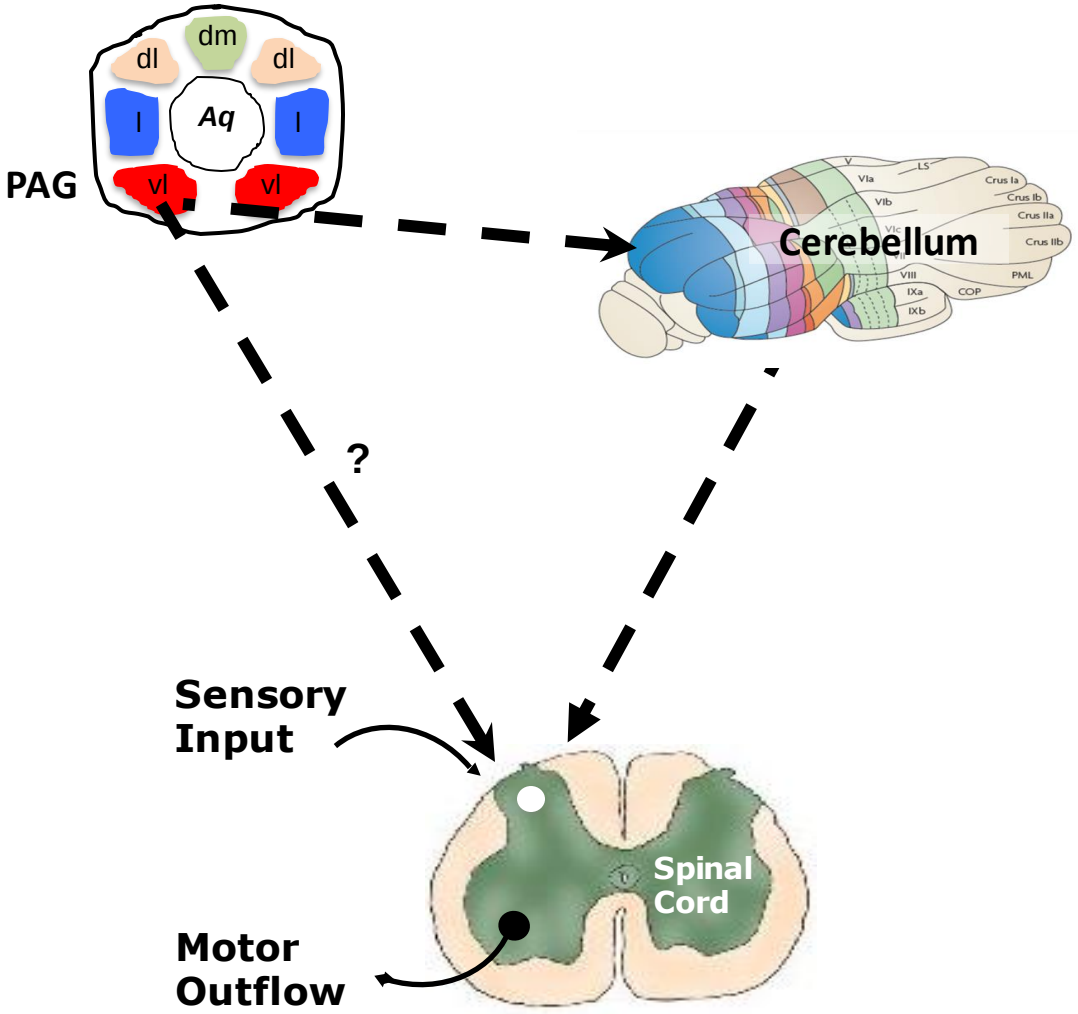
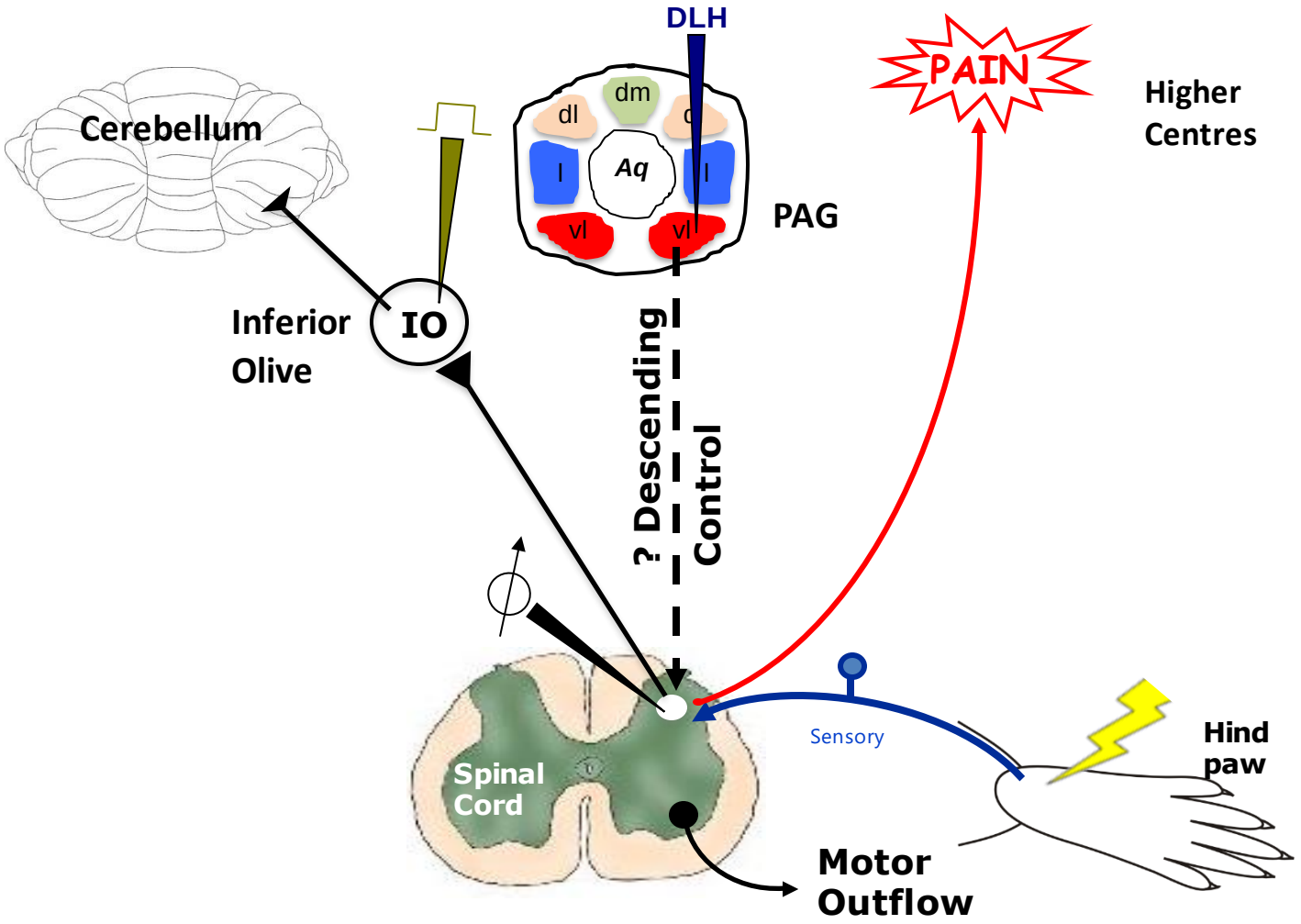


Main Question

- Neural pathways & mechanisms that connect the PAG to distinct motor responses and sensory control?
  - **vlPAG – cerebellum links and interactions?**

vlPAG - Cerebellum Interactions



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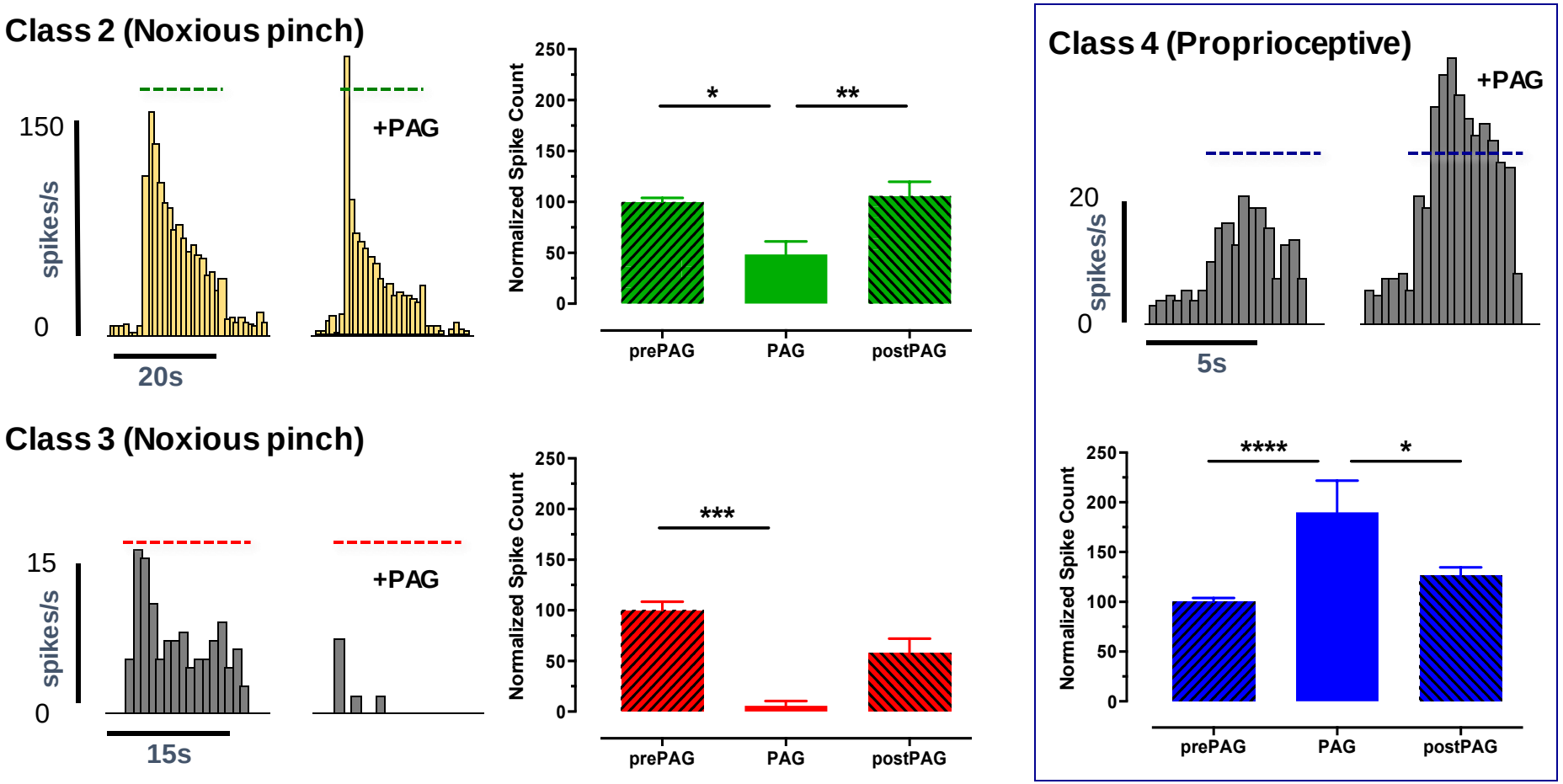
vlPAG descending control of spino-olivary neurons



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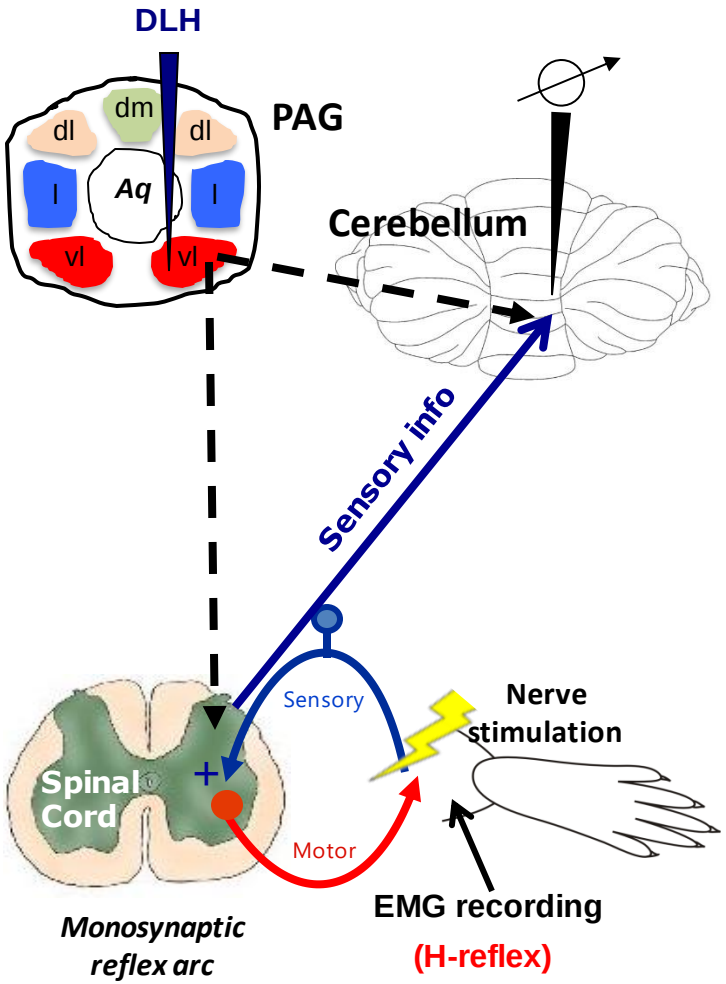
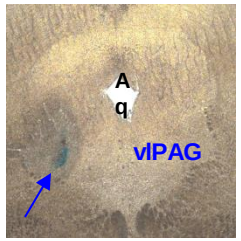
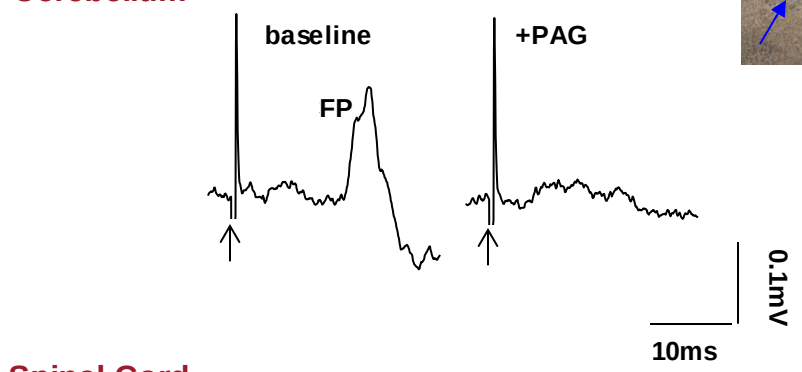
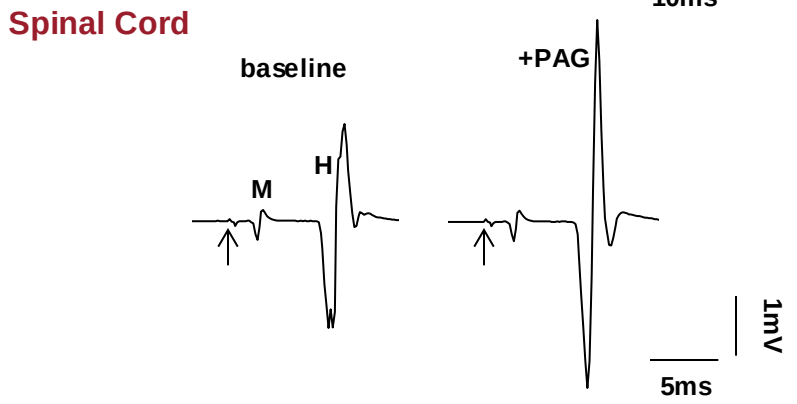
vlPAG descending control influences sensory and motor components of motor circuits









Koutsikou et al (2015) J Neurosci 35: 14132-14147
Cerminara, Koutsikou et al (2009) EJN

SUMMARY II

- **vlPAG is an important source of descending control at the level of the spinal cord:**
  - Reduces nociceptive information (antinociception)
  - Reduces withdrawal responses
  - Facilitates spinal reflexes

- **vlPAG is source of descending control of sensory information to the cerebellum:**
  - Reduces nociceptive information (antinociception)
  - Facilitates proprioceptive information
  - Exerts differential effects on sensory and motor functions simultaneously

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Summary III

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- **vlPAG is source of descending control of sensory information to the cerebellum:**
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  - Facilitates proprioceptive information
  - Exerts differential effects simultaneously
- **vlPAG – Cerebellar Vermal Lobule VIII physiological connections:**
  - via the Inferior Olive (electrophysiological and anatomical evidence)

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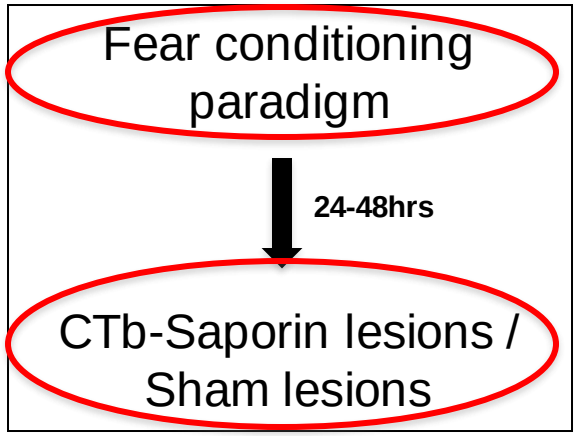
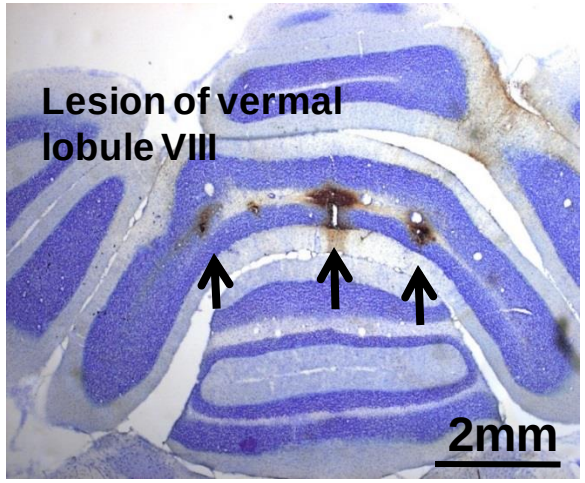
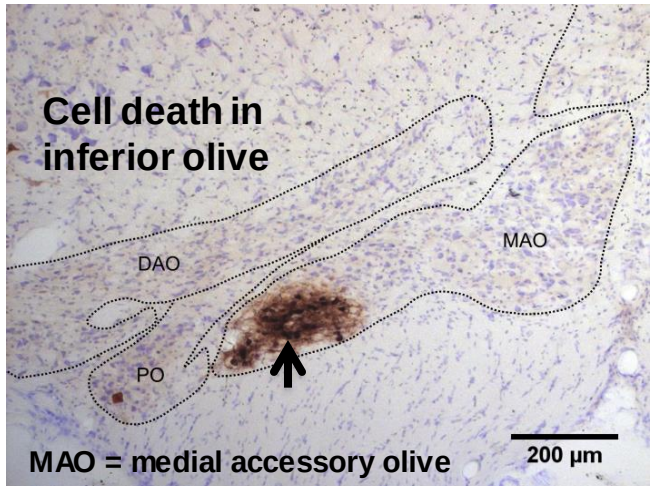
Functional significance of vlPAG – cerebellar vermal lobule VIII link



Cerebellar Cortex



Inferior olive



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Olivo-cerebellar lesions reduce freezing behavior

Fear conditioning paradigm

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Sham / CTb-Sap lesions

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Motor / Anxiety tests

↓

Fear memory retrieval

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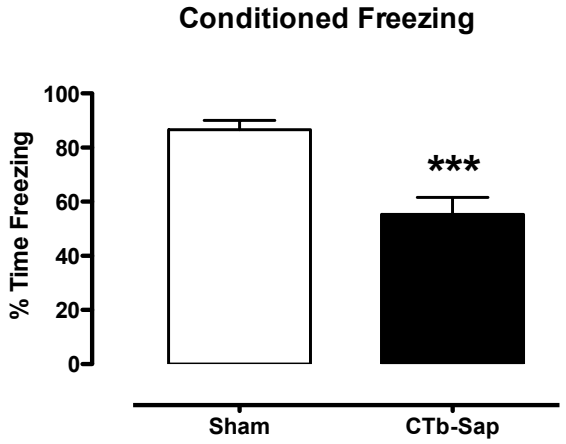
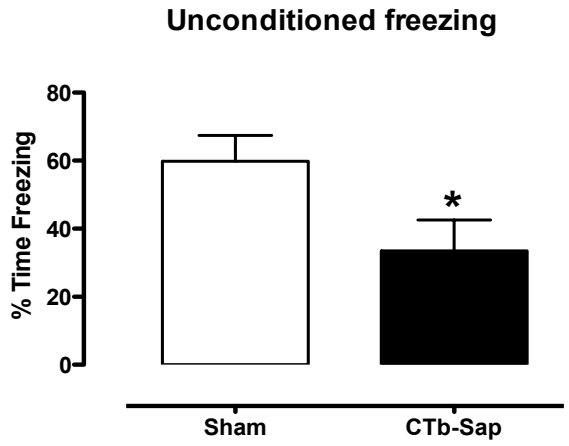
Innate (unconditioned) fear test using cat odour





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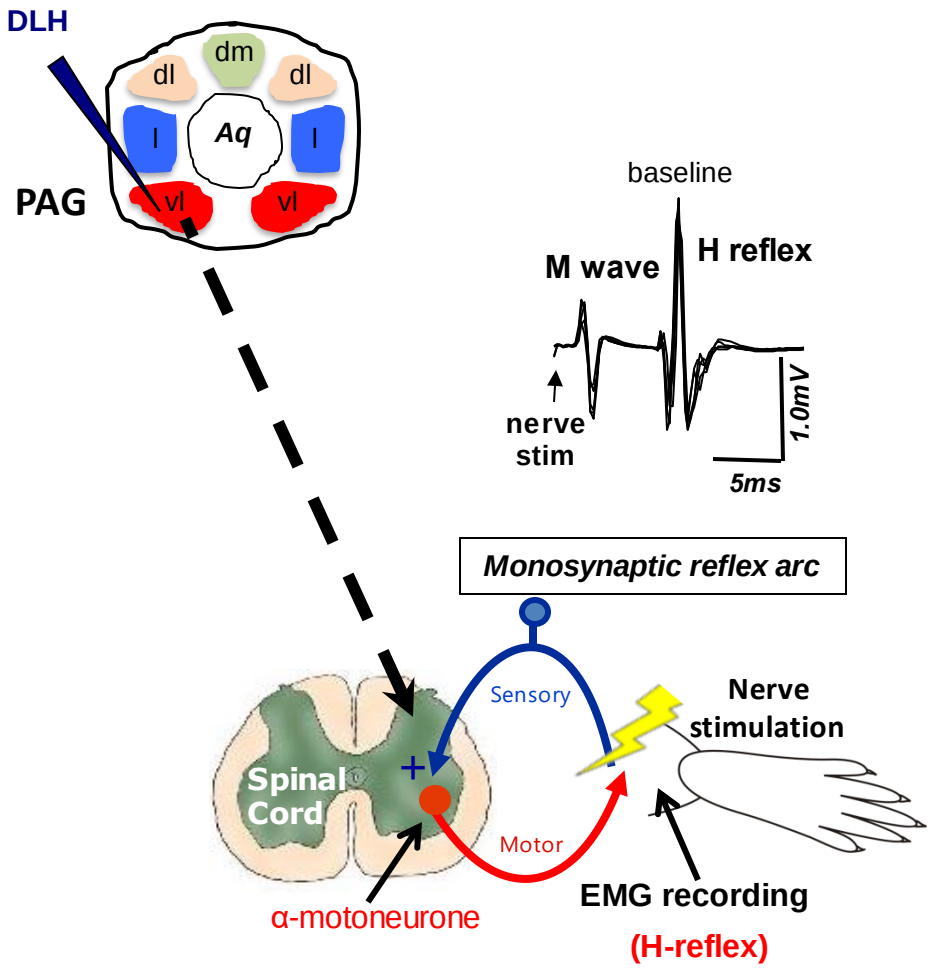
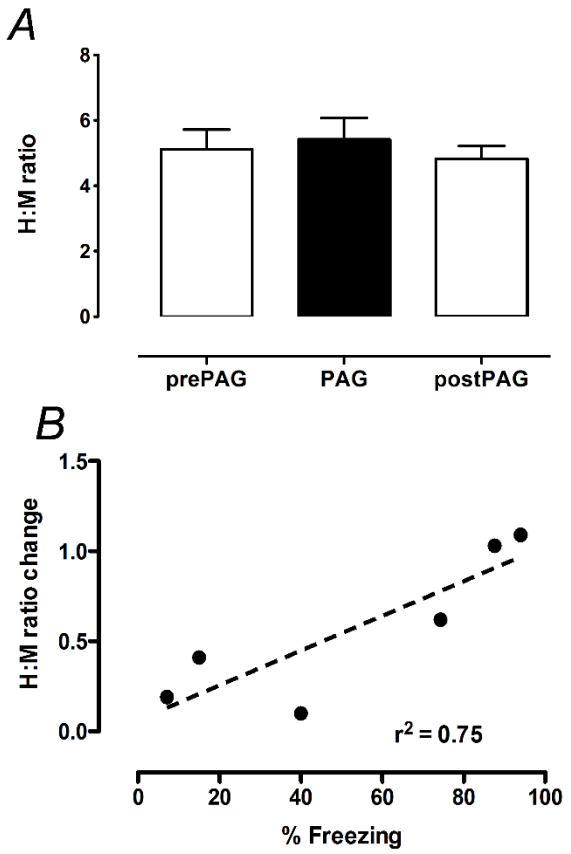
https://physoc.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1113%2Fjphysiol.2013.268714&file=Video_S2_SuppInfo.wmv

Olivo-cerebellar lesions prevent H-reflex facilitation





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SUMMARY IV

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- **vlPAG is source of descending control of sensory information to the cerebellum:**
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  - Exerts differential effects simultaneously
- **vlPAG – Cerebellar Vermal Lobule VIII physiological connections:**
  - via the Inferior Olive
- **Cerebellar Vermal Lobule VIII lesion reduces vlPAG mediated:**
  - Conditioned & unconditioned freezing behavior
  - H-reflex facilitation

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CONCLUDING REMARKS

- **Cerebellar Vermal Lobule VIII circuits are functionally important in:**
  - ✧ Connecting vlPAG to spinal motor apparatus

- **PAG - cerebellar lobule VIII neural substrates may contribute to:**
  - ✧ generation, co-ordination and precise execution of survival behaviours that link fear and pain

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BBSRC, MRC, Wellcome Trust

THANK YOU

HAPPY CHRISTMAS