The Central Neural Foundations of Awareness and Self-Awareness

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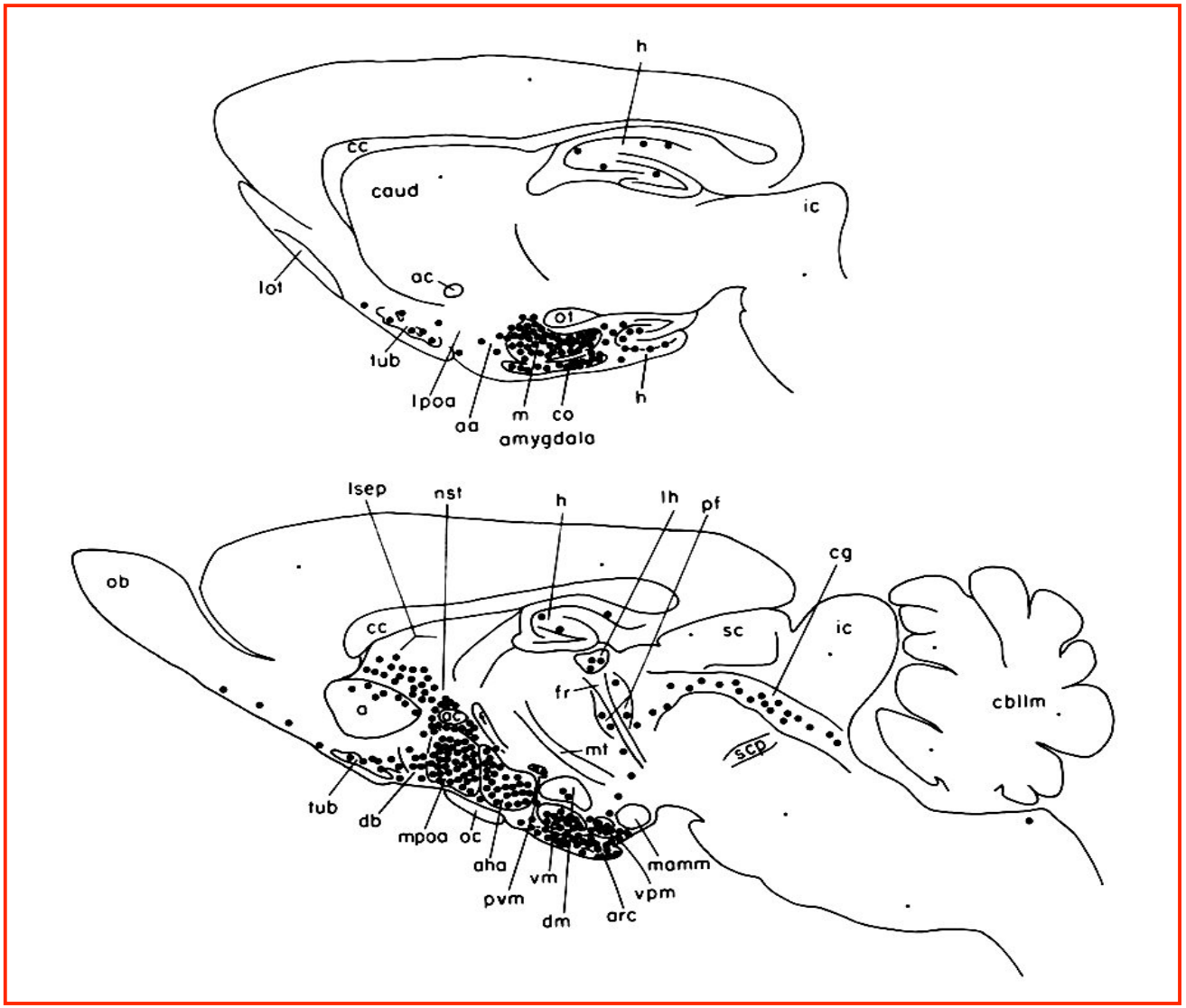
- How to analyze mechanisms for a mammalian behavior.
- CNS arousal: concepts.
- CNS arousal: mechanisms. (neural, molecular, maths)
- CNS arousal and awareness: clinical.

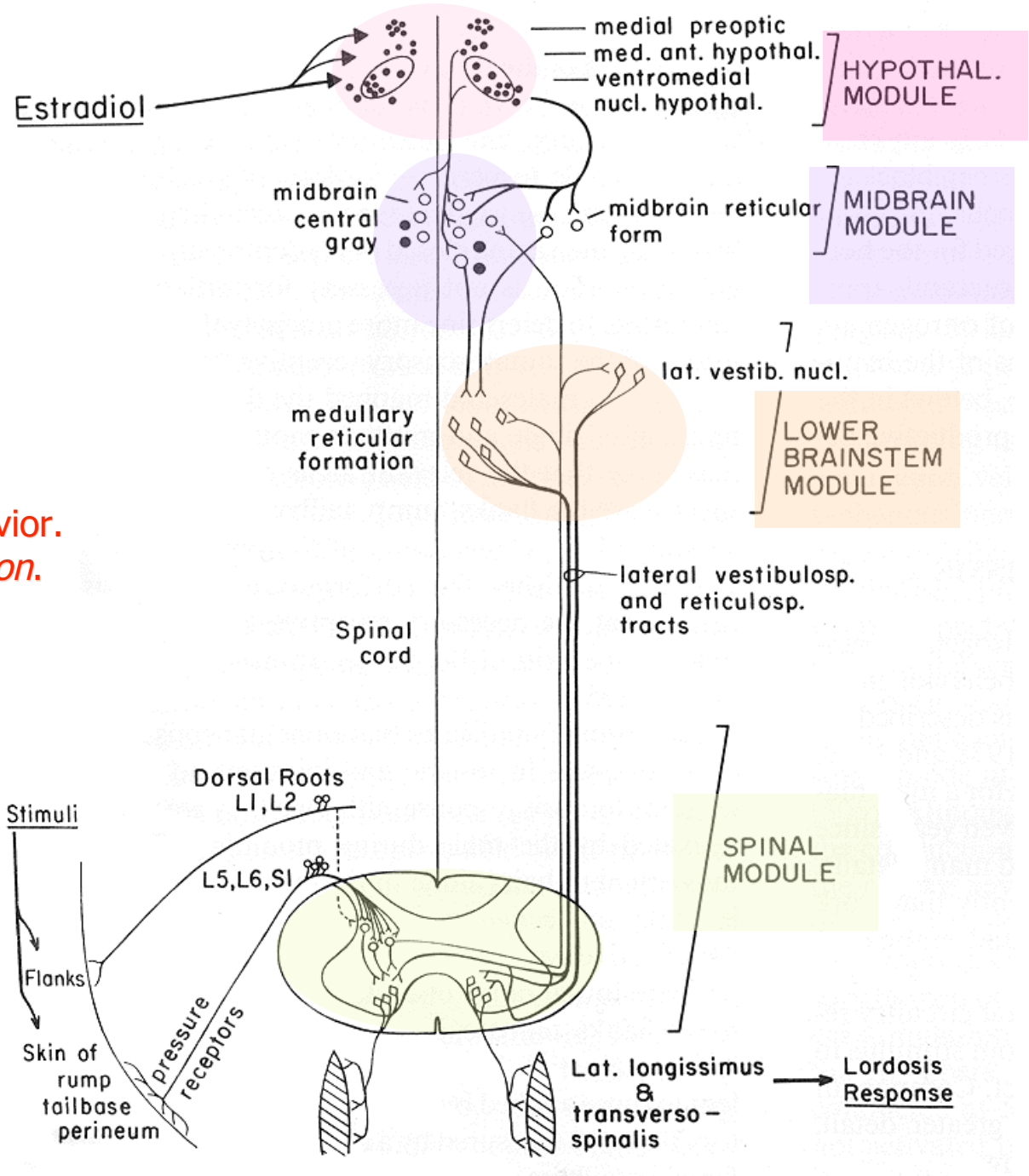
The Receptors

(Pfaff, Science 1968; J. Comp. Neurology, 1973)



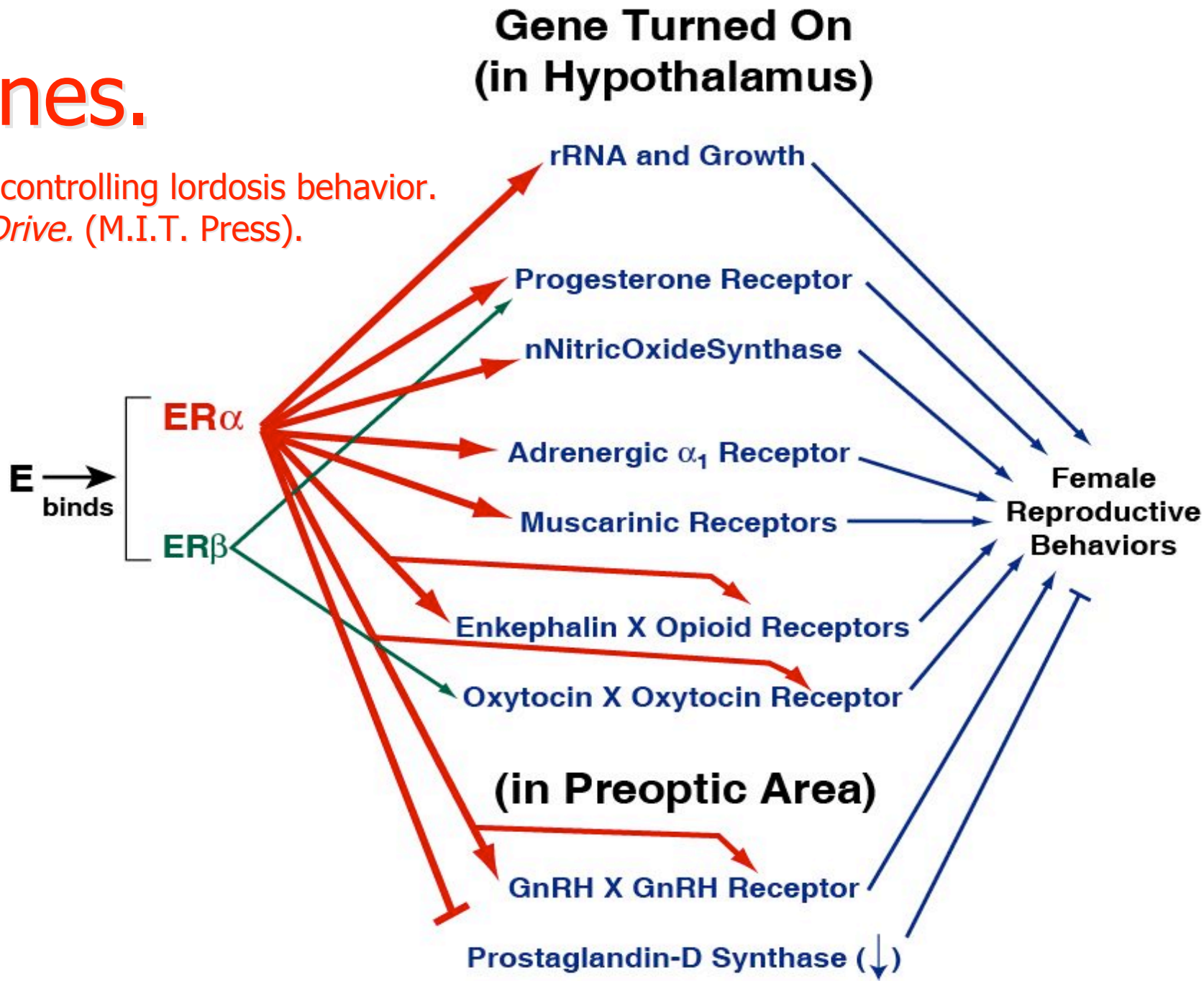
Neural circuit.

Neural circuit for lordosis behavior.
From *Estrogens & Brain Function*.
(Springer-Verlag).



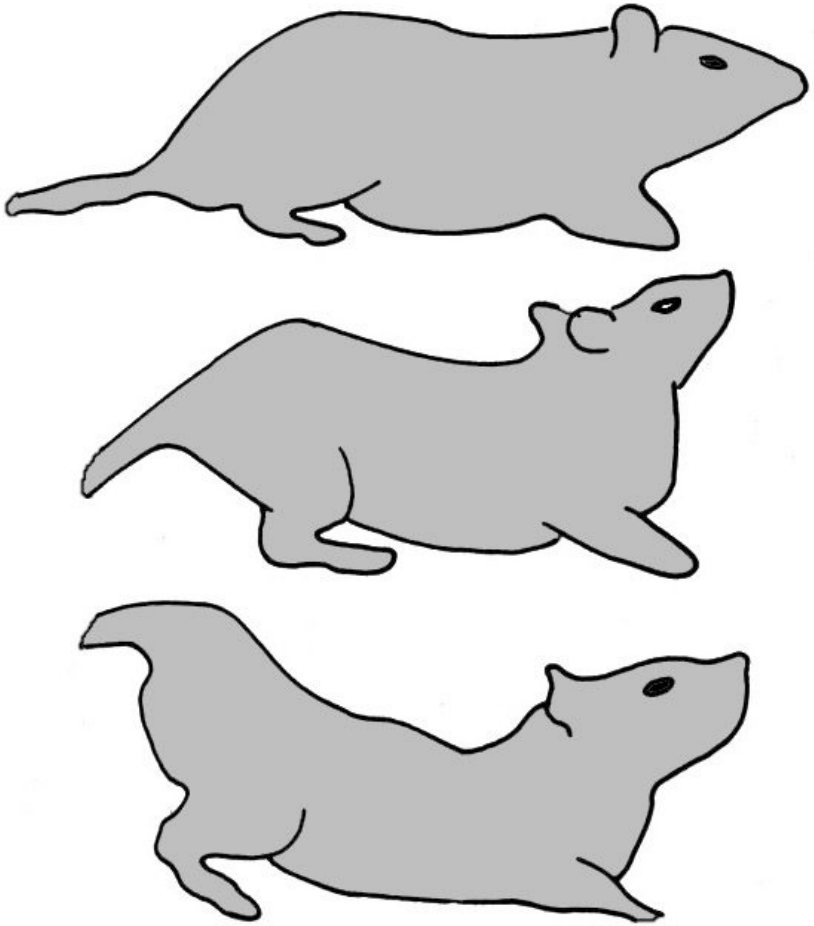
Genes.

Genes controlling lordosis behavior.
From *Drive.* (M.I.T. Press).



The Behavior

('Estrogens and Brain Function')



- Steroid hormones coordinate brain function with rest of body to ensure reproduction appropriate to environment.

- Mechanisms understood from receptor chemistry (Angstroms) through seasonality (light years).

Conclusion

- Specific biochemical reactions in specific nerve cell groups of the mammalian brain determine a biologically crucial behavior.

Question answered:

"Is it possible to explain mechanisms for any mammalian behavior?"

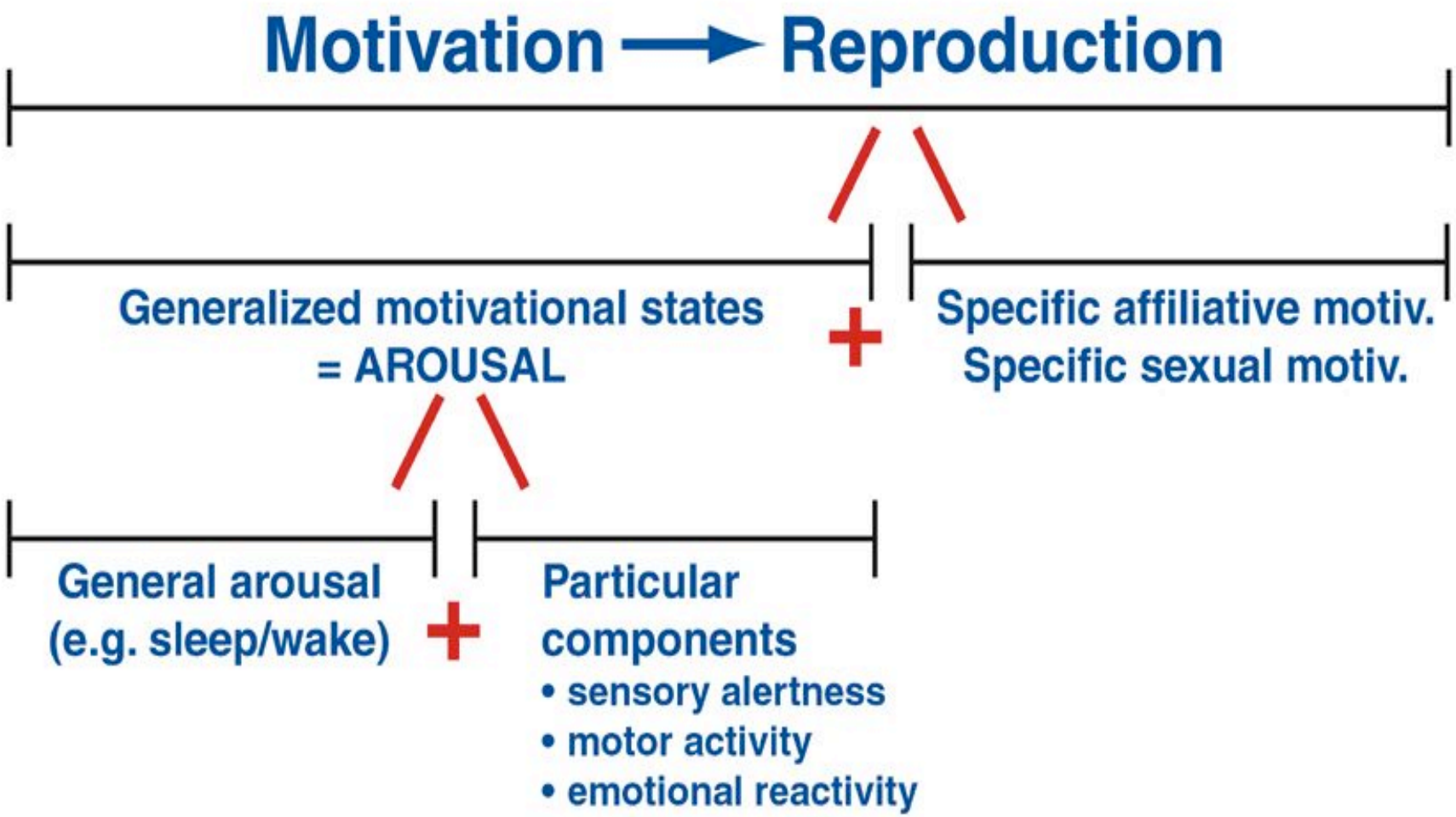
YES.

(II.) New Question:

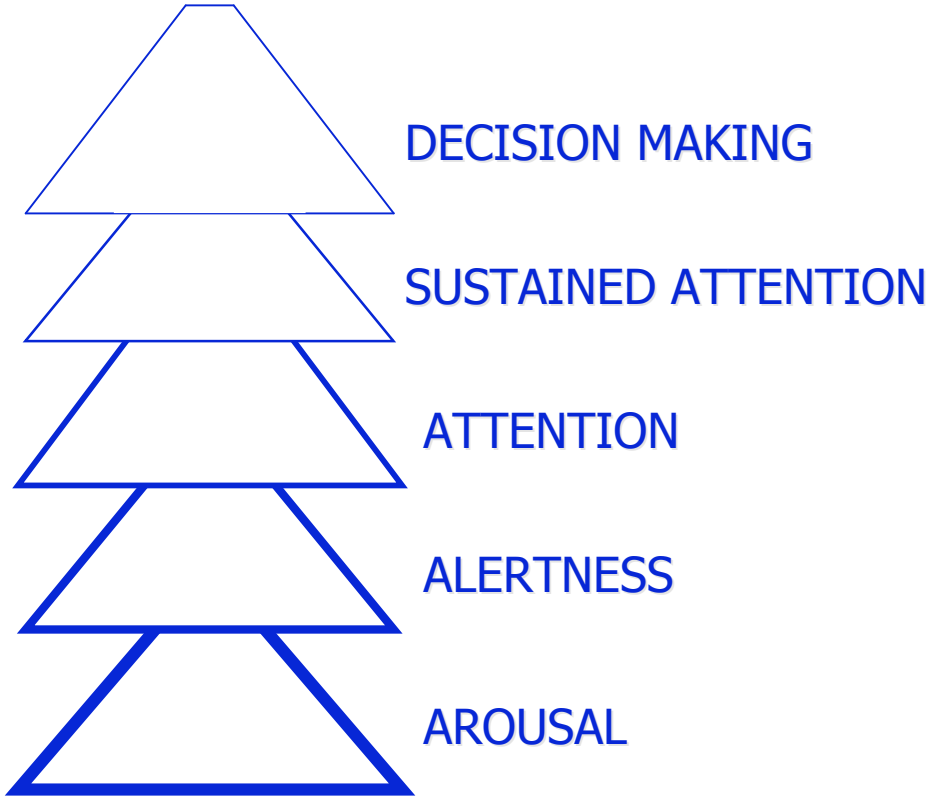
"Can we approach mechanisms for the fundamental force in the CNS, which underlies all mammalian behaviors?"

YES.

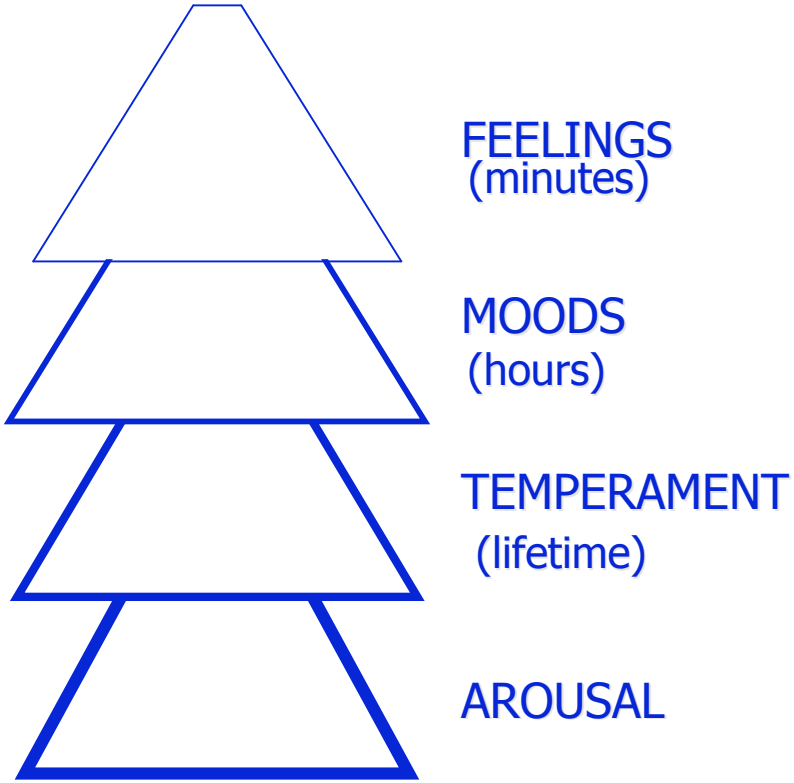
Literature Review:



COGNITIVE FUNCTION



EMOTIONAL FUNCTION



Fundamental Arousal of Brain and Behavior: Applications

- Stupor, vegetative, coma
- Aging
- Alzheimer's
- ADHD
- Autism
- Anesthesia
- Sleep Disorders
- Mood Disorders (Depression, Bipolar Disorders)
- Vigilance/Military
- Vigilance/Shift Work
- Vigilance/Dangerous Occupations
- Toxicology (e.g., Lead in water)
- Fatigue states (CFIDS, FMS, Gulf War)

Operational Definition of Arousal

A more aroused animal or human is:

i. More alert to sensory stimuli in all modalities.

ii. Emitting more voluntary motor activity.

iii. More reactive emotionally.

$$A = F_g(A_g) \bullet (F_1(A_{s_1}) + F_2(A_{s_2}) \ldots + \ldots F_{s_n}(A_{s_n}))$$

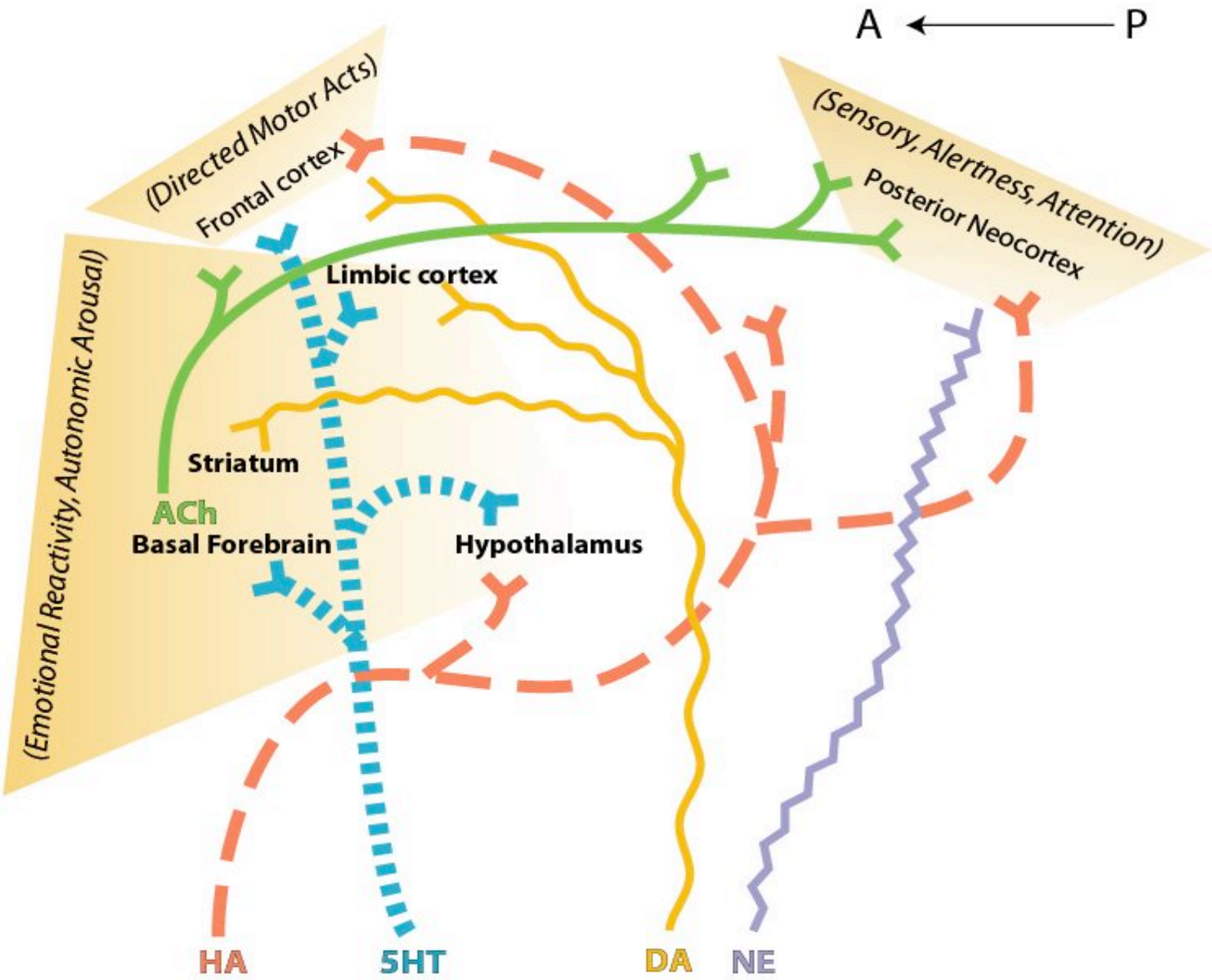
Where A is the state of arousal of the CNS at any moment.

Ag= generalized arousal.

As_n, a specific form of arousal.

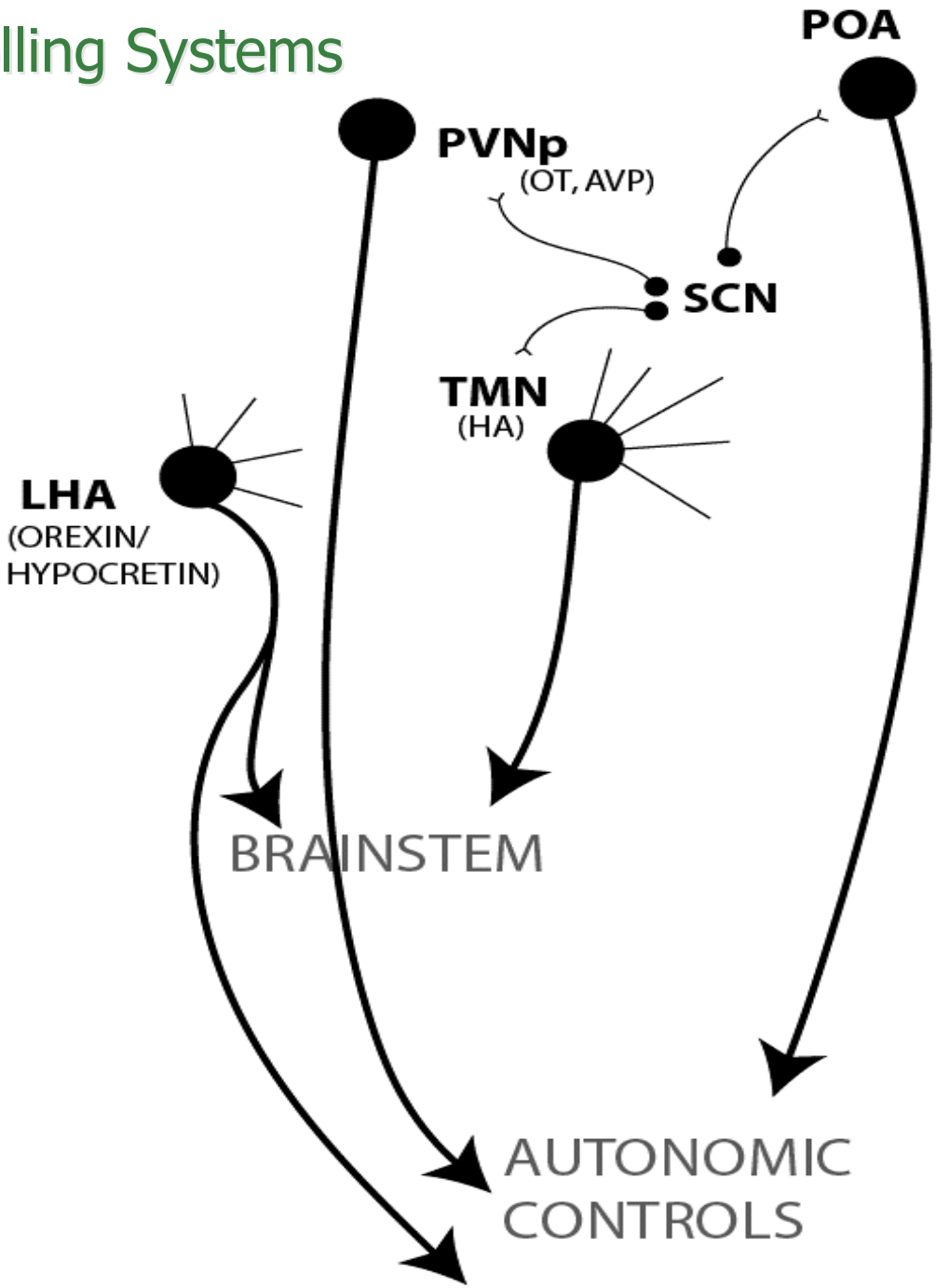
III. CNS arousal mechanisms

- Neuroanatomical
- Neurophysiological
- Functional genomics
- Information theory



Ascending Activating Systems

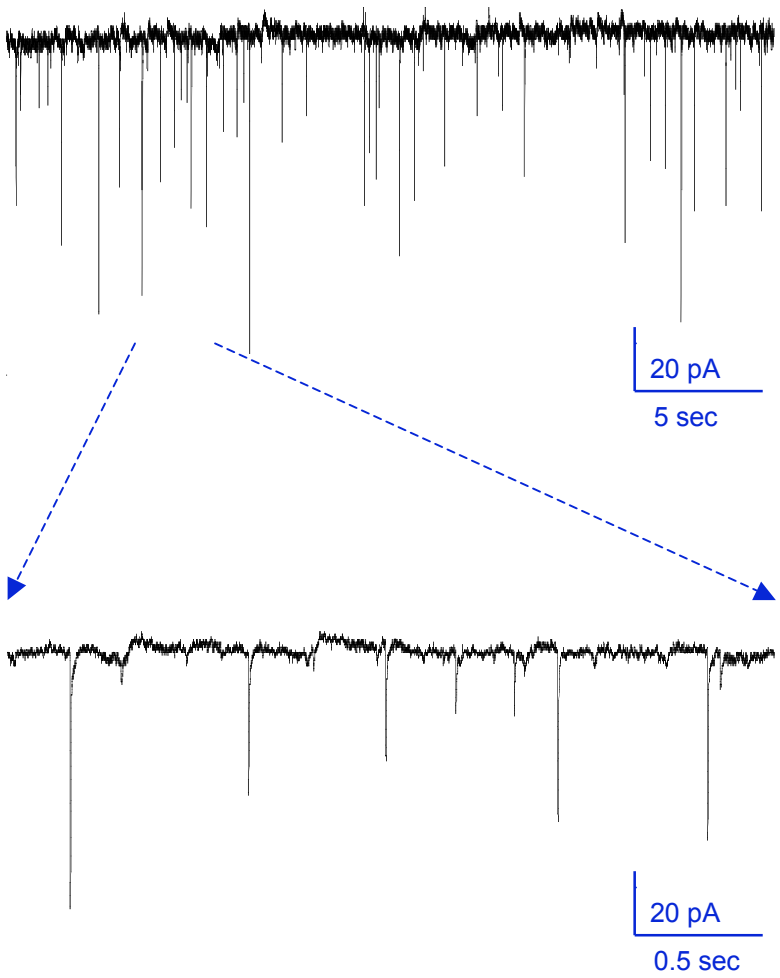
Descending Arousal-controlling Systems



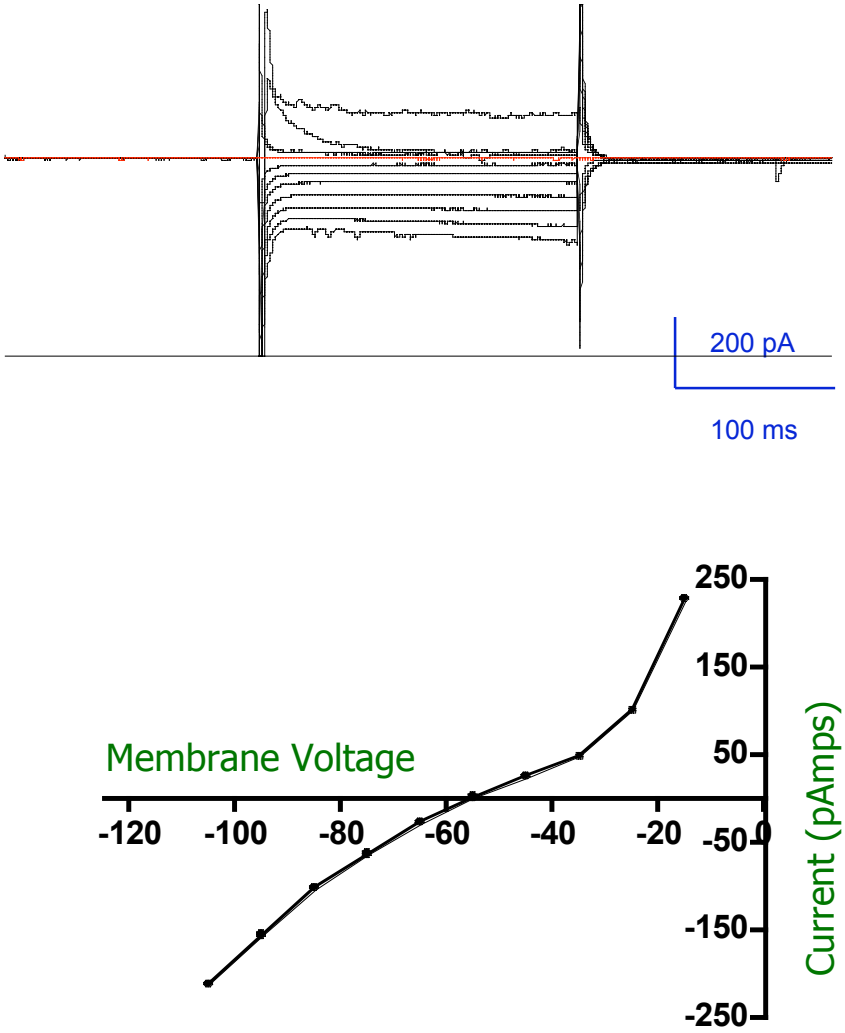
Patch clamp recordings from 'master cells' for arousal in mouse medullary reticular formation: Purposes

- Discover cellular properties that produce their causation of arousal, even panic.
  - Thresholds, excitability, activation kinetics, inactivation kinetics, positive feedback?
- Discover transmitters and peptides they respond to
  - Norepinephrine, histamine, glutamate

Spontaneous synaptic activity in a large medullary reticular neuron.

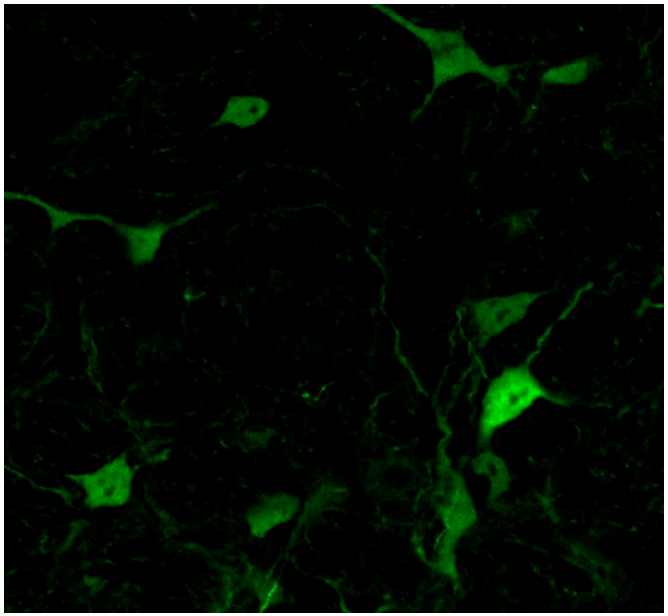


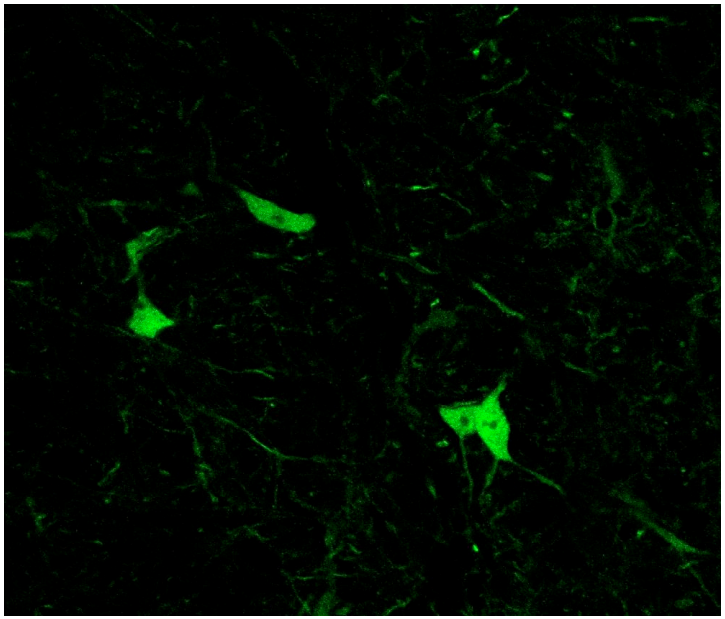
Generating a Current/Voltage curve from this neuron.



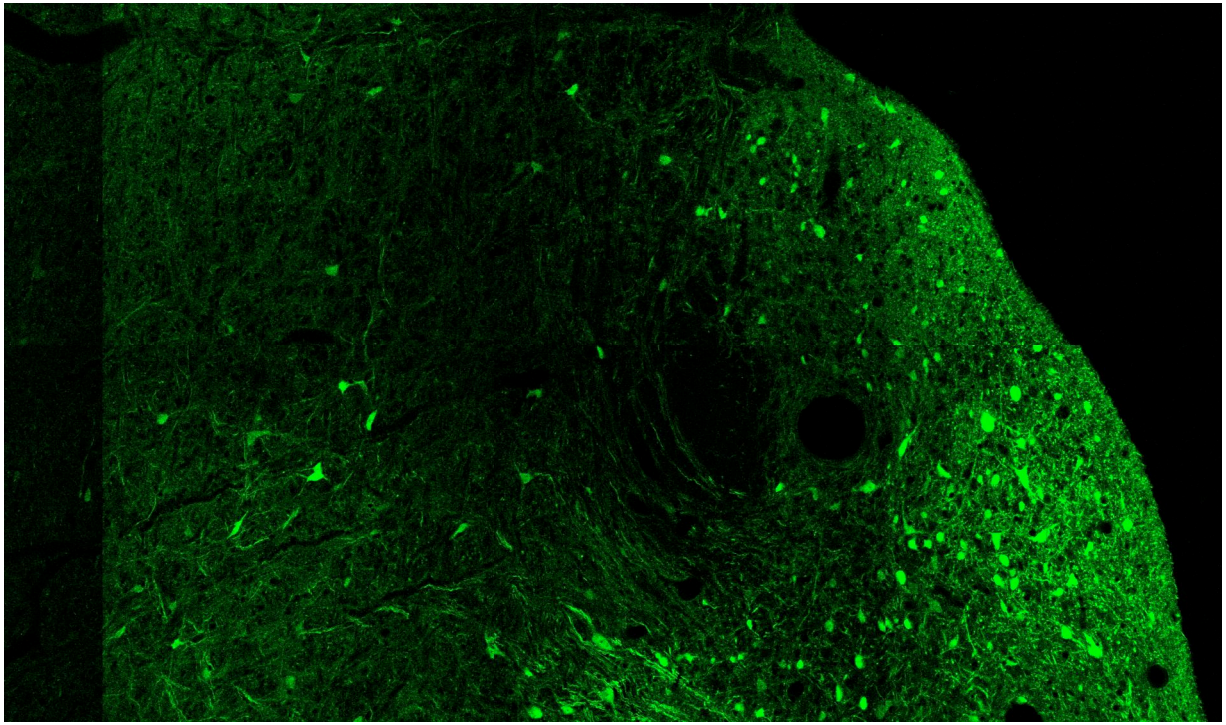
Jin Zhou, Anna Lee, Don Pfaff

“Master cells” for arousal express from the Connexin-36 promoter





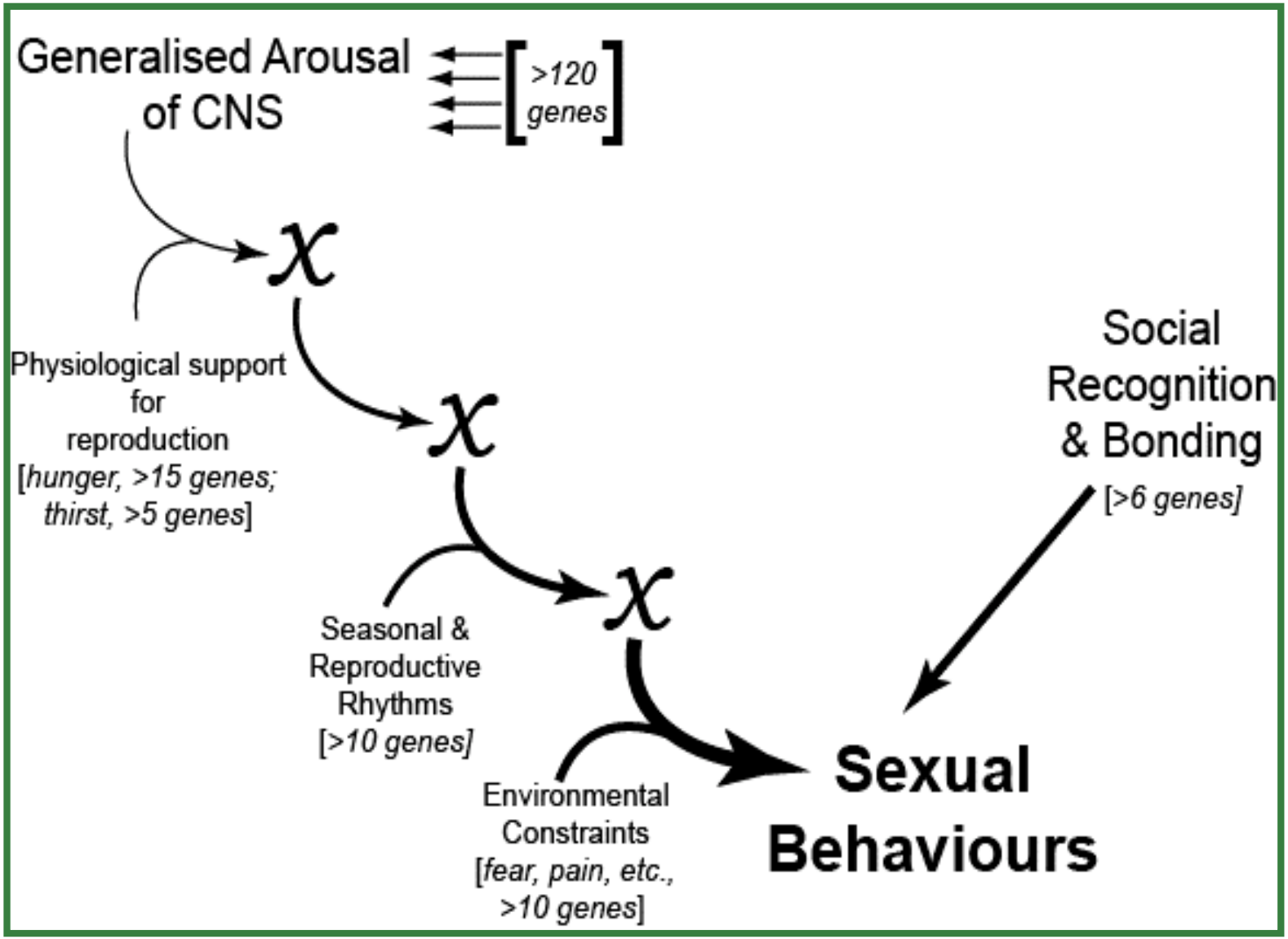
Thus, their activity may be able to be amplified rapidly.



Proof of Principle: Genomics of CNS Arousal (***A***) is Experimentally Tractable

3 Genes	3 Methods in Mouse CNS Functional Genomics	3 Results using our ***A*** assay
ER, Nuclear receptor	Null Mutation	ER α but not ERβ → ***A*** ↑
Histamine Receptor, Type 1	Mol. Pharmacology	HA through H1 → ***A*** ↑
PGDS, Enzyme	Anti-sense Oligos	PGD in POA → ***A*** ↓

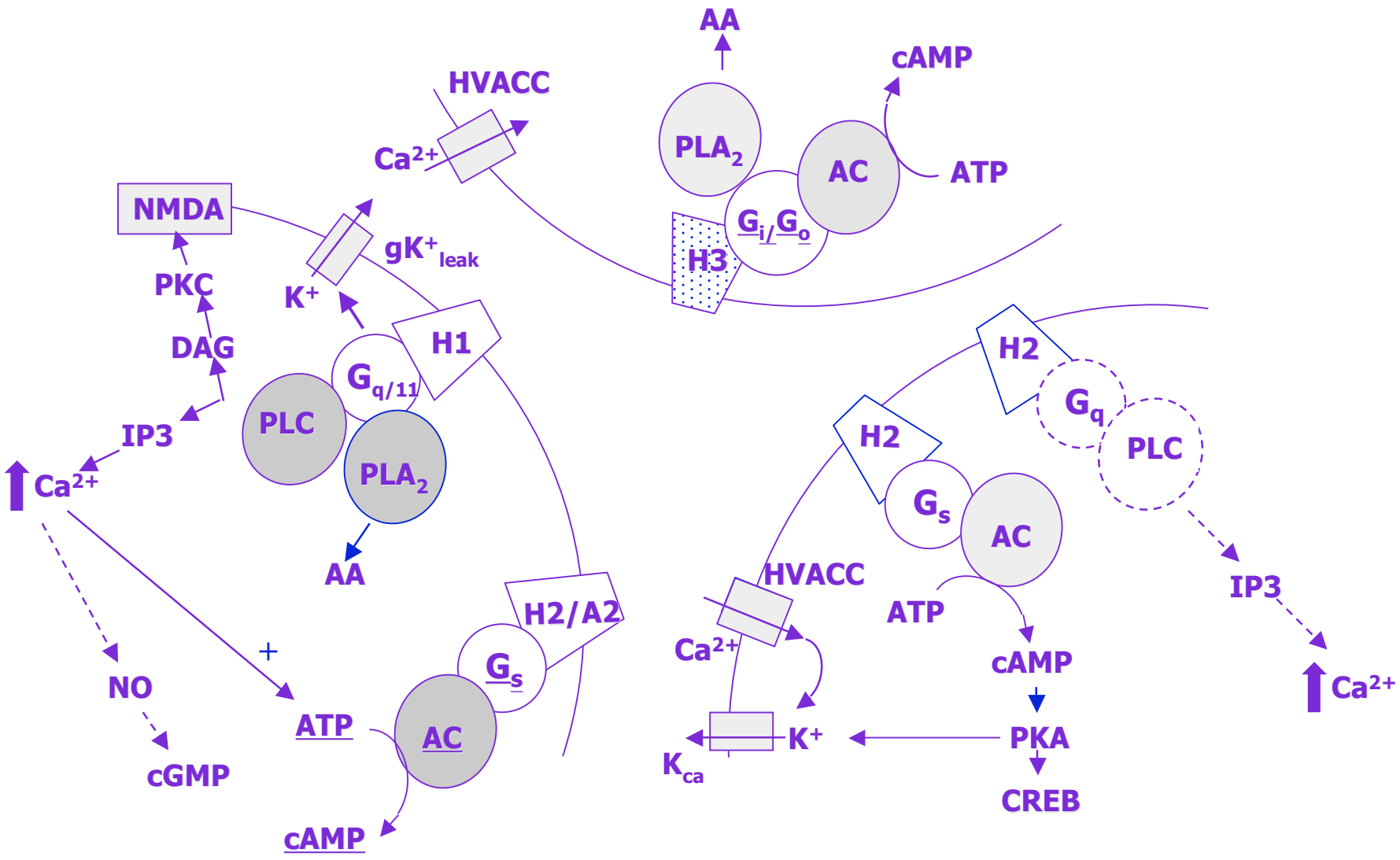
Scheme of gene/environment interactions from CNS arousal to sexual behaviour.



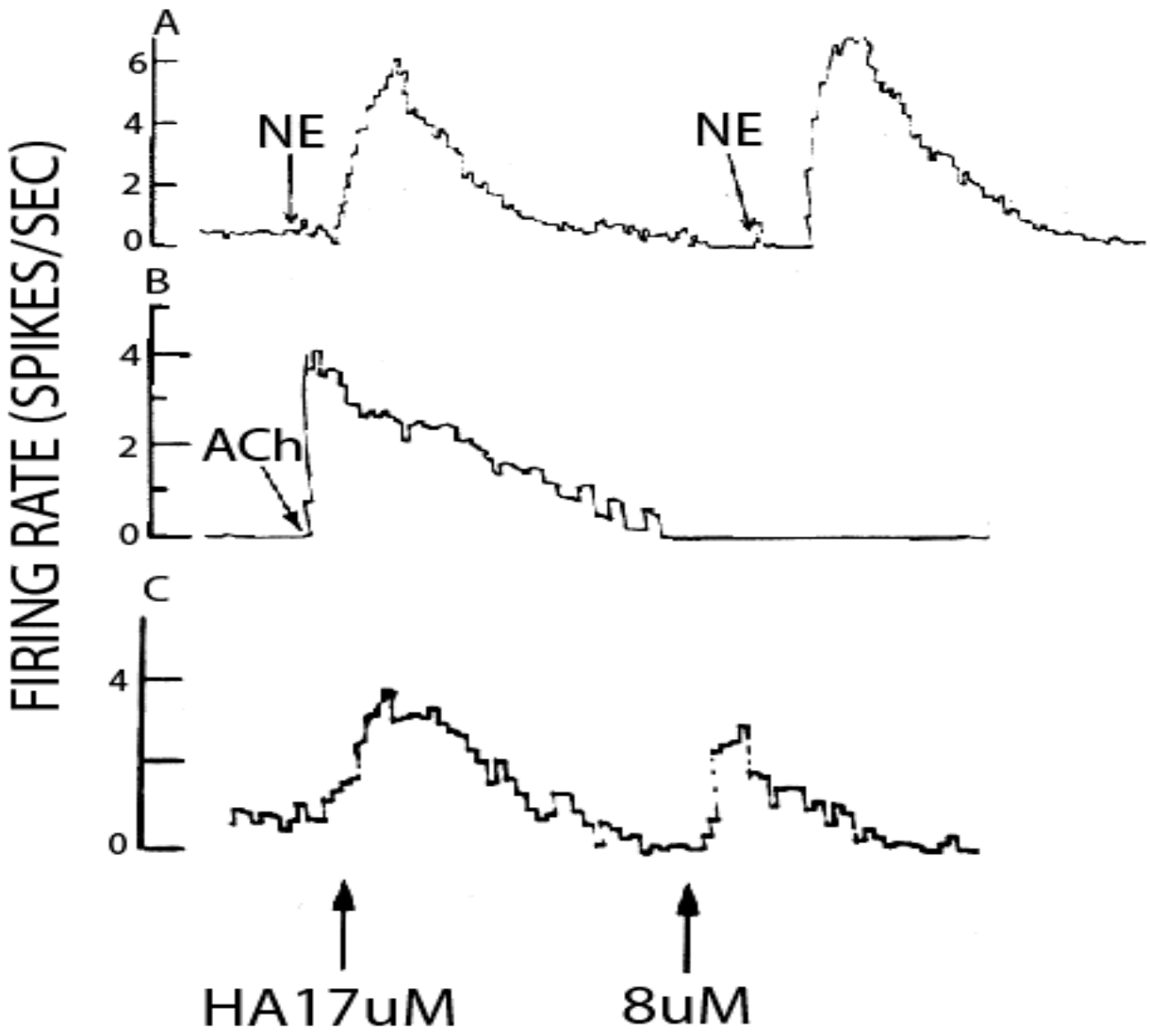
How do generalized arousal mechanisms influence particular arousal states, thus to facilitate specific behaviors?

- Current work = patch clamping on hypothalamic neurons controlling sexual arousal:
    - HA increases
    - μ opioid agonist decreases

Histamine Receptor Signal Transduction Pathways



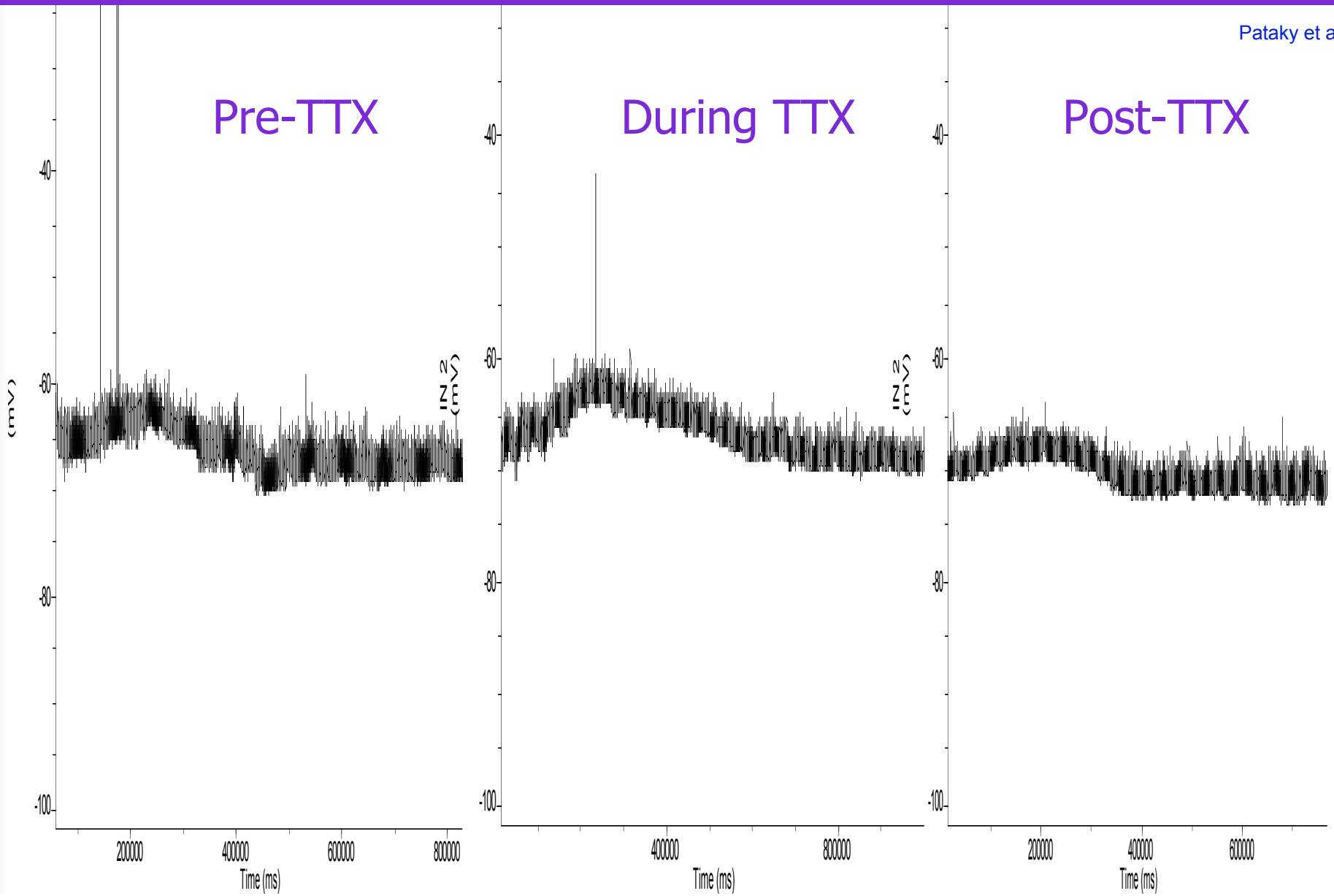
Generalized Arousal Transmitters on VMN Neurons



Lee-Ming Kow et al

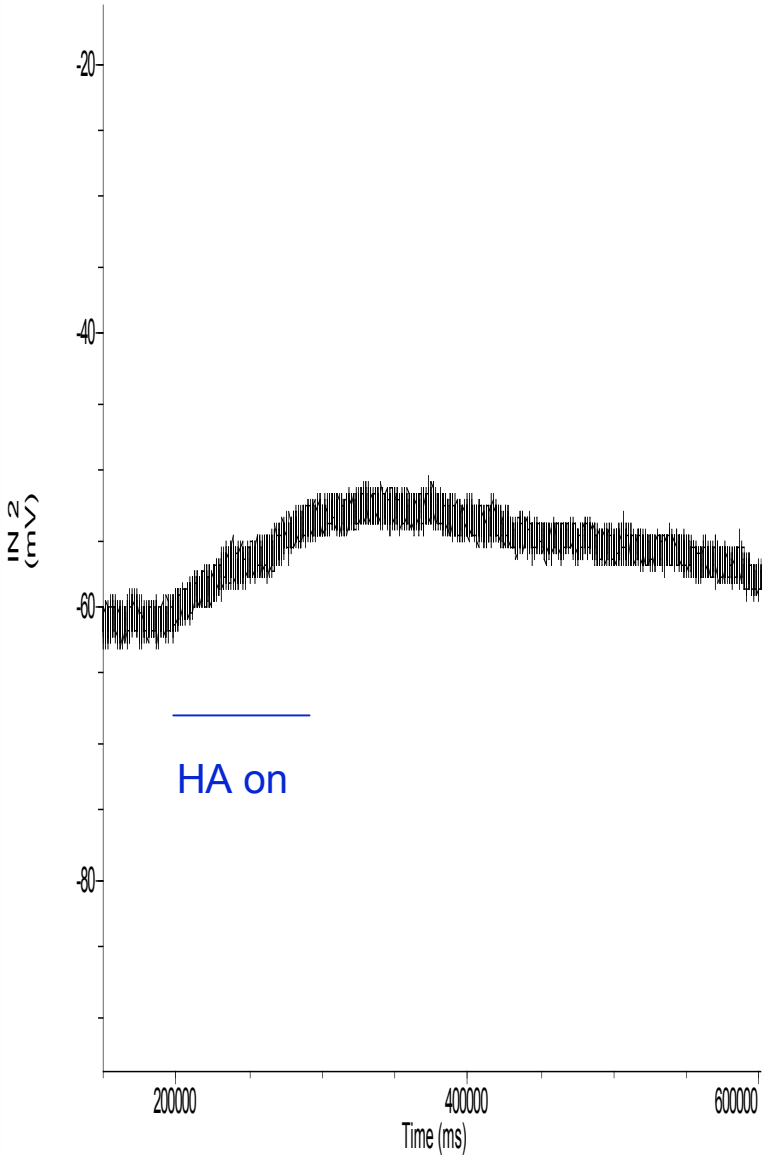
Sodium channel blocker, TTX, had no effect on histamine-induced depolarization

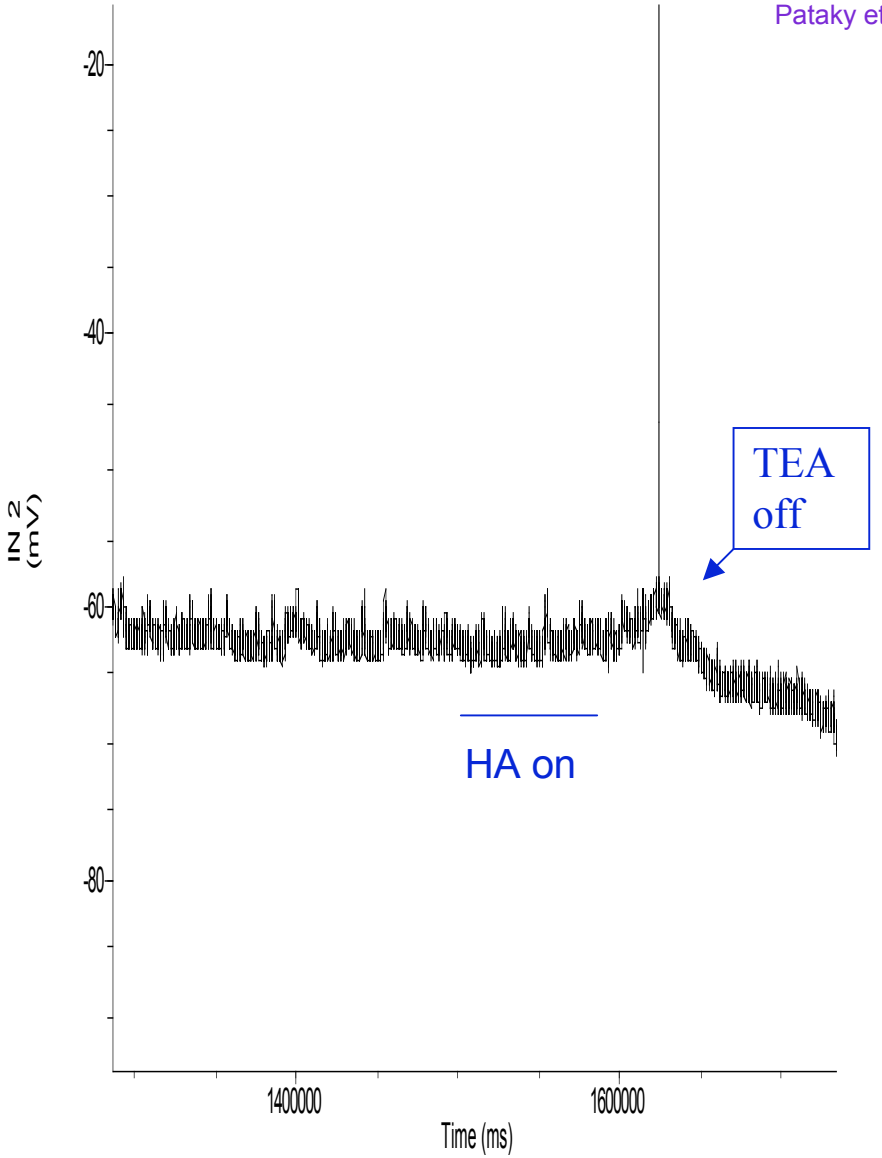
Pataky et al.



Histamine depolarization was abolished by potassium channel blocker TEA

Pataky et al.





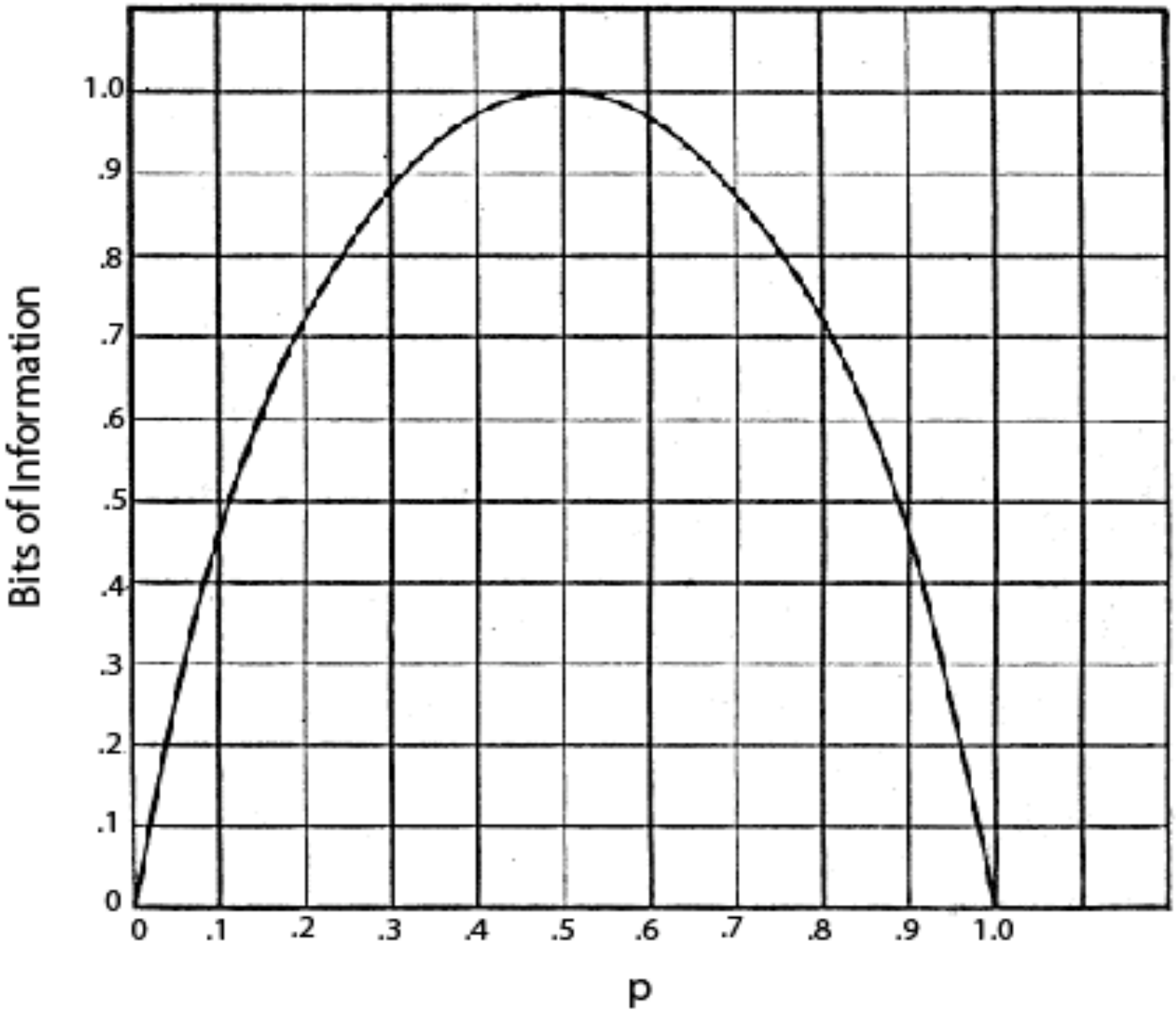
- Thus, HA produced in TMN hypothalamic neurons acts through H1 receptors and conventional signal transduction pathways to reduce potassium currents in VMN hypothalamic neurons. The consequences are increased sex behavior and reduced aggressive behavior.

Idea: Information theory maths shed light on CNS arousal mechanisms

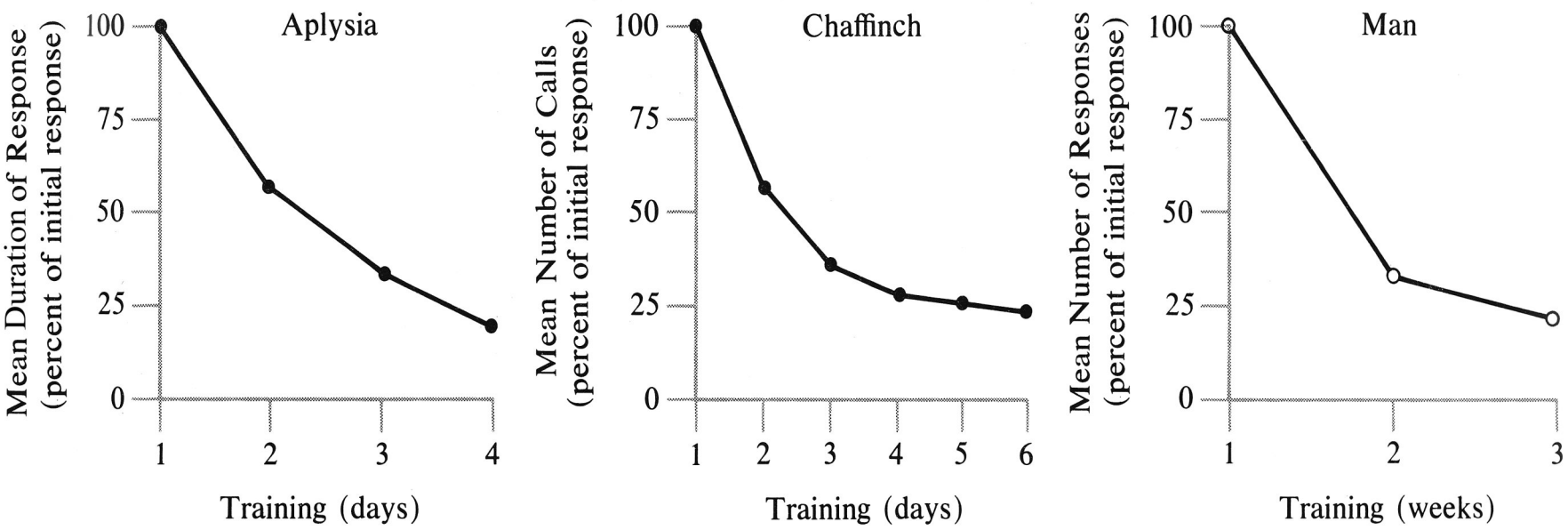
- Arousal-related neurons respond best to high-information (salient, surprising, unpredictable) stimuli (Harvard U. Press, 2005)
- Claude Shannon devised an intuitively pleasing, mathematically precise definition of information as follows:

$$H(x) = \sum p(x) \log_2 {}^{1}\!/_{p(x)}$$

Where H is the total amount of "Shannon" information and p(x) is the probability of event x.


Bits of Information
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
0
.1
.2
.3
.4
.5
.6
.7
.8
.9
1.0
p

Arousal / Information theory thinking naturally yields a universal phenomenon: HABITUATION.

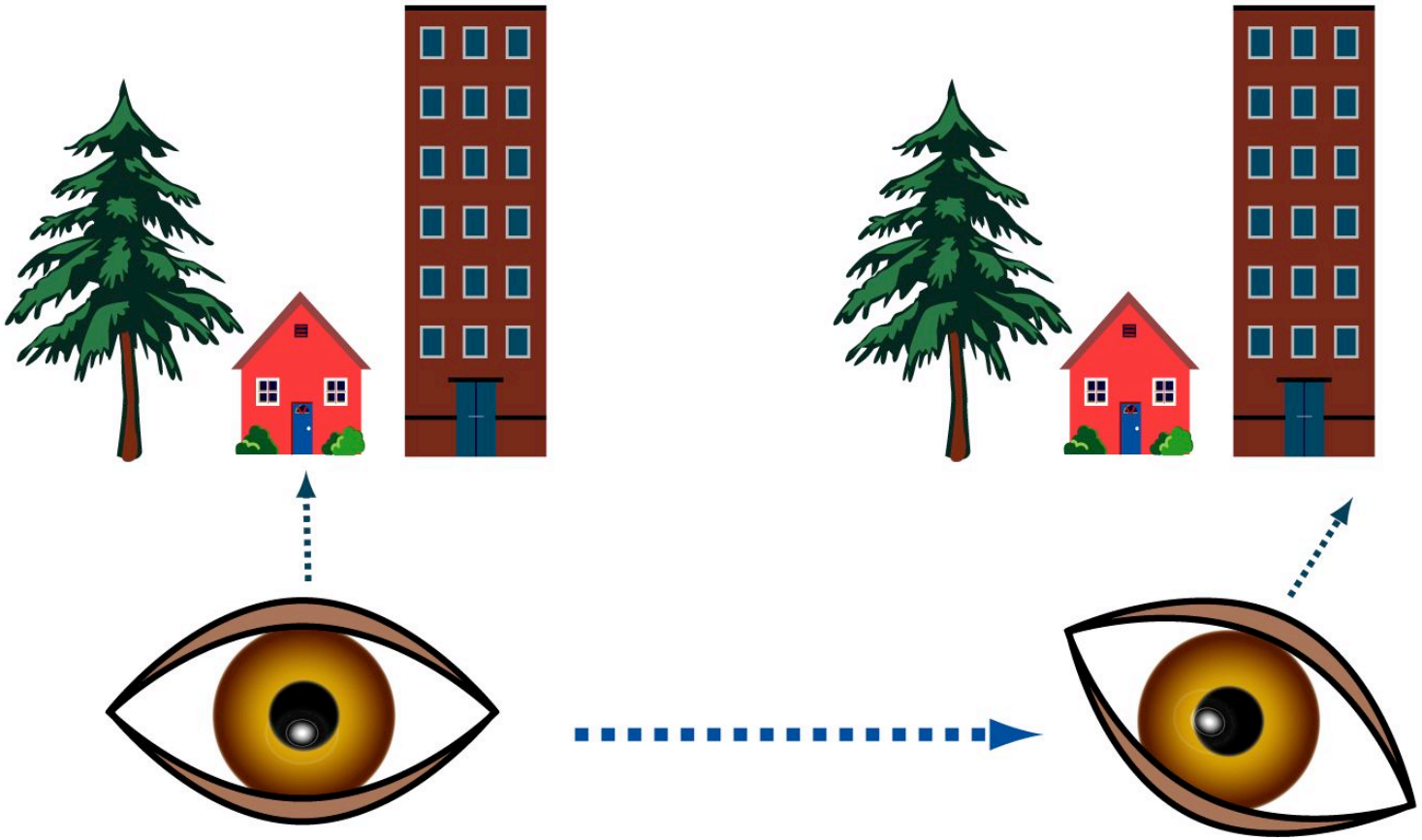


IV. Arousal and Awareness: Human

Theory of the representation of one's acts to oneself.

Practice: In patients suffering vegetative and minimally conscious states.

The Basis of Self Awareness in Neurophysiology. “Reafferenz Theory”.



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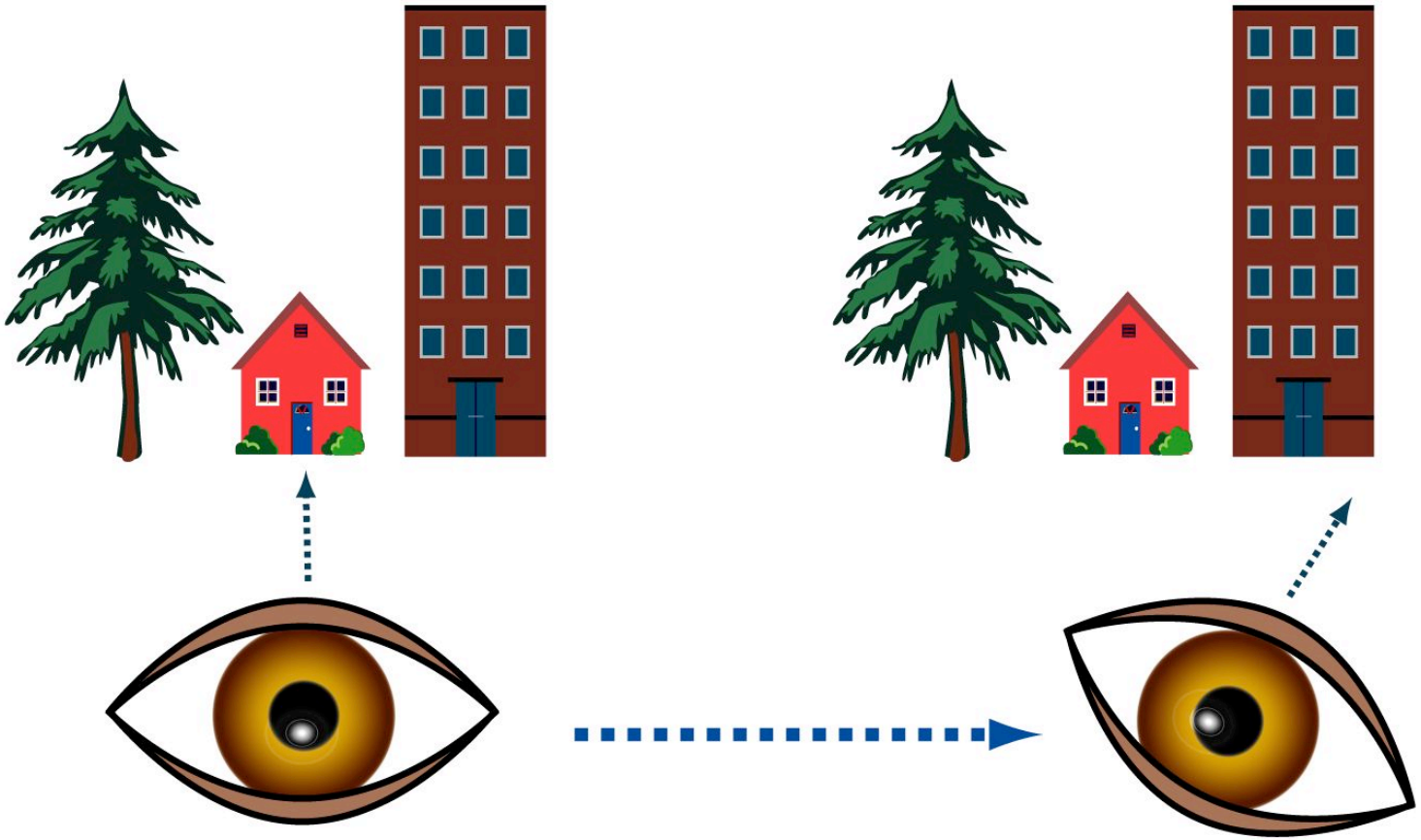

Oculomotor
COMMAND signal=

DID THE WORLD
MOVE TO THE LEFT?

NO

"corollary discharge" → visual system.

The Basis of Self Awareness in Neurophysiology. “Reafferenz Theory”.

- Stability of Visual Field
- Corollary discharge for all motor acts
- Corollary discharge for (internal) verbal acts= representation to oneself as oneself.
- CNS evolution ⇨ higher “layers” of awareness.

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Voss H.U., Ulug A.M., Watts R., Heier L.A., McCandliss B., Kobylarz E., Giacino, J, Ballon D., Schiff N.D. (2006) Axonal Regrowth in late recovery from the minimally conscious state? *Journal of Clinical Investigation* (in press)

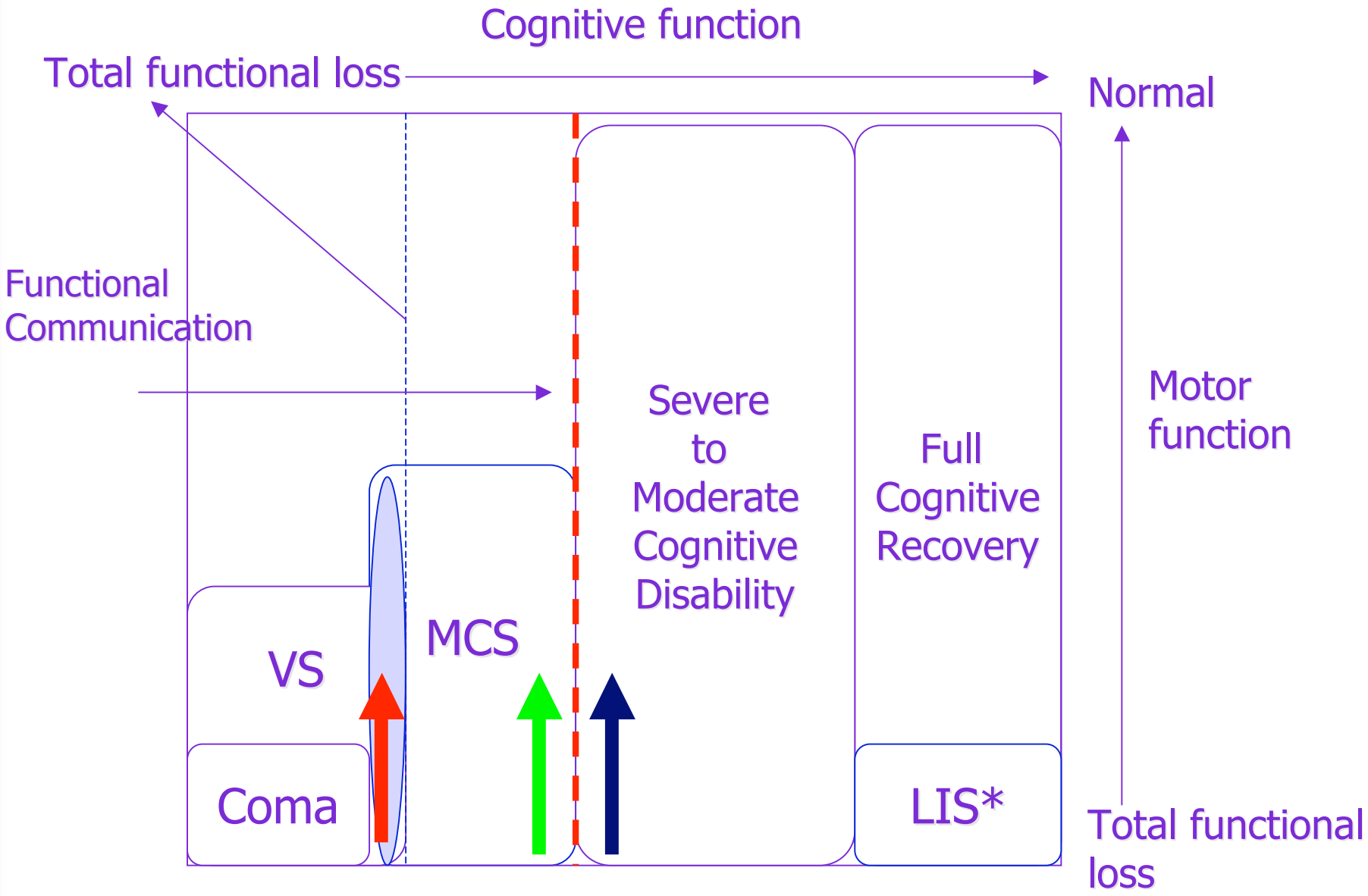
Schiff, N, Rodriguez-Moreno, D, Kamal, A, Kim, K.H., Giacino, J, Plum, F and Hirsch, J. (2005) fMRI reveals large-scale network activation in minimally conscious patients. *Neurology* 64: 514-523

Schiff, N.D. (2005) Modeling the minimally conscious state: measurements of brain function and therapeutic possibilities. *Progress in Brain Research* 150: 477-497

Laureys, S.L., Owen, A.M., and Schiff, N.D. (2004) Brain function in coma, vegetative state and related disorders. *Lancet Neurology* 3(9):537-46.

Schiff, N., Ribary, U., Moreno, D., Beattie, B., Kronberg, E., Blasberg, R., Giacino, J., McCagg, C., Fins, J.J., Llinas, R. and Plum, F. (2002) Residual cerebral activity and behavioral fragments in the persistent vegetative state. *Brain* 125(6): 1210-1234.

Conceptualizing global disorders of consciousness



(*Schiff, ND,* The Neurology of Impaired Consciousness, Cognitive Neurosciences III, MIT Press)

B. Effect of Excitatory State or Levels of Consciousness

The spontaneous electrical rhythms of the brain are most sensitive to functional states best described under the heading of alterations in the level of consciousness or attention. The alpha and beta rhythms

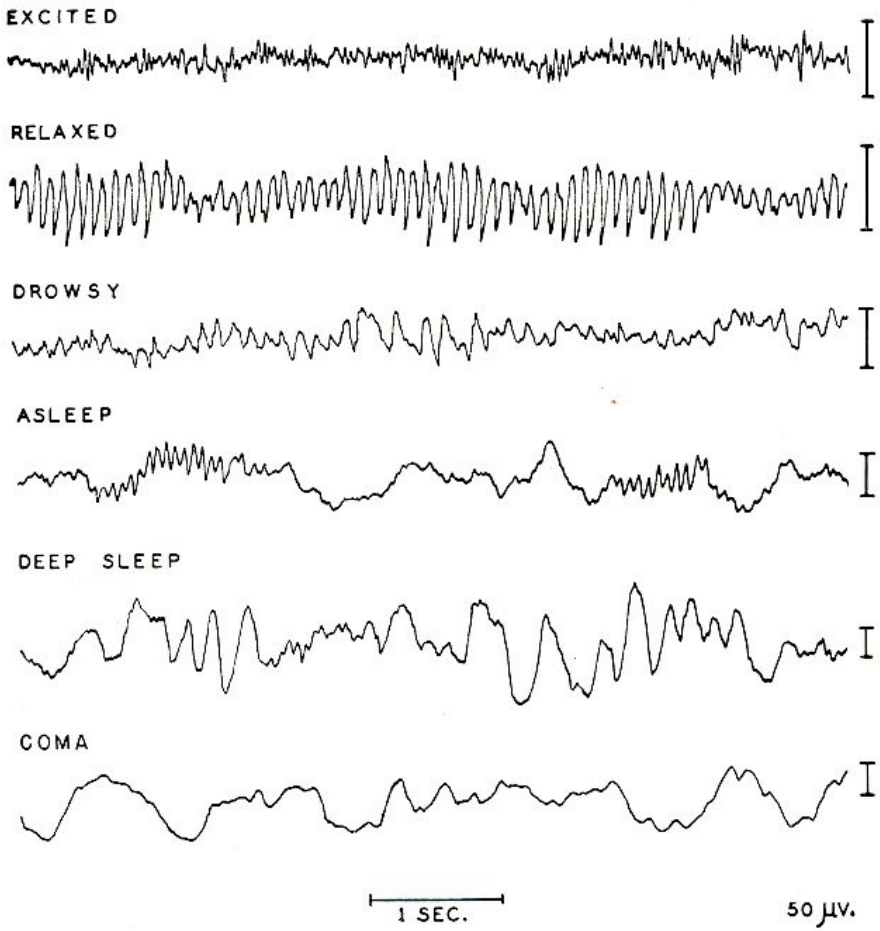


FIG. V-2.

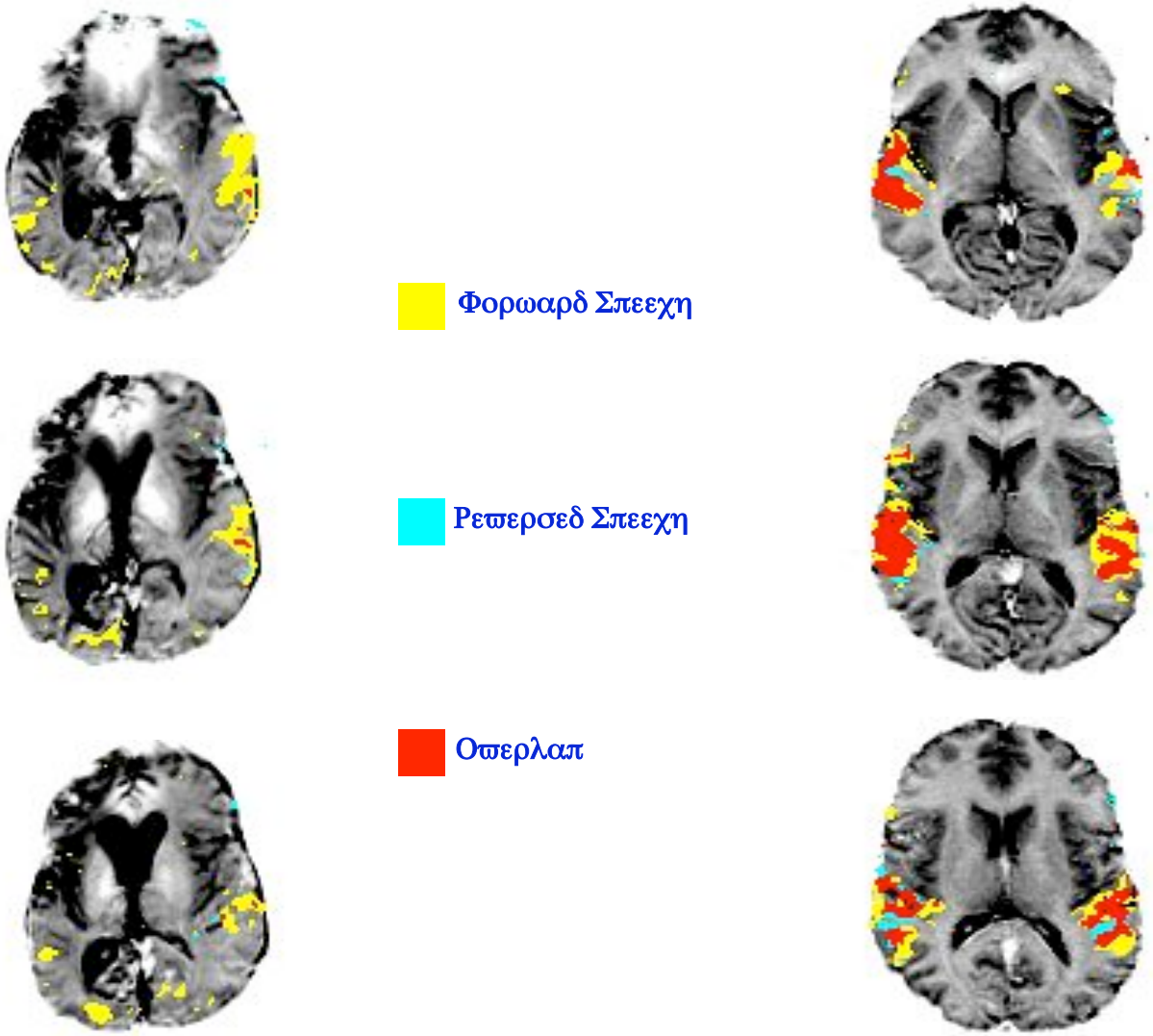
FIG. V-2. Characteristic electroencephalograms during variations in states of consciousness.

Minimally conscious state EEG patterns may be similar to normal wakefulness

Vegetative state EEG patterns are typically similar to coma

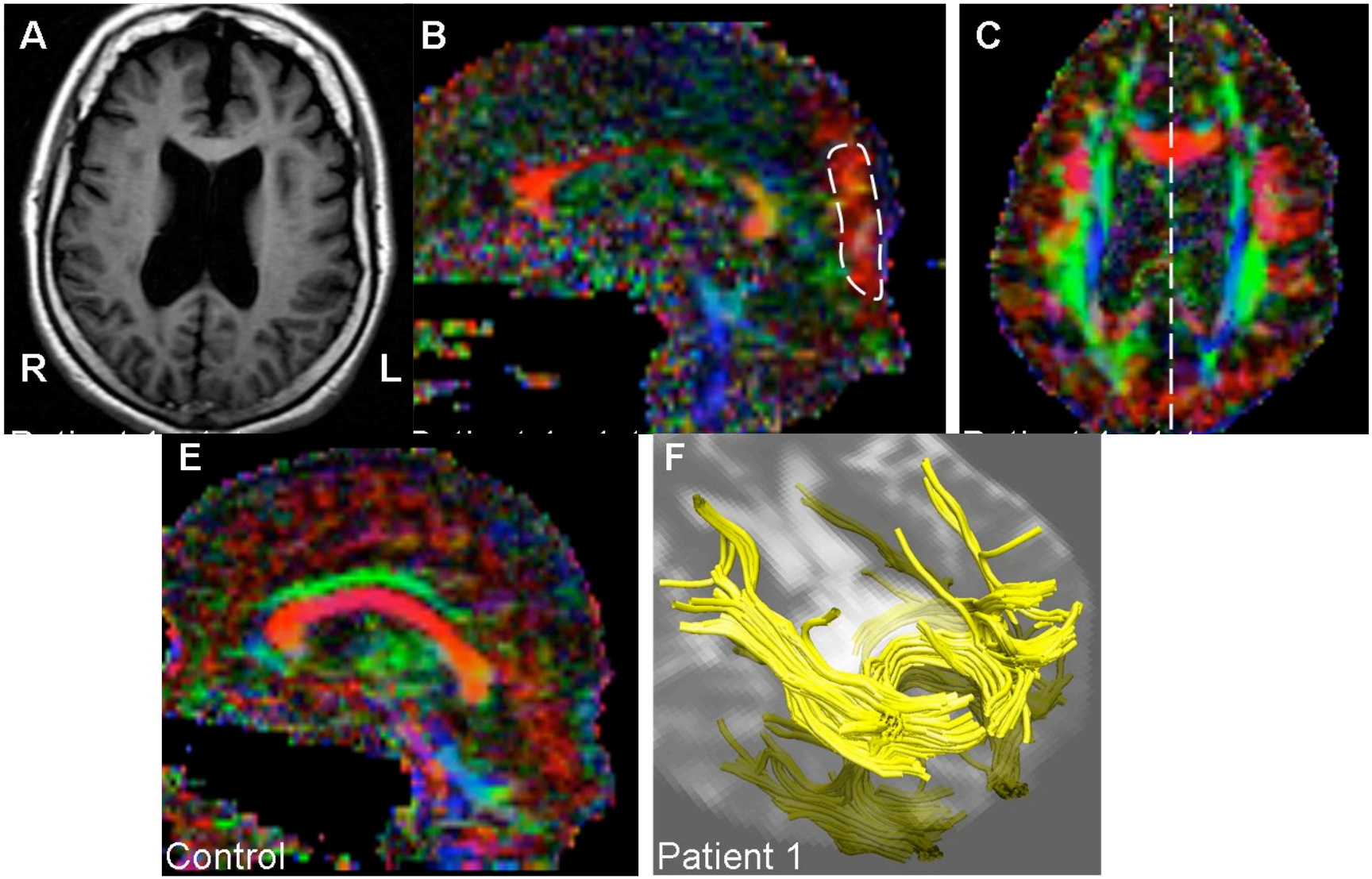
Minimally Conscious State Patient

Normal Subject



Schiff, N, Rodriguez-Moreno, D, Kamal, A, Kim, K, Giacino, J, Plum, F and Hirsch, J. fMRI reveals large-scale network activation in minimally conscious patients.
***Neurology* (2005) 64: 514-523**

Evidence of structural reorganization of cerebral white matter in late (19 years) emergence from the minimally conscious state



H. U. Voss, A. M. Ulug, R. Watts, L. A. Heier, B. D. McCandliss, S. Niogi, E. J. Kobylarz, J. Giacino,D. Ballon, N. D. Schiff. Axonal regrowth in late recovery from the minimally conscious state? *J Clinical Investigation* (in press)

Overall Summary

1. *Looking back*: In hypothalamic neurons expressing ERs, E influences several genomic modules to control a spinal-midbrain-spinal behavior circuit for lordosis behavior. This work demonstrated that specific chemical reactions in specific parts of the brain determine a specific behavior.

2. *Looking forward*: Underlying all mammalian behaviors is CNS arousal: Precise operational definition features sensory alertness, motor activity and emotional reactivity. We have a "high throughput" assay.

Overall Summary, Continued

3) We understand how generalized arousal forces impact specific arousal states: e.g. HA, NE and ACh, themselves hormone dependent, increase electrical activity in behavior-controlling hypothalamic neurons.
4) Creation of models for diffuse brain damage in mice will lead to strategies for amelioration and recovery from brain damage.