Breathing: The master clock for orofacial rhythms?

David Kleinfeld
5 March 2014
Kavli Institute for Theoretical Physics, UC Santa Barbara

Team Neurophysics (http://physics.ucsd.edu/neurophysics/)

PhD students

R. W. Berg
T. W. Cacciatore
G. O. Clay
J. C. Curtis
J. D. Driscoll
K. Ganguly
D. N. Hill
D. C. Jeong
V. Joseph
A. I. Kurnakova
D. W. Matthews
S. B. Mehta
N. Mercer
J. D. Moore
N. Nishimura
T. A. Parsons
L. F. Schroeder
P. S. Tsai

Postdocs

K. F. Ahrens
P. Blinder
P. J. Drew
M. S. Fee
E. Grannon
C. Mateo
L. Mellander
C. Ruehlmann
C. B. Schaffer
A. Y. Shih
R. A. Stepnoski
S. Venkatachalam

Project scientists

P. M. Knutsen
A. Muller
Q.-T. Nguyen
J. C. Prechtl
P. S. Tsai
R. Wessel

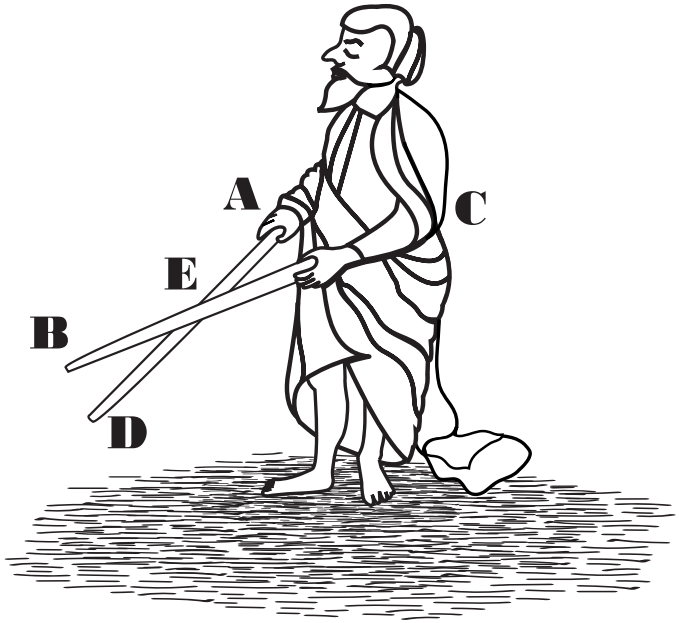
With thanks for past and ongoing financial support

BEBRF, HFSP, HBP, NIH (Director's Pioneer Award, NCRR, NIA/CNCRS, NIBIB/BRP, NIDA, NIDA/CEBRA, NIDCD, NIMH, NIMH/EUREKA & NINDS), NSF (DBI, IBN, IGERT, & Physics), Packard, Roche, Whitehall, US/Israel BSF, & UCSD CBAM

Senior collaborators

E. Ahissar
K. Akassoglou
M. Anderson
G. E. Blonder
P. D. Brodfueher
T. H. Bulloch
G. Cauwenberghs
H. J. Chiel
L. B. Cohen
K. R. Delaney
W. Denk
M. Deschenes
A. Devor
M. E. Diamond
J. H. Duyn
F. F. Ebner
G. B. Ermentrout
A. L. Fairhall
D. E. Feldman
Y. Freund
B. Friedman
T. Furuta
A. Gelperin
E. Golanov
D. Golomb
O. Griesbeck
A. Groisman
S. Haidarliu
F. Helmchen
P. E. Hockberger
T. E. Hughes
A. I. Ifarraguerri
S. Iyengar
R. S. Johnson
Z. Kam
H. J. Karten
J. P. Kaufhold
W. B. Kristan
H. Levine
V. Lev-Ram
P. D. Lyden
P. P. Mitra
A. L. Obaid
B. Pesaran
R. C. Reid
B. M. Salzberg
R. M. Shapley
B. I. Shraiman
P. A. Slesinger
H. Sompolinsky
J. A. Squier
H. Suhl
K. Svoboda
D. W. Tank
P. W. Taylor
R. Y. Tsien
F. Wang
J. Waters
B. A. Williams
R. Yuste
H. P. Zeigler

Descartes' (1637) blind man scanning walking sticks to locate an object



Rats rhythmically scan their vibrissae to locate nearby objects

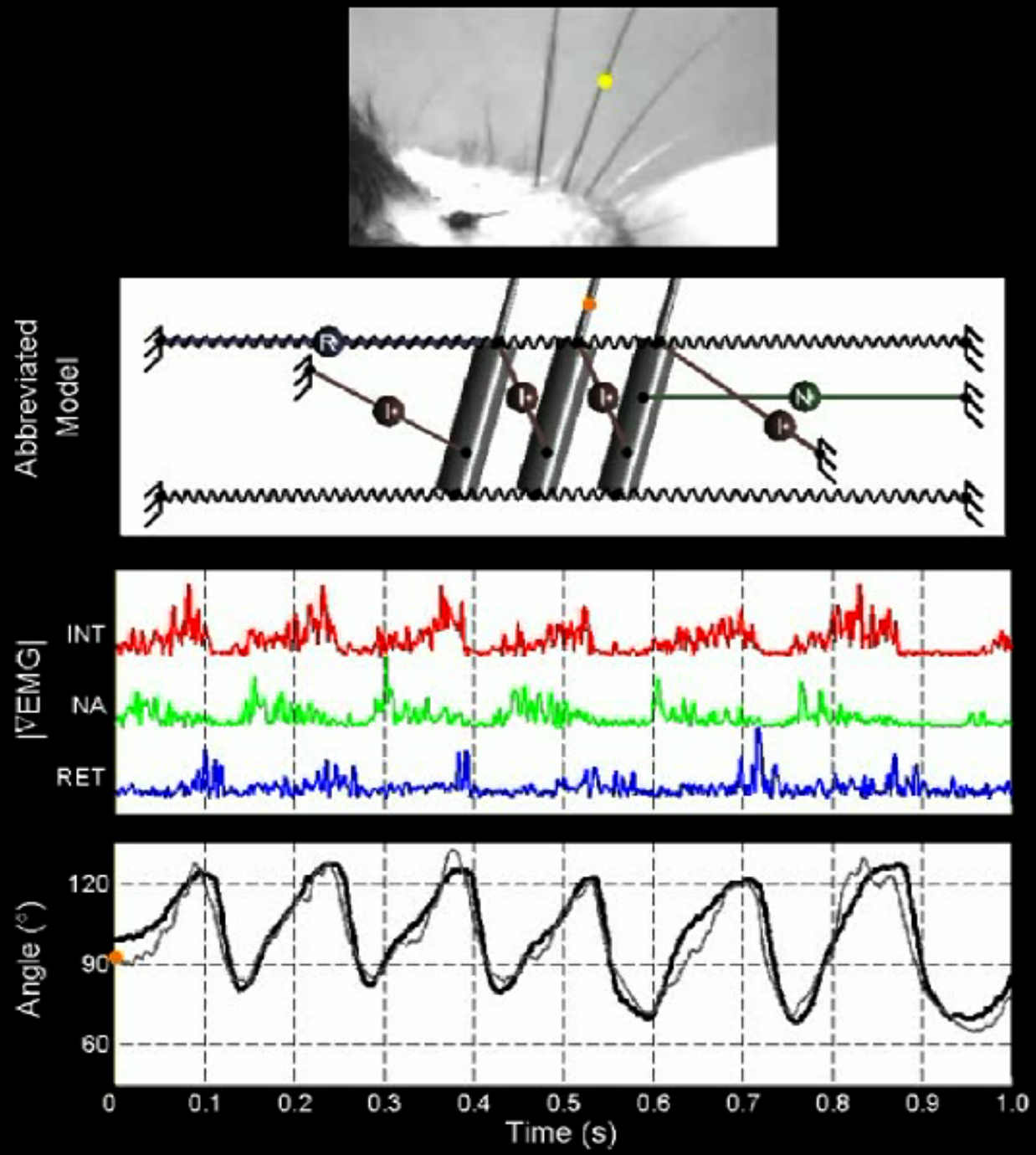
Breathing: The master clock for orofacial rhythms?

- **Review of whisking**

- Brainstem circuits for control of rapid vibrissa motion
  - Relation of whisking and breathing
  - Circuit basis for a whisking pattern generator

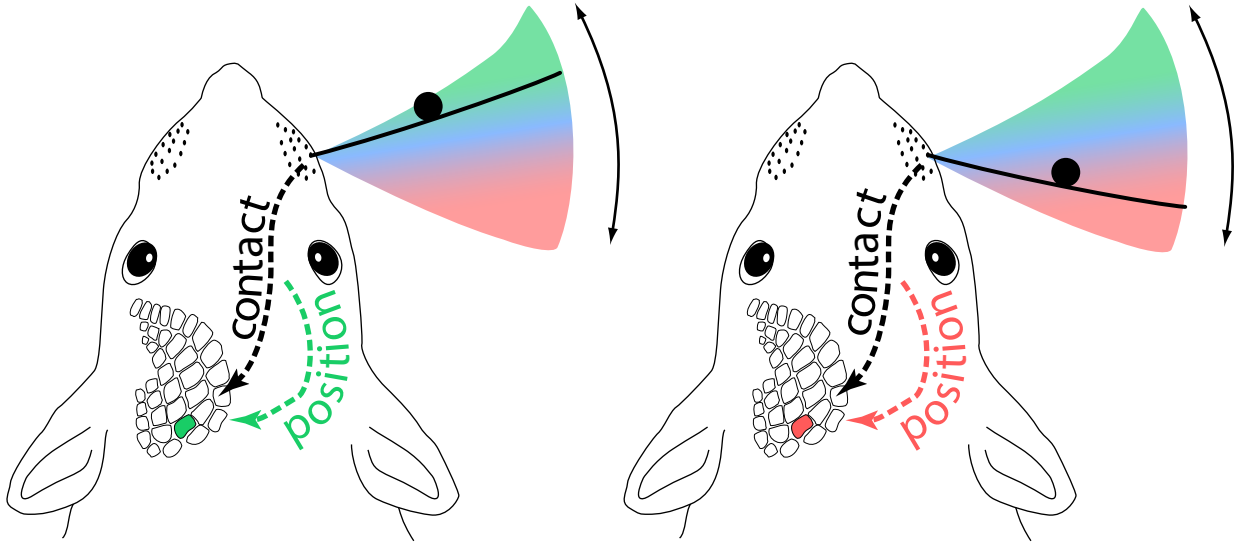
- Cortical control of slowly evolving whisking parameter

- Brainstem modulation of the sensory stream
  - Breathing as the origin of phase coding for perceptual binding

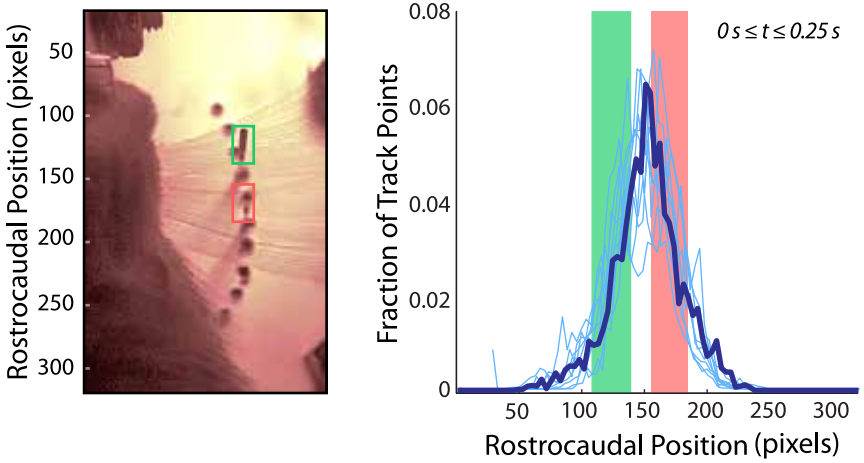


Hill, Bermejo, Zeigler and Kleinfeld (2008)

Paradigm to test if rodents code the azimuthal position of their vibrissae

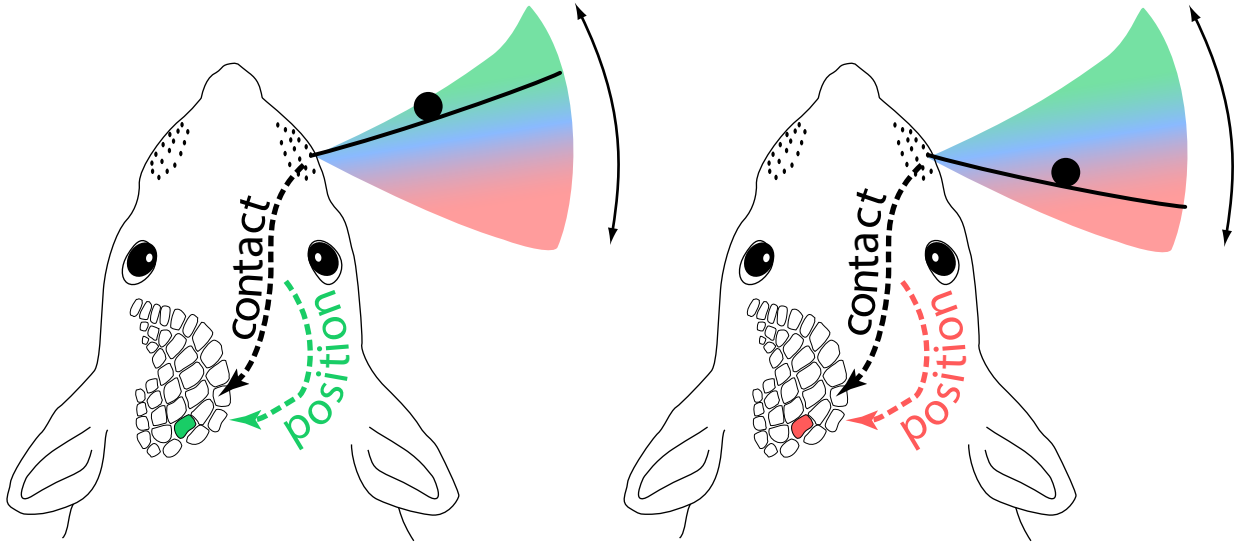


Rodents whisk over a restricted range that encompasses both stimuli

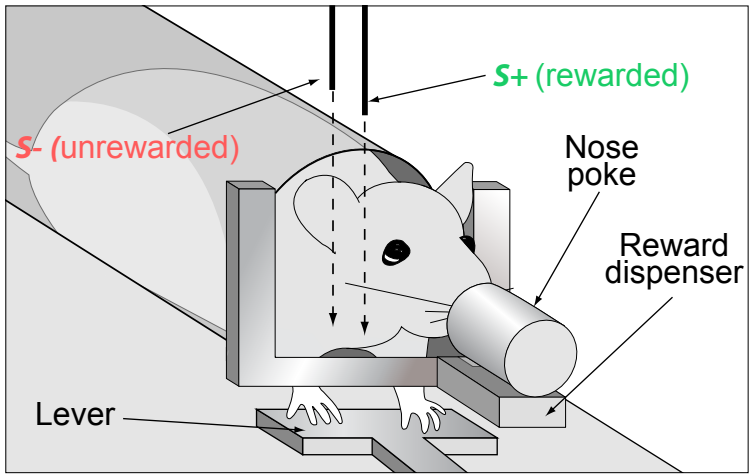


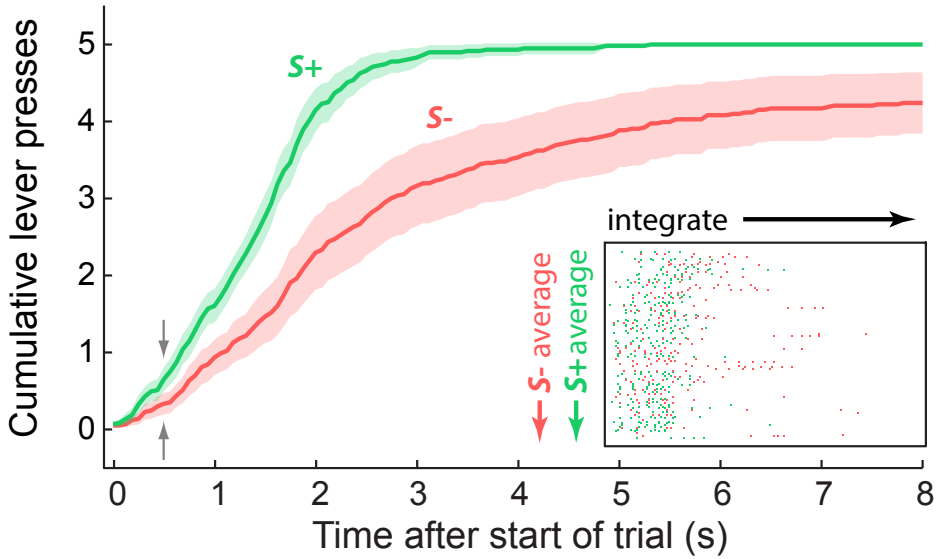
Mehta, Whitmer, Figueroa, Williams & Kleinfeld (PLoS Biology 2007)

Paradigm to test if rodents code the azimuthal position of their vibrissae



Behavioral evidence that rodents know the position of their vibrissae

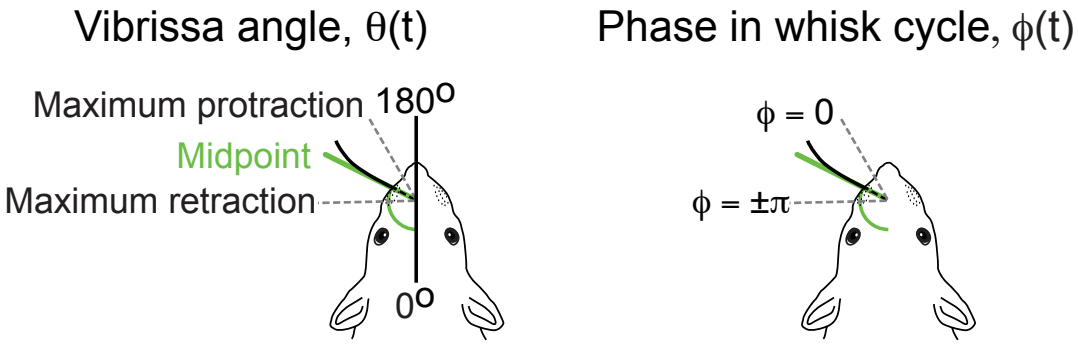




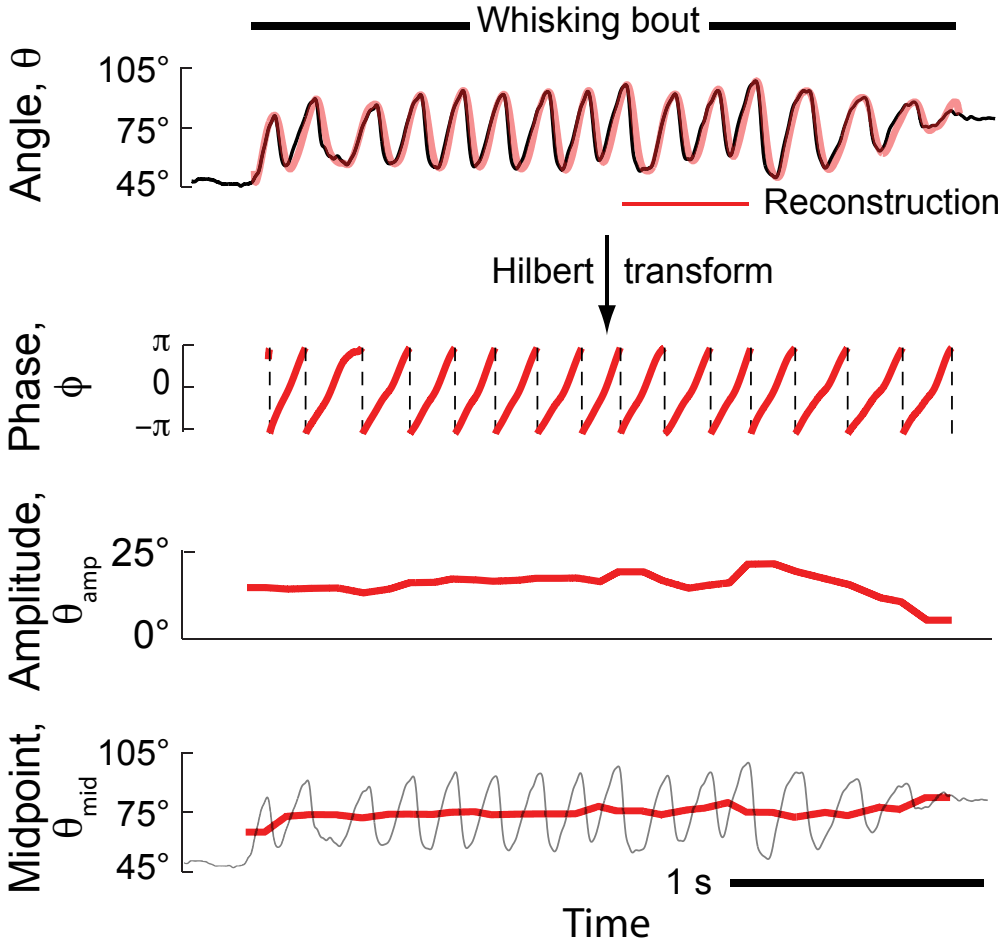
Mehta, Whitmer, Figueroa, Williams & Kleinfeld (PLoS Biology 2007)

see, for mice, O'Connor, Clack, Huber, Komiyama, Myers & Svoboda (J Neuroscience 2010)

Angular versus phase coordinates for whisking



Decomposition of the whisking signal into phase, amplitude and midpoint



Lesson

Whisking is generated by a control signal of the form

$$\theta(t) = \theta_{amplitude}(t) \cdot \cos \phi(t) + \theta_{midpoint}(t)$$

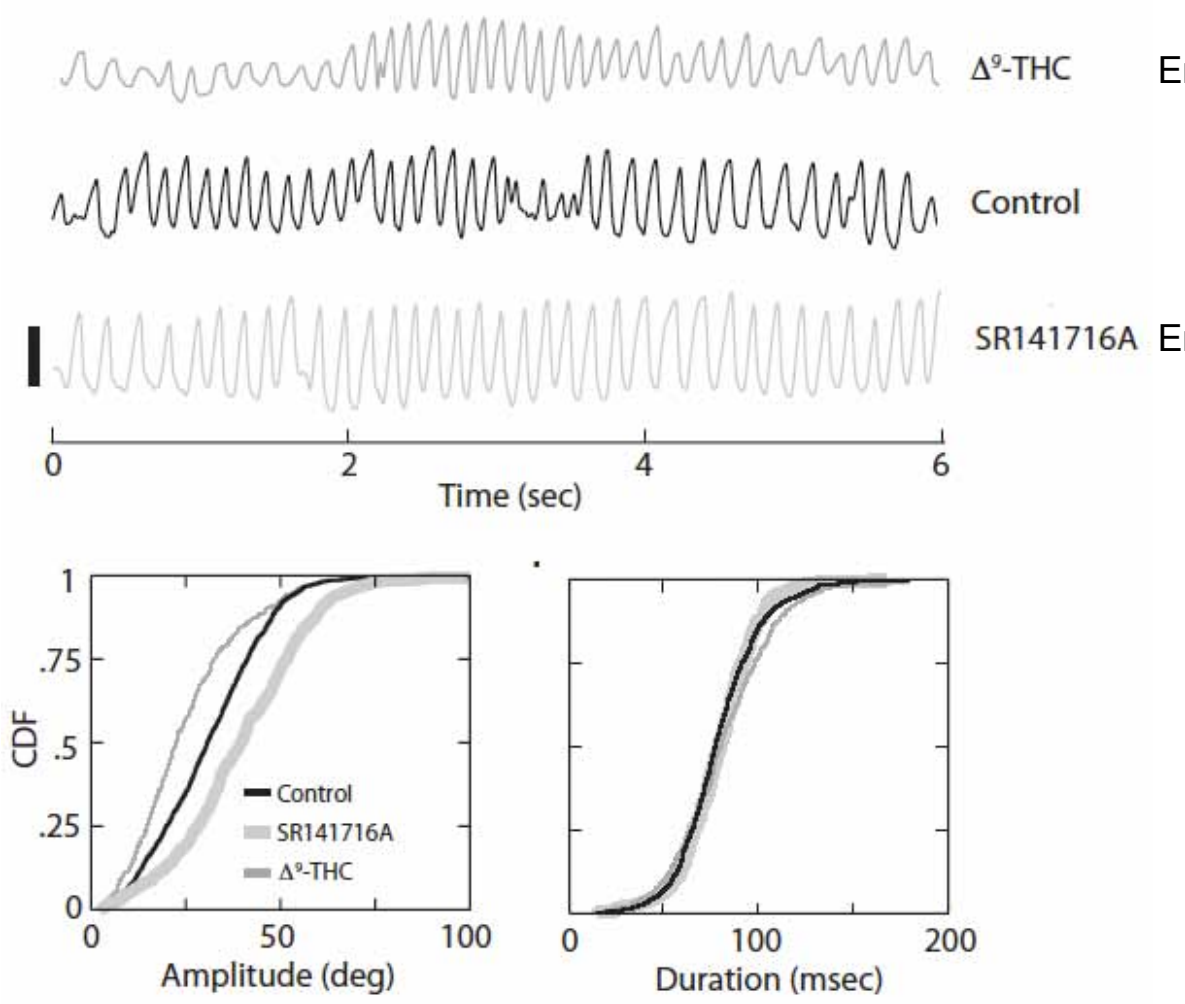
slow fast slow

with $d\phi(t)/dt = 2\pi f_{whisk}$ for rhythmic whisking

Question

Where, if anywhere, is the locus for generation of the fast signal?

Pharmacological decoupling of the control for whisking amplitude and frequency (Pietr, Knutsen, Shore, Ahissar & Vogel 2010)

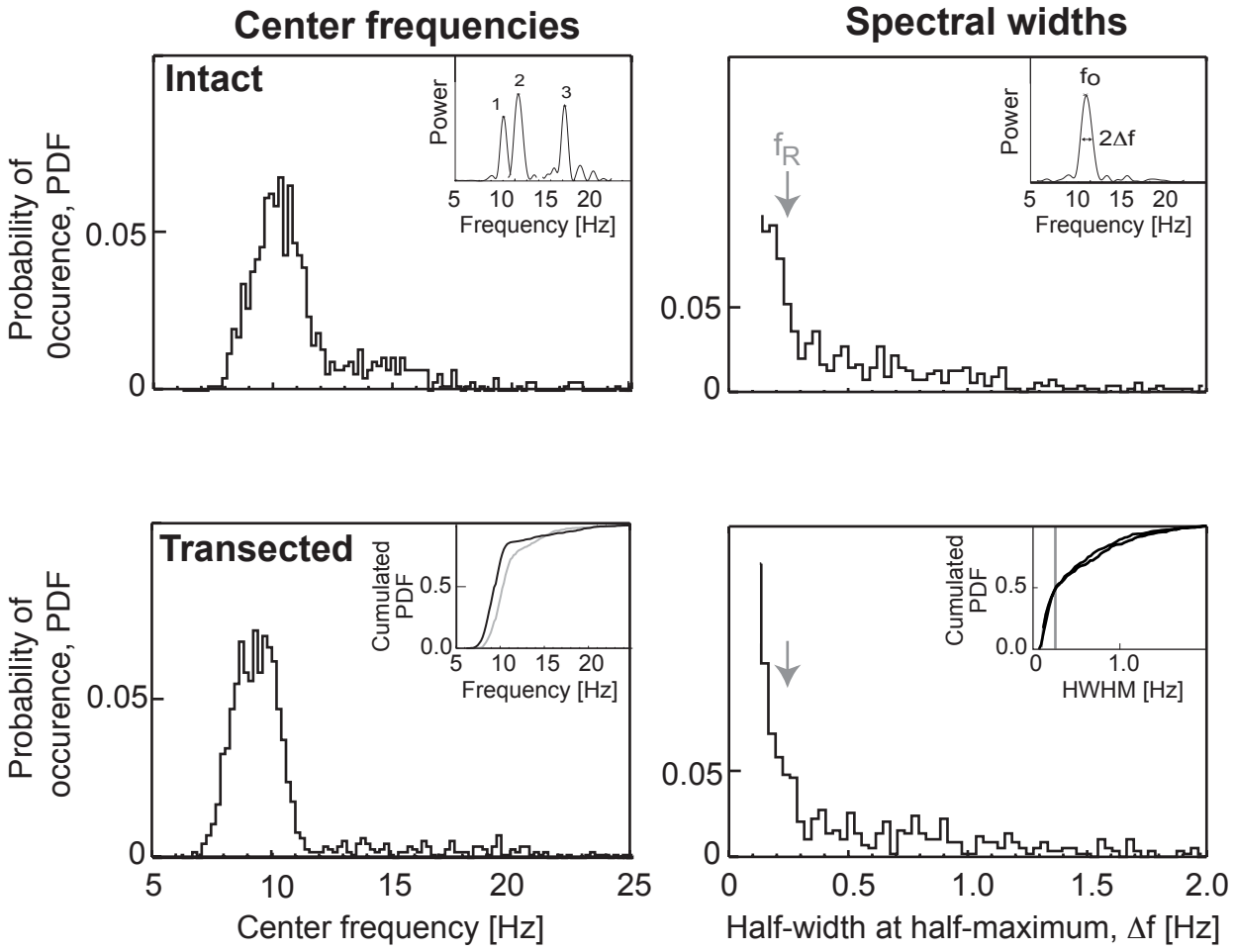


Endocannabinoid agonist

Endocannabinoid antagonist

Suggests selected control of fast versus slow whisking parameters

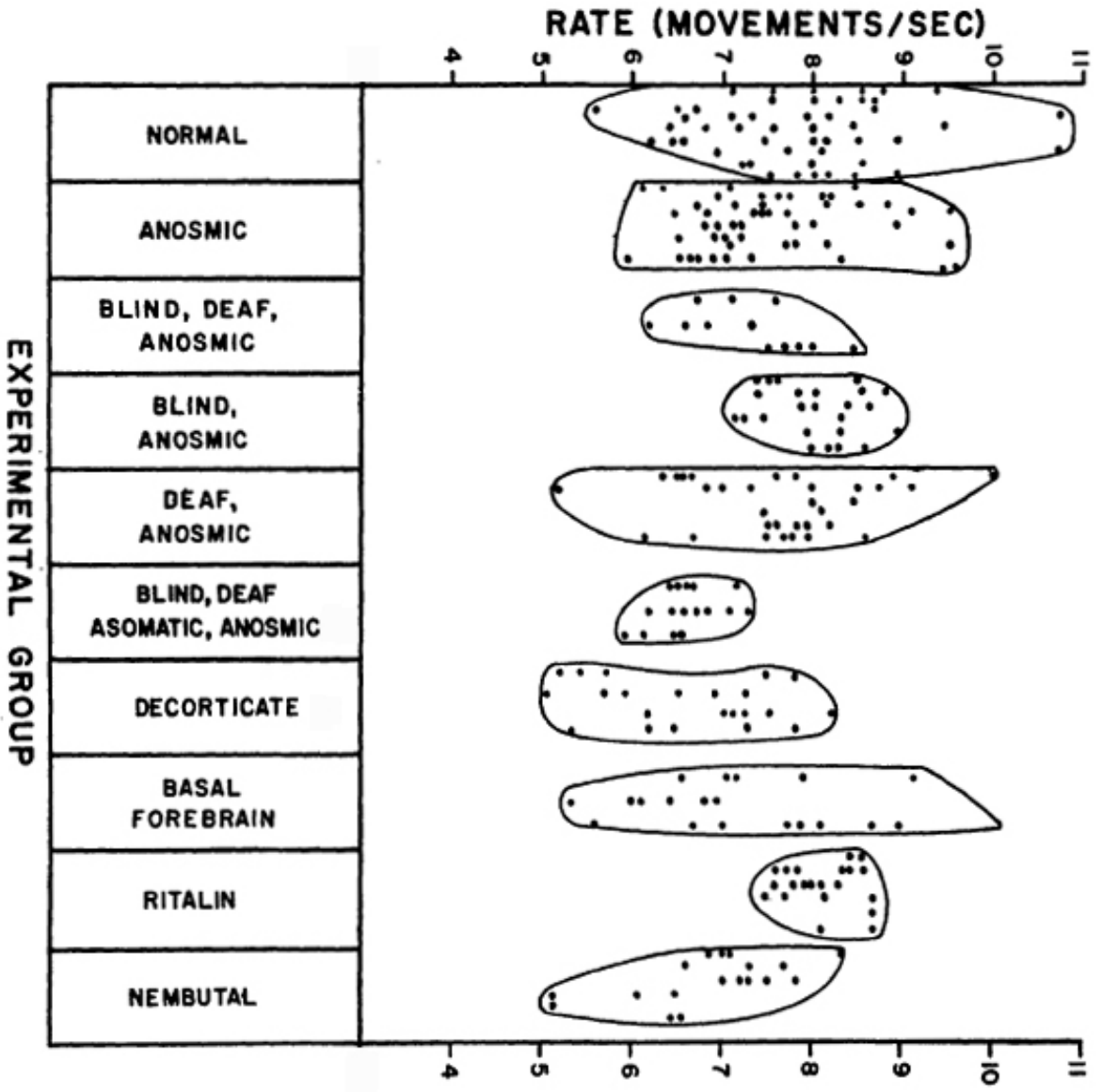
Whisking occurs without sensory feedback



Implies presence of a CPG

Berg & Kleinfeld (2004 J Neurophysiol)

Rhythimic whisking can occur without forebrain structures (Welker 1964)



This and related data suggests a brainstem CPG (Gao, Bermejo & Zeigler 2001)

Breathing: The master clock for orofacial rhythms?

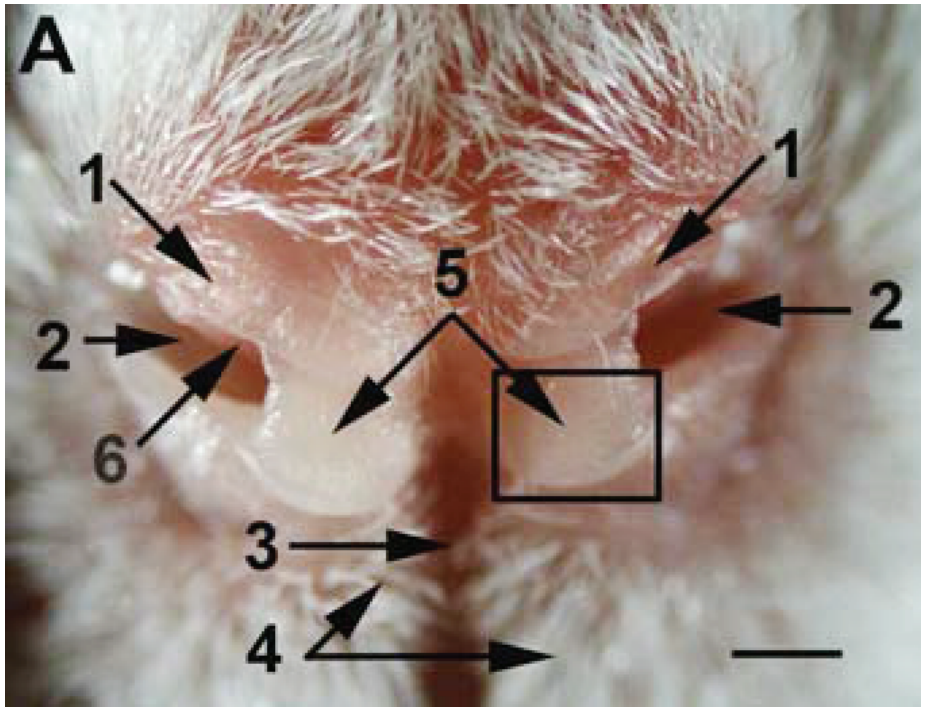
- Review of whisking

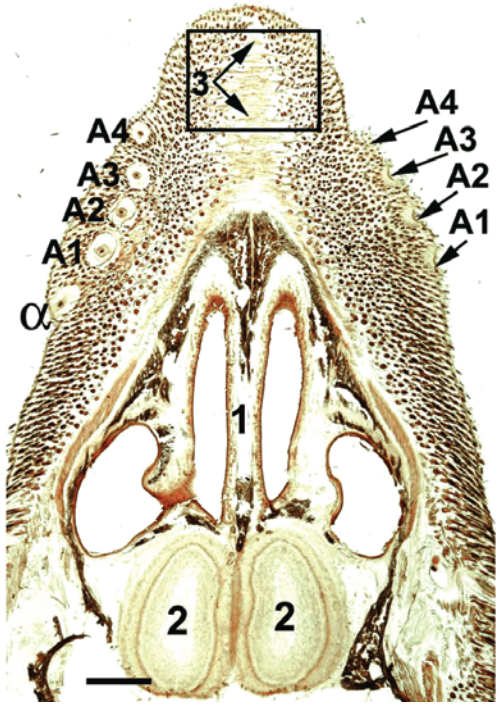
- **Brainstem circuits for control of rapid vibrissa motion**
  - **Relation of whisking and breathing**
  - Circuit basis for a whisking pattern generator

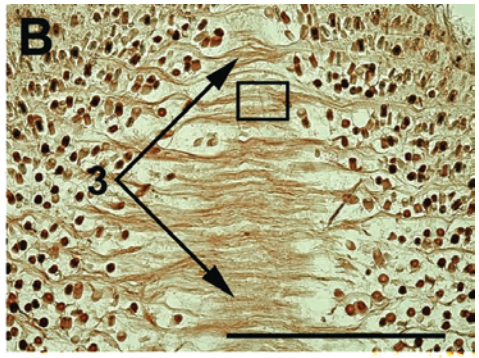
- Cortical control of slowly evolving whisking parameter

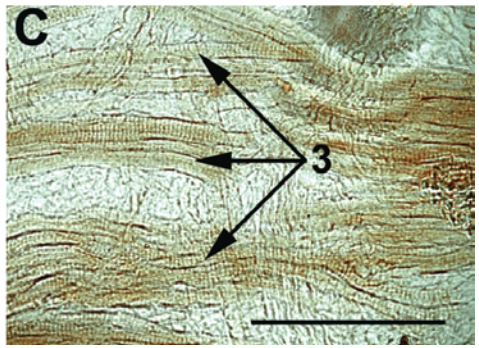
- Brainstem modulation of the sensory stream
  - Breathing as the origin of phase coding for perceptual binding

Common muscles in the rhinarium are involved in sniffing and whisking



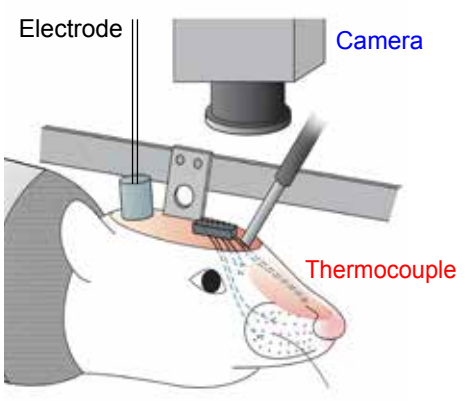




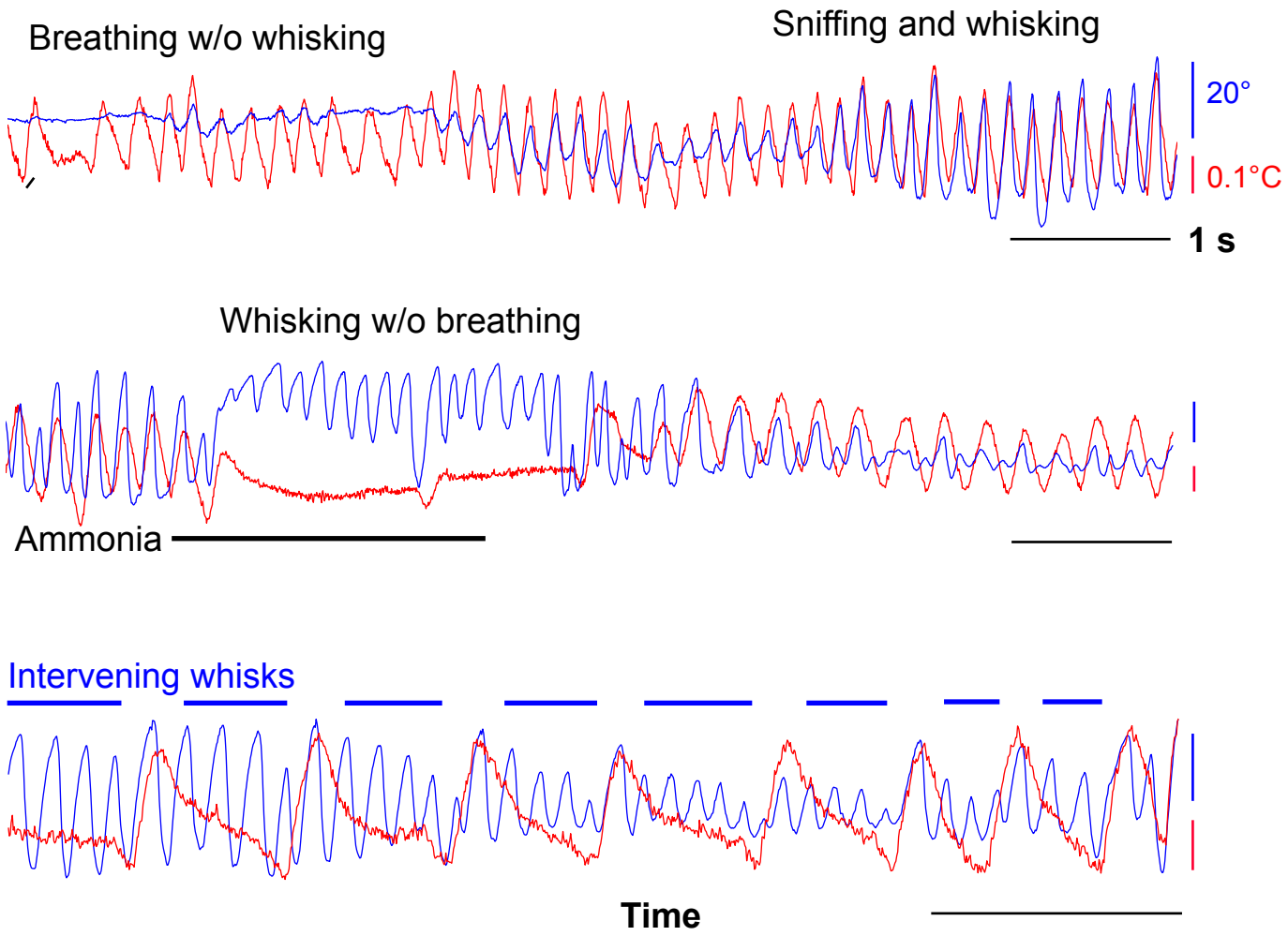


M. transversus nasi

Haidarliu, Golomb, Kleinfeld & Ahissar (Anat Rec 2012)

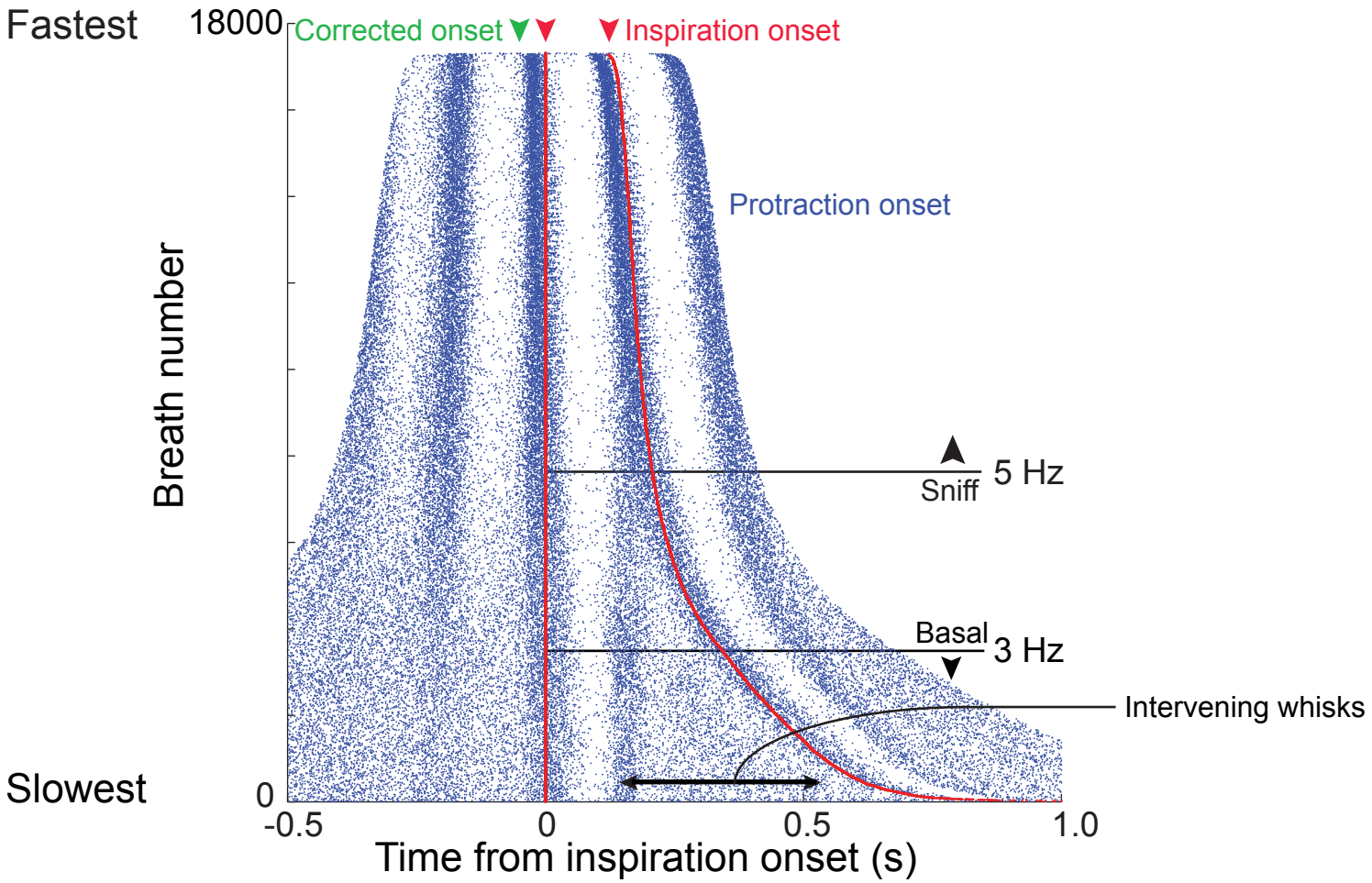


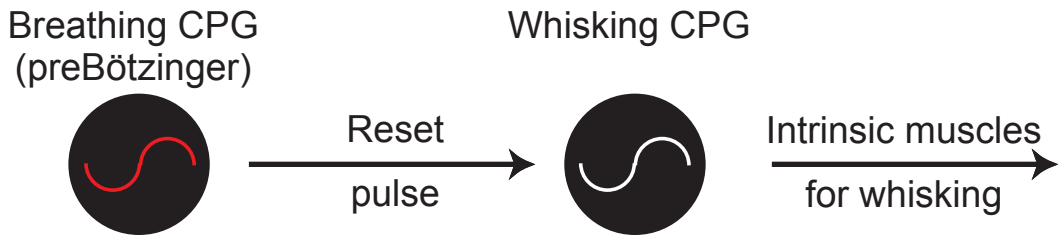
Phase resetting of rhythmic whisking by breathing (sniffing & basal respiration)



Moore*, Deschenes*, Furuta, Huber, Smear, Demers & Kleinfeld (Nature 2013)

Respiration resets whisking oscillations





Moore*, Deschenes*, Furuta, Huber, Smear, Demers & Kleinfeld (Nature 2013)

Lesson

PreBötzinger respiratory complex is involved in protraction phase of whisking pattern generation

Breathing: The master clock for orofacial rhythms?

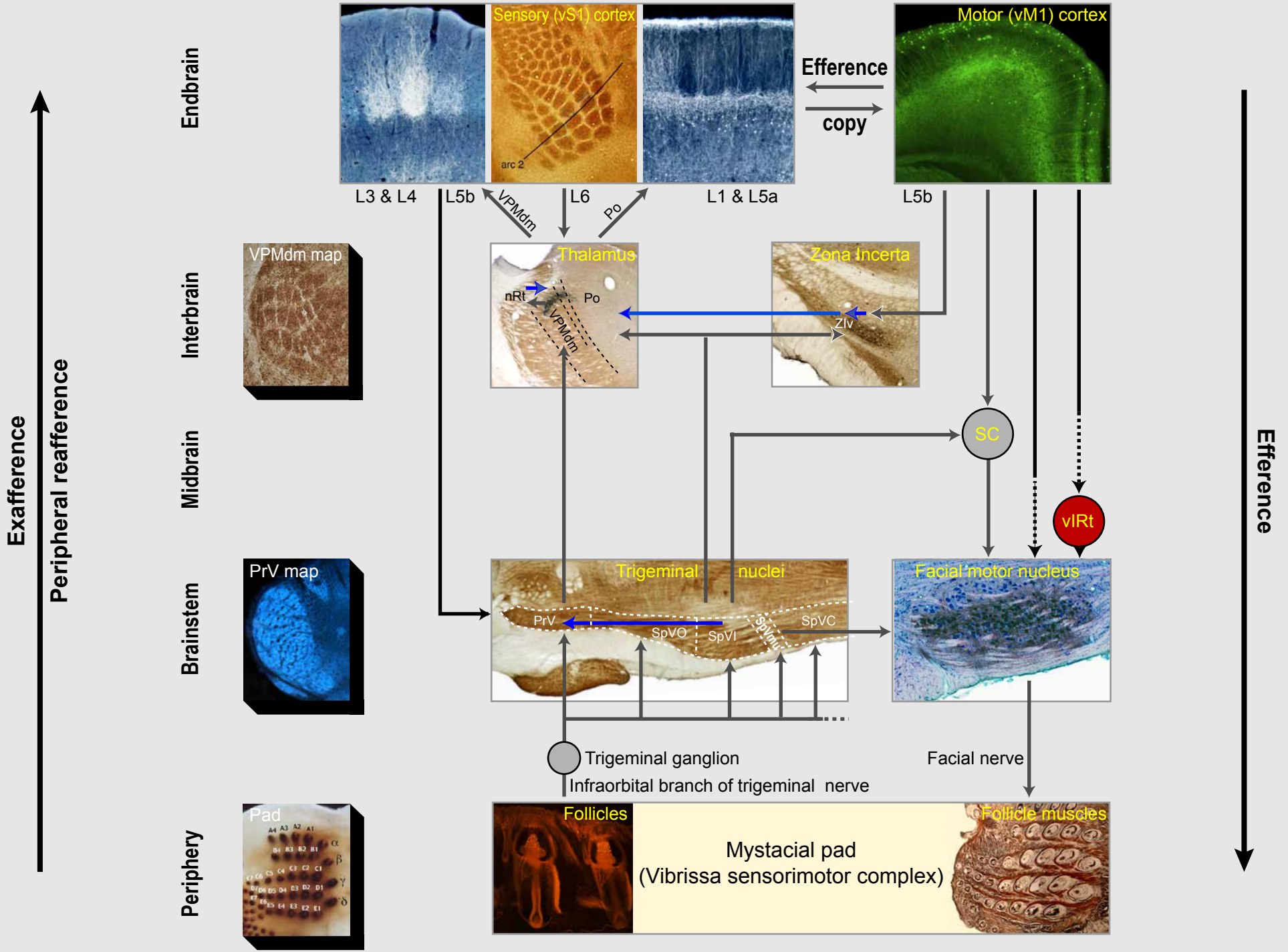
- Review of whisking

- **Brainstem circuits for control of rapid vibrissa motion**
  - Relation of whisking and breathing
  - **Circuit basis for a whisking pattern generator**

- Cortical control of slowly evolving whisking parameter

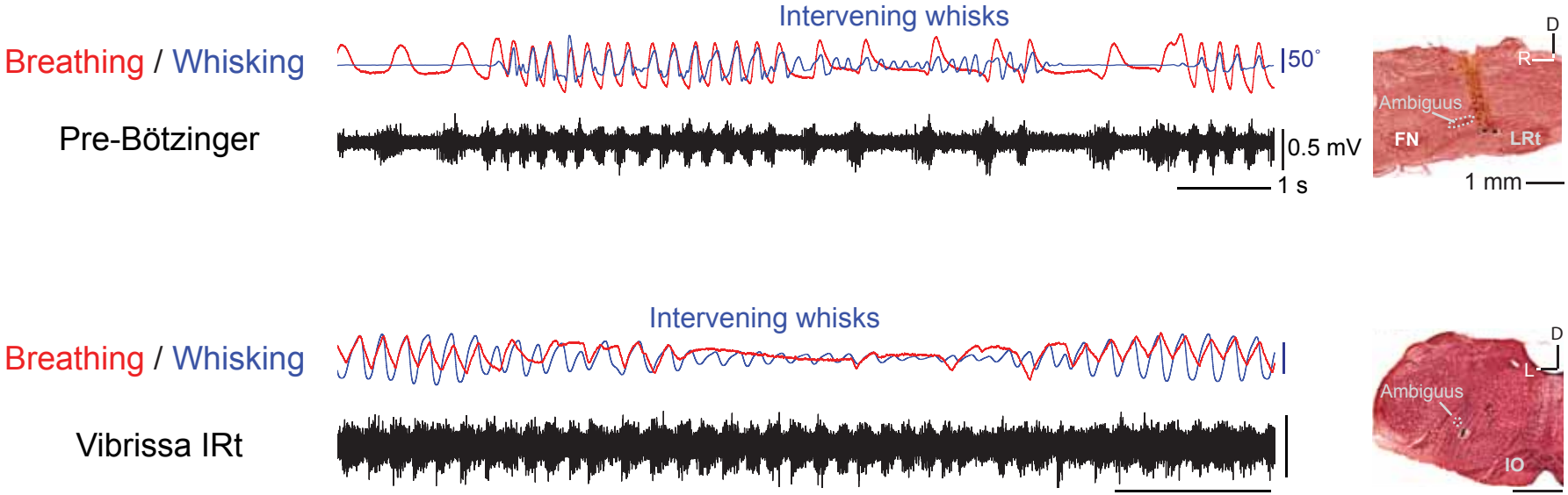
- Brainstem modulation of the sensory stream
  - Breathing as the origin of phase coding for perceptual binding

Signal flow and computing in sensorimotor loops of the vibrissa system

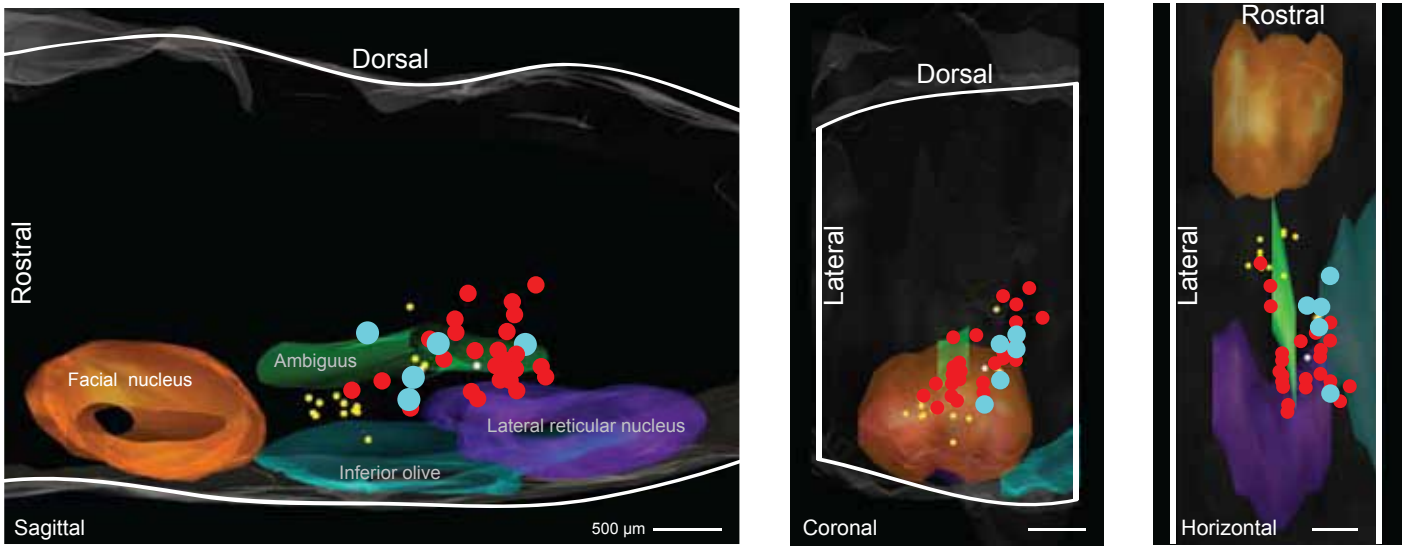


Modified from Kleinfeld & Deschenes (Neuron 2011)

Units in the intermediate reticular formation (IRt) that report inspiration versus protraction



- Inspiratory / protraction
- Whisking



Moore*, Deschenes*, Huber, Smear, Demers & Kleinfeld (under revision)

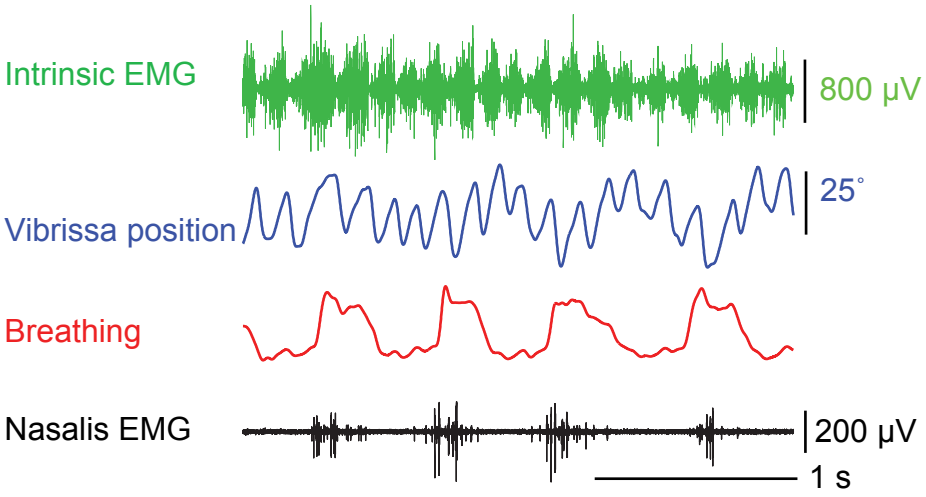
Lesson

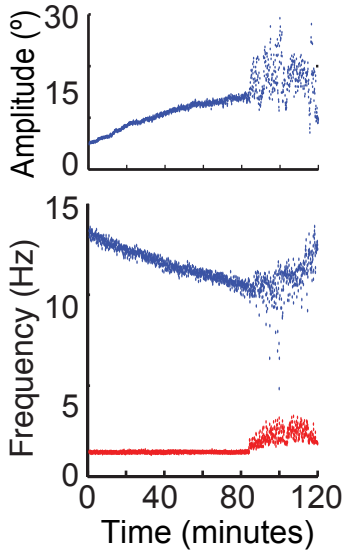
A newly recognized zone of neurons in the lRt formation code rhythmic motion of the vibrissa

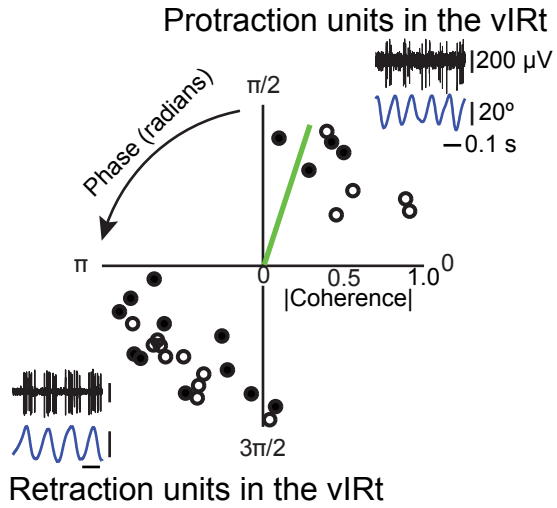
Question

Are these units sufficient to drive rhythmic motion?

Kainic acid activates the vIRt, which drives facial motoneurons







Moore*, Deschenes*, Furuta, Huber, Smear, Demers & Kleinfeld (Nature 2013)

Lesson

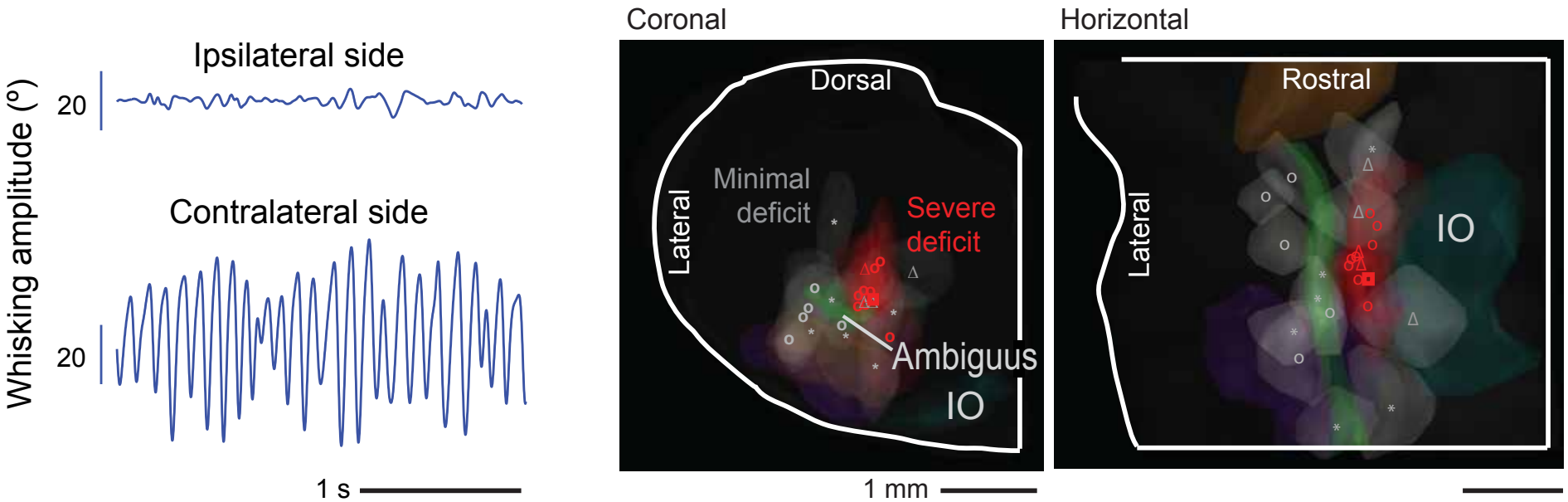
A newly recognized zone of neurons in the IRt formation can drive rhythmic motion of the vibrissa

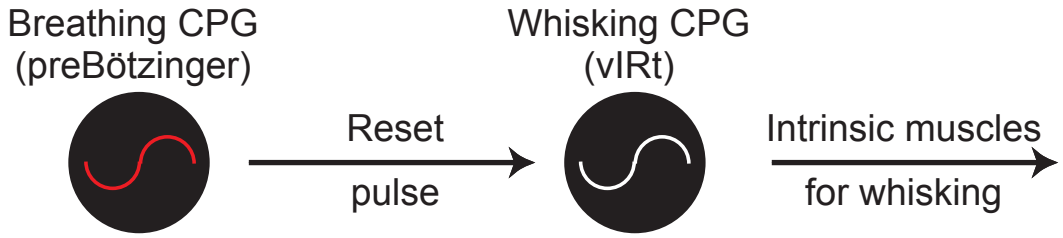
Question

Are these units necessary to drive rhythmic motion?

Lesion of the vlRt blocks exploratory whisking

o Electrolytic
Δ Sindbis virus
◘ Ibotenic acid





Moore*, Deschenes*, Furuta, Huber, Smear, Demers & Kleinfeld (Nature 2013)

Lesson

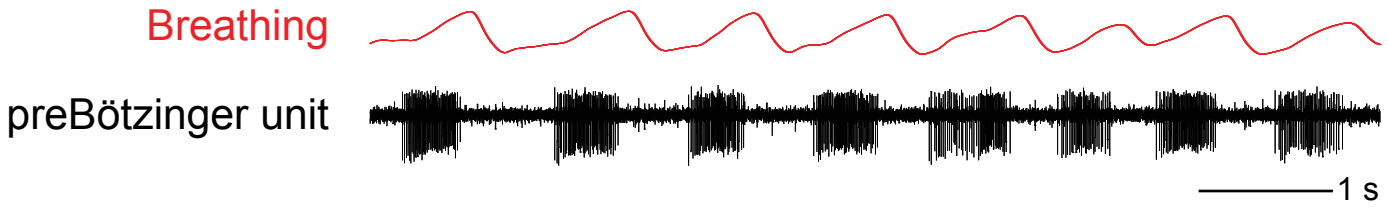
Units in the vlRt are necessary for rhythmic motion of the vibrissae

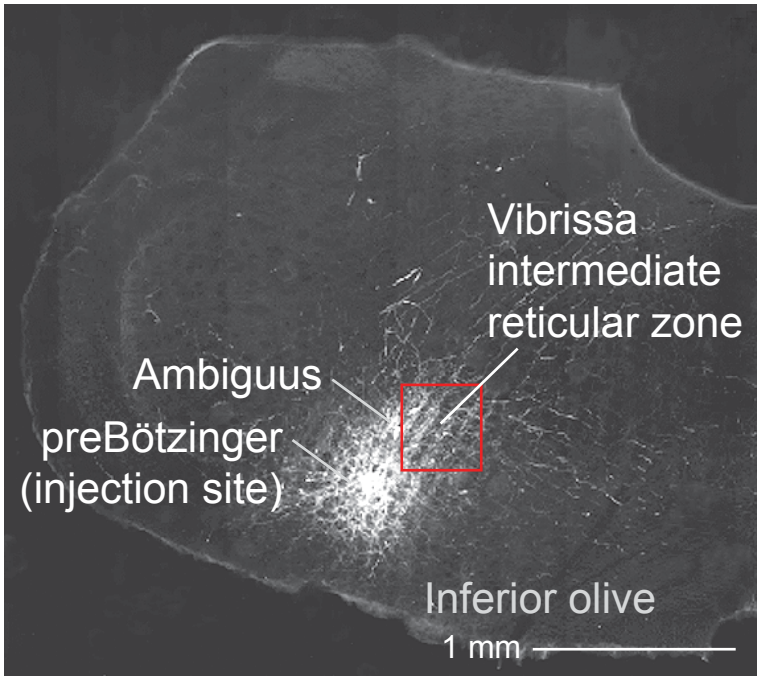
Question

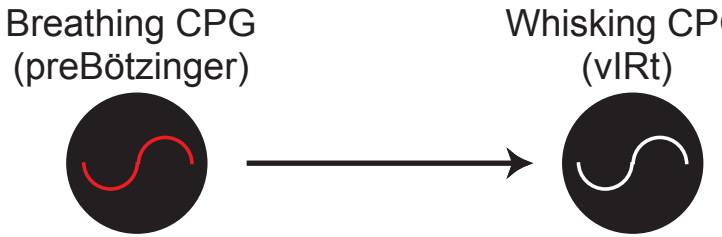
Can we identify the monosynaptic connections of a minimal breathing and whisking circuit?

PreBötzinger units project to the vibrissa zone of the lRt

(anteriograde labeling with biotinylated dextran amine)



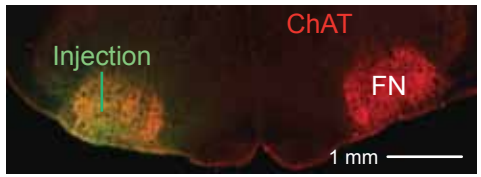


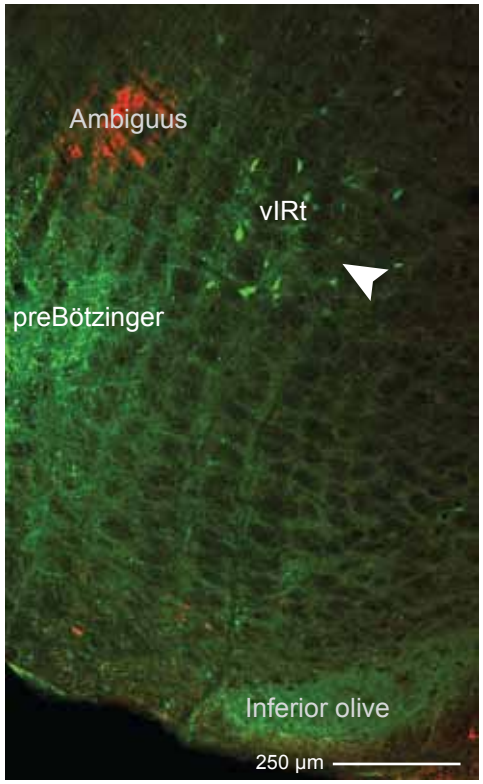


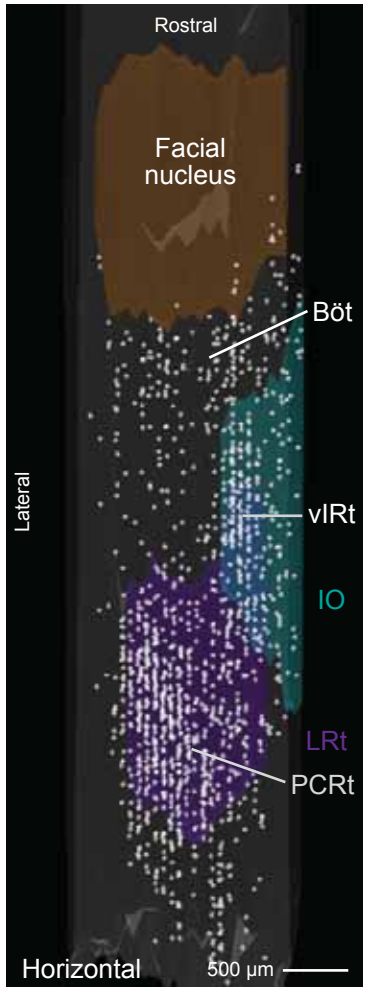
Moore*, Deschenes*, Huber, Smear, Demers & Kleinfeld (under revision)

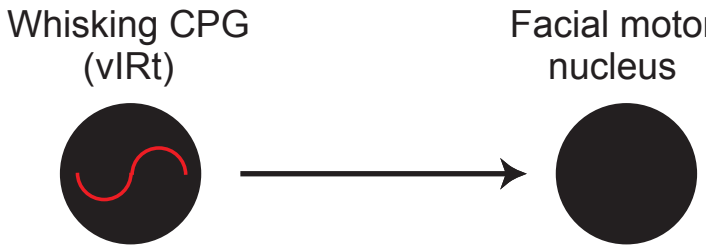
The facial nucleus receives input from the vibrissa zone of the IRt

(retrograde labeling with Neurobiotin™)



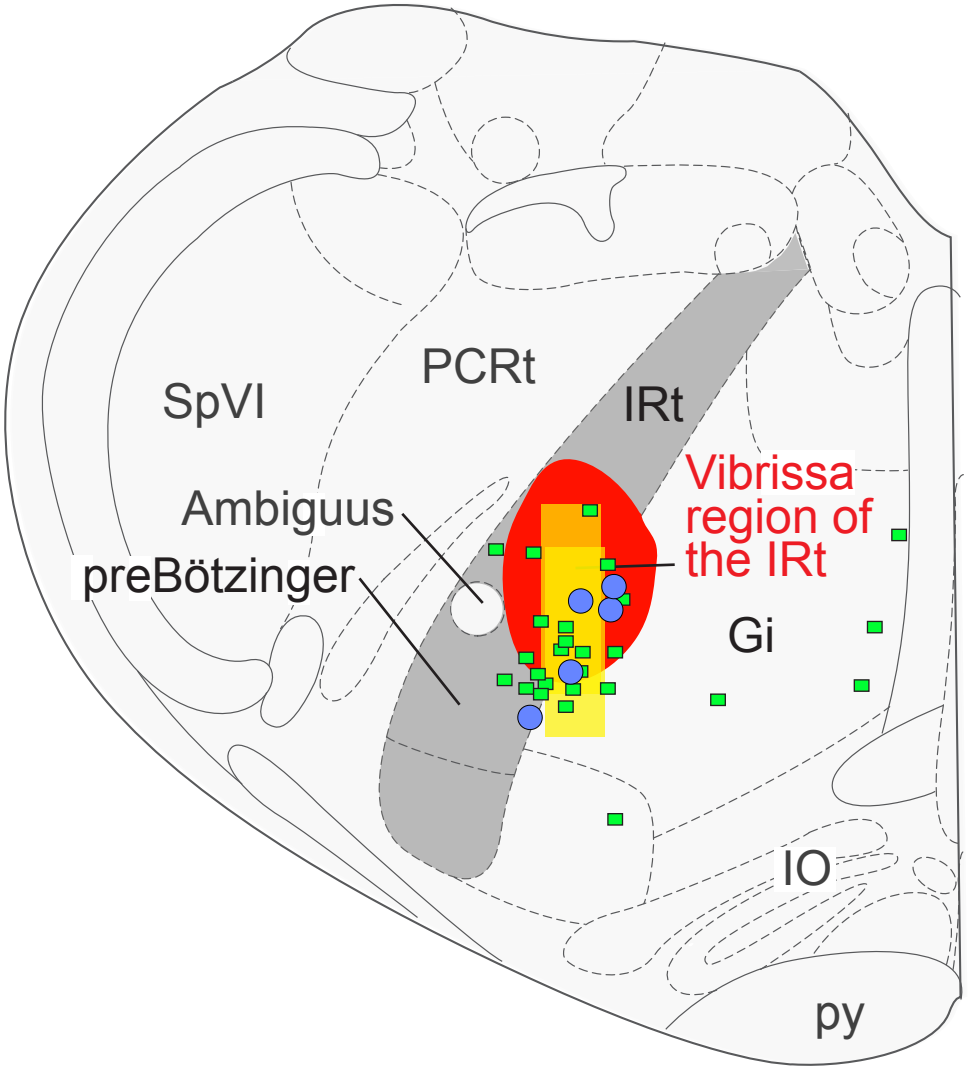






Moore*, Deschenes*, Huber, Smear, Demers & Kleinfeld (under revision)

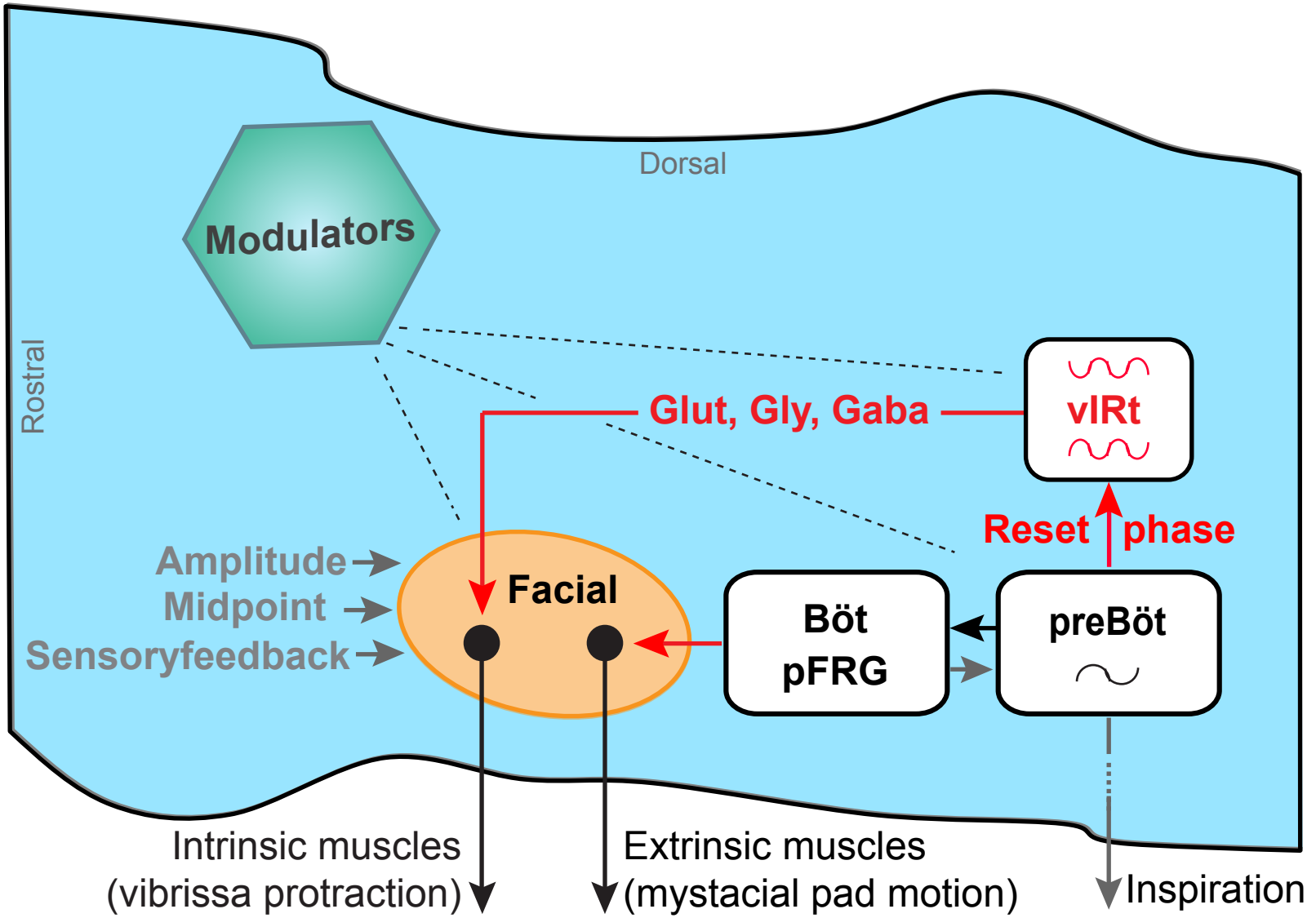
Compendium of evidence for a vibrissa pattern generator zone in the intermediate reticular formation (vIRt)



- Premotor to facial nucleus
- Effective whisking lesion
- Rhythmic whisking units
- Kainic acid induced whisking units

Moore*, Deschenes*, Furuta, Huber, Smear, Demers & Kleinfeld (Nature 2013)

Minimal model of the brainstem rhythmic generator for whisking



Adapted from Moore*, Deschenes*, Furuta, Huber, Smear, Demers & Kleinfeld (Nature 2013)

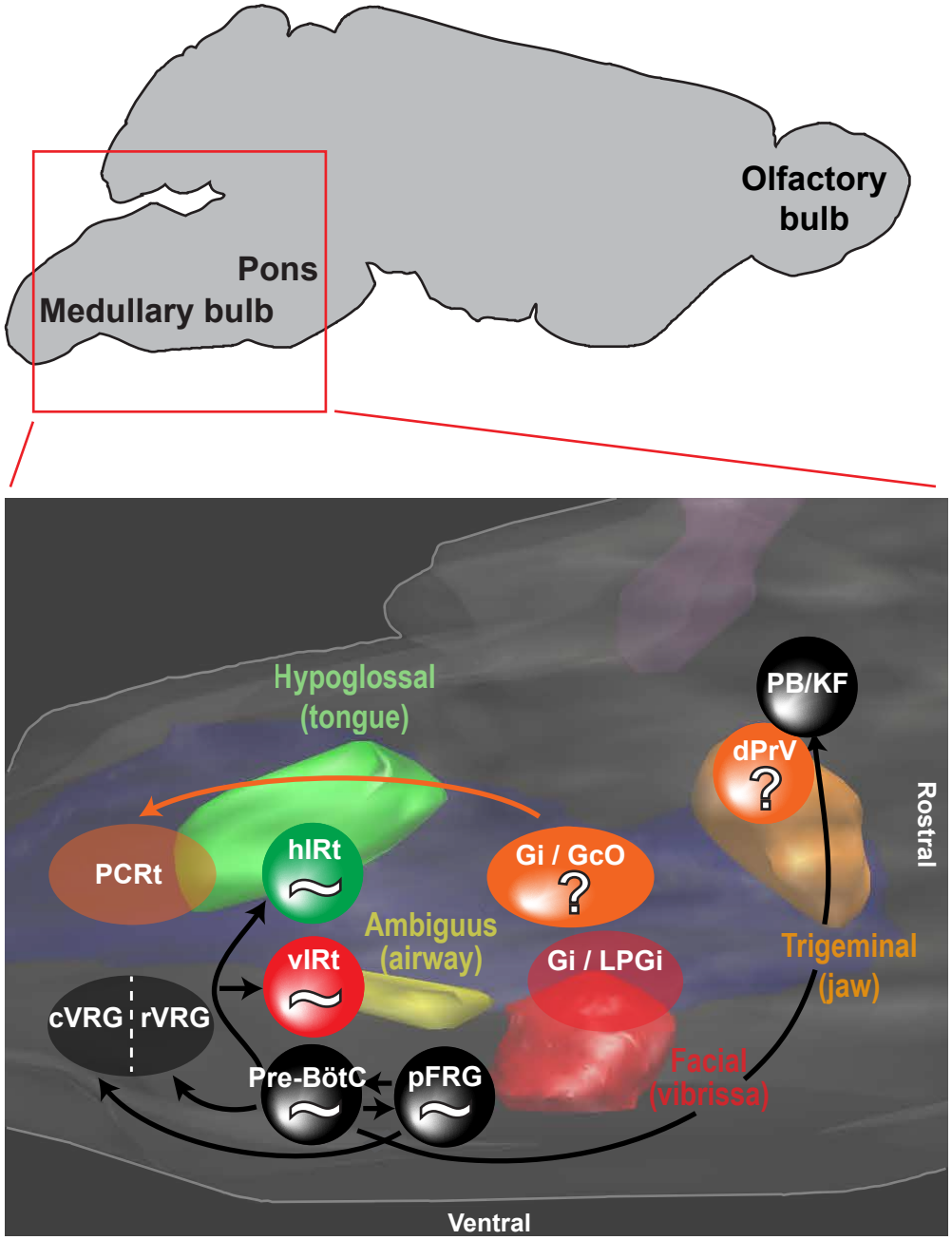
Summary lesson

Breathing coordinates rhythmic whisking

Conjecture

Primacy of inhalation as a *master clock* for orofacial behaviors

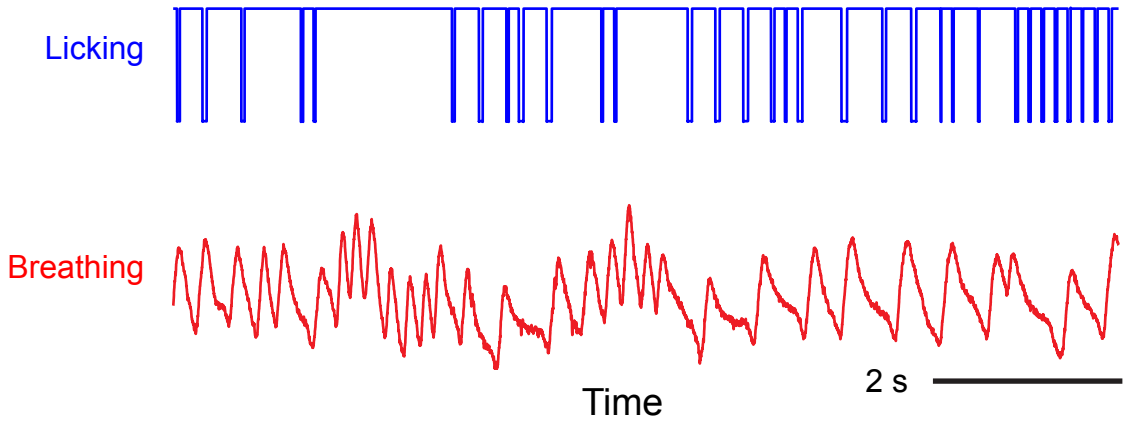
Connections to brainstem motor nuclei involved in orofacial control

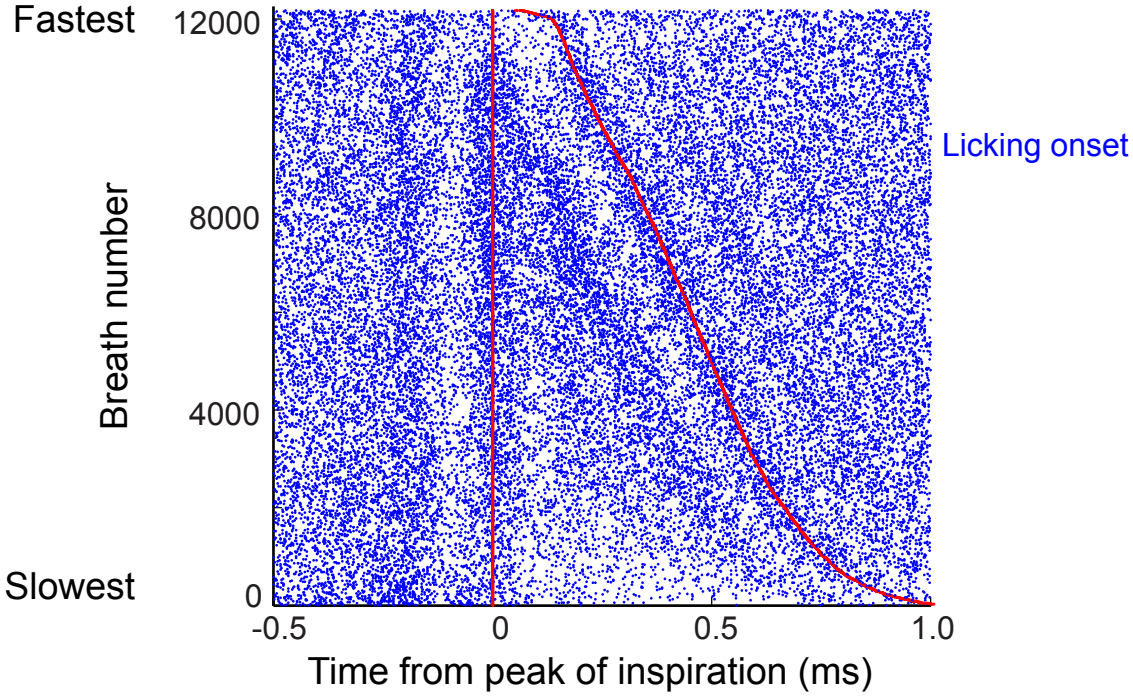


Kleinfeld, Deschenes, Wang & Moore (Nature Neuroscience 2014)

Coordination of licking with breathing

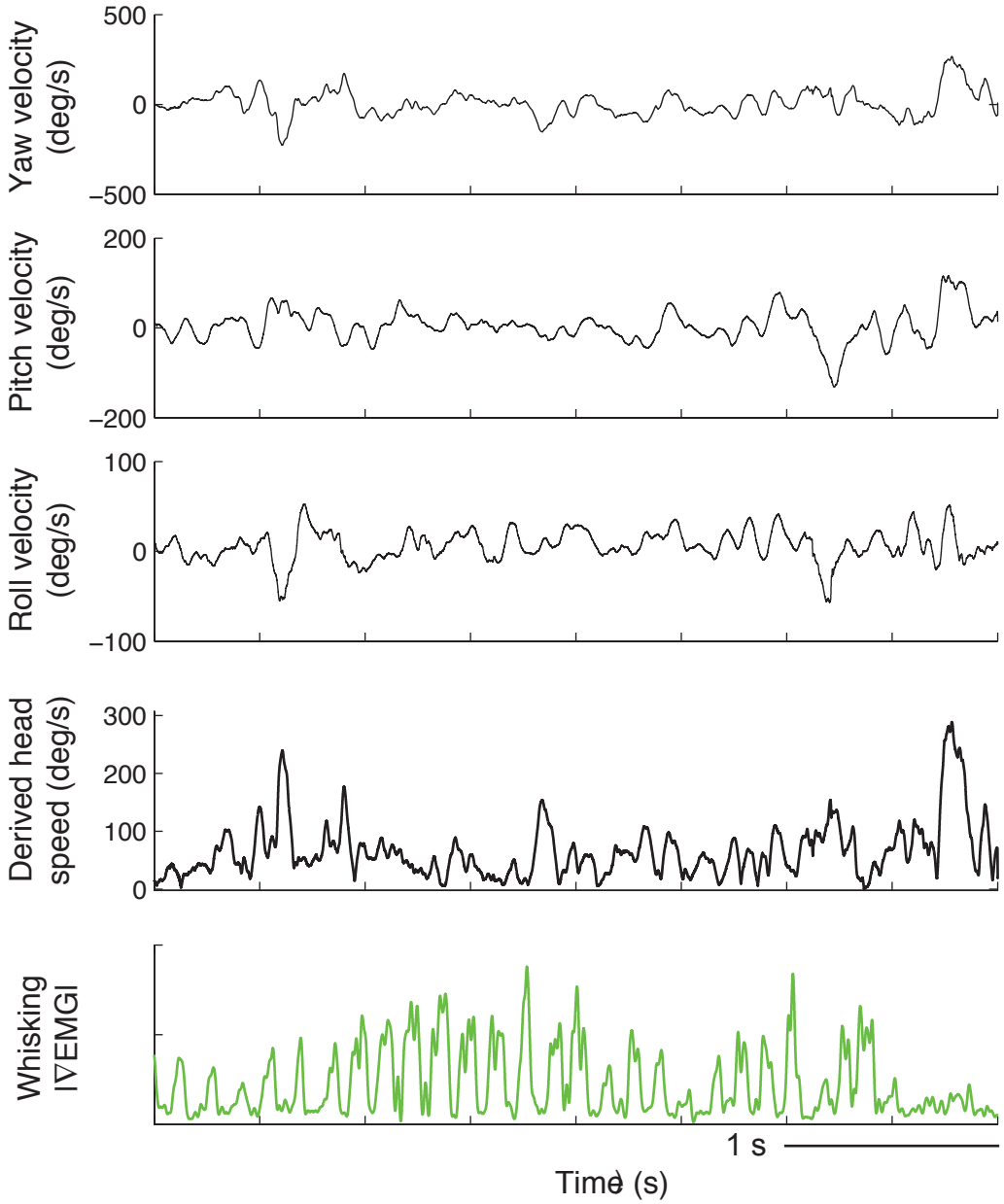
(following Travers, Dinardo & Karimnamazi, Neurosci Biobehav Rev 1997)

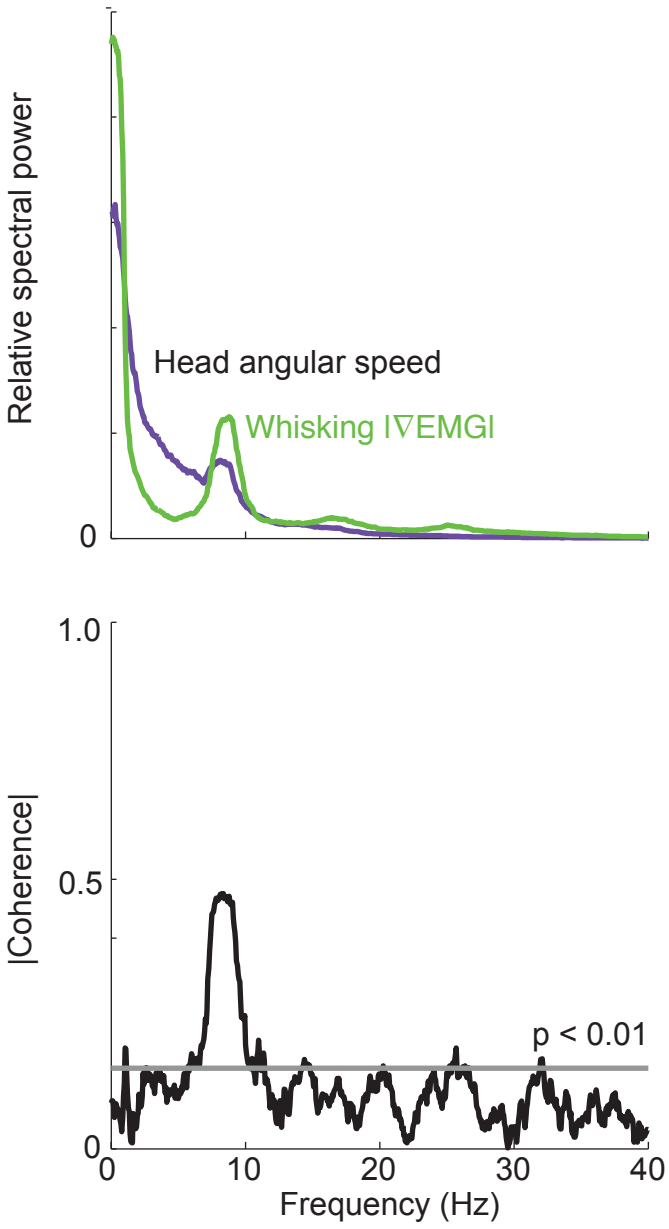




Moore, Deschenes & Kleinfeld (unpublished)

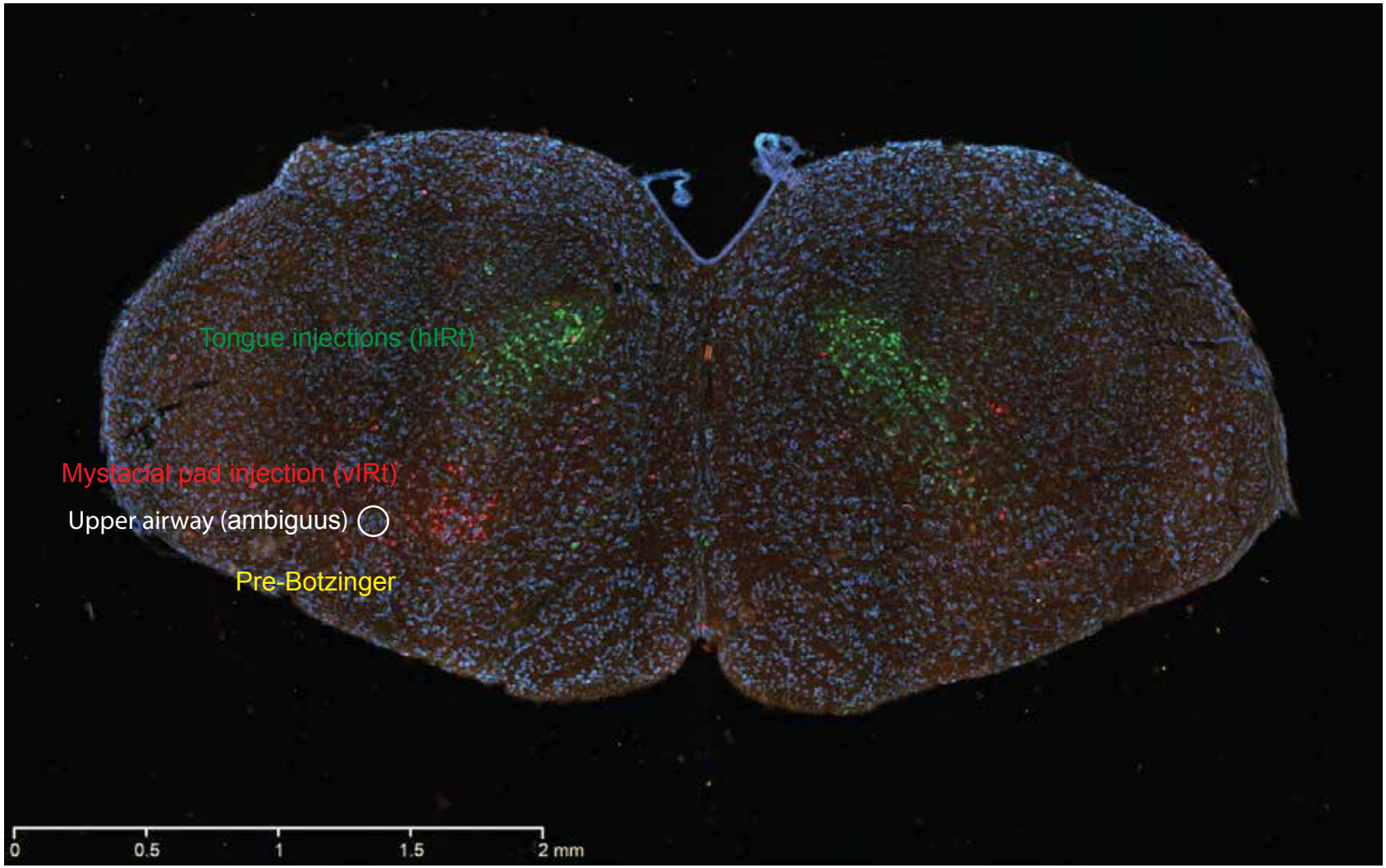
Preliminary data on coordination of head bobbing with whisking





Moore, Deschenes & Kleinfeld (unpublished)

Preliminary support of “Master clock bus” via dual labeling with ΔG-XFP rabies in chat-G mice



Moore, Stanek, Deschenes, Kleinfeld, Wang (unpublished)

Breathing: The master clock for orofacial rhythms?

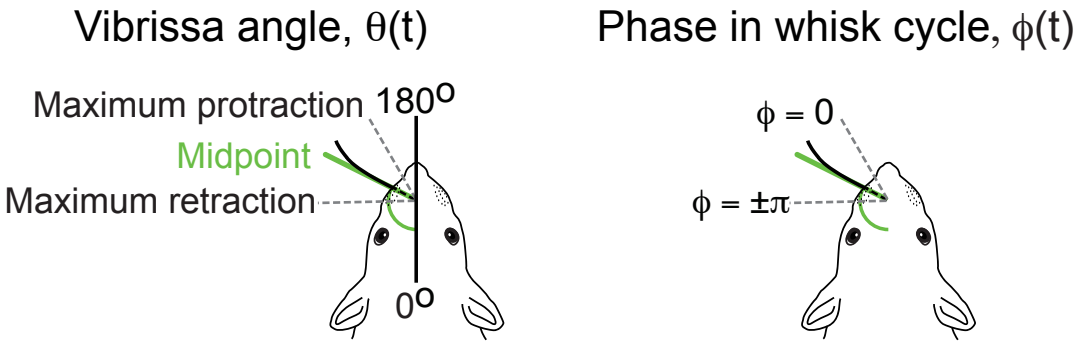
- Review of whisking

- Brainstem circuits for control of rapid vibrissa motion
  - Relation of whisking and breathing
  - Circuit basis for a whisking pattern generator

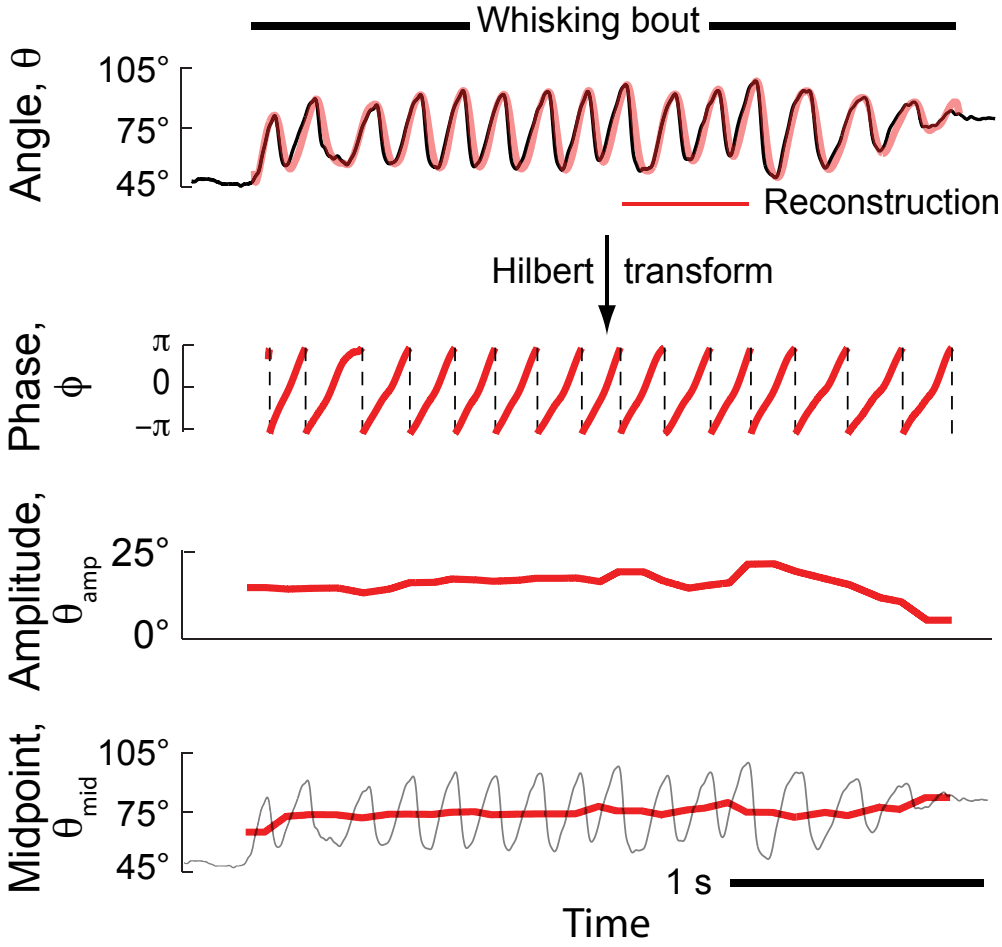
- **Cortical control of slowly evolving whisking parameter**

- Brainstem modulation of the sensory stream
  - Breathing as the origin of phase coding for perceptual binding

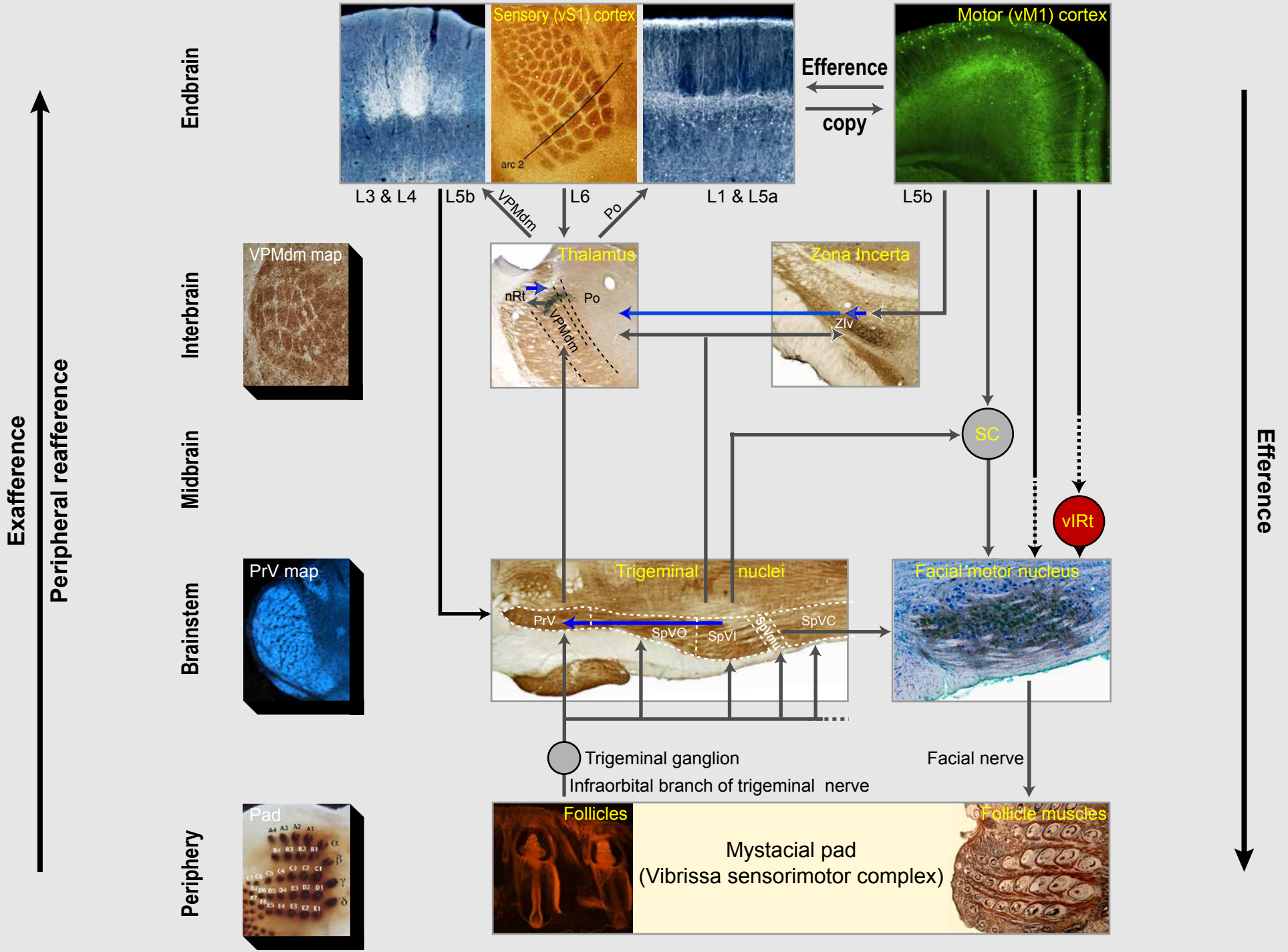
Angular versus phase coordinates for whisking



Decomposition of the whisking signal into phase, amplitude and midpoint

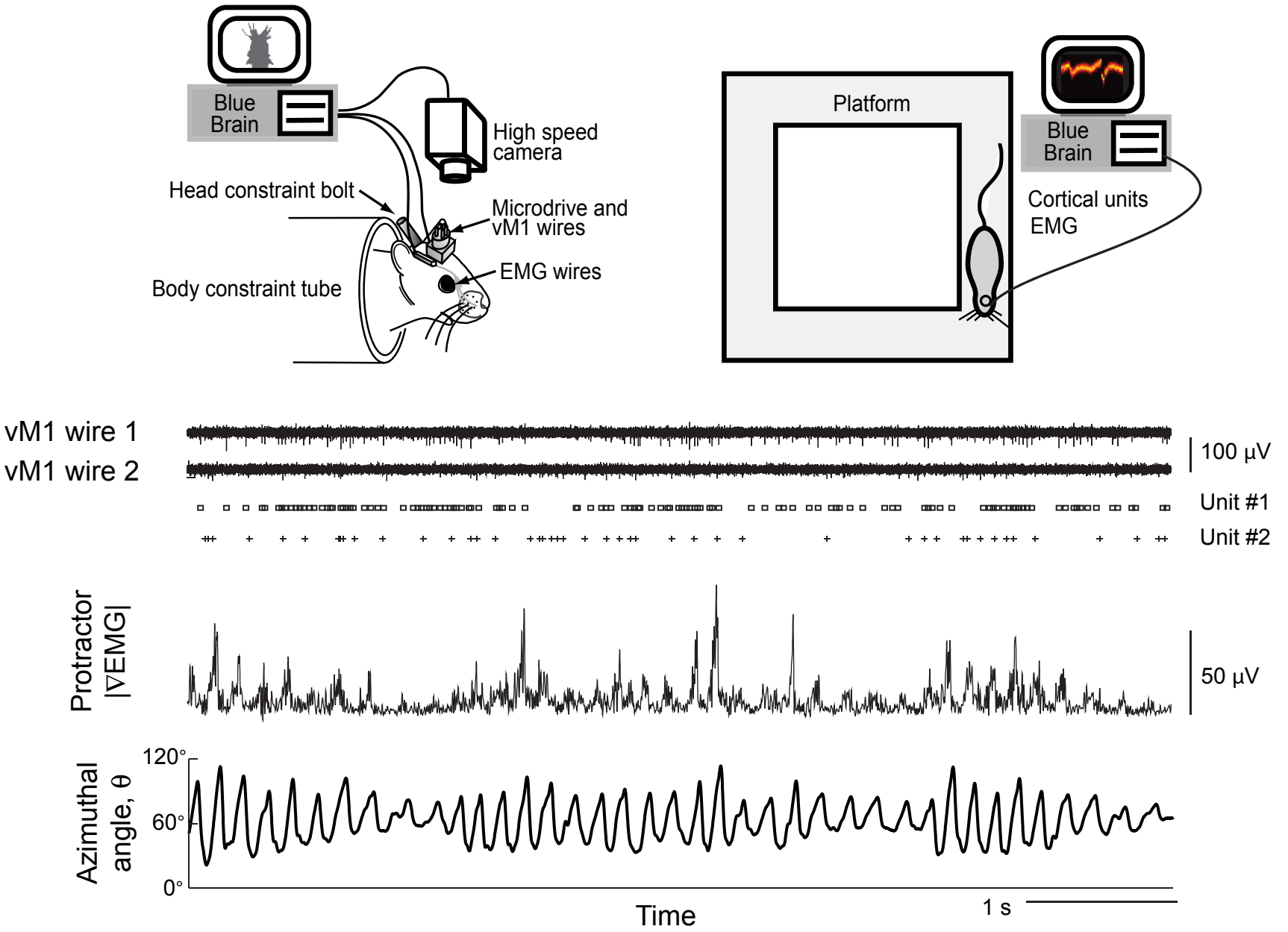


Signal flow and computing in sensorimotor loops of the vibrissa system



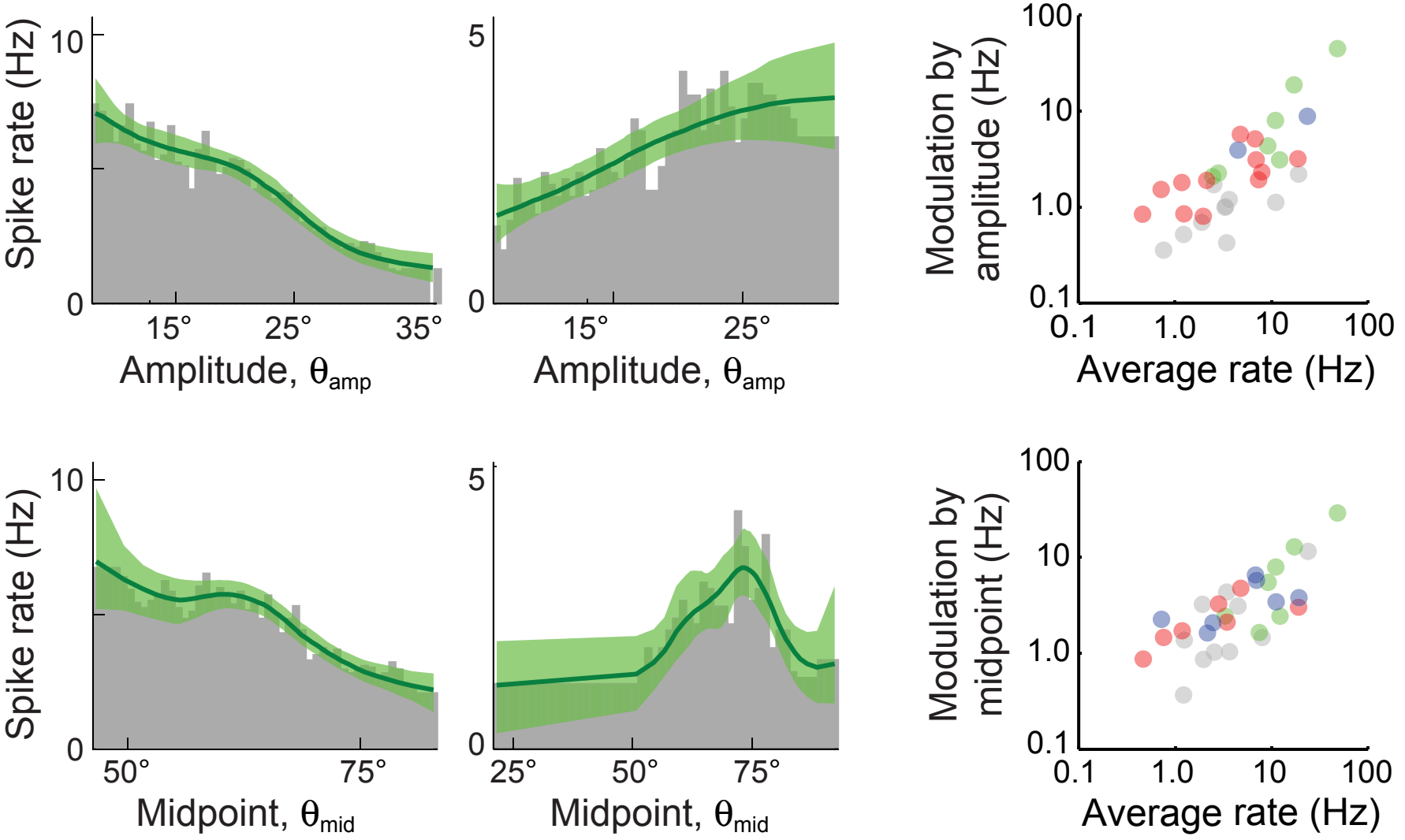
Modified from Kleinfeld & Deschenes (Neuron 2011)

Whisking and unit activity in vibrissa primary motor (vM1) cortex



Hill, Curtis, Moore & Kleinfeld (Neuron 2011)

Rodent vM1 cortex reports the slowly varying amplitude and midpoint of whisking



Hill, Curtis, Moore & Kleinfeld (Neuron 2011)

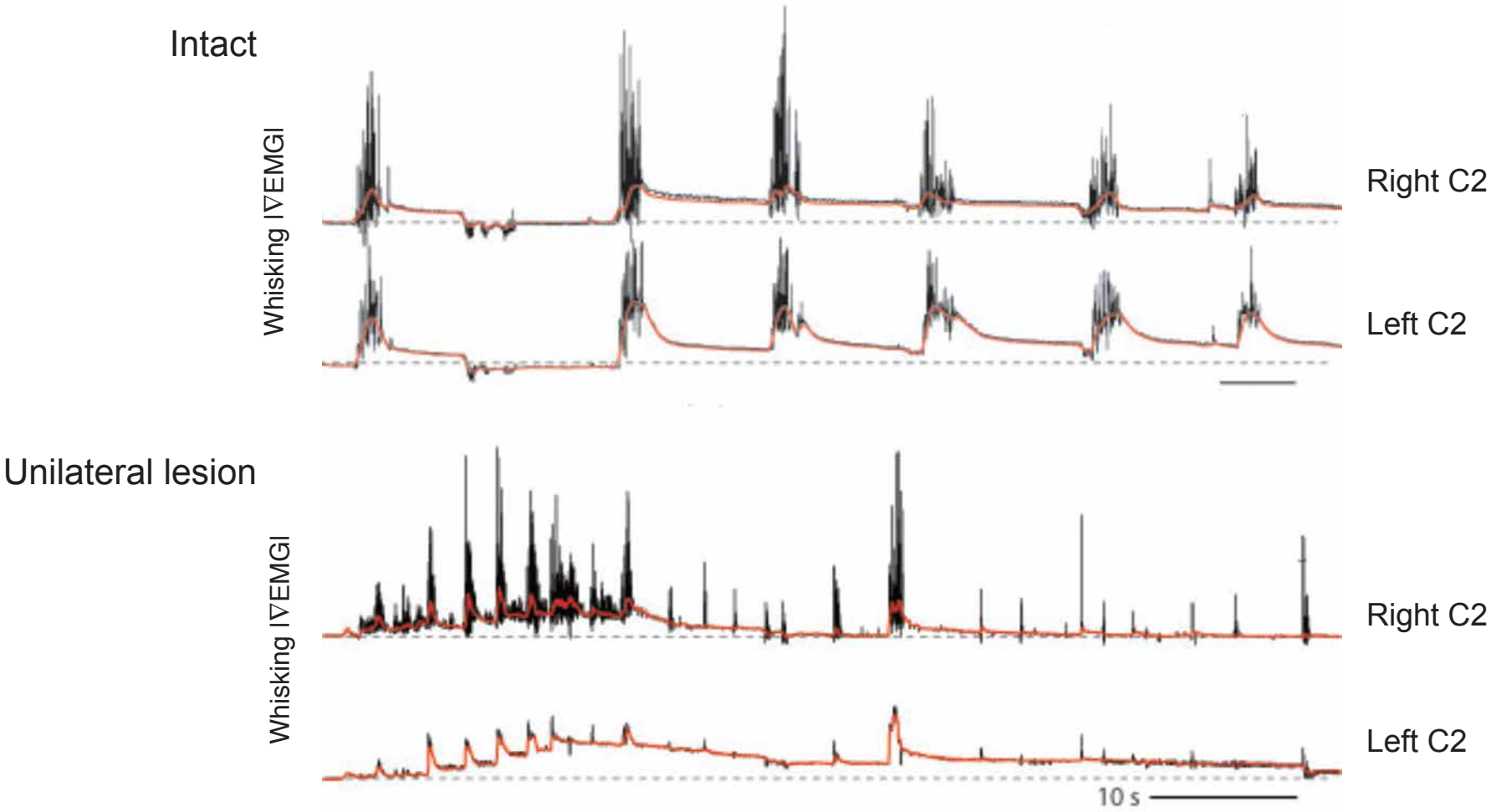
Lesson

Motor (vM1) cortex codes slowly varying envelope – amplitude and midpoint - of vibrissa position

Question

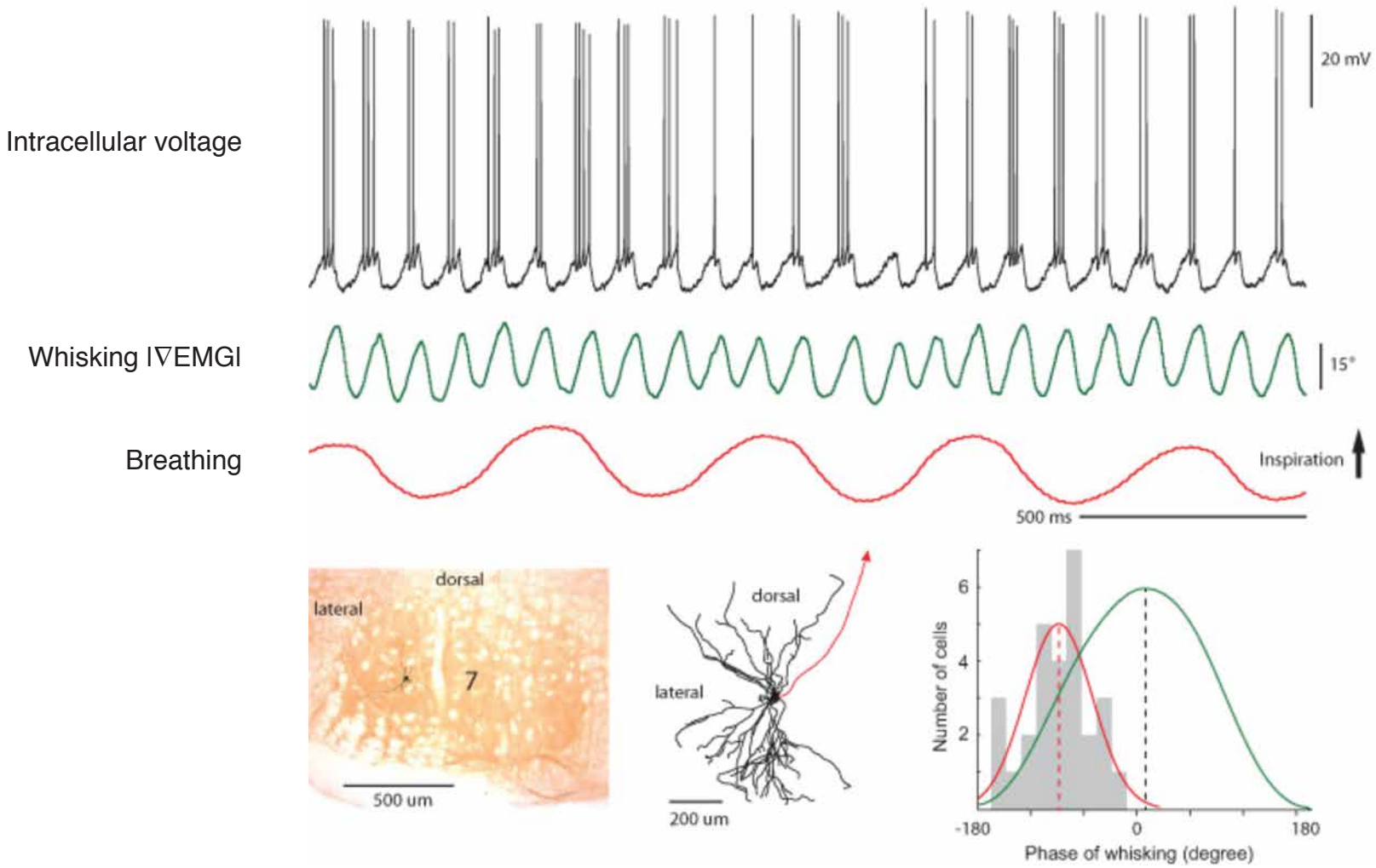
Is there a vibrissa "midpoint" or offset nucleus in the brainstem?

Lesion of the whisking oscillator (vlRt) does *not* effect the midpoint: Preliminary evidence for decoupled fast versus slow brainstem control



Deschenes, Moore & Kleinfeld (unpublished)

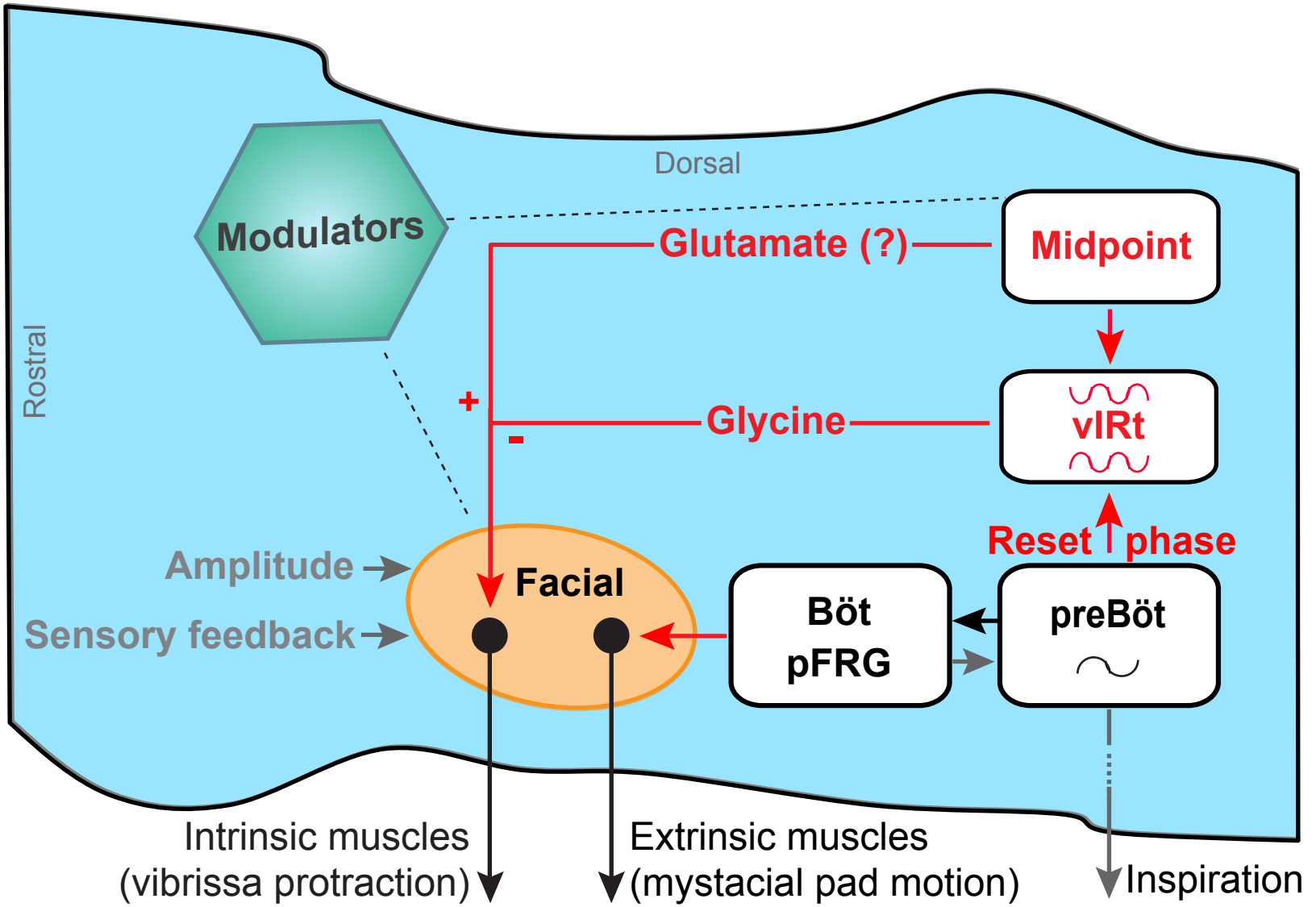
Preliminary evidence that facial motoneurons receive inhibitory (strychnine-sensitive) rhythmic drive (Deschenes, unpublished)



$$\theta(t) = \theta_{midpoint}(t) - \theta_{amplitude}(t) \times \cos \varphi(t)$$

slow slow fast

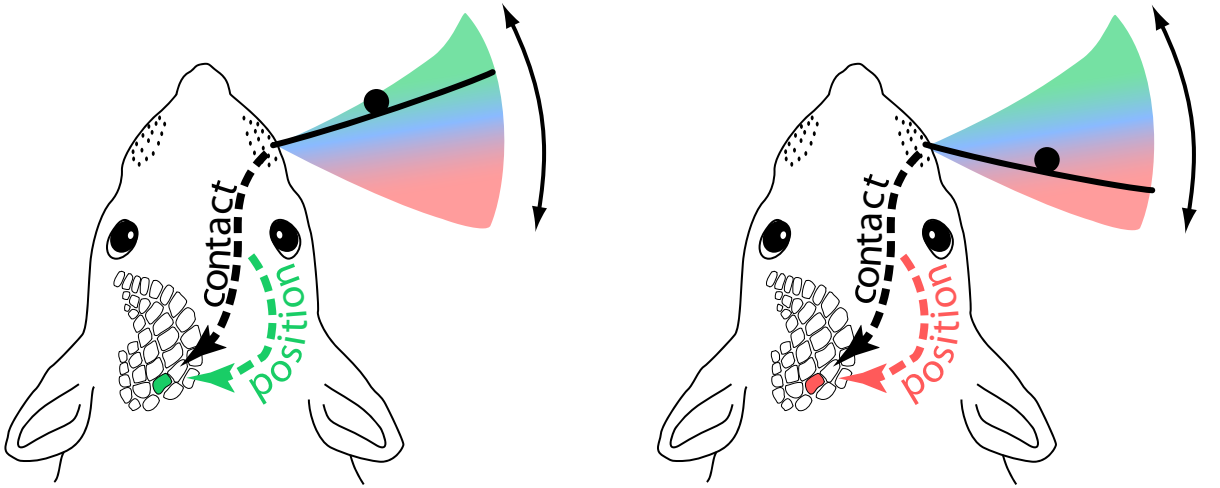
Minimal model of the brainstem generator for whisking (similarties to spinal circuits for rhythmic locomotion)



Breathing: The master clock for orofacial rhythms?

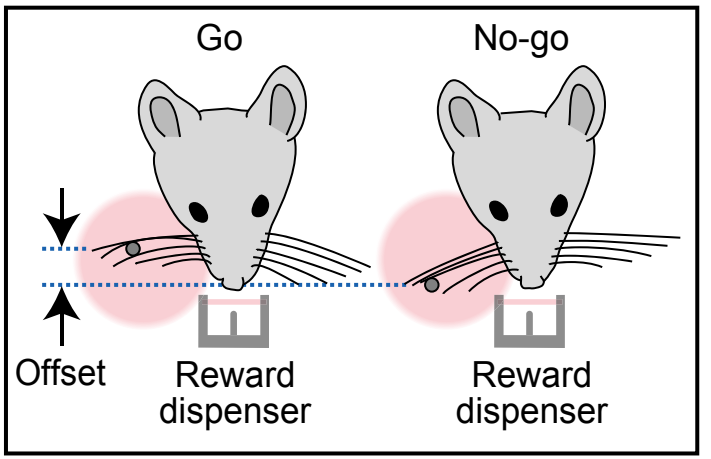
- Review of whisking
- Brainstem circuits for control of rapid vibrissa motion
  - Relation of whisking and breathing
  - Circuit basis for a whisking pattern generator
- Cortical control of slowly evolving whisking parameter
- **Brainstem modulation of the sensory stream**
  - **Breathing as the origin of phase coding for perceptual binding**

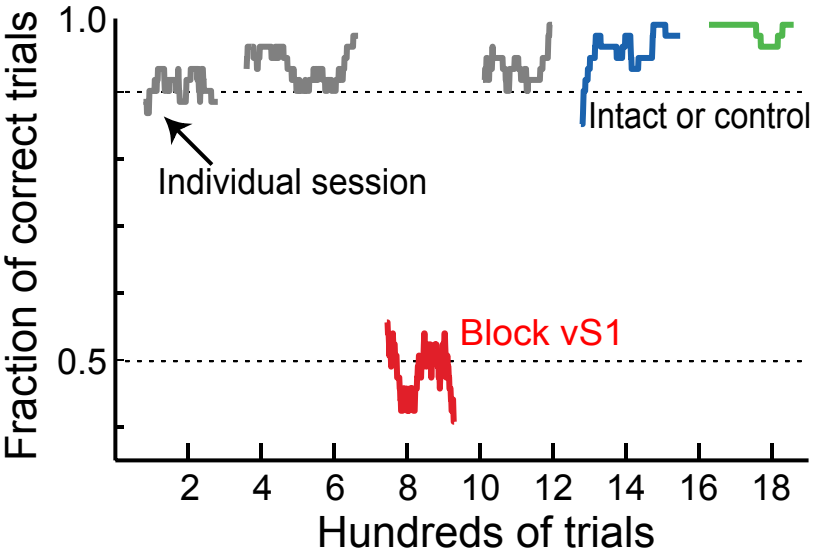
Paradigm to test if rodents code the azimuthal position of their vibrissae



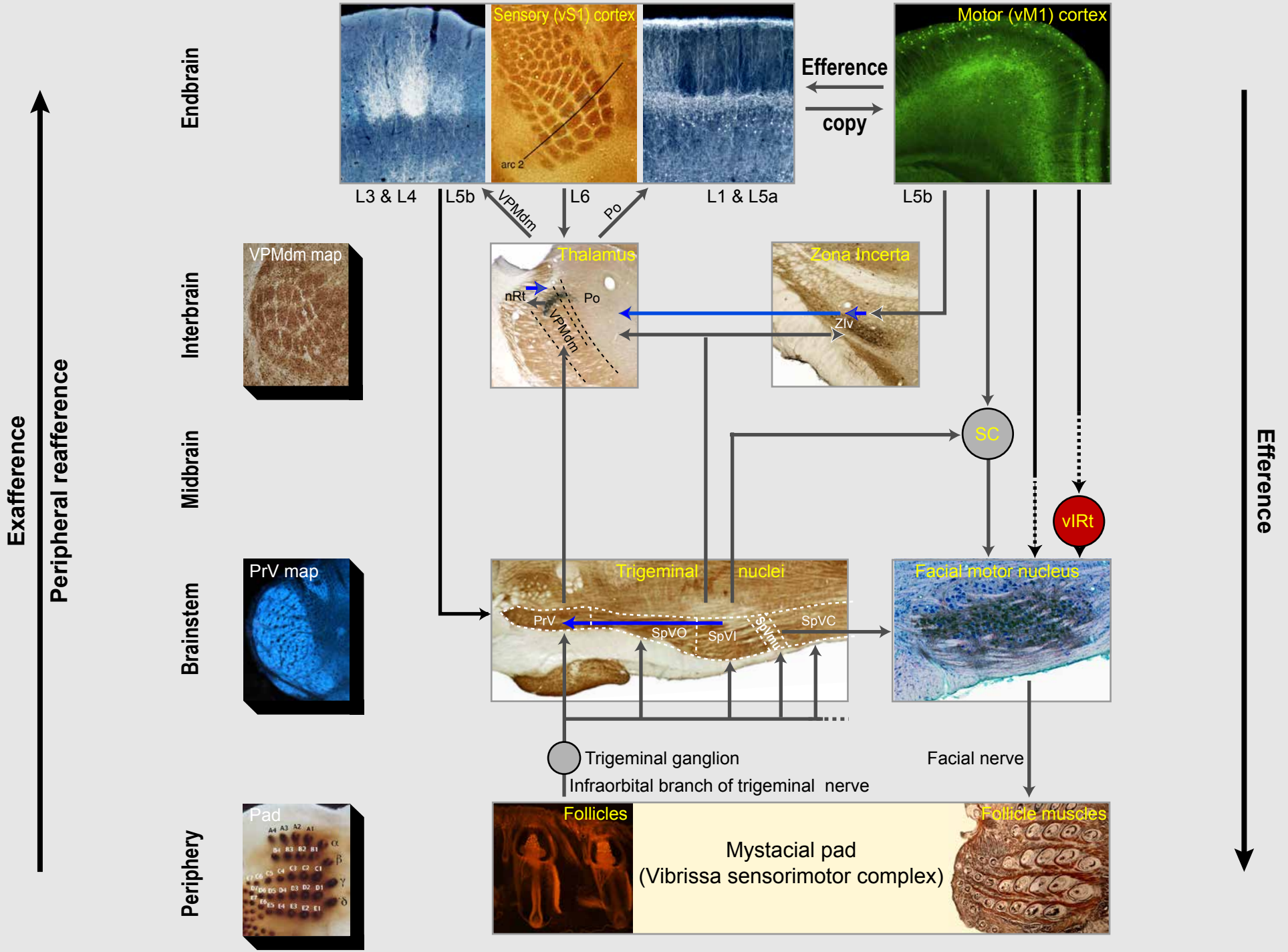
Evidence that vS1 cortex is necessary to report vibrissa position

(O'Connor, Clack, Huber, Komiyama, Myers & Svoboda, Journal of Neuroscience 2010)





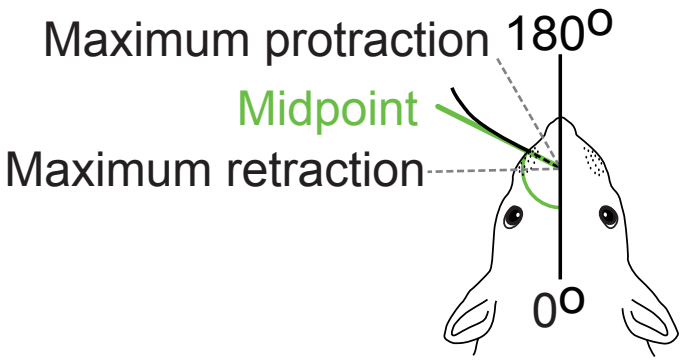
Signal flow and computing in sensorimotor loops of the vibrissa system



Modified from Kleinfeld & Deschenes (Neuron 2011)

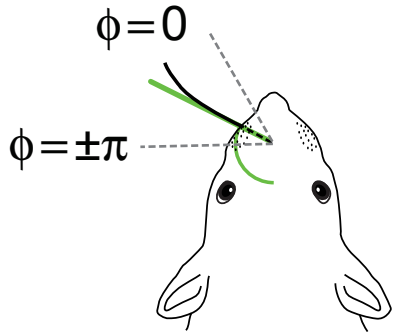
Is the vibrissa touch response conditioned solely by phase?

Touch referenced to vibrissa angle, $\theta(t)$



versus

Touch referenced to phase in whisk cycle, ϕ (t)

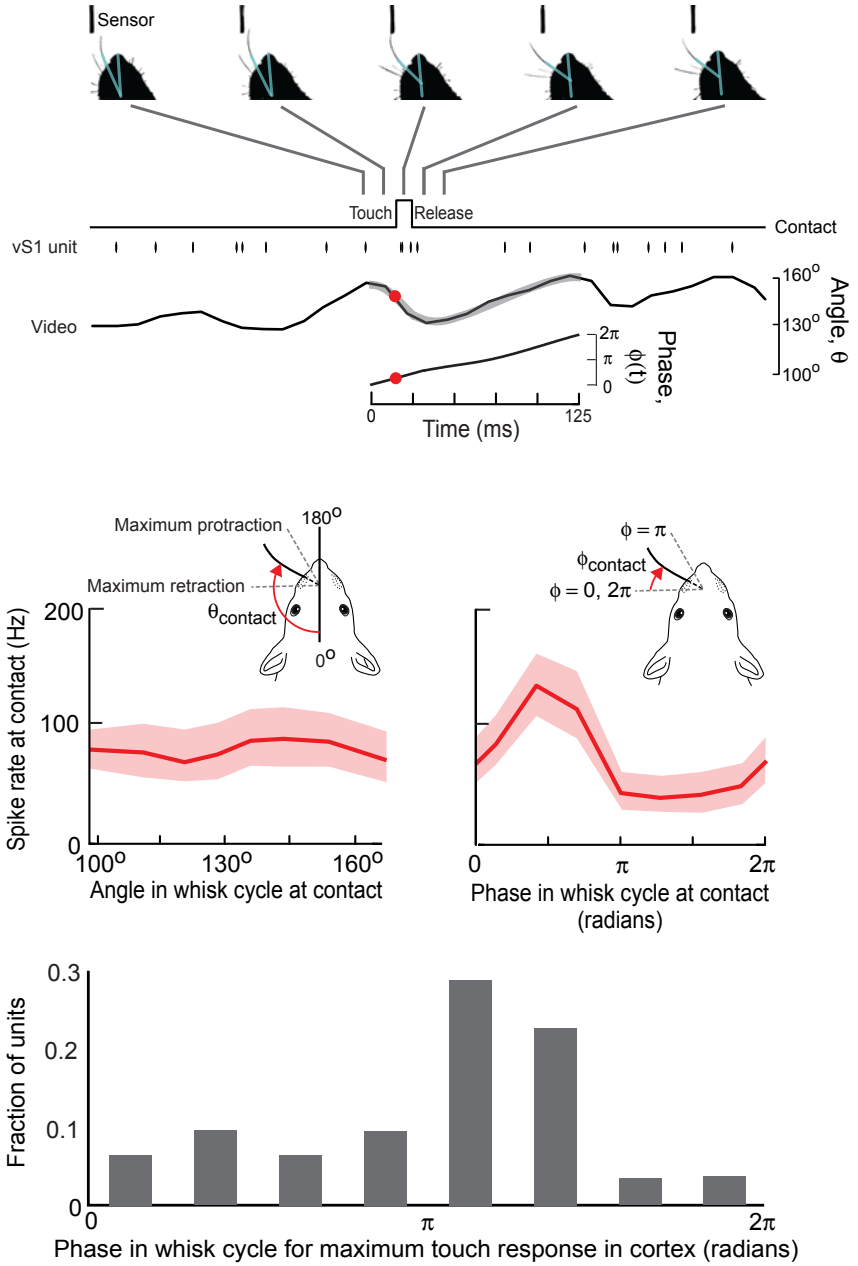


$$\theta(t) = \theta_{amplitude}(t) \cdot cos\ \phi(t) + \theta_{midpoint}(t)$$

slow fast slow

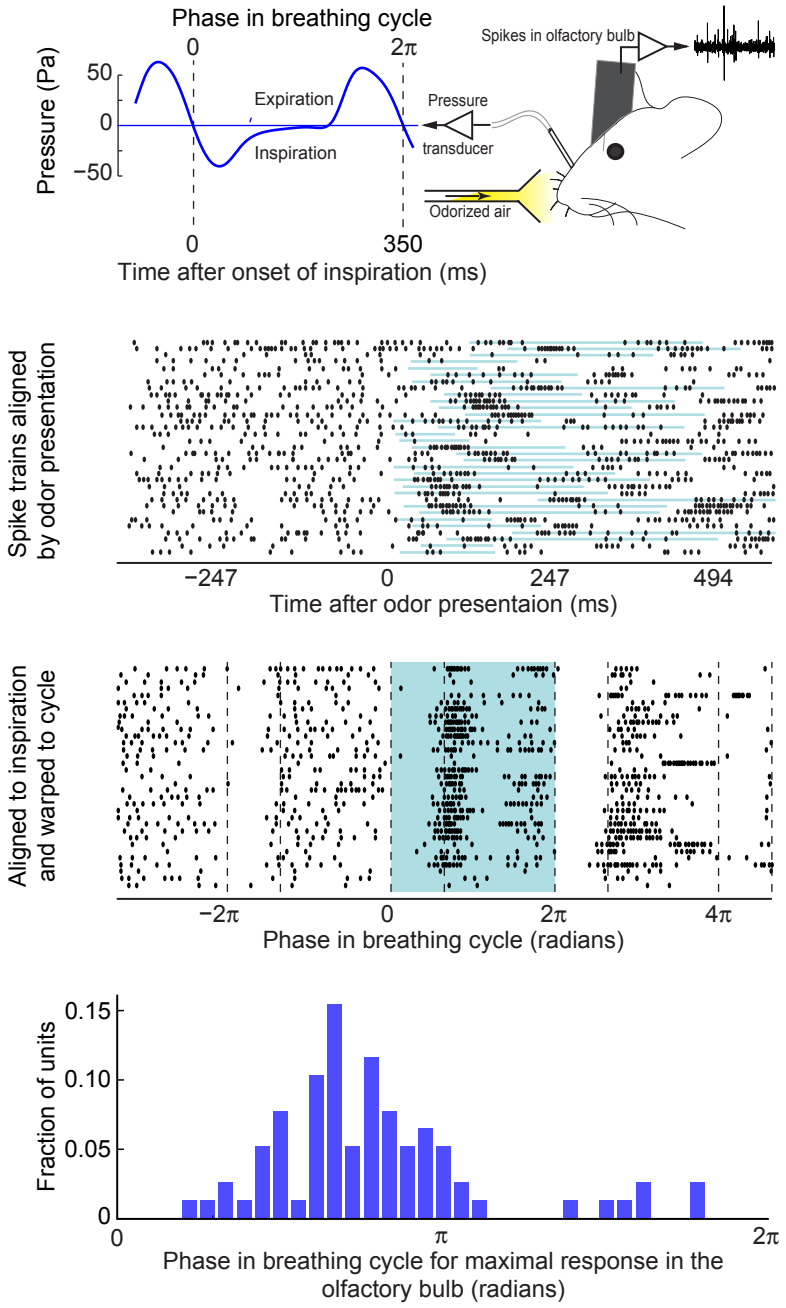
with $d\phi(t)/dt = 2\pi f_{whisk}$ for rhythmic whisking

Vibrissa S1 cortex codes azimuth of vibrissa touch by phase in the whisk (= respiratory) cycle

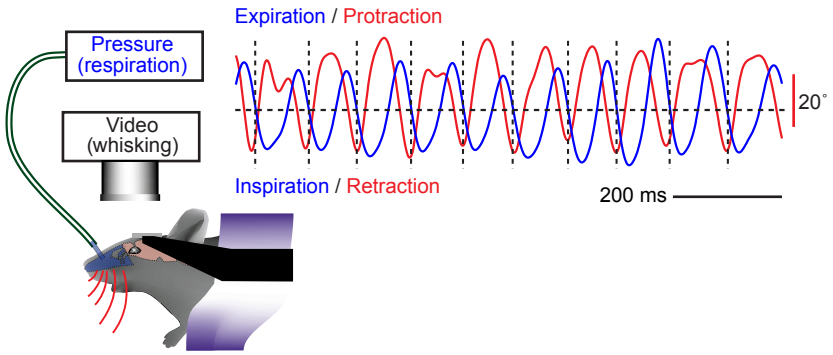


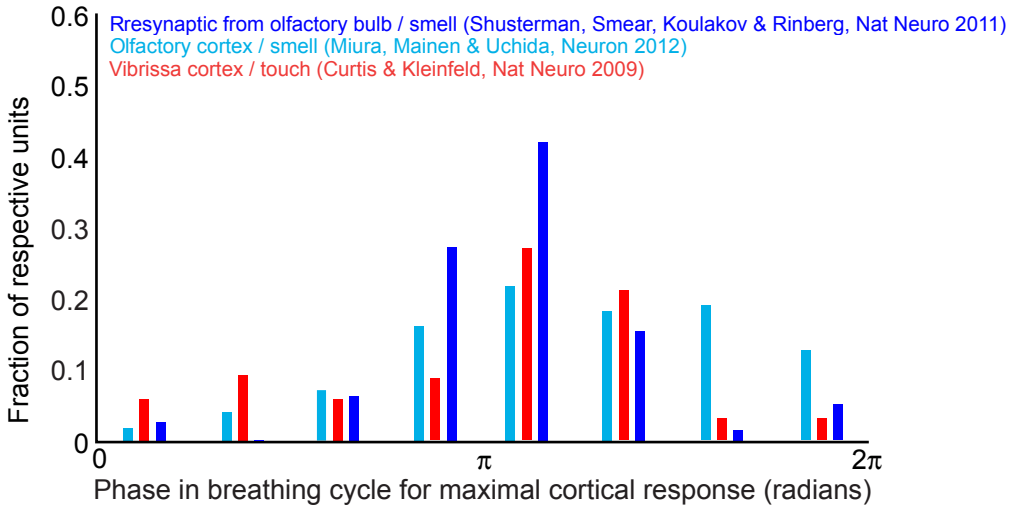
Curtis & Kleinfeld (Nature Neuroscience 2009)

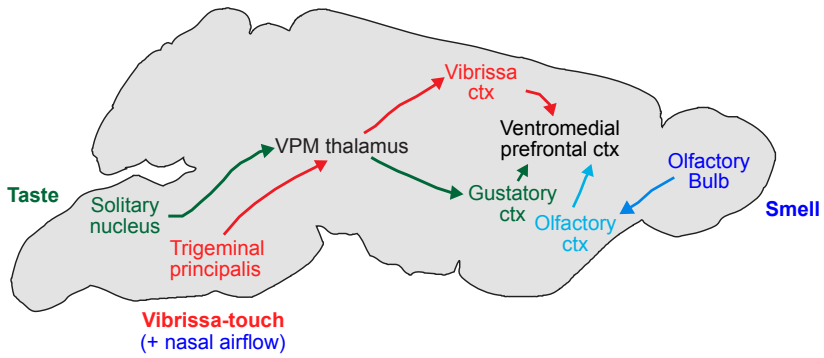
Olfactory bulb codes odor by phase in respiratory (= whisk) cycle
(Shusterman, Smear, Koulakov & Rinberg Nature Neuroscience 2011)



Coordination of sniffing and whisking and their spiking representation in sensory cortices







Kleinfeld, Deschenes, Wang & Moore (Nature Neuroscience 2014)

Lesson

A common clock for the phase sensitivity of sniffing and whisking

Conjecture

Inhalation as the *master clock* to bind percepts based on orofacial (smell, touch, and taste) inputs

Breathing: The master clock for orofacial rhythms?

Thank you for your attention!