DEVELOPMENT OF AROUSAL CONCEPTS

- **Waking** is a complex state. It is characterized by: 1) Perceptions that are influenced by external and internal sensory input; 2) Capacity of directing attention and accessing memory faithful to recent history; 3) Readjustment of posture, array of motor output; 4) Emotions that are focused to percepts and thoughts .(Hobson and Pace-Schott, 2002)

- **1930s**: wakefulness is maintained by afferent input to the brain and sleep ensues when that input is removed, as in the 'cerveau isole' cat, or falls below a certain critical level, as in normal sleeping (Bremer, Deafferentation theory)

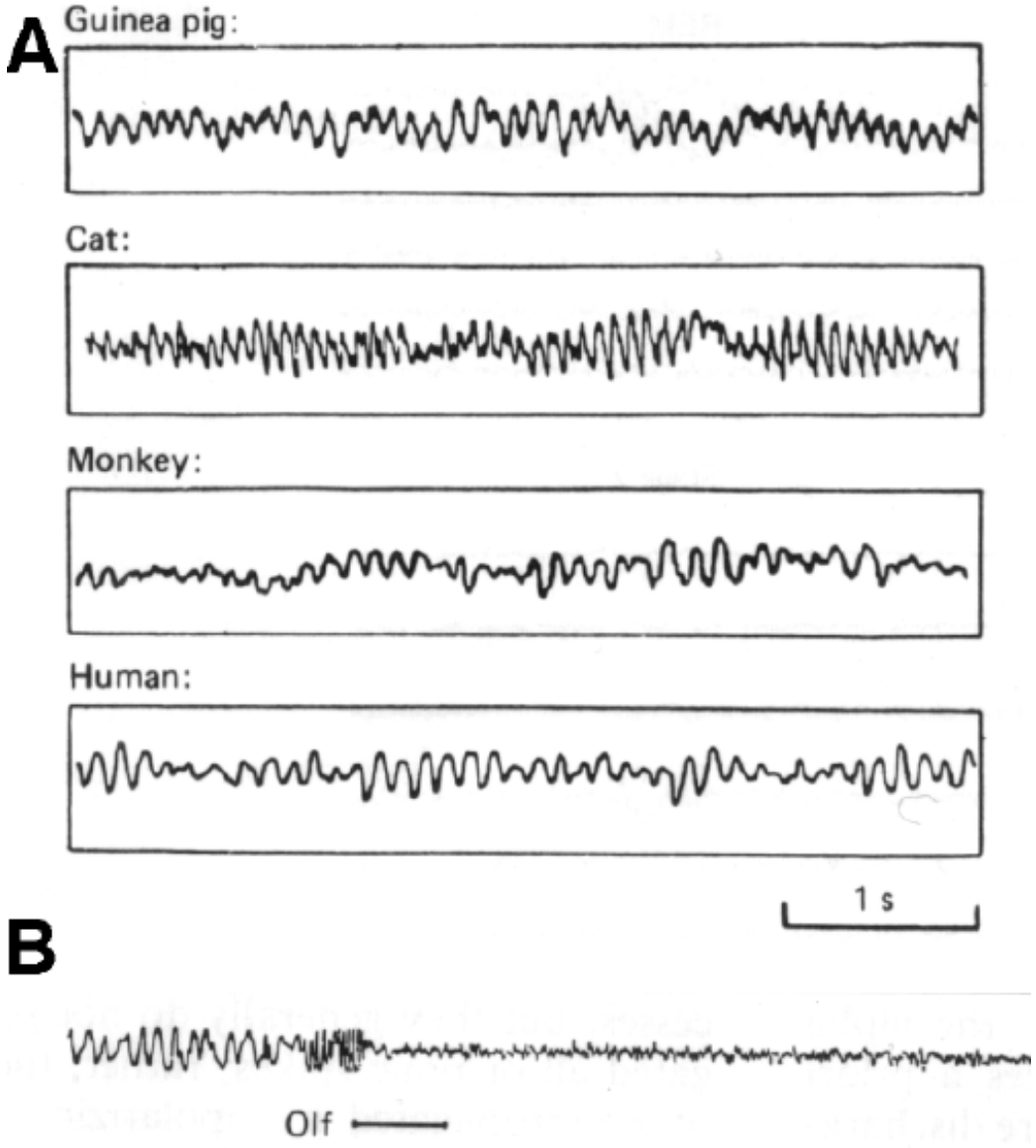
- **1950s**: the brain actively controls its own state by the ascending reticular activating system (Magoun-Moruzzi).

- **1965s**- the concept of an undifferentiated reticular formation is gradually replaced by the description of transmitter-specific cell groups in the brainstem, the basal forebrain and the hypothalamus that send widely branching axons to the cortex and other parts of the brain.

- **1980s**- thalamo-cortical oscillations; neuromodulators trigger intrinsically generated oscillatory pattern in cooperating cortical cells. Arousal is a switch from slow to fast oscillatory pattern (Steriade, McCormick, Llinas, Singer, Buzsaki).

- **1990s**- The subjective experience of various states can tentatively be linked to the accompanying changes in systematic variations in balance between various neuromodulators. The characteristic imaging data in various states are likely to relate to the shifts in regional metabolism and blood flow that are orchestrated by the these neuromodulators.

- **2003** Arousal provides the motivational force that activates behavior (Pfaff)

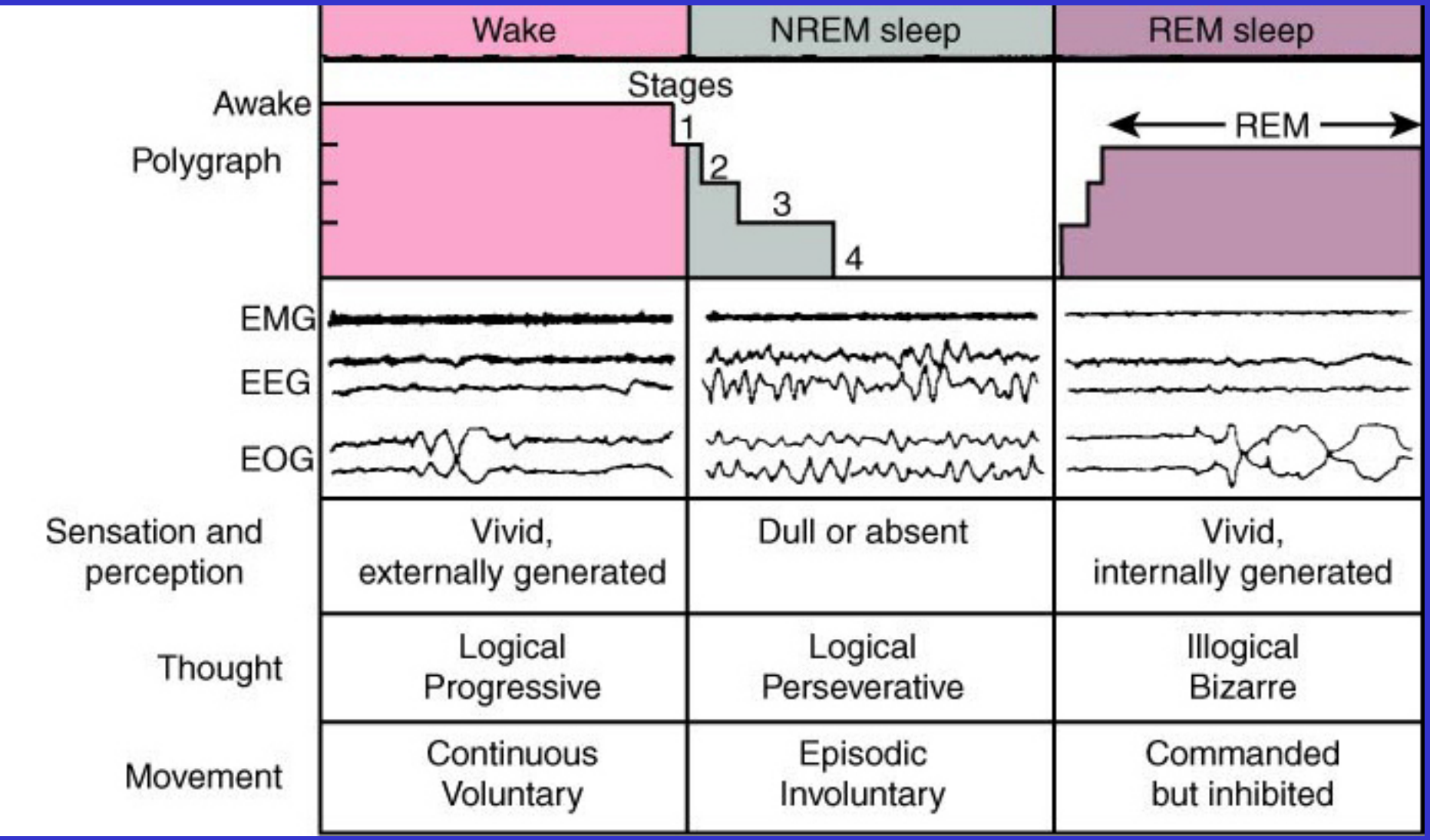


Alpha rhythm

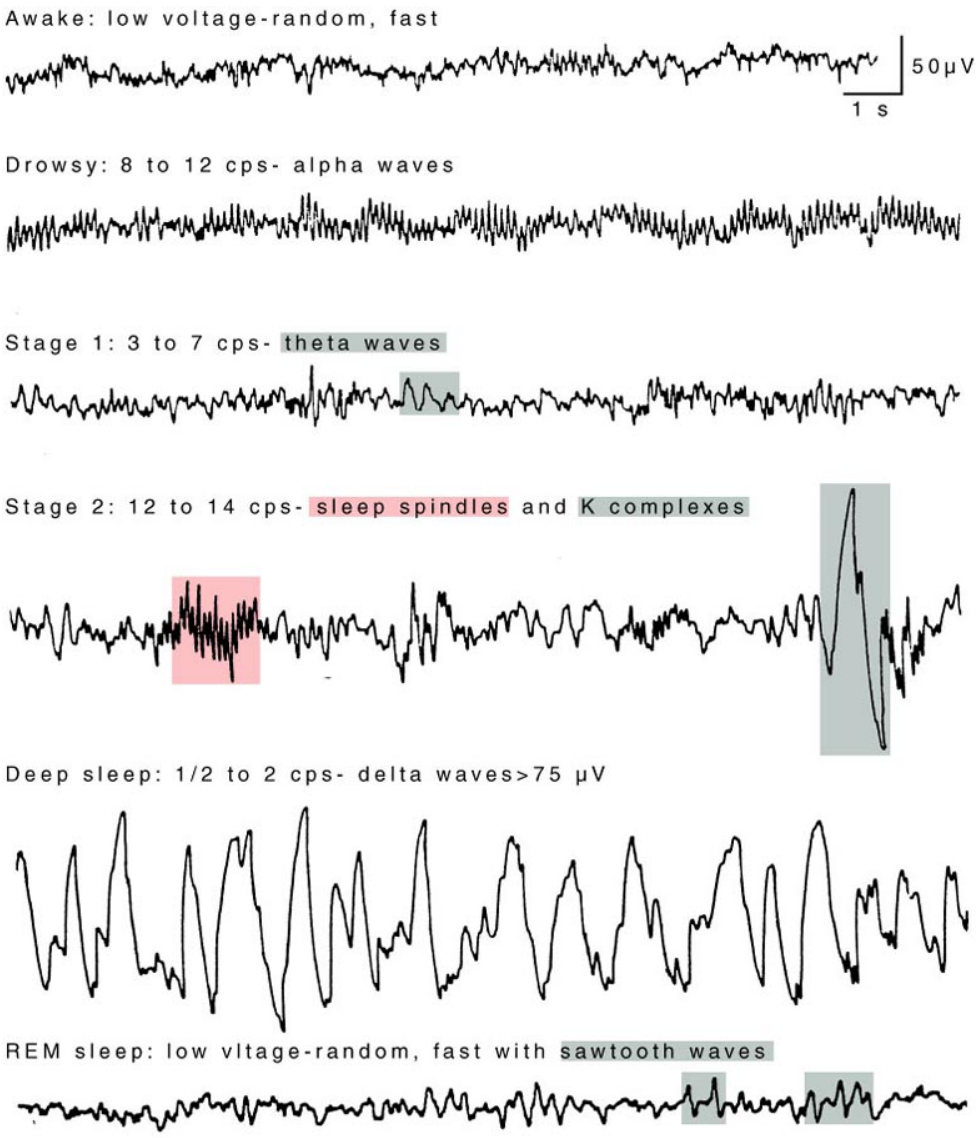
A: EEG records showing alpha rhythm from four species (Brazier, 1960).

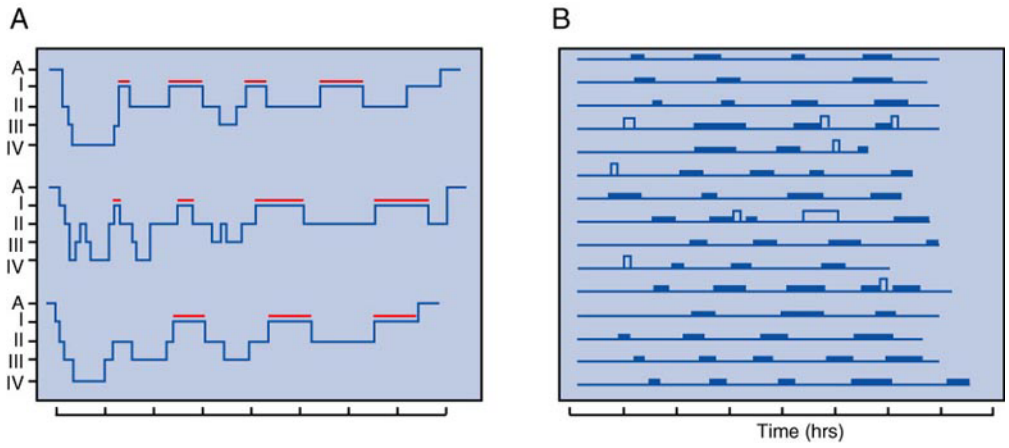
B: Desynchronization of the EEG of a rabbit by an olfactory stimulus (Green and Arduini, 1954).

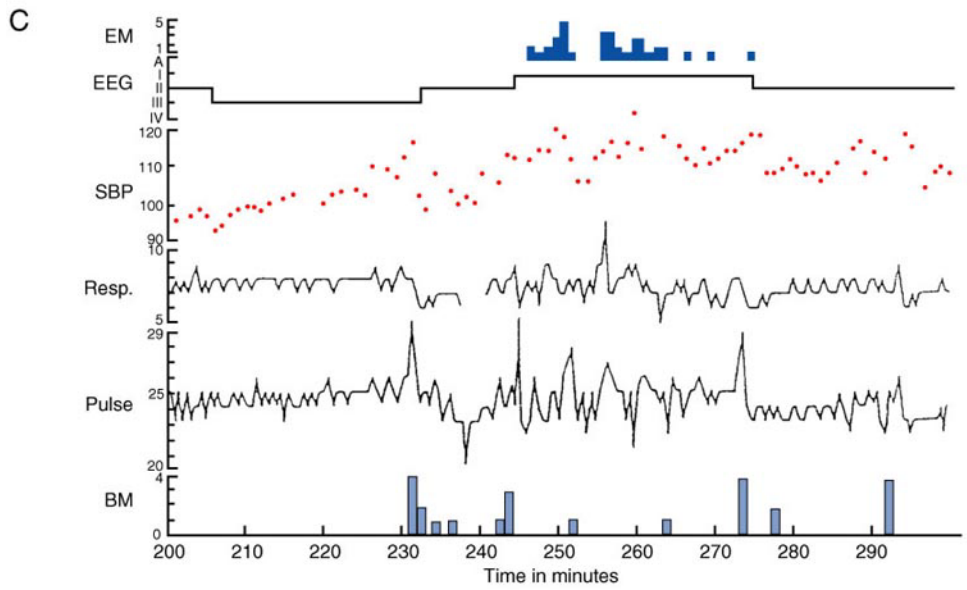
Behavioral states in humans

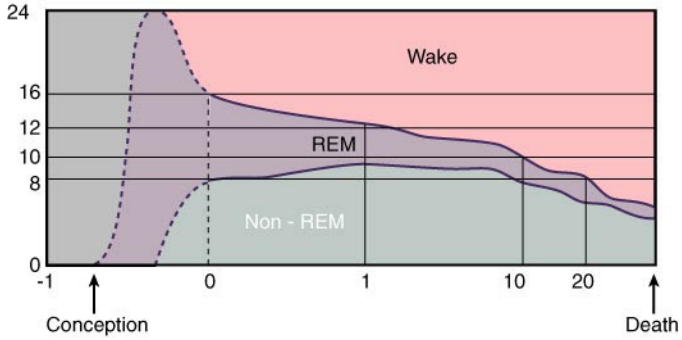


Hobson and Pace-Schott, 2003

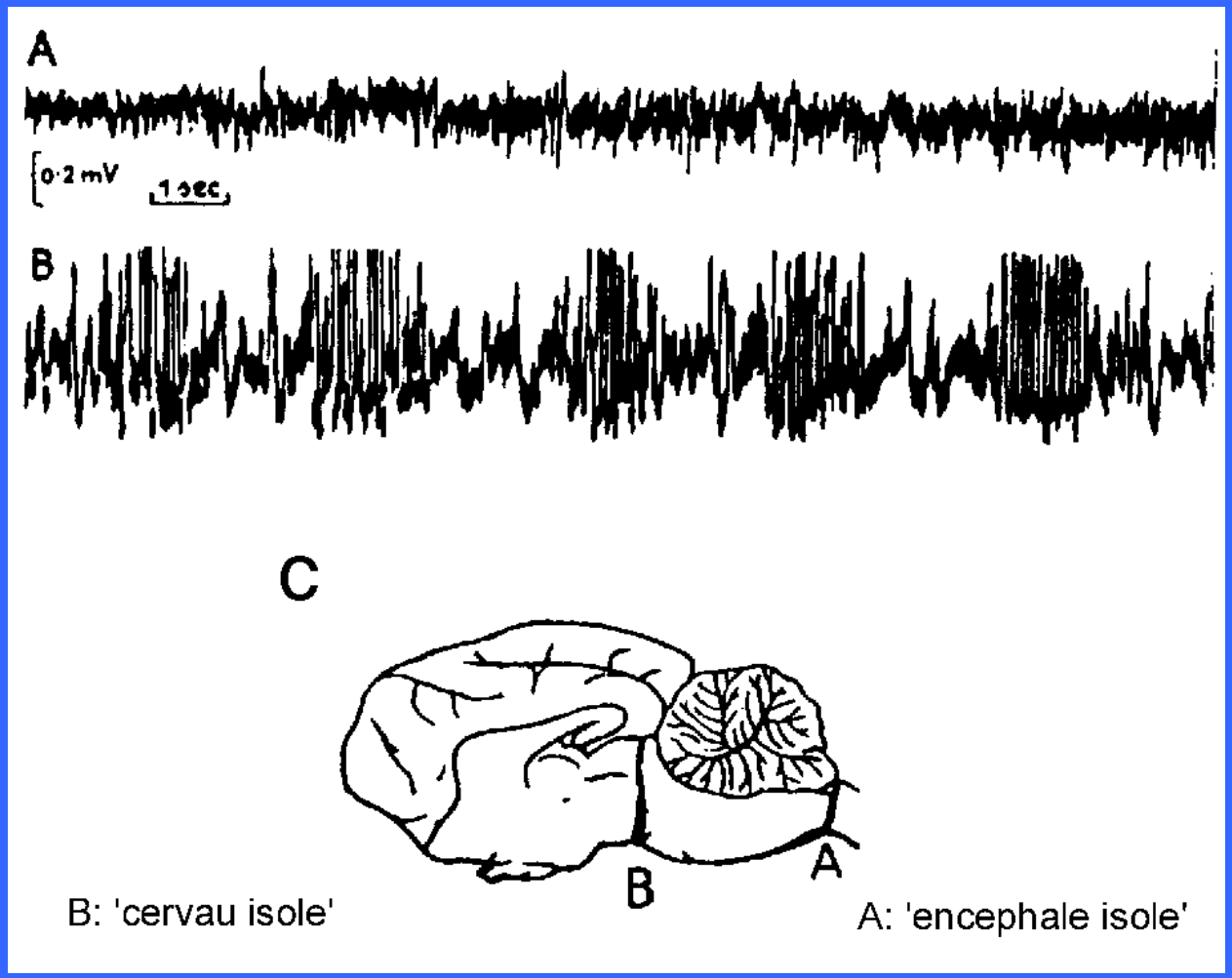






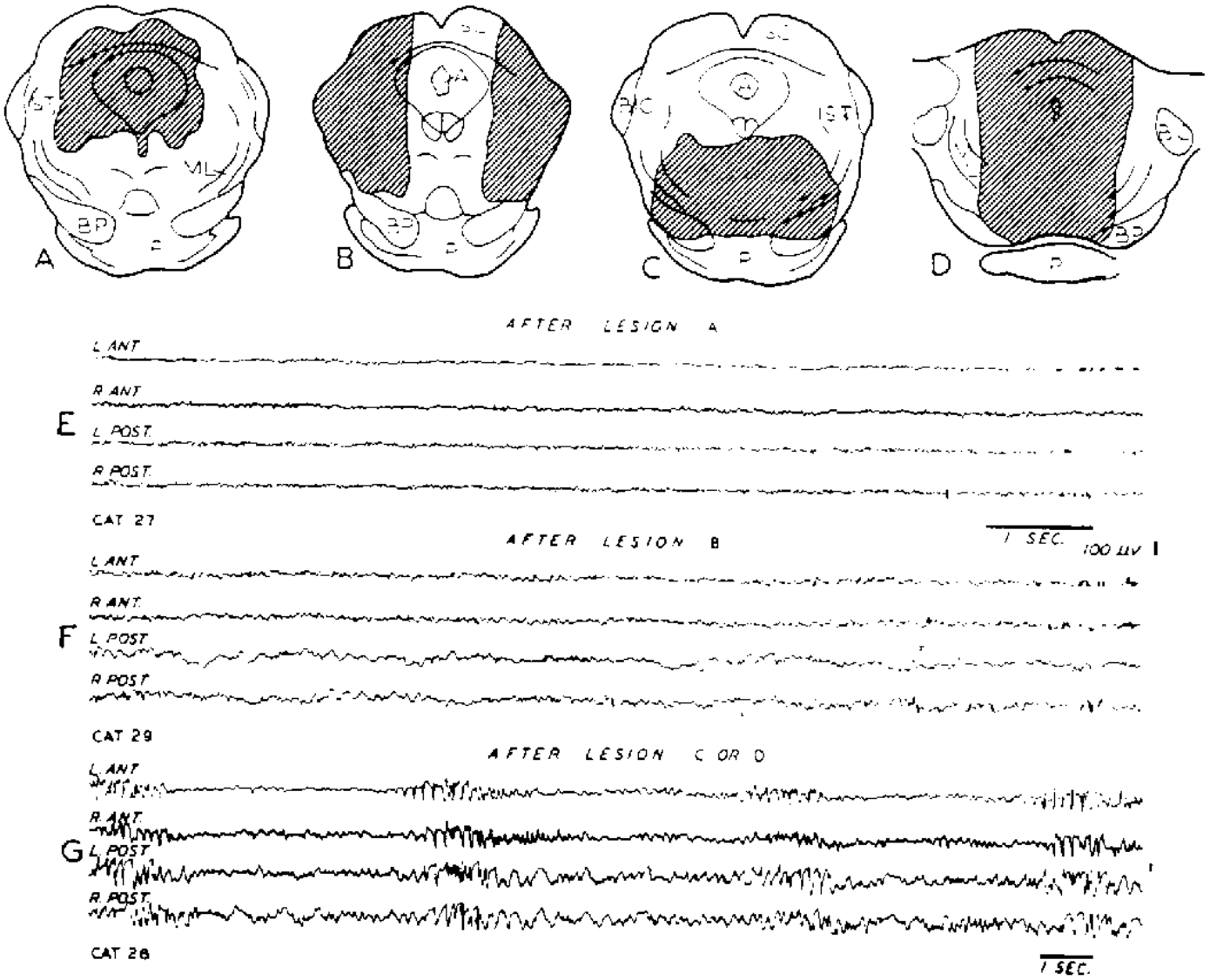


EEG with brainstem transections

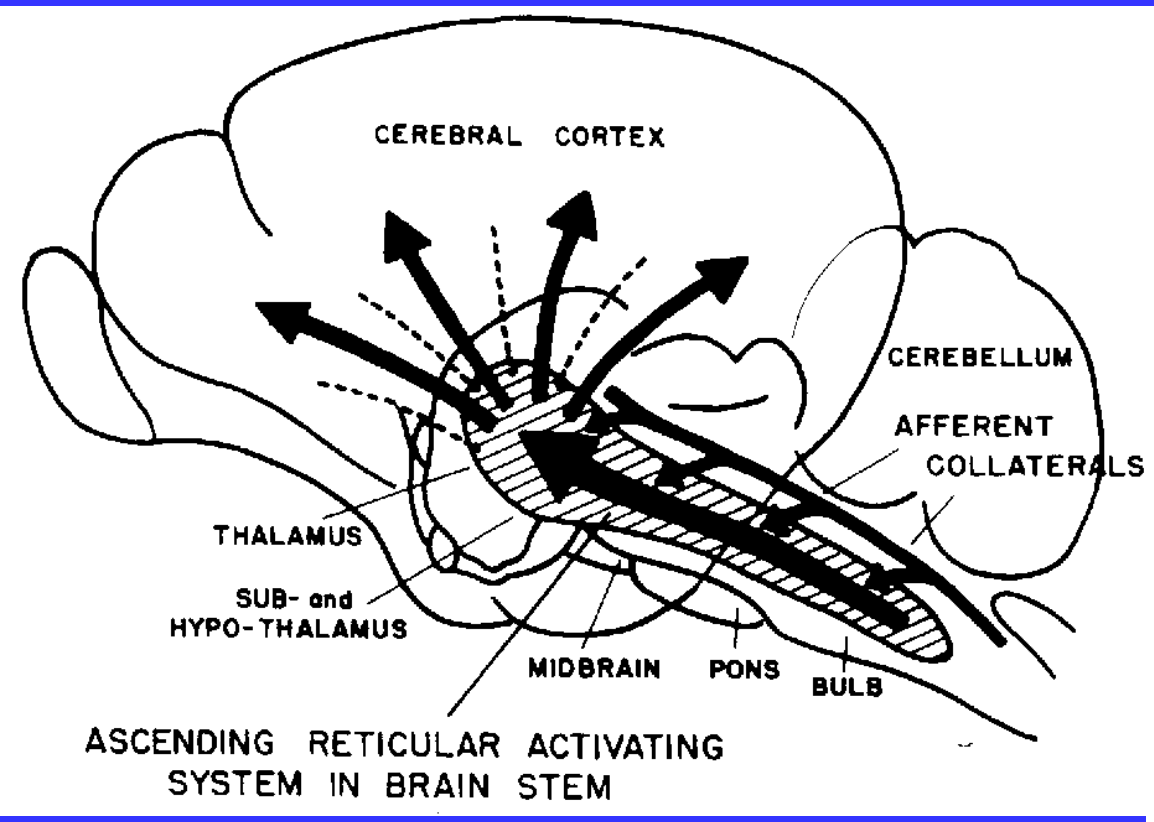


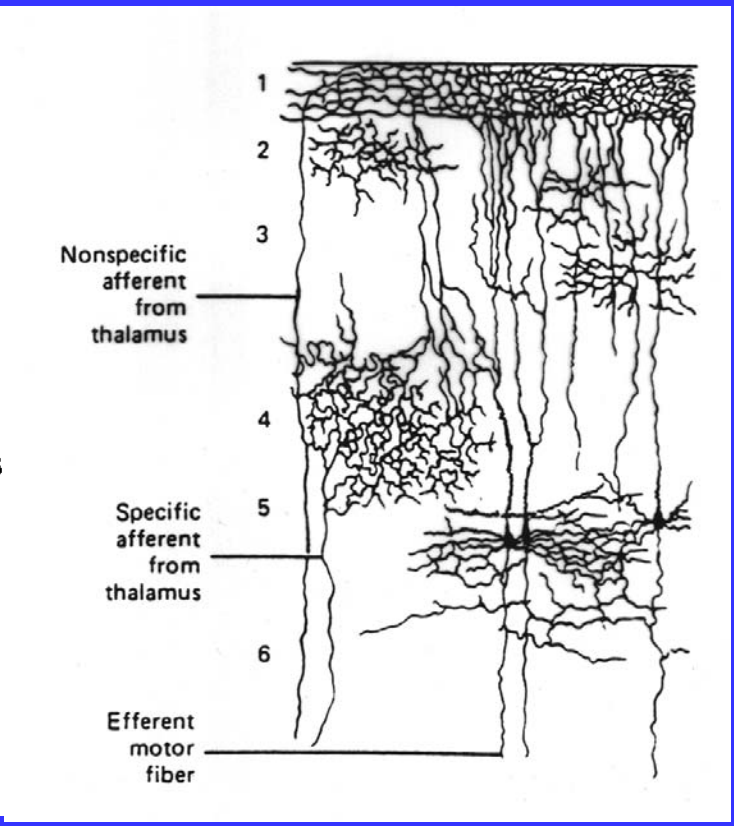
A: Cortical LVFA typical of the alert state in cat (transection at ‘A’).
B: Spindling with cut at ‘B’ (Bremer, 1937).

EEG with brainstem lesions (Lindsley et al., ’49)



Ascending modulatory systems: The past

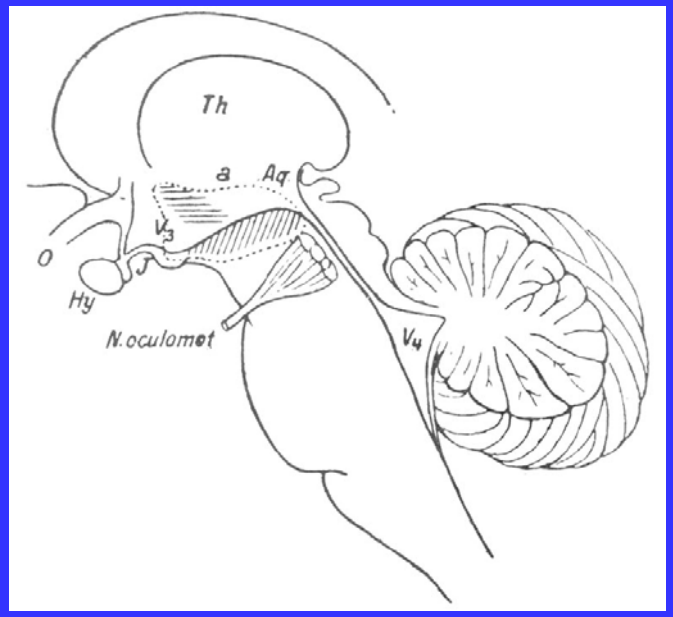




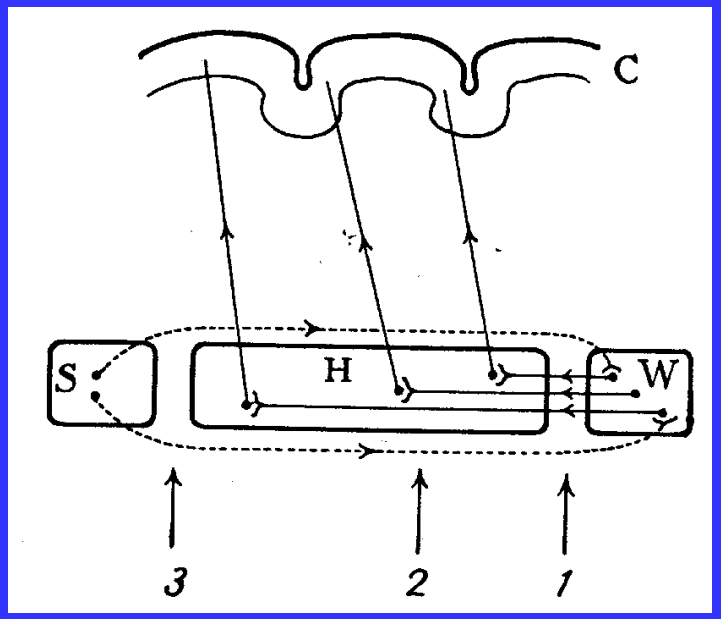
Magoun, Moruzzi et al, 1951

Lorente de No, 1938

Hypothalamic sleep-wake ‘centers’

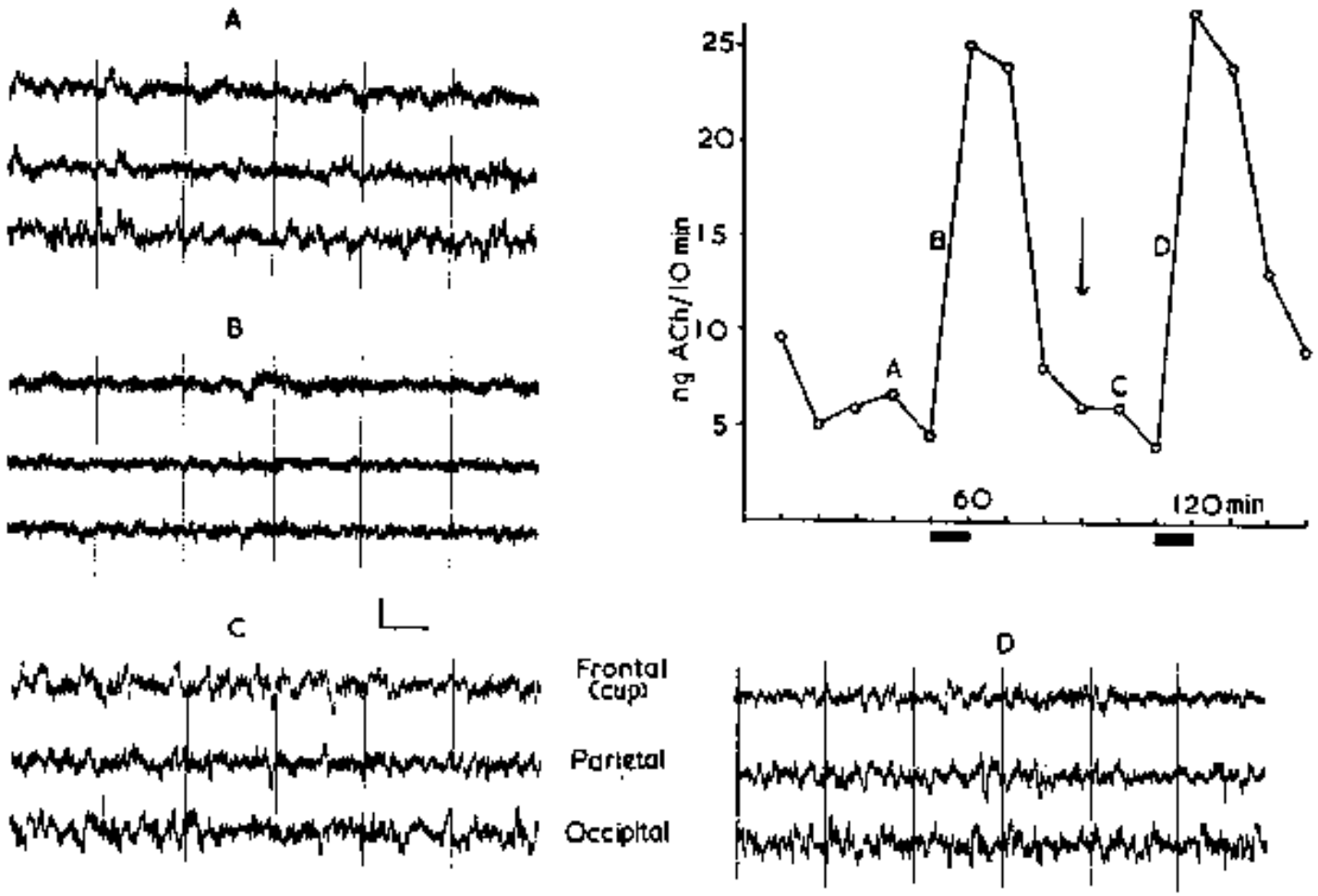


Von Economo, 1931



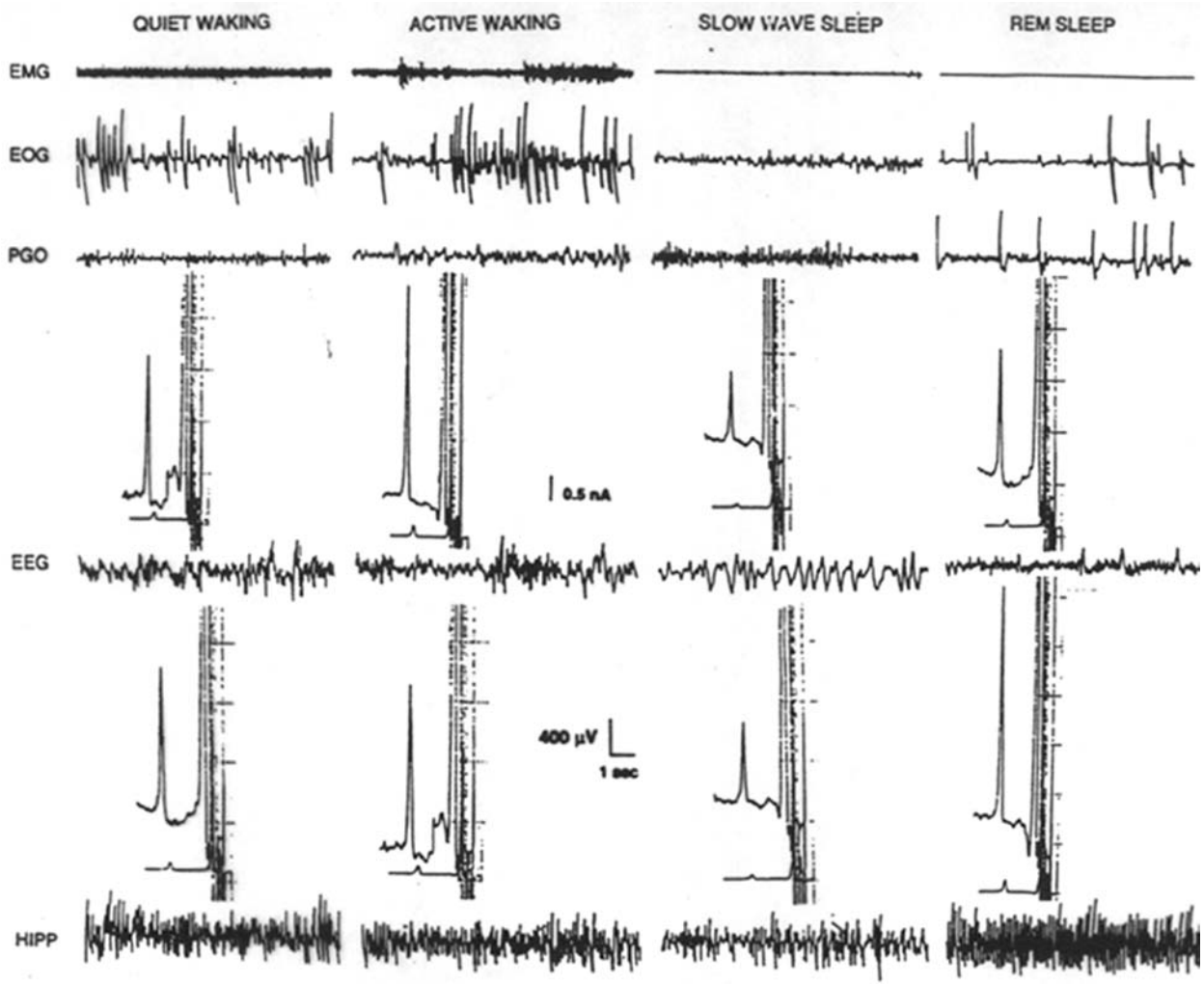
Nauta, 1946

Cortical EEG and ACh output I



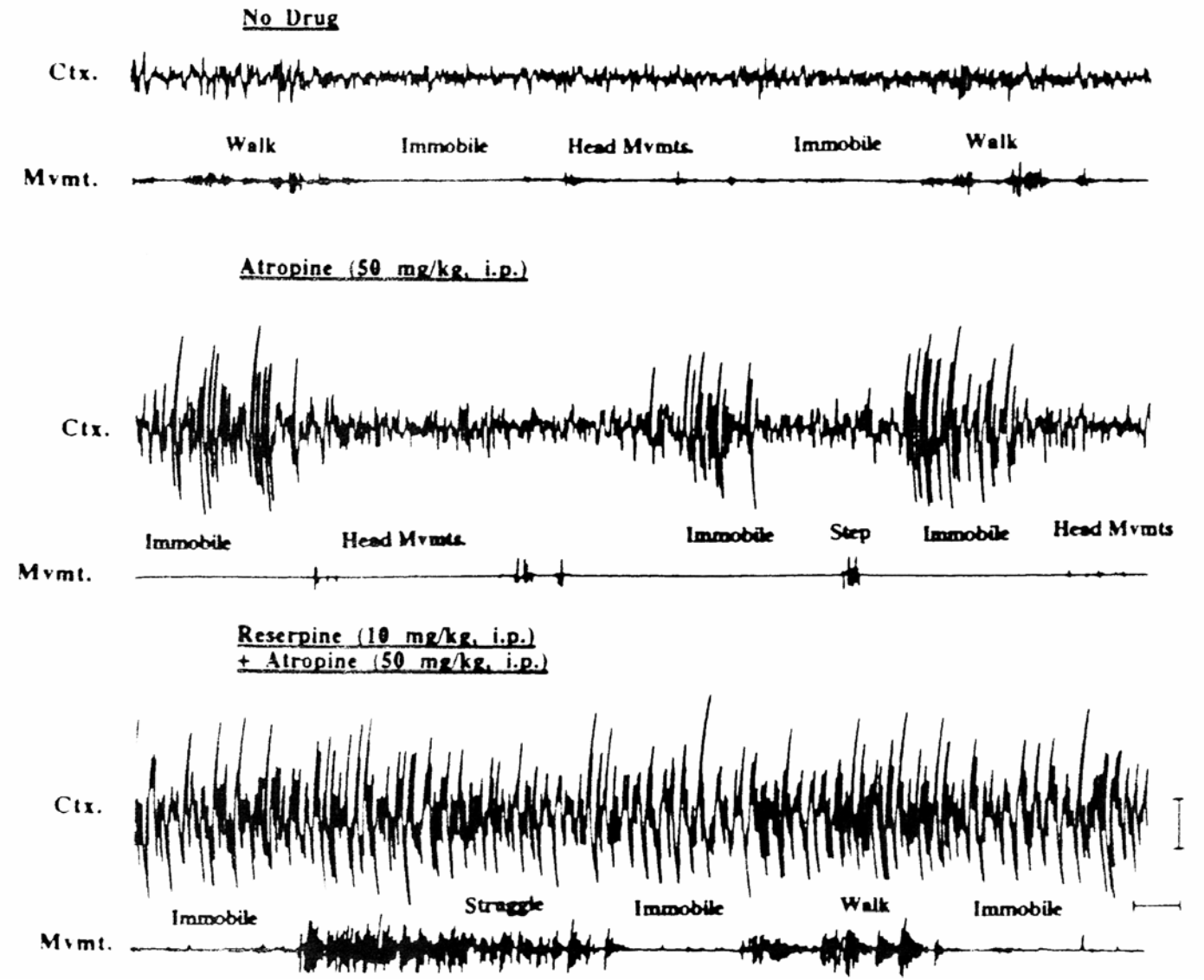
During period marked by thick line, stimulation of the RF. At arrow, 1mg/kg atropine injected iv. EEG calibration: 0.1 mV, 1 sec (Szerb et al., 1965).

Correlation of EEG and ACh output II

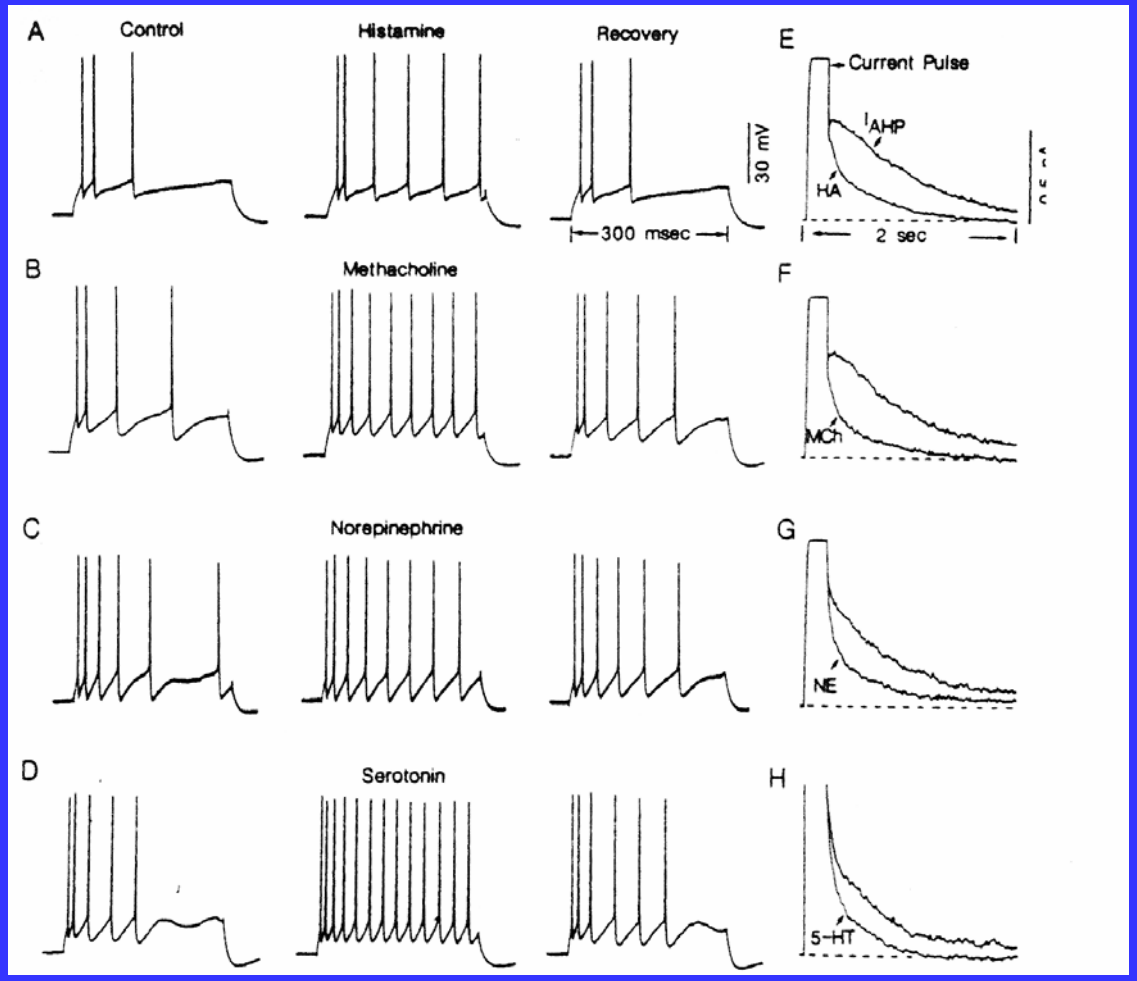


Correlation of EEG and ACh output in cortex and hippocampus in freely-moving cat (Marrosu et al., 1995)

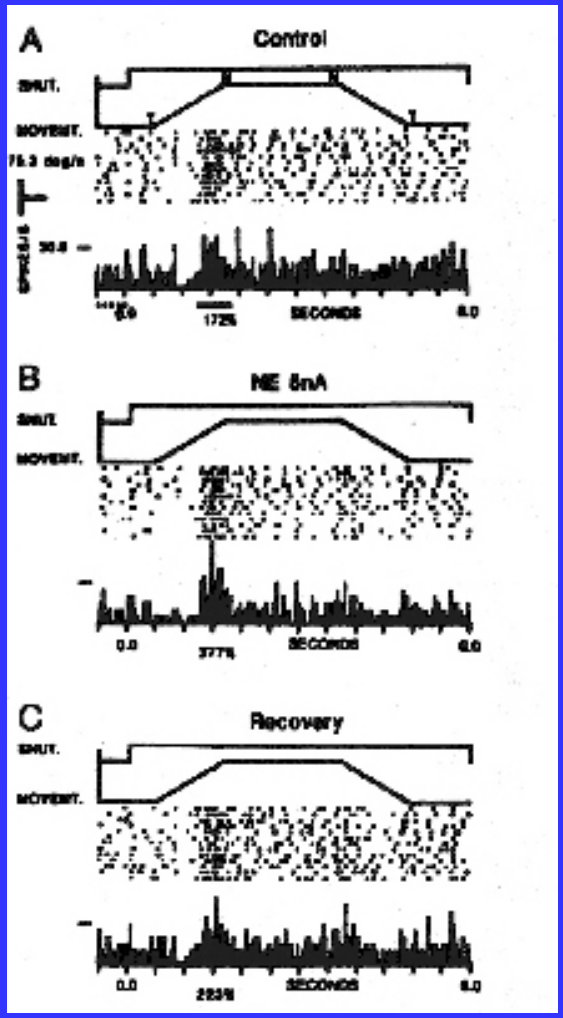
EEG, behavior, transmitter interactions



Effect of neuromodulators on cortical firing and network function

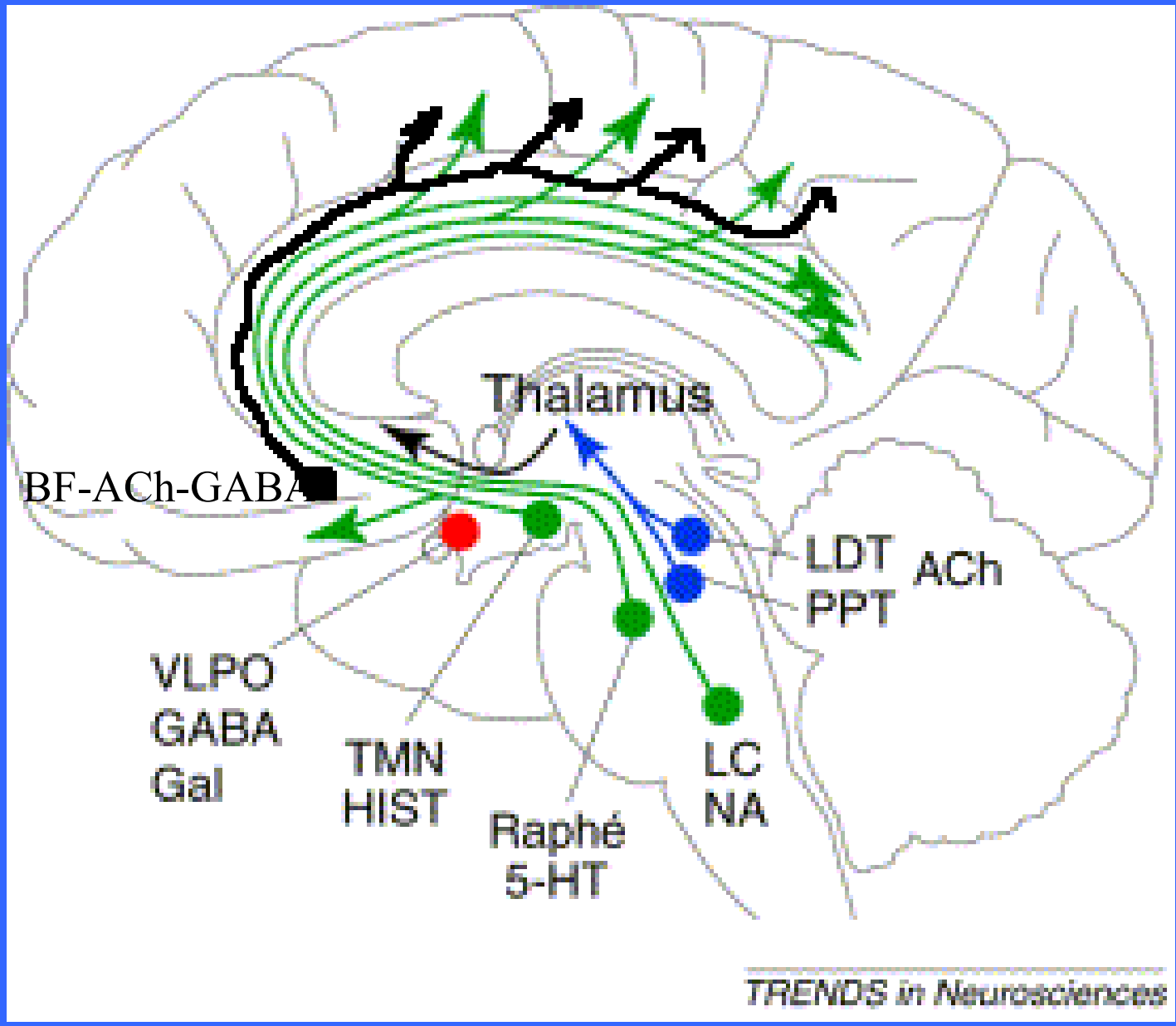


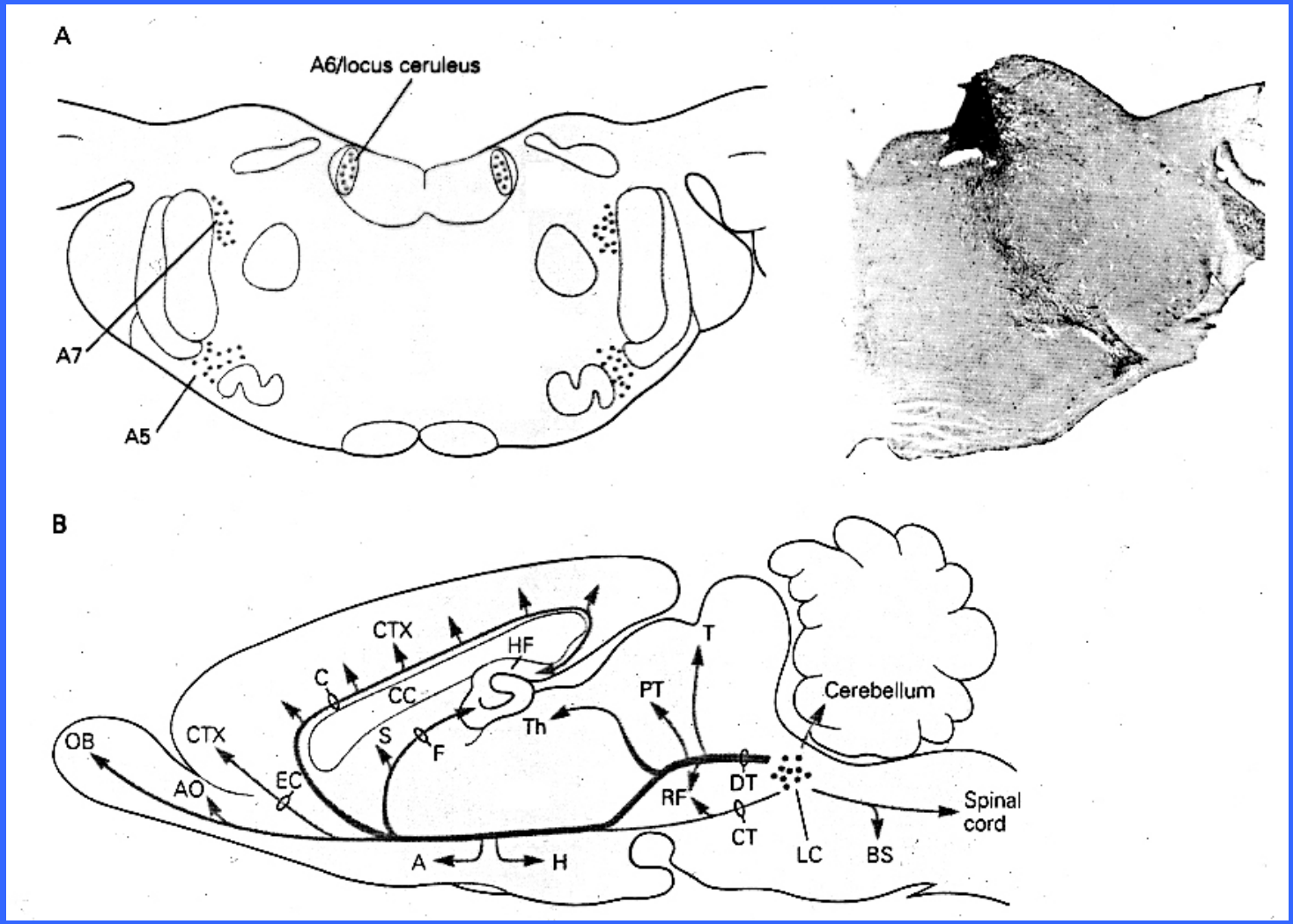
A-D: current clamp; E-H voltage clamp mode; McCormick and Williamson, 1989



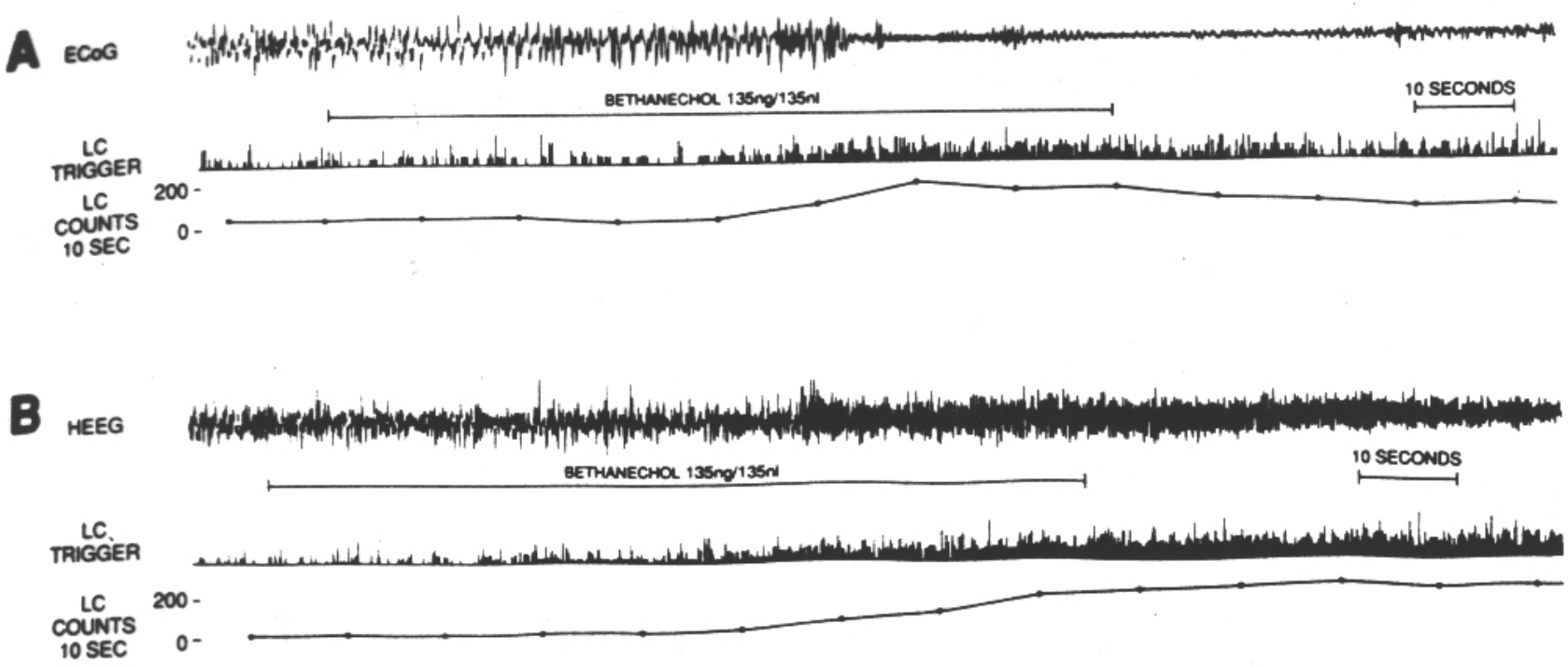
Waterhouse et al., 1990

Subcortical modulatory cell groups (Saper)



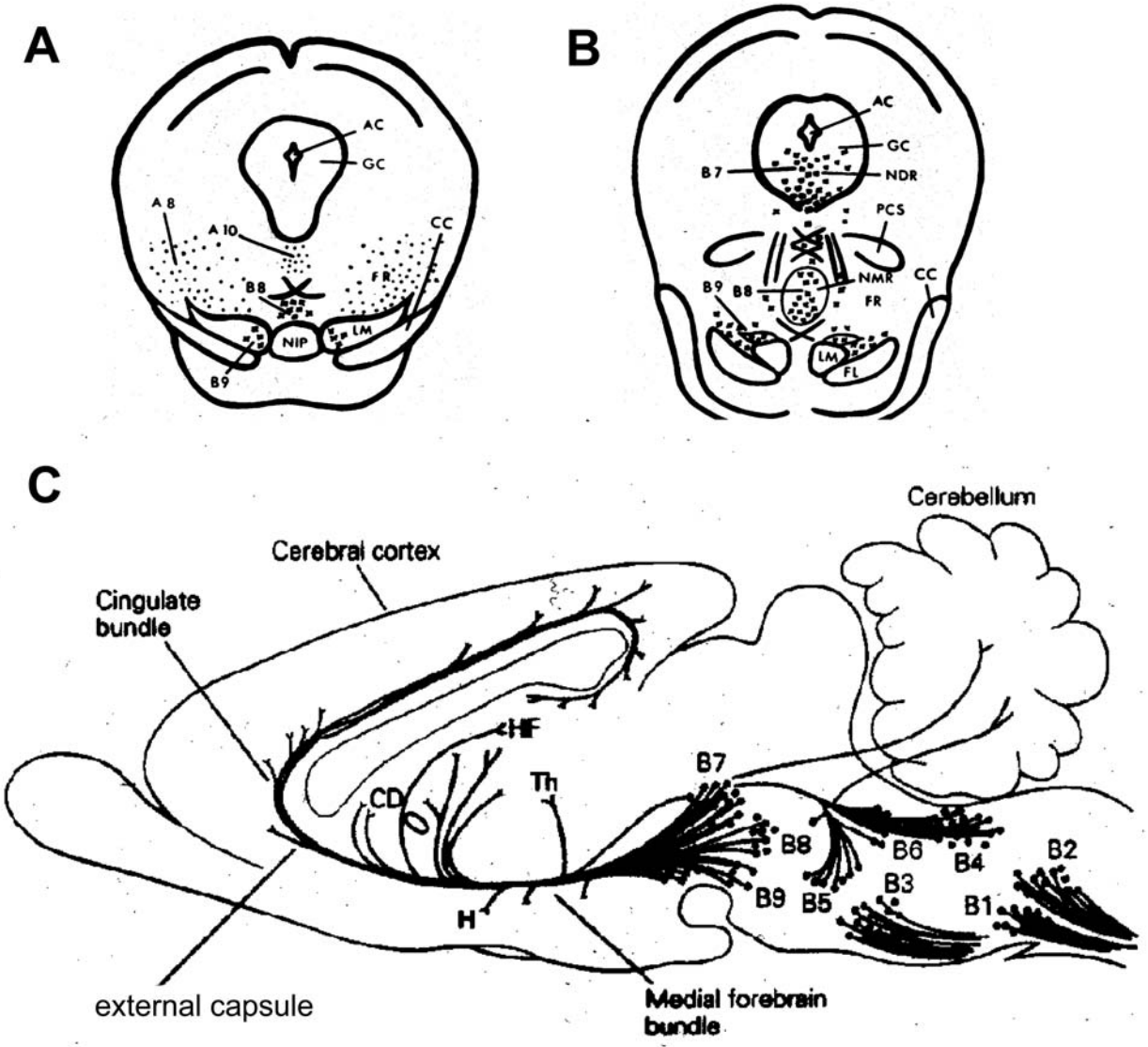


LC provides a major ascending output to the thalamus and cerebral cortex as well as descending projections to the brainstem, cerebellum and spinal cord.



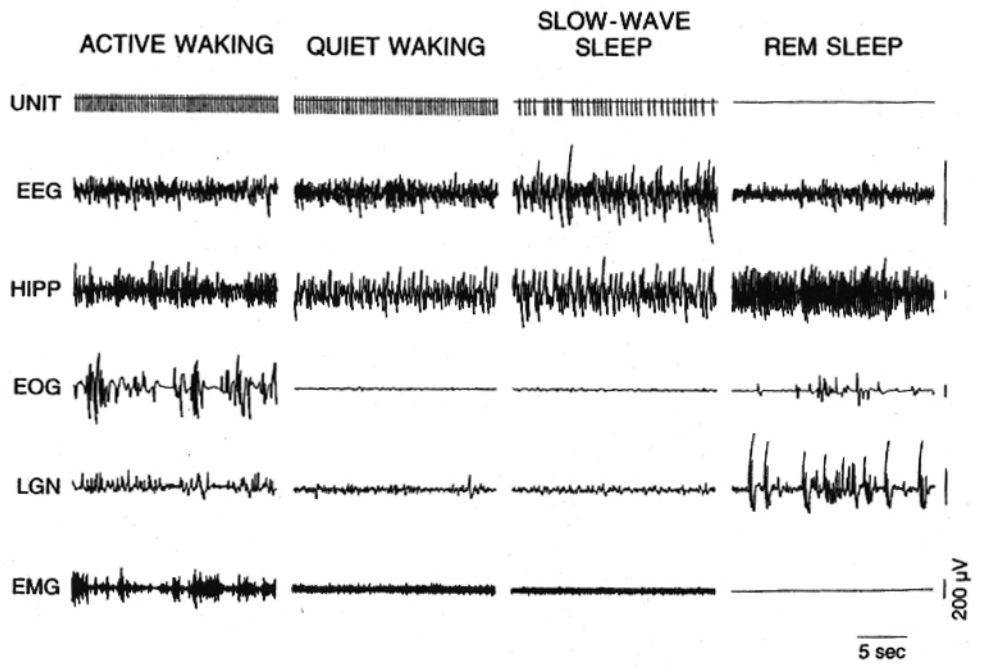
Relationship of LC activity to cortical ECoG (**A**)and hippocampal EEG (HEEG, **B**) before, during and after peri-LC bethanechol infusion. The raw trigger output from LC activity is shown in the middle trace, and the integrated trigger output(10 sec intervals)is in the bottom trace.As LC activity is seen to increase during the latter part of the infusion, reduced amplitude and increased frequency become evident in the ECoG trace. As LC activity begins to decrease, ECoG amplitude begins to increase and its frequency decreases.Similar changes can be observed in the HEEG (Aston-Jones)

Serotoninergic neurons along the midline of the brainstem



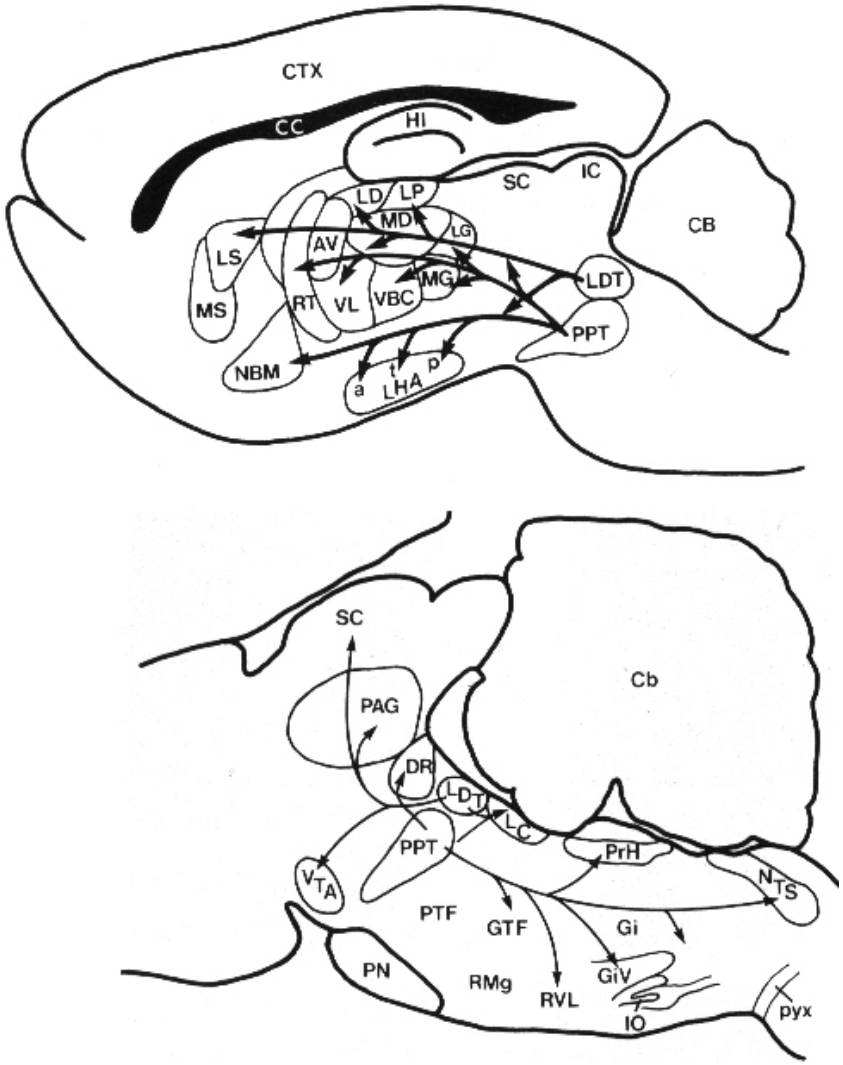
A, B coronal, **C** sagittal sections. Neurons in the B1-B3 groups project to the lower brains stem and spinal cord. Neurons in the raphe pontis (B6), median raphe (B7) and dorsal raphe (B8) project to the upper brainstem, hypothalamus, thalamus and cerebral corte.,

DR neuron activity and EEG

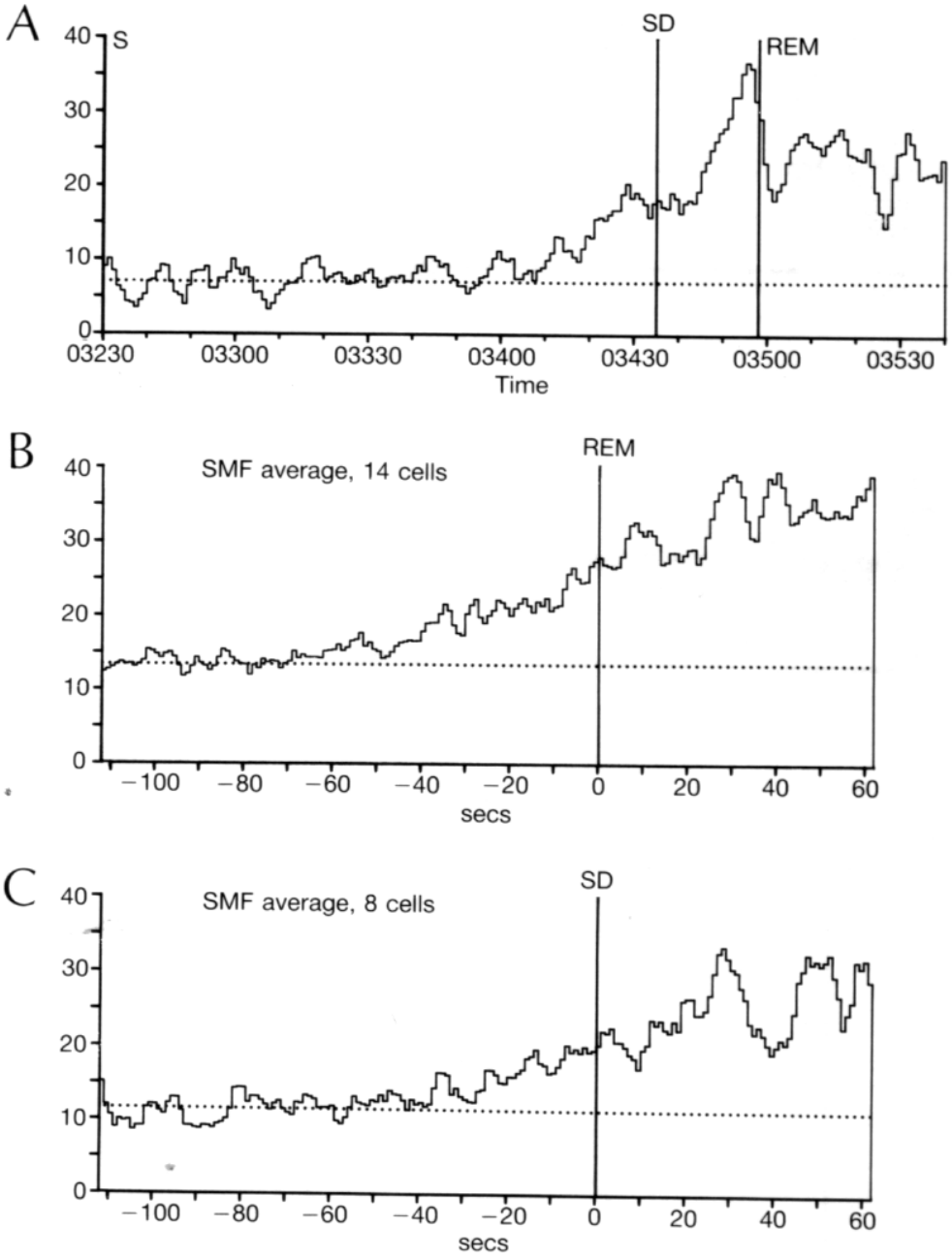


Polygraph records showing the activity of a typical dorsal raphe (DR) neuron and gross potentials across the sleep/wake cycle.Note the positive relationship between the firing rate and the level of behavioral arousal, as well as the cessation of unit activity during REM sleep. During REM sleep, ponto-geniculo-occipital (PGO) waves can be seen in the LGN trace and prominent rhythmic slow activity (theta) in the hippocampus (HIPP) trace (Jacobs and Fornal, 1999).

The mesopontine cholinergic nuclei



Summary of ascending and descending projections of the latero-dorsal (LTD) and pedunculo-pontine (PPT) tegmental nuclei. The most substantial ascending projections are to the thalamus, including relay and limbic nuclei. This pattern of thalamic innervation is in marked contrast to the surrounding tegmentum which innervates midline and intralaminar nuclei. The PPT also innervates the reticular (RT) nucleus, however, this nucleus also receive a substantial cholinergic innervation from the basal forebrain. A major target of the descending projection is the medial pontine reticular formation (Wainer et al., 1993).



PPT neuron firing and EEG

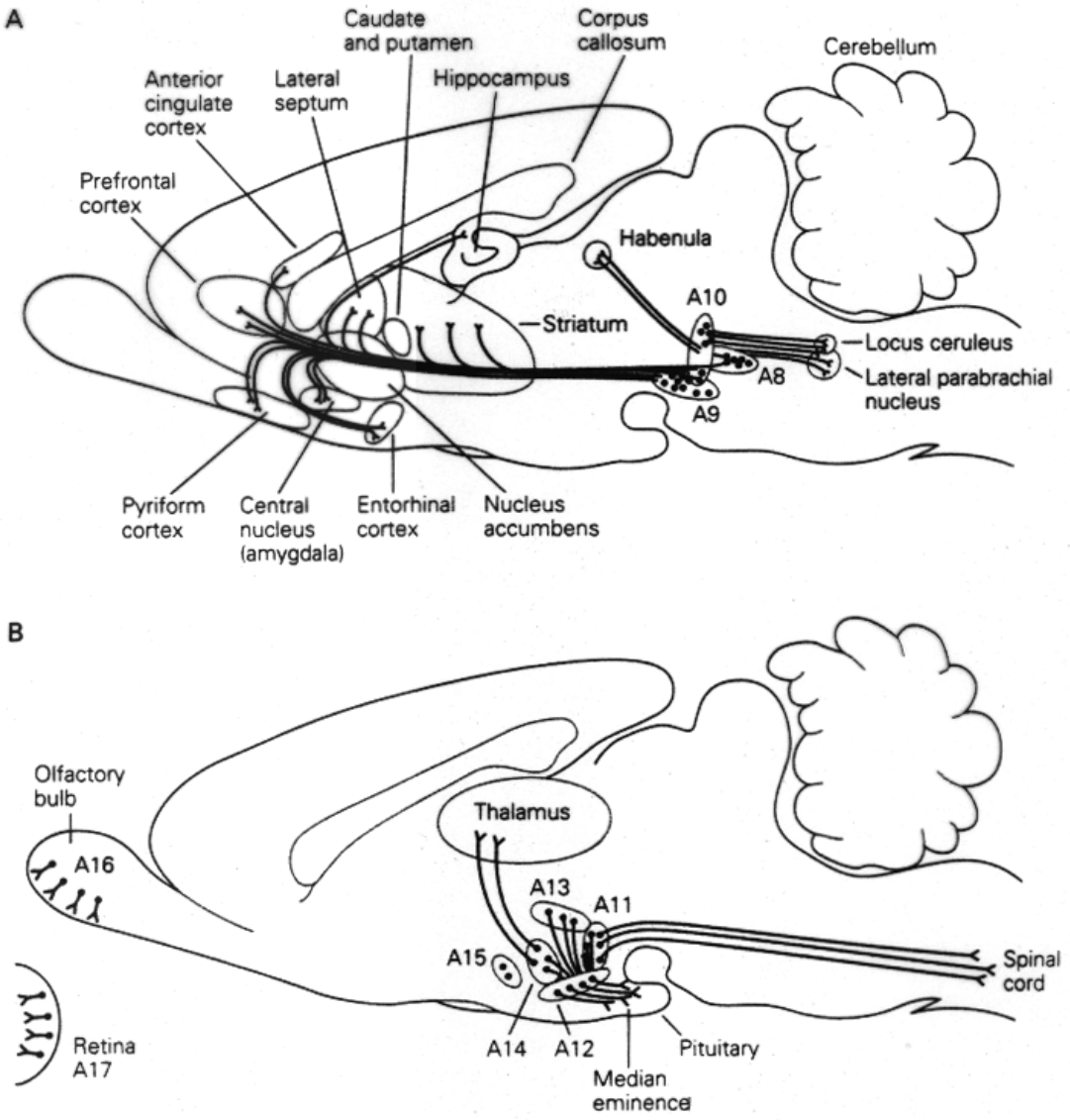
Brainstem PPT neurons of cat increase firing rates in advance of EEG desynchronization during REM sleep.Sequential mean frequency (SMF) of one (A), 14 (B) and eight PPT neurons.S= synchronized sleep, SD= transitional epoch. Time 0 of SD epoch is the appearance of the first PGO wave. The spontaneous firing baseline in S is indicated by dotted line. (Steriade, Data, Oakson, Pare).

Dopaminergic neurons in the brain

Dopaminergic neurons in the brain stem and hypothalamus.

A. Dopaminergic neurons in the substantia nigra (**A9** group) and the adjacent retrorubral field (**A8** group) and ventral tegmental area (**A10** group) provide a major ascending pathway that terminates in the striatum, the frontotemporal cortex, and the limbic system, including the central nucleus of the amygdala and the lateral septum.

B. Hypothalamic dopaminergic neurons in the **A11** and **A13** cell groups, in the zona incerta, provide long descending pathways to the autonomic areas of the lower brain stem and the spinal cord. Neurons in the **A12** and **A14** groups, located along the wall of the third ventricle, are involved with endocrine control. Some of them release dopamine as a prolactin release inhibiting factor in the hypophysial portal circulation.



Activity of DA neurons relate to prediction of reward

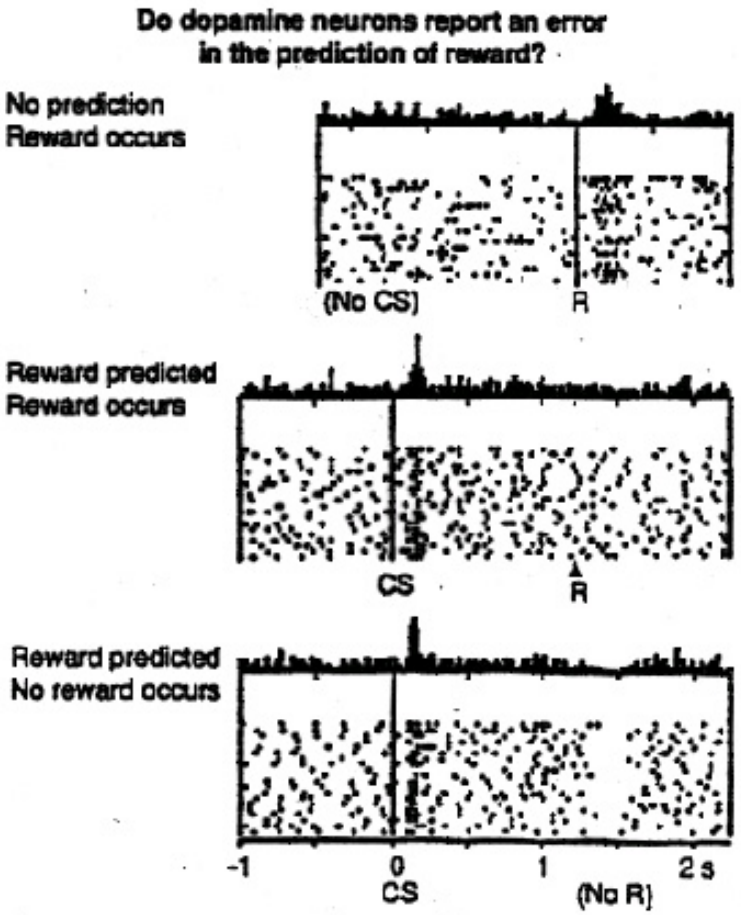
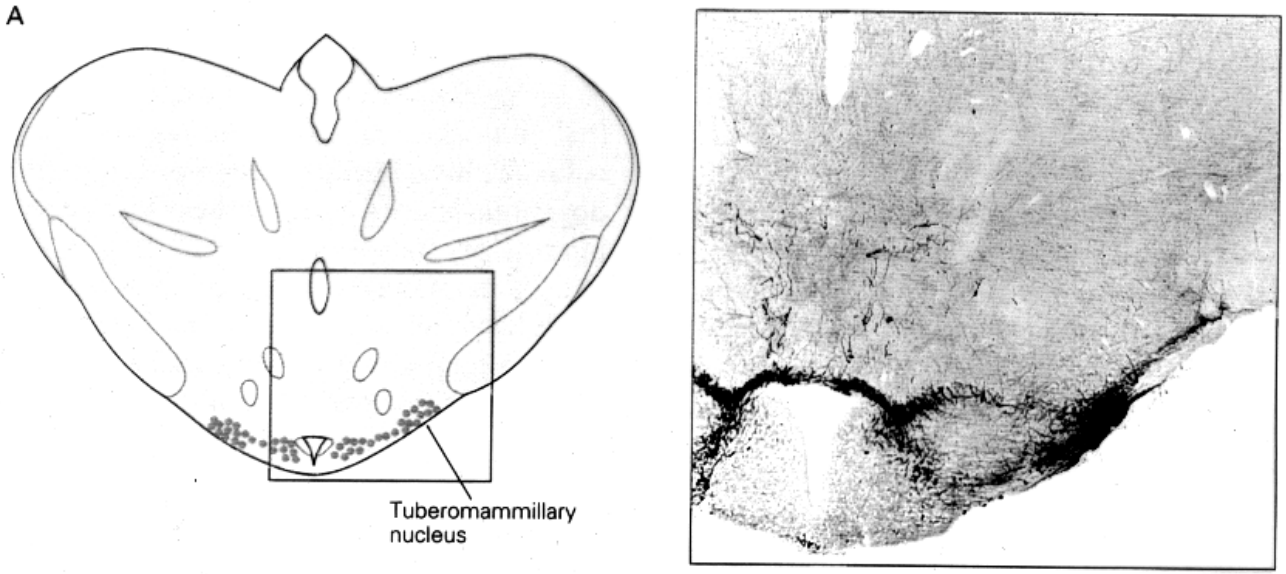
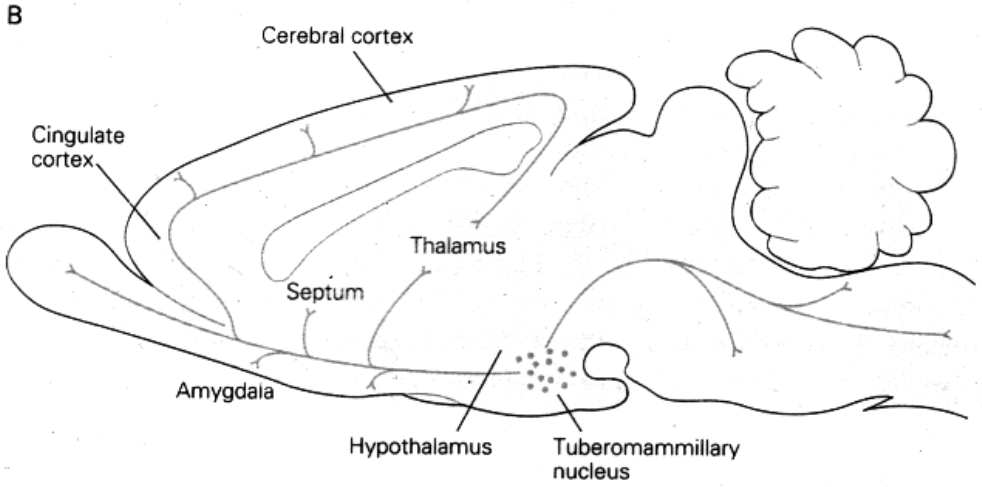


Fig. 1. Changes in dopamine neurons' output code for an error in the prediction of appetitive events. (**Top**) Before learning, a drop of appetitive fruit juice occurs in the absence of prediction—hence a positive error in the prediction of reward. The dopamine neuron is activated by this unpredicted occurrence of juice. (**Middle**) After learning, the conditioned stimulus predicts reward, and the reward occurs according to the prediction—hence no error in the prediction of reward. The dopamine neuron is activated by the reward-predicting stimulus but fails to be activated by the predicted reward (right). (**Bottom**) After learning, the conditioned stimulus predicts a reward, but the reward fails to occur because of a mistake in the behavioral response of the monkey. The activity of the dopamine neuron is depressed exactly at the time when the reward would have occurred. The depression occurs more than 1 s after the conditioned stimulus without any intervening stimuli, revealing an internal representation of the time of the predicted reward. Neuronal activity is aligned on the electronic pulse that drives the solenoid valve delivering the reward liquid (top) or the onset of the conditioned visual stimulus (middle and bottom). Each panel shows the peri-event time histogram and raster of impulses from the same neuron. Horizontal distances of dots correspond to real-time intervals. Each line of dots shows one trial. Original sequence of trials is plotted from top to bottom. CS, conditioned, reward-predicting stimulus; R, primary reward.

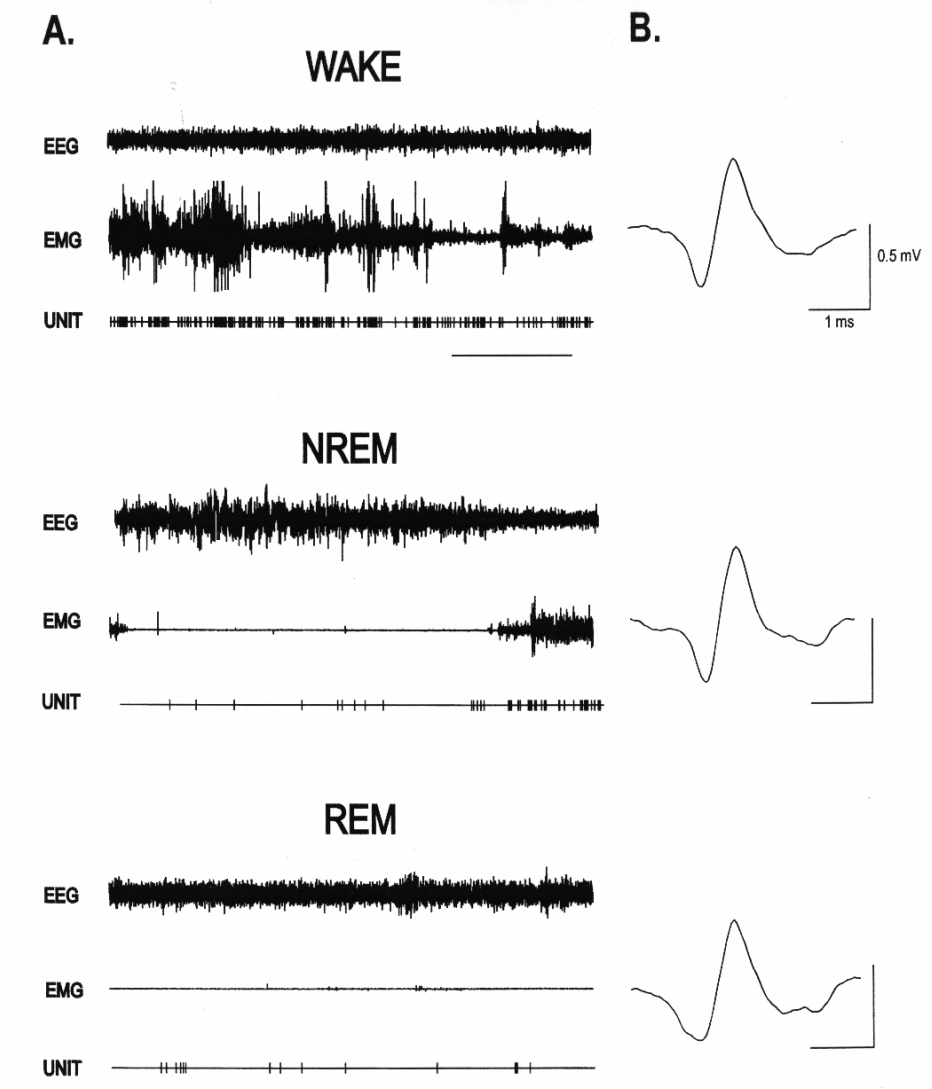
Histaminergic neurons in the postero-lateral hypothalamus





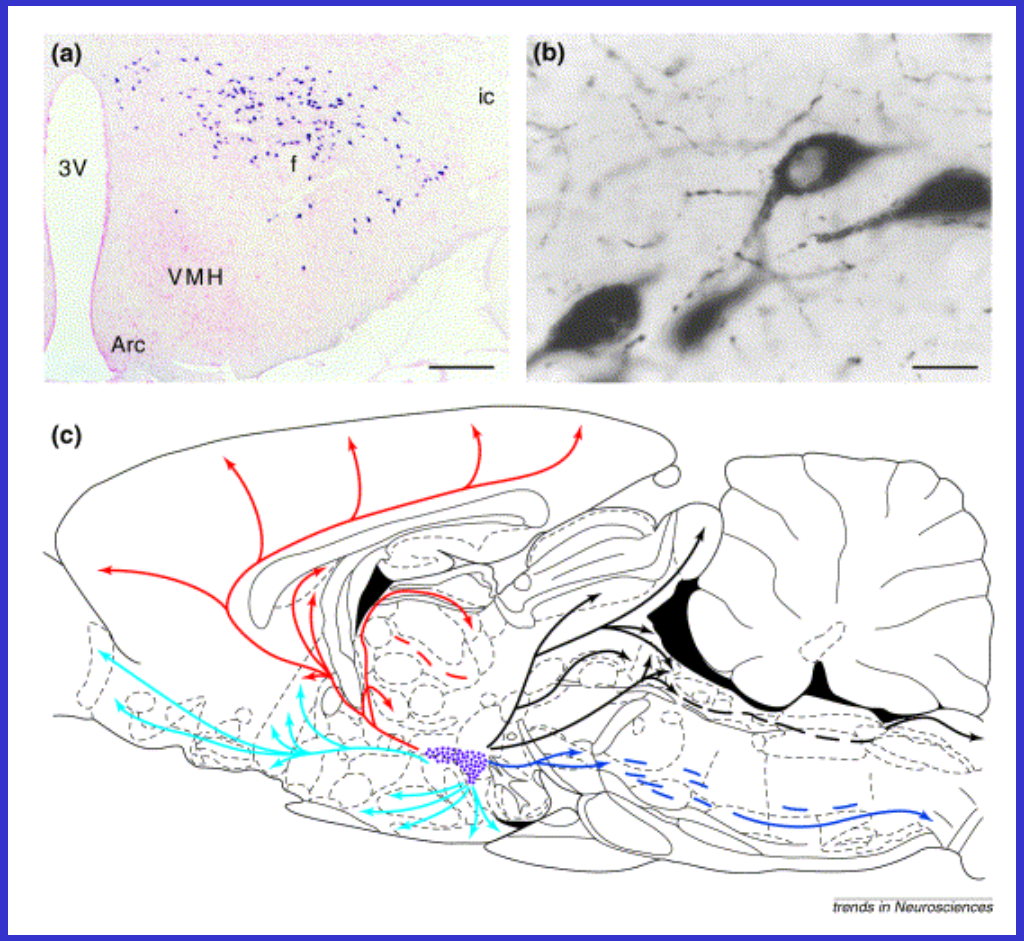
Histaminergic cells are clustered in the tuberomammilary nucleus in the posterior-lateral hypothalamus. The histaminergic neurons innervate the entire neuraxis, from the cerebral cortex to the spinal cord (From Saper, 2000)

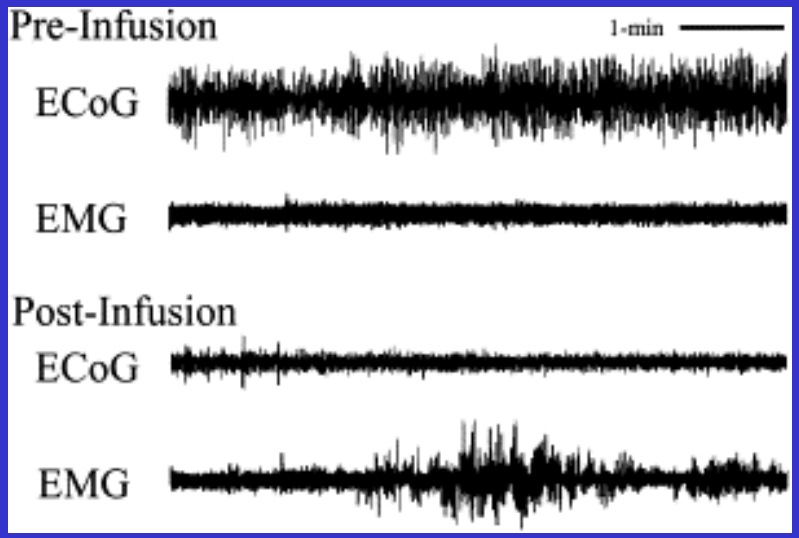
Waking-related neuron in the post-lat. hypothalamus



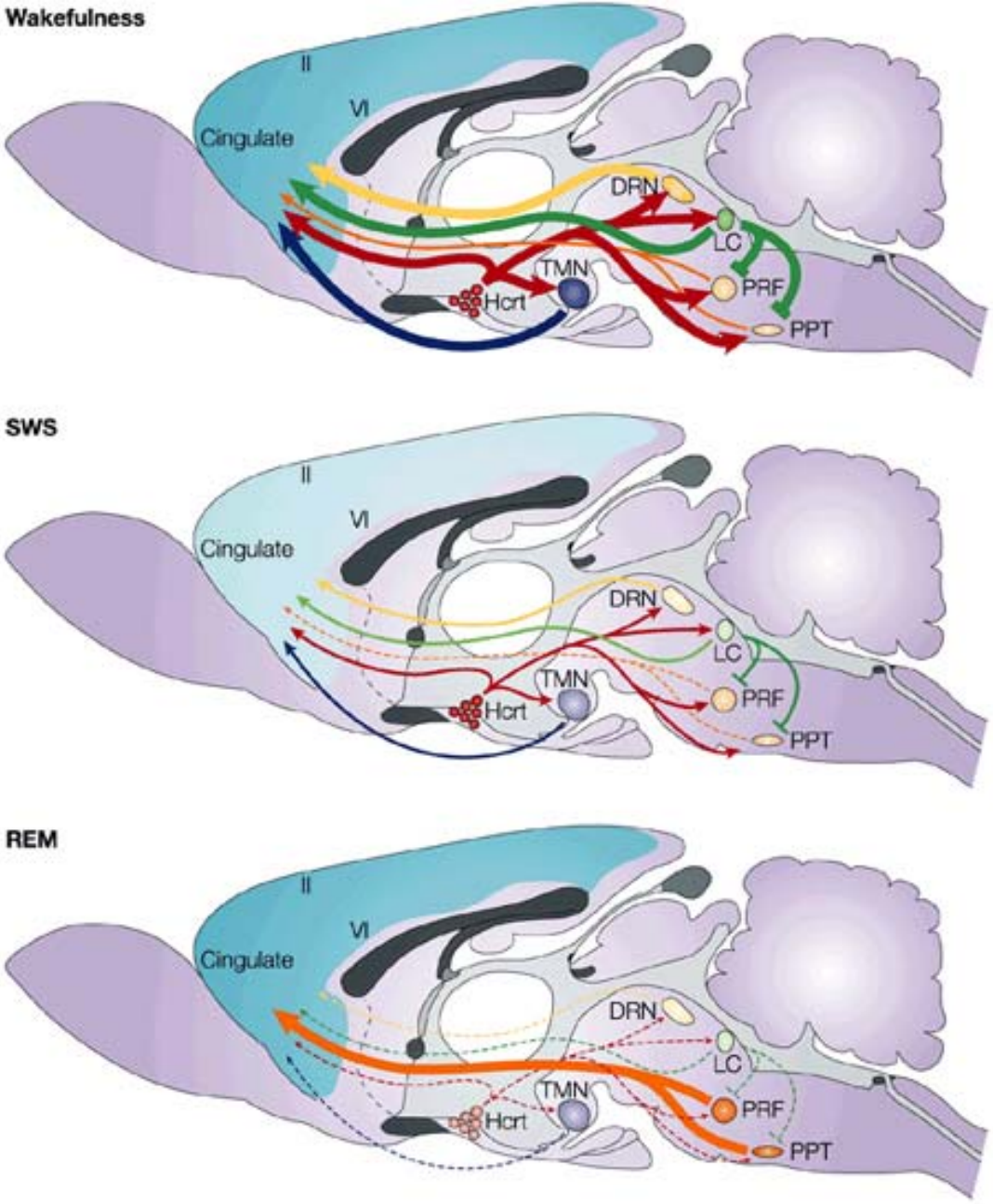
Waking-related neuron in the post-lat hypothalamus, in the area that is rich in histaminergic neurons. Unit firing in waking: 2.03 Hz, NREM: 0.15 Hz and REM sleep: 0.14 Hz. Note the resumption of firing coincident with the appearance of waking in the second trace. Steininger et al., 1999.

The orexin/hypocretin system of the lateral hypothalamus





Ascending modulatory systems: The present



DRN-5HT

LC-NE

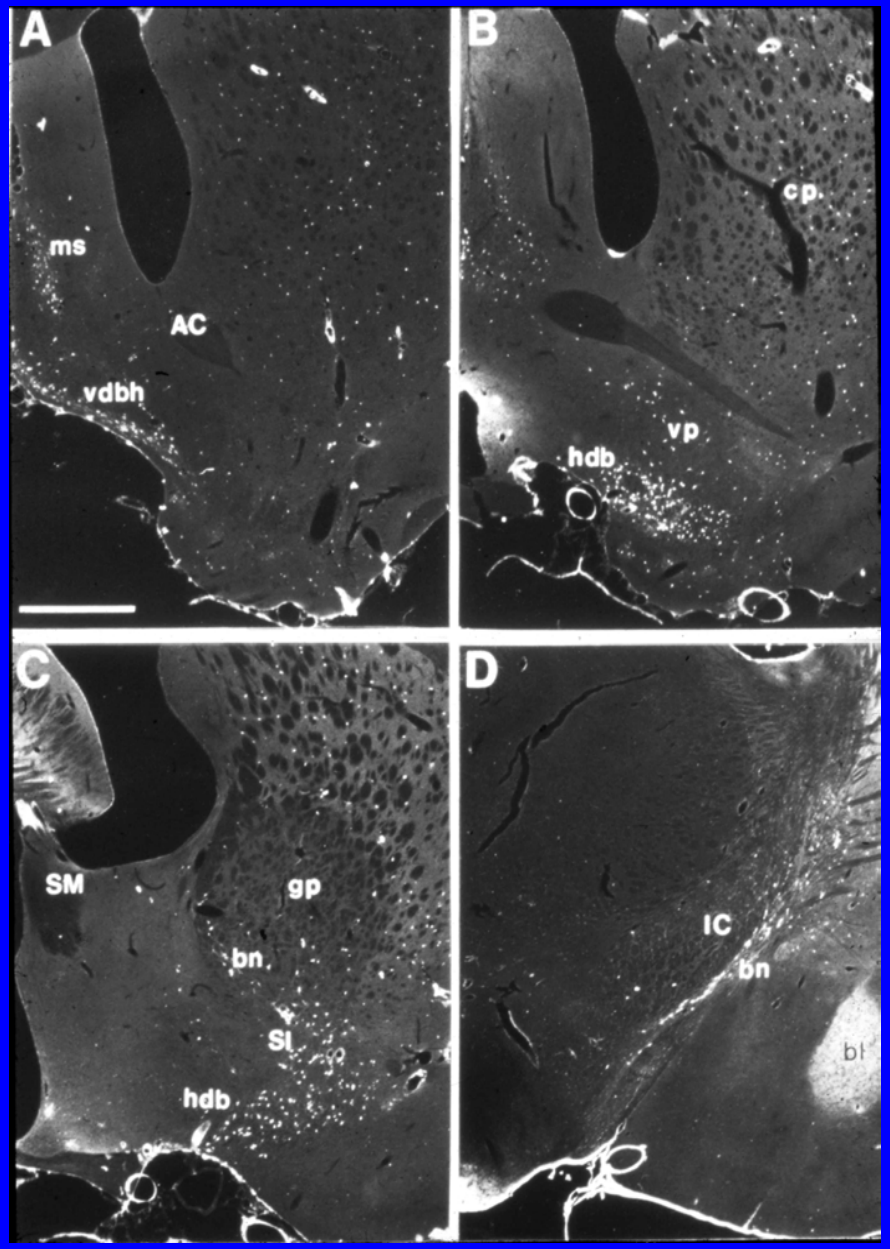
PPT-ACh

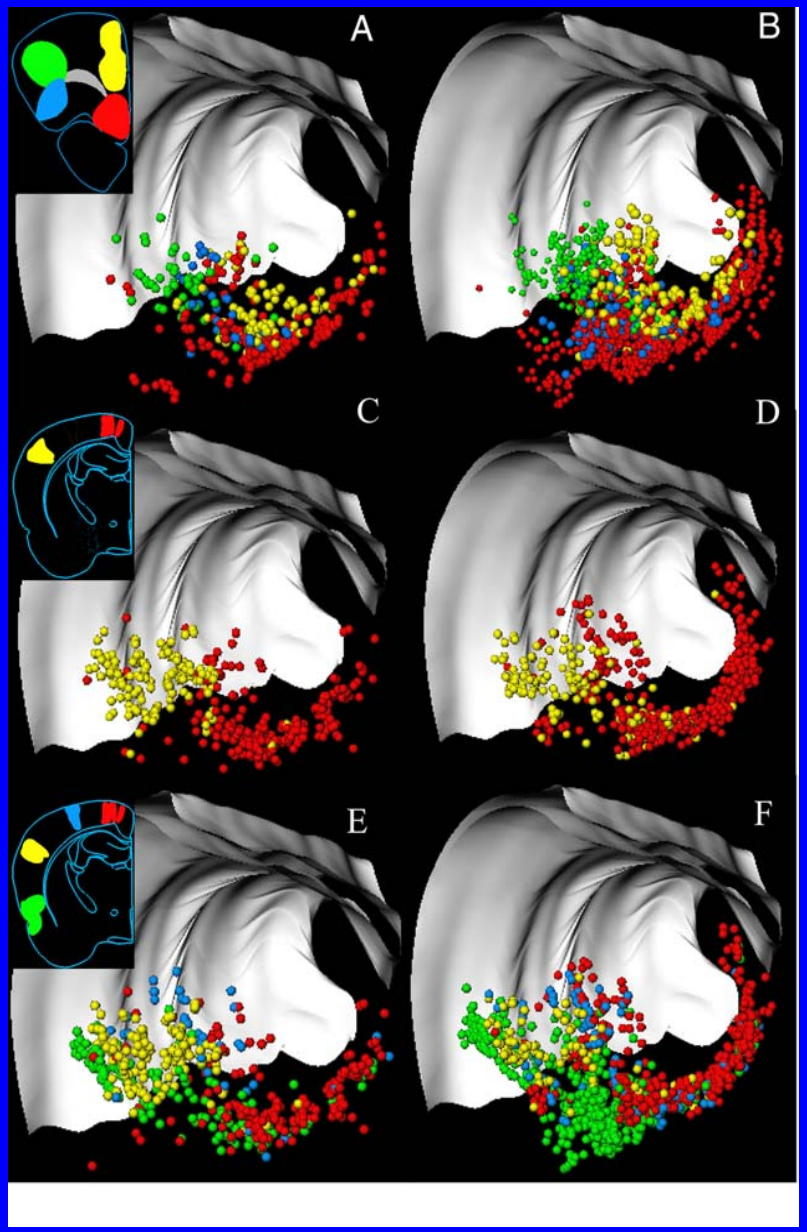
TMN-His

Hcrt/Orexin

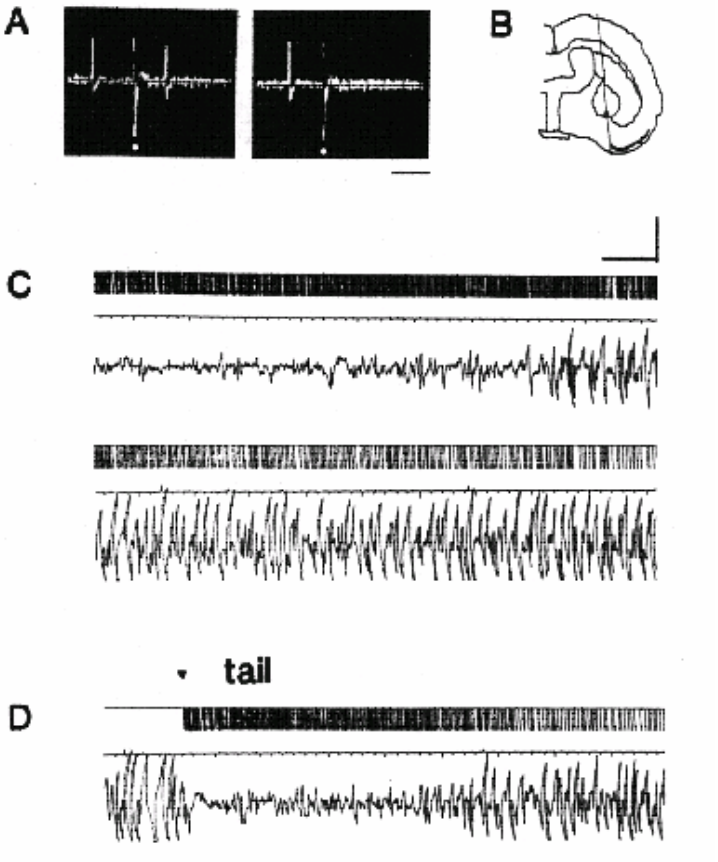
Sutcliffe and De Lecea, 2002;

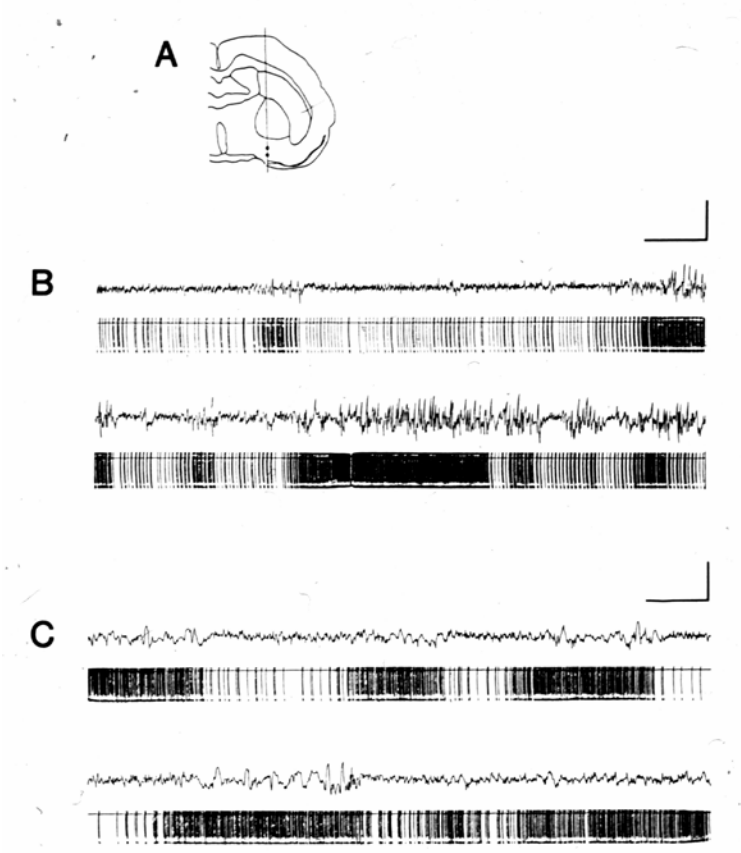
DISTRIBUTION OF CHOLINERGIC CORTICOPETAL NEURONS IN RAT





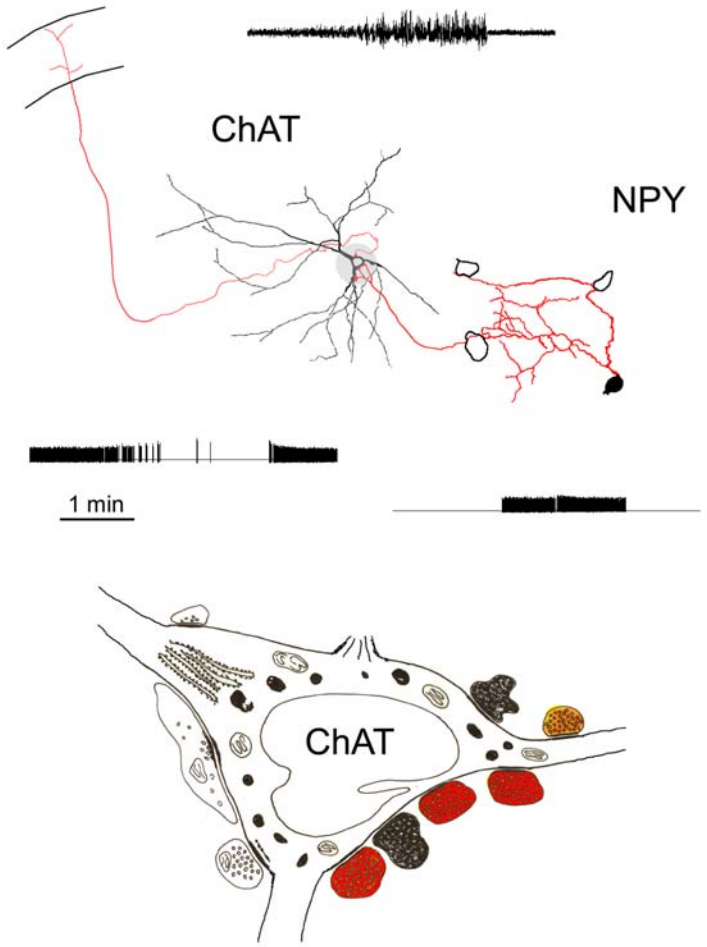
BF neurons are electrophsyiologically heterogeneous



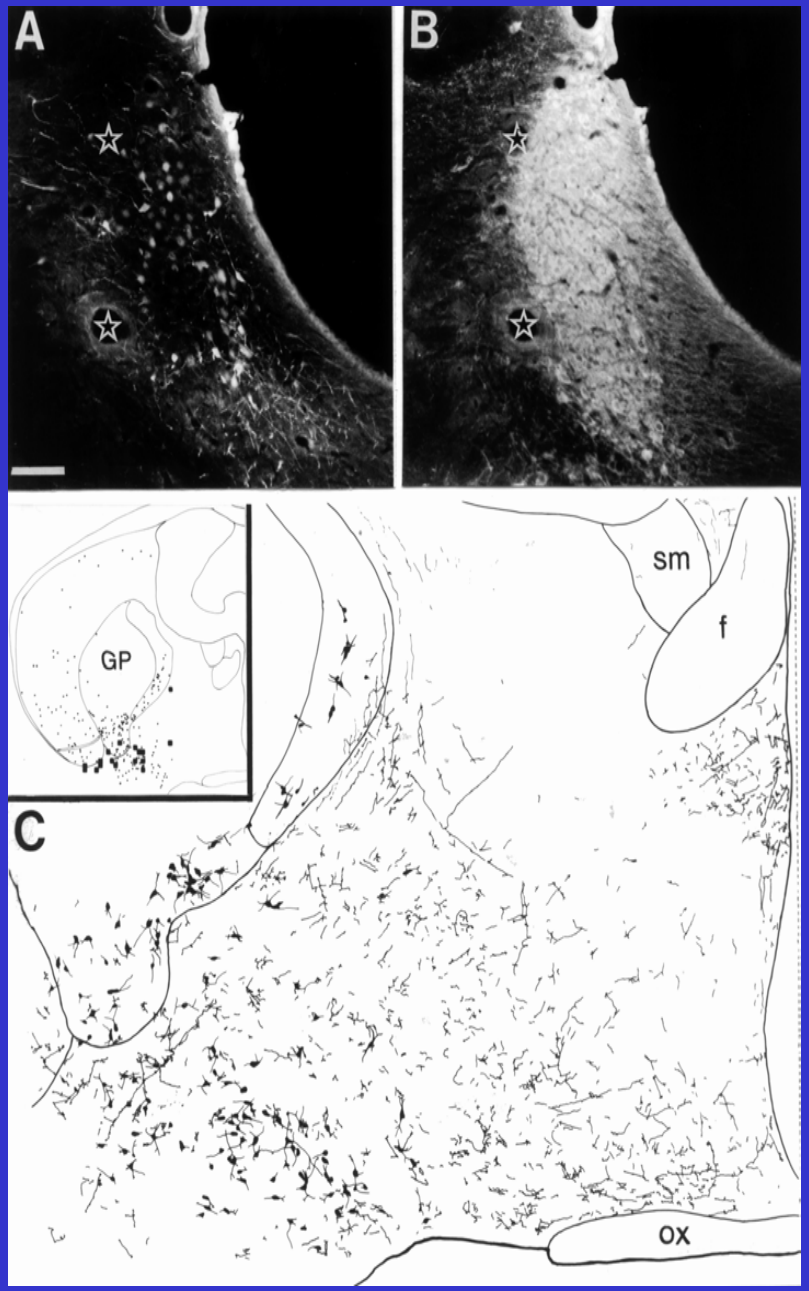


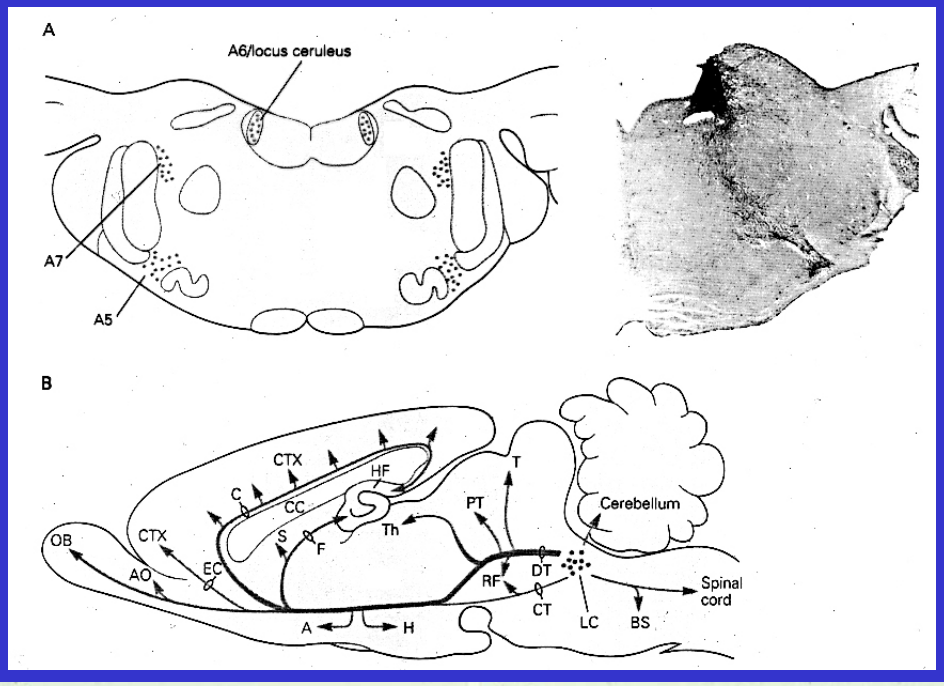
Detari et al., 1987

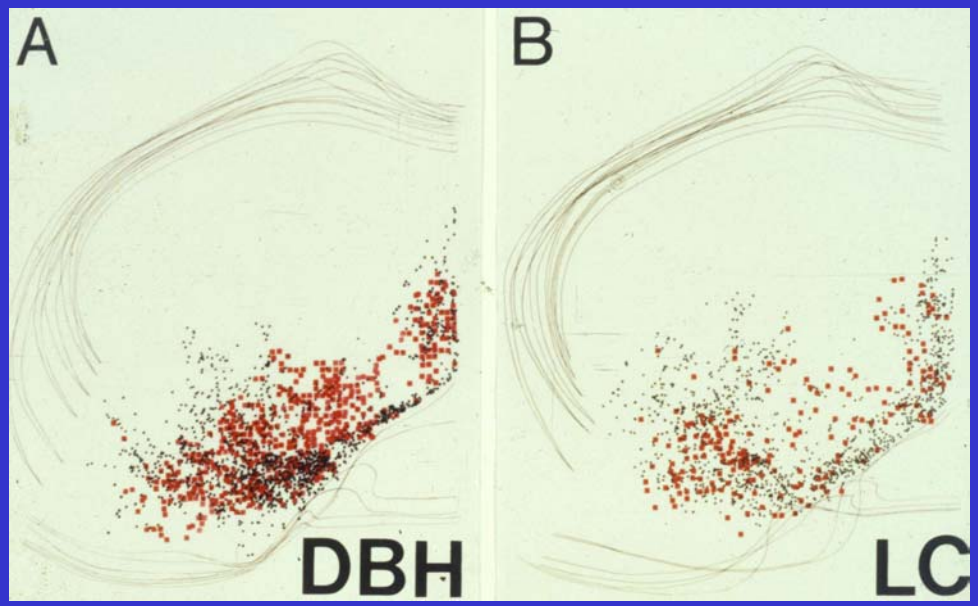
Putative functional circuitry in the BF



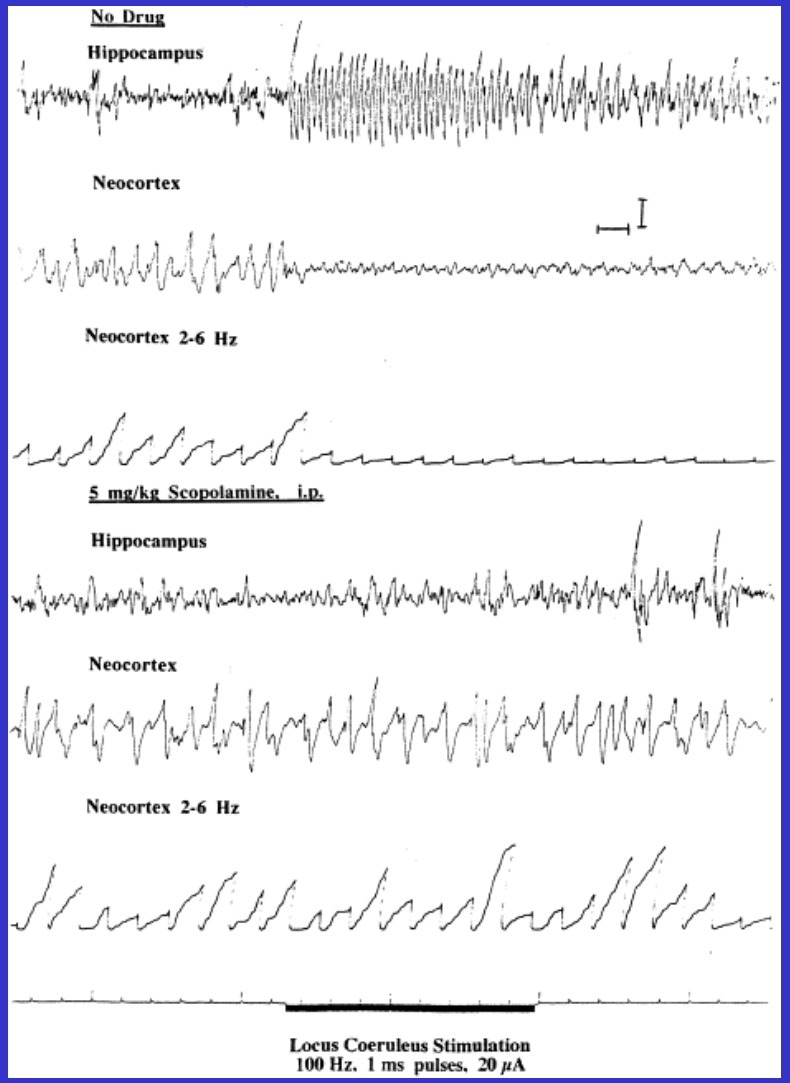
Diffuse input to BF: LC axons



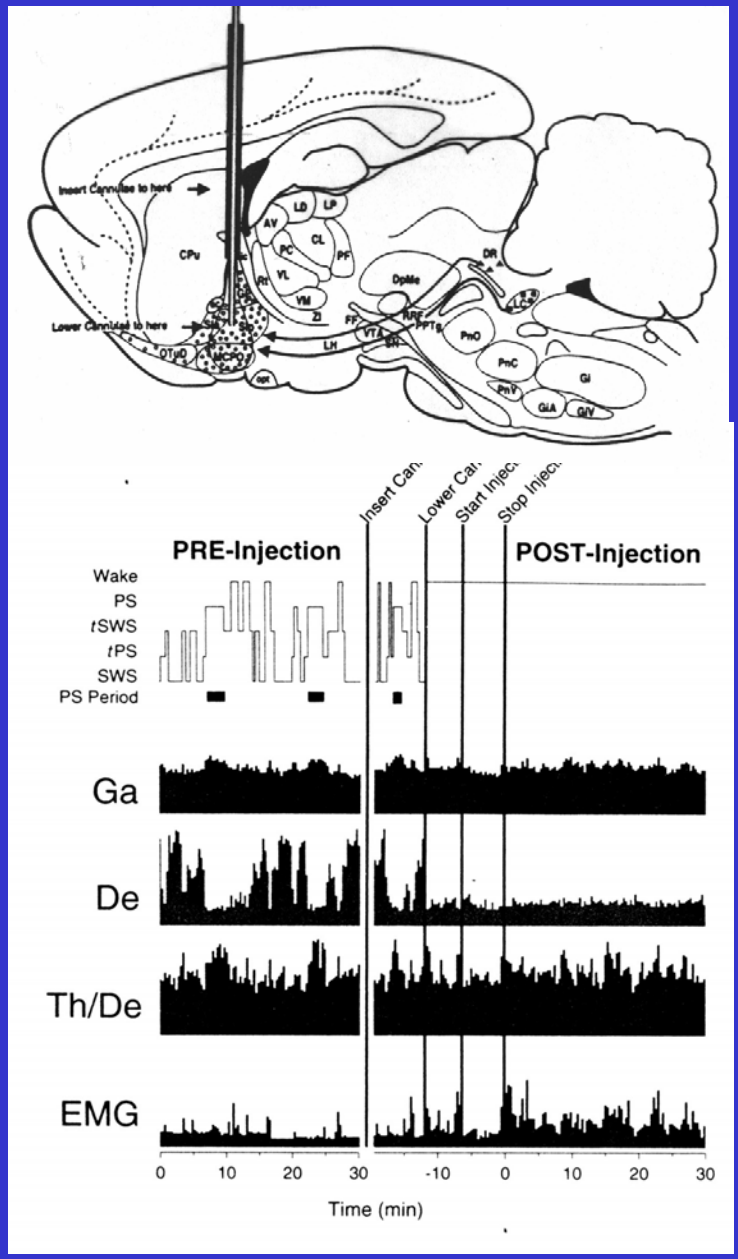




LC can affect the cortex via the BF

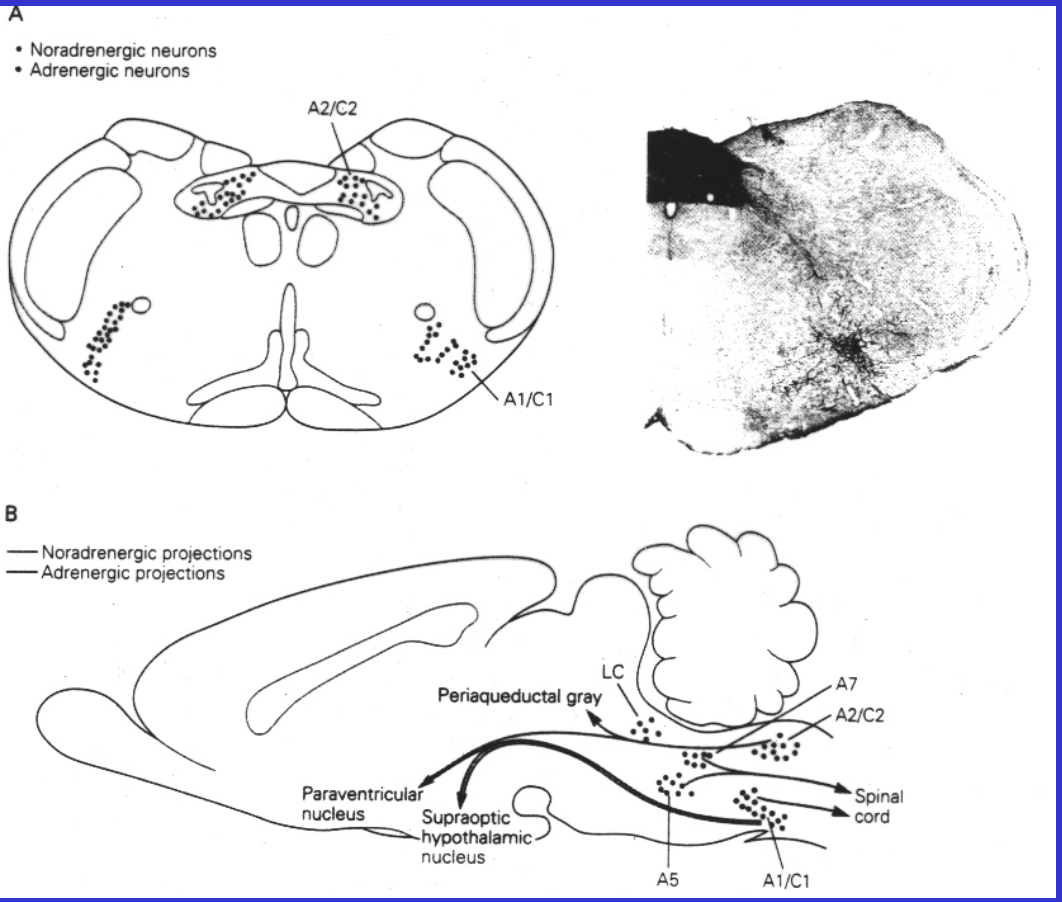


Dringenberg and Vanderwolf, 1998

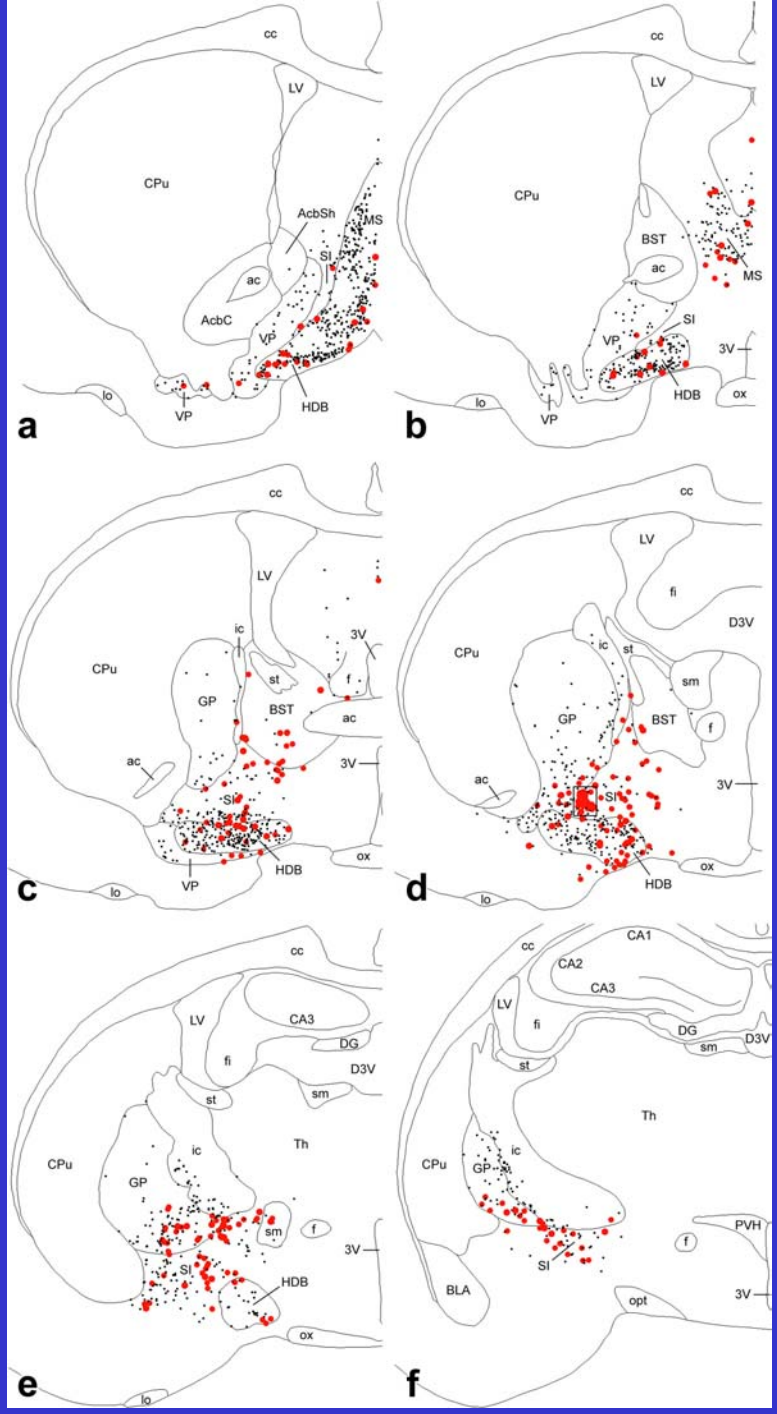


Cape and Jones, 1998

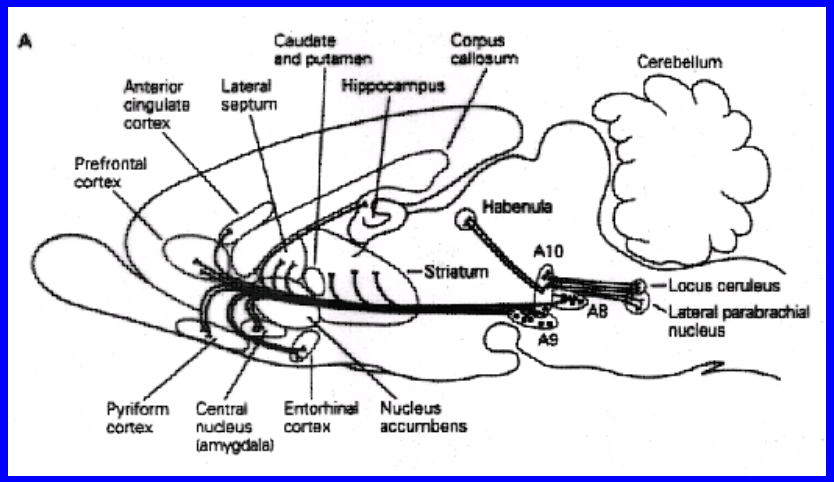
Diffuse input to BFC cells: adrenaline input from the medulla

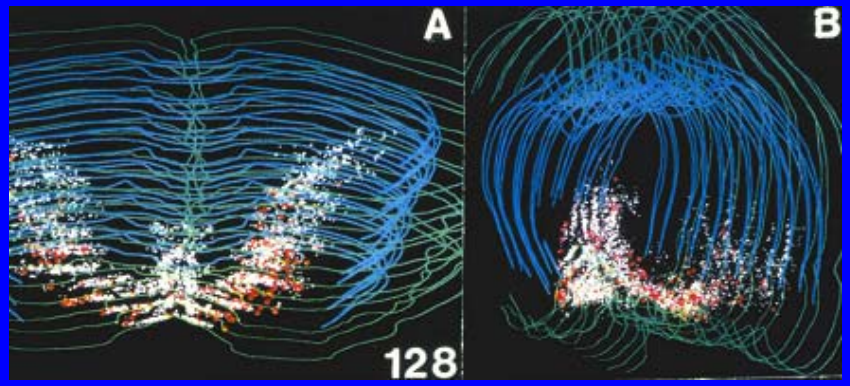


Hajszan and Zaborszky, 2002

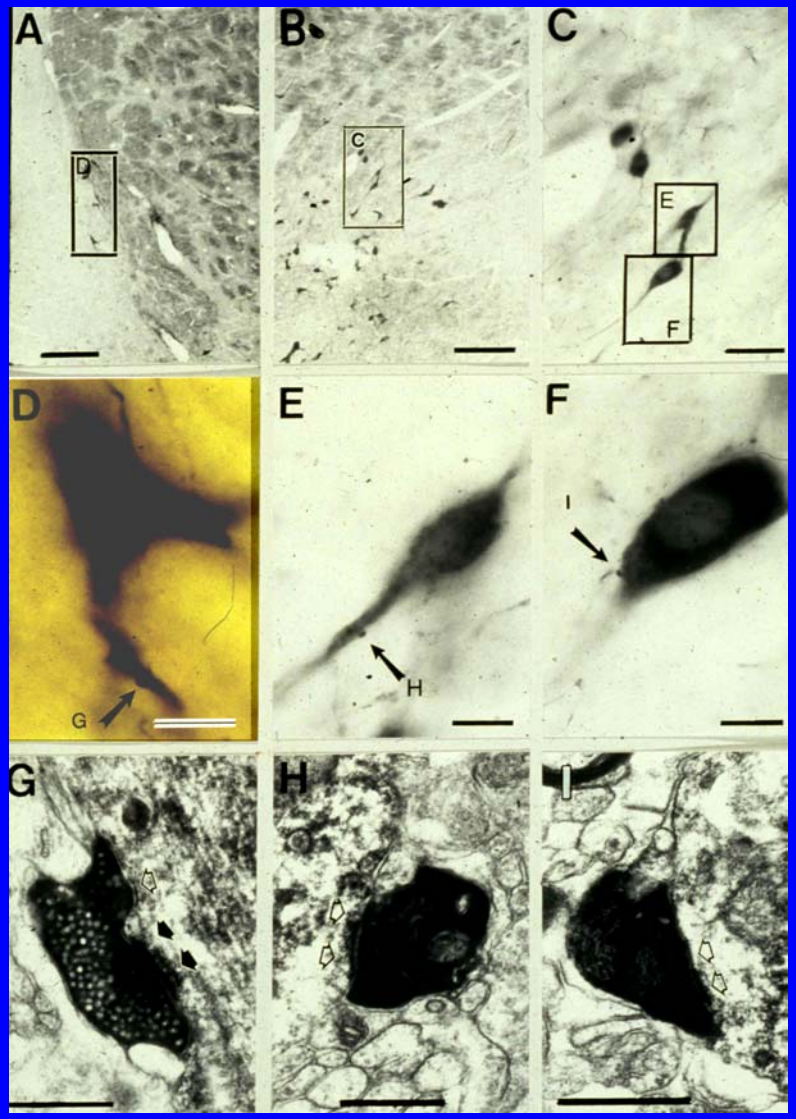


CHOLINERGIC NEURONS RECEIVE SYNAPSES FROM THE MIDBRAIN DOPAMINERGIC AREA



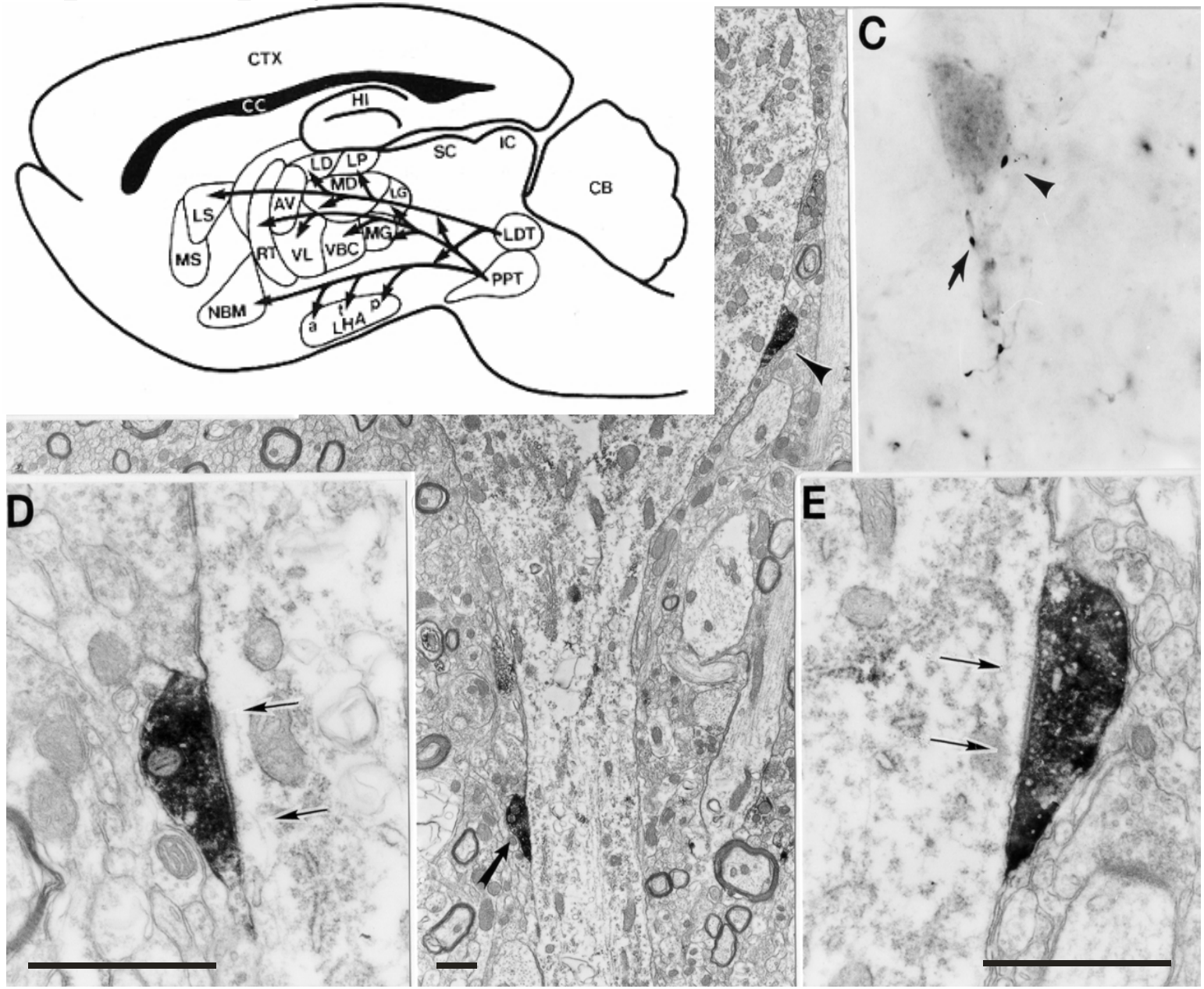


Ventral midbrain axons contact CH and PV cells in the BF

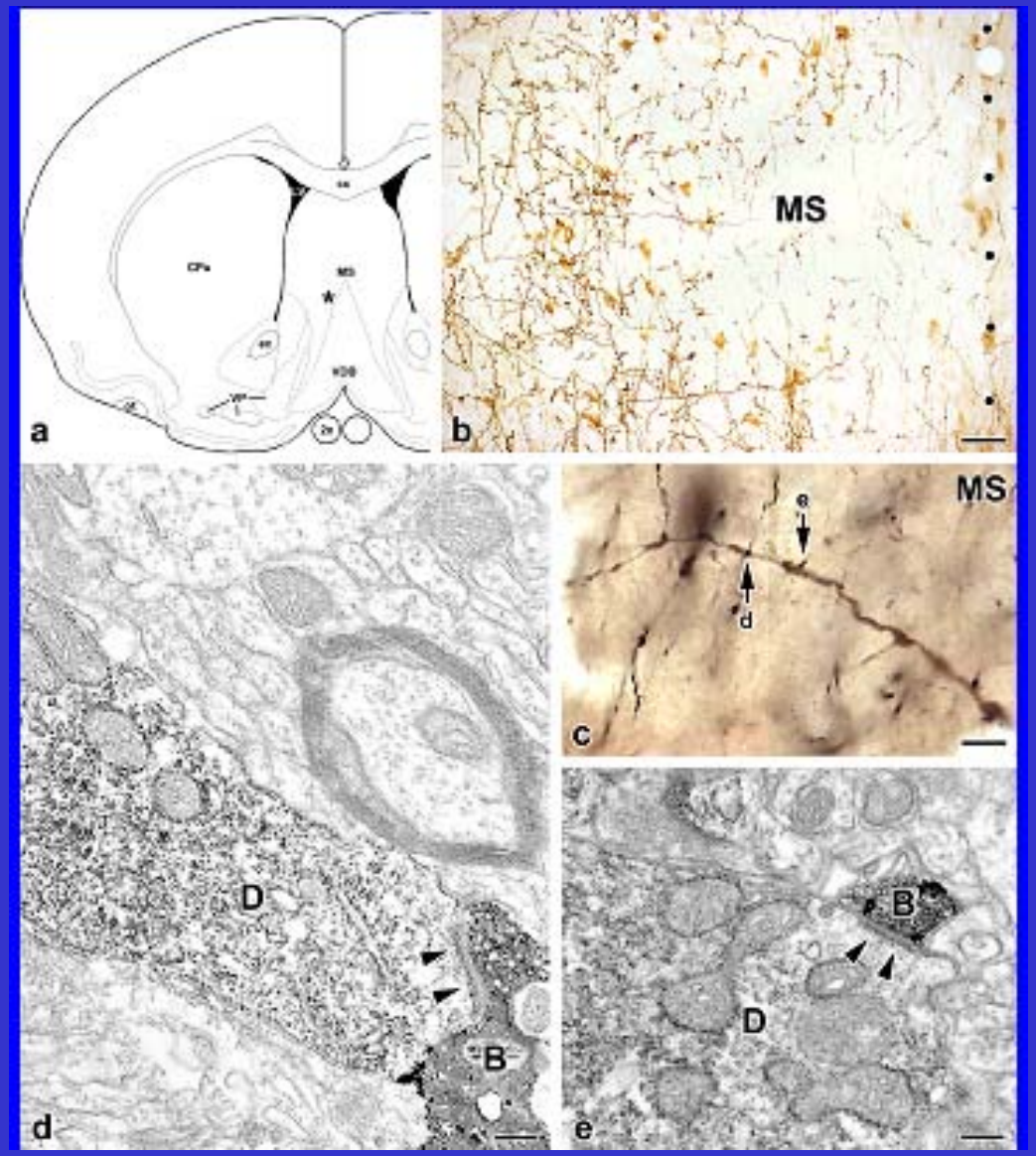


Gaykema and Zaborszky, 1996

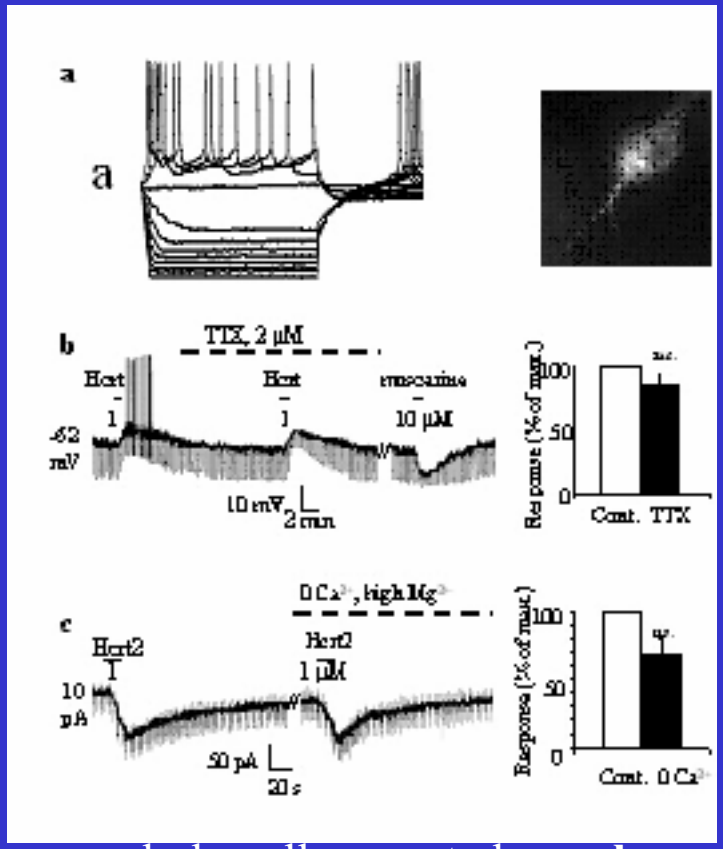
Mesopontine projections to PV (and CH) neurons in the BF



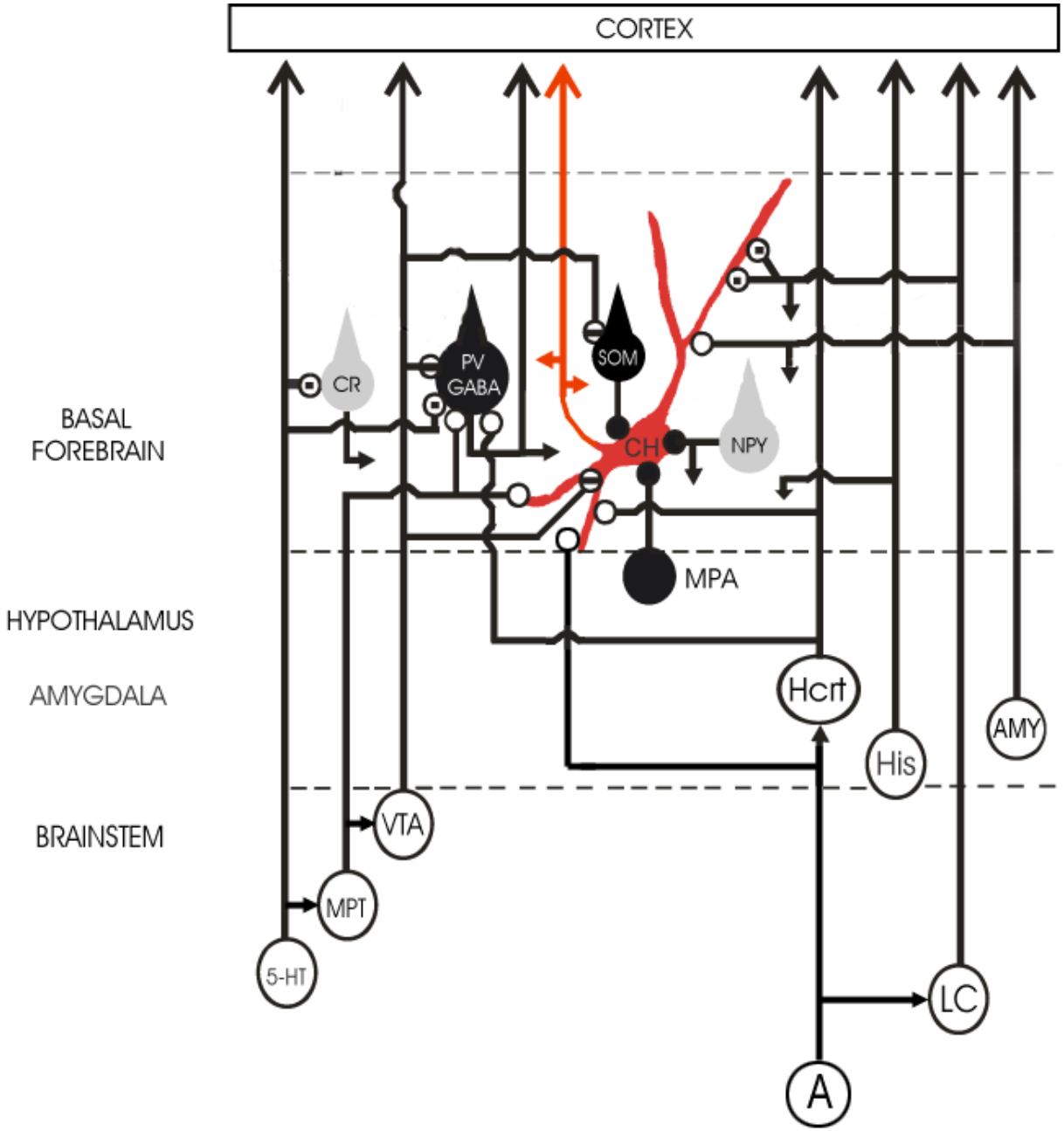
Diffuse input to BF: hypocretin axons



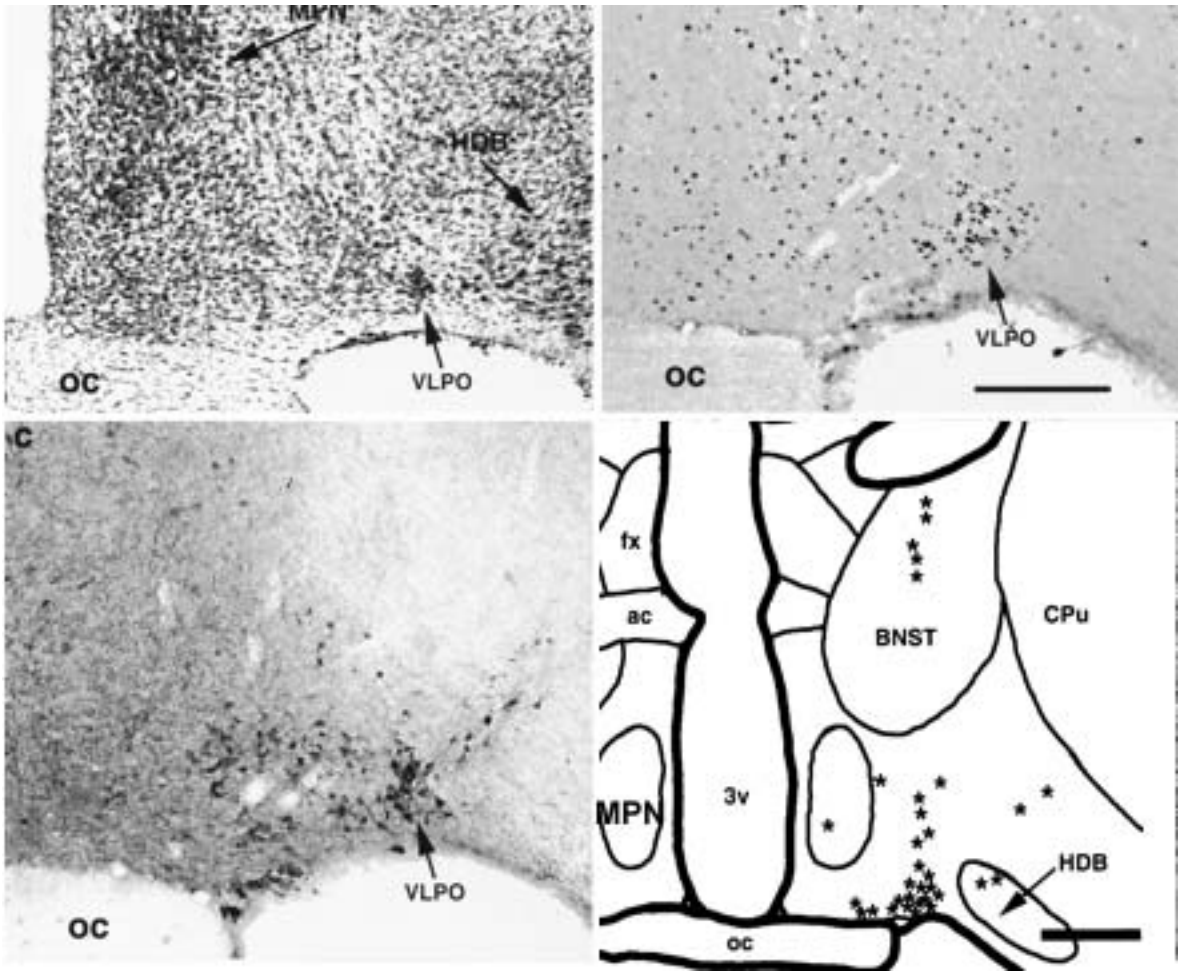
Wu, Zaborszky, Hajszan, van den Pol, Alreja, in press



a: whole-cell current clamp; **b**: current clamp showing the depolarizing effect of Hcrt. **c**: voltage clamp (-65 mV) in which Hcrt2 induced an inward current that persisted in zero Ca2+, high Mg2+ ACSF.

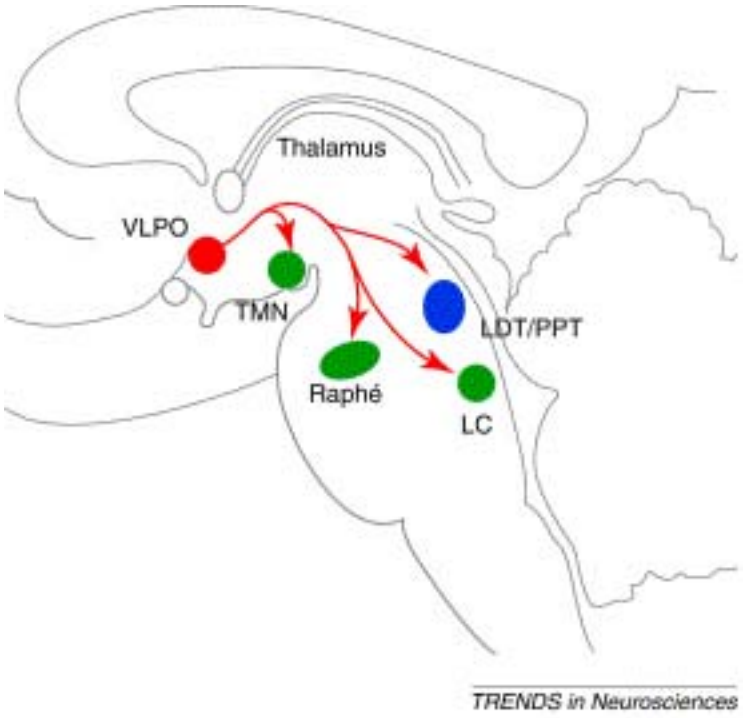

CORTEX
BASAL FOREBRAIN
HYPOTHALAMUS
AMYGDALA
BRAINSTEM
CR
PV GABA
SOM
CH
NPY
MPA
Hcrt
His
AMY
VTA
MPT
5-HT
LC
A

Sleep-active neurons in the VLPO



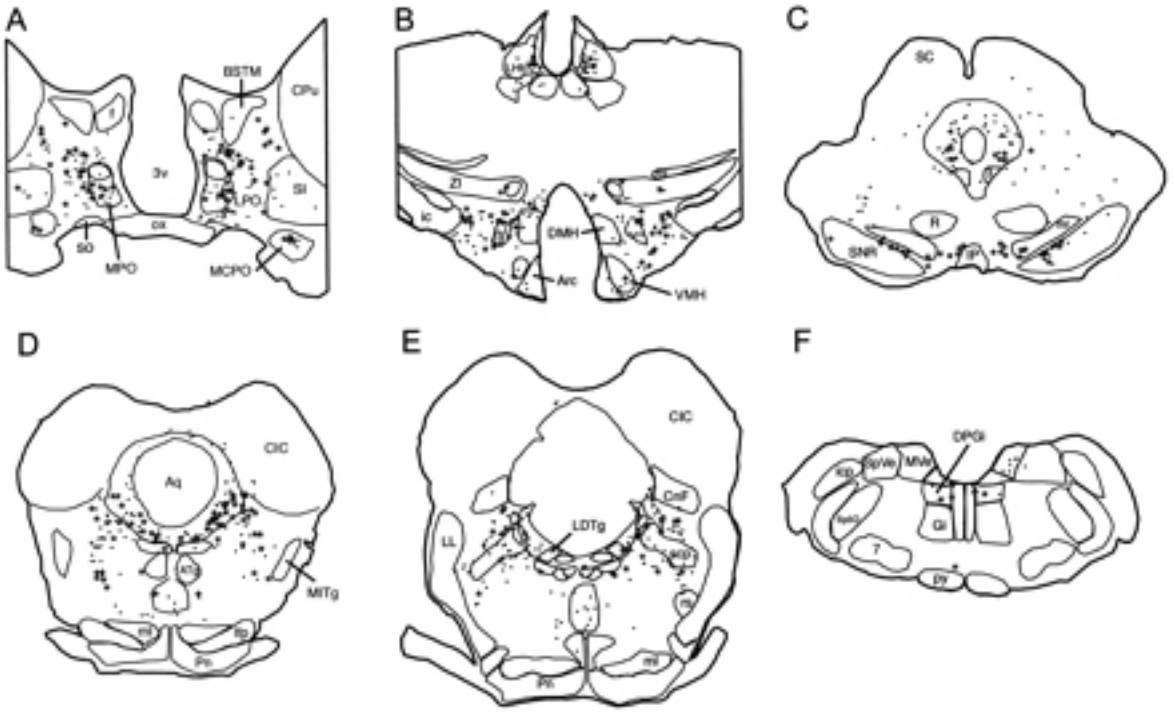
A: Giemsa-stained section showing a small triangular cluster of cells (ventrolateral preoptic nucleus).b: Fos-ir neuronal nuclei in the VLPO after 1 hr period spent predominantly asleep. C: the VLPO is demarcated as a galanin/GABA positive cell group. Lower right: retrogradely labeled neurons that project to the tuberomammilary nucleus(Sherin et al., 1998).

Projections from the VLPO



Saper et al., 2001

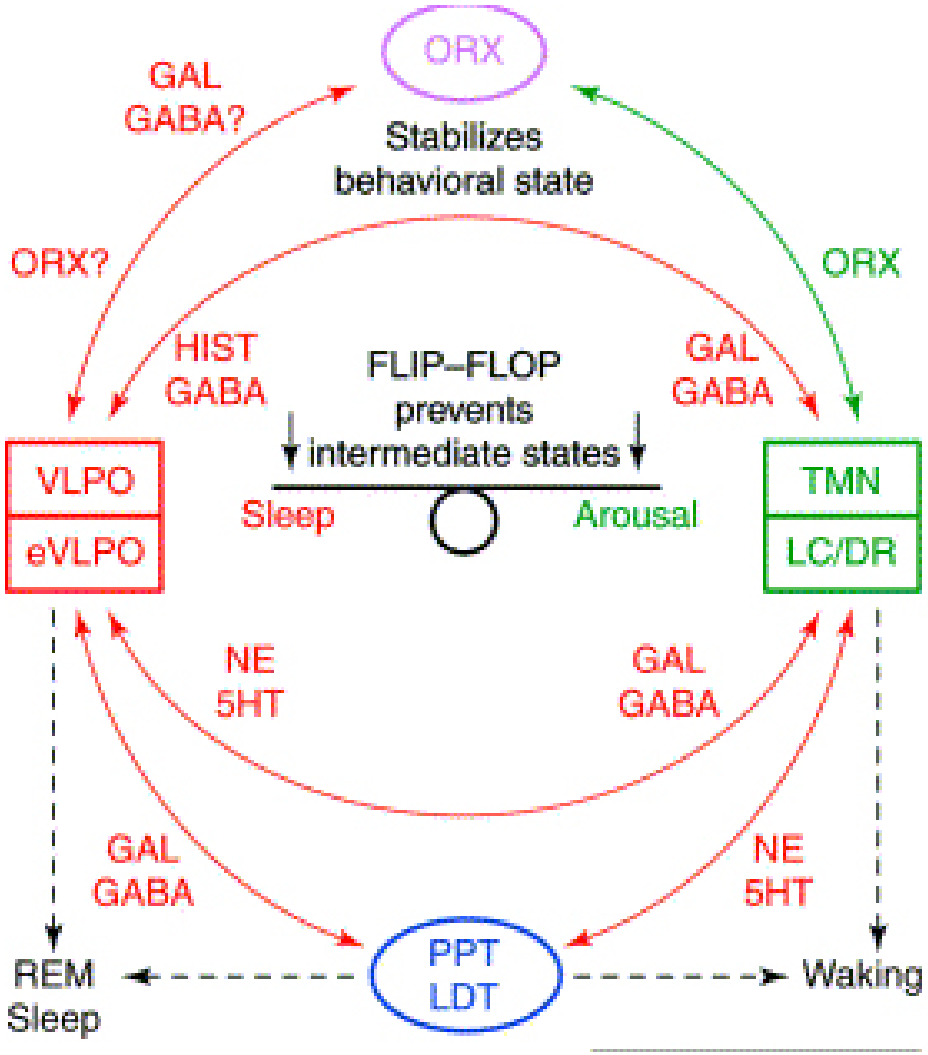
GABA release in the DR during REM



GABAergic afferents to the DRNm using retrograde tracing with cholera toxin B and glutamic acid decarboxylase immunohistochemistry. Stars corresponds to double-labeled cells. Note abundant projection from the medial (MPO) and lateral preoptic area (LPO) and pontine ventarl periaqueductal gray (Gervasoni et al., 2000).

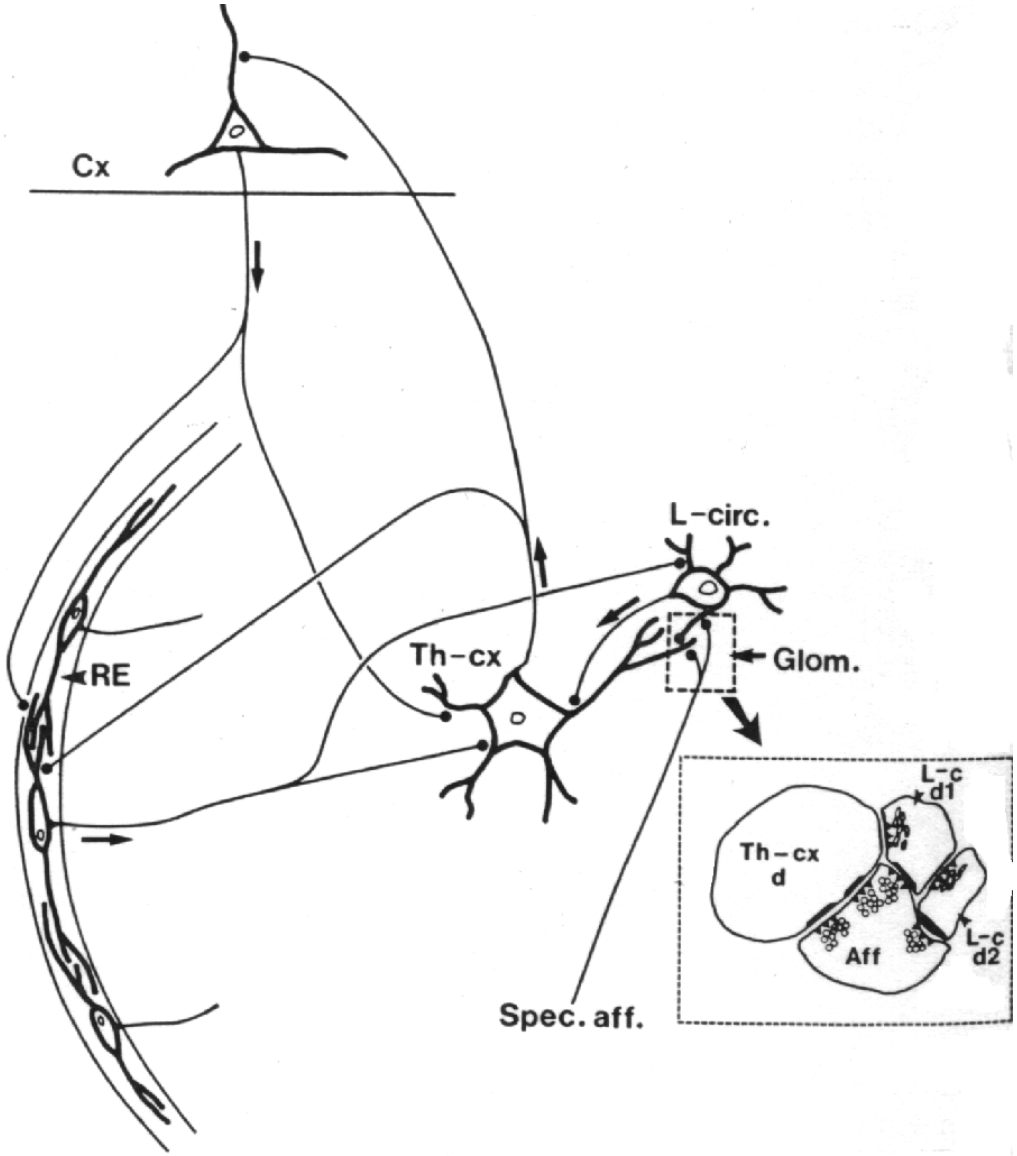
The cessation of firing of 5-HT raphe neurons is a key controlling event of REM. REM sleep is accompanied by a selective increase in GABA release, but not glutamate in the DRN in naturally sleeping cats (Nitz and Siegel, 1997).

The flip-flop switch



A model for reciprocal interactions between sleep- and wake-promoting brain regions, which produces a flip–flop switch. Aminergic regions such as the TMN, LC and DR promote wakefulness by direct excitatory effects on the cortex and by inhibition of sleep-promoting neurons of the VLPO. During NREM sleep, the VLPO inhibits amine-mediated arousal regions through GABAergic and galaninergic (GAL) projections. The inhibition of the amine-mediated arousal system disinhibits VLPO neurons, further stabilizing the production of sleep. Orexin/ (ORX) neurons in the lateral hypothalamic area might further stabilize behavioral state by increasing the activity of aminergic neurons, thus maintaining consistent inhibition of sleep-promoting neurons in the VLPO and REM-promoting neurons in the PPT–LDT (Saper et al., 2001).

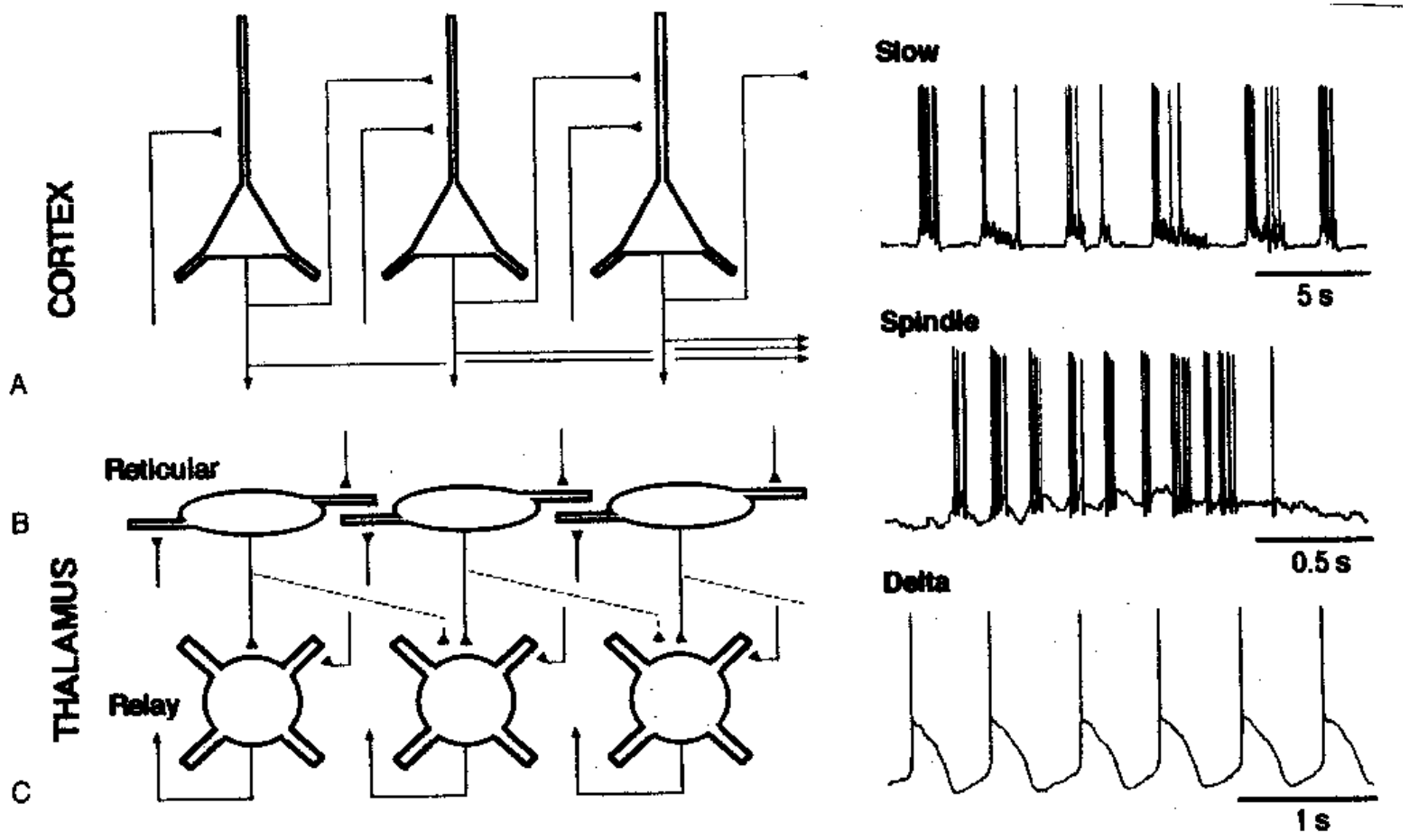
Synaptic organization of the thalamus



RE: reticular thalamic nucleus; Th-cx: thalamocortical n.; Cx: pyramidal n.; L-circ: local circuit n.; Inset: synaptic contacts within a glomerulus

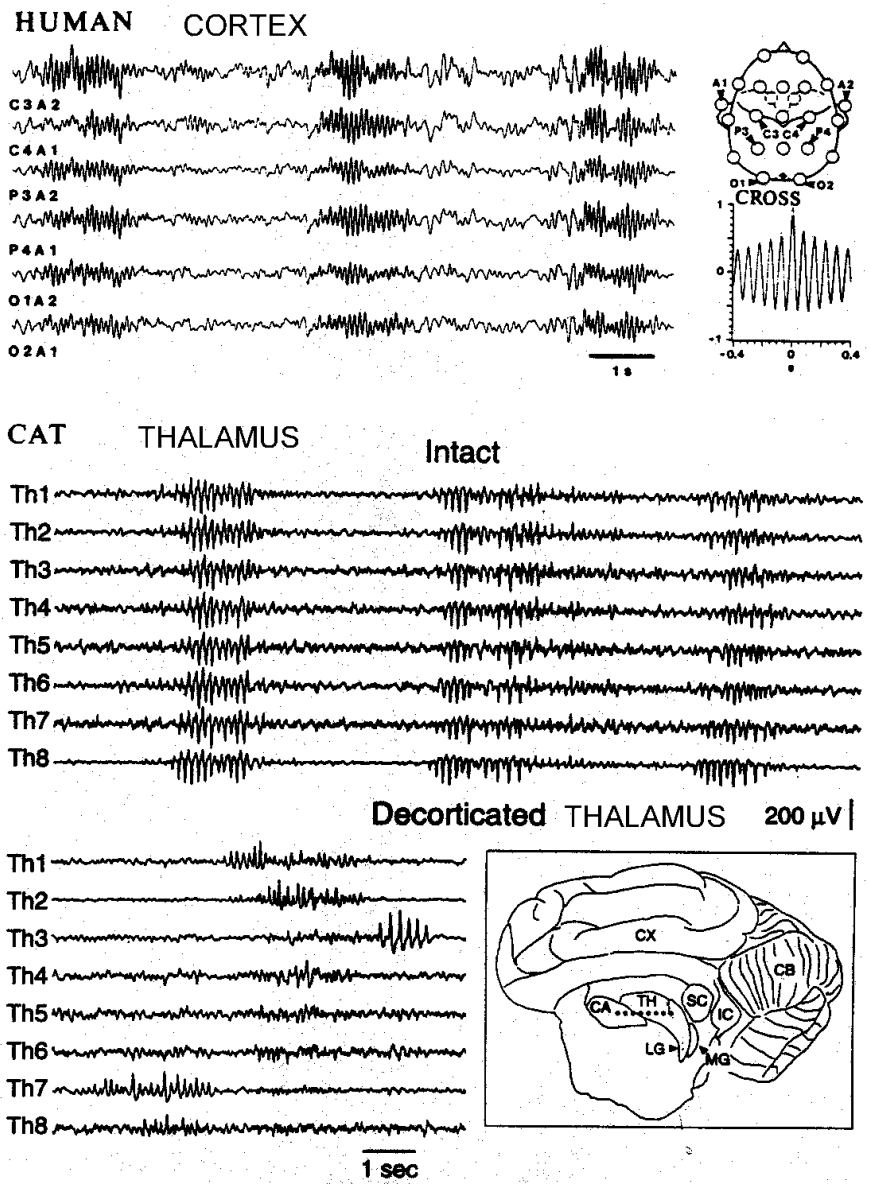
(Llinas and Steriade, 1988)

Different types of NREM sleep oscillations



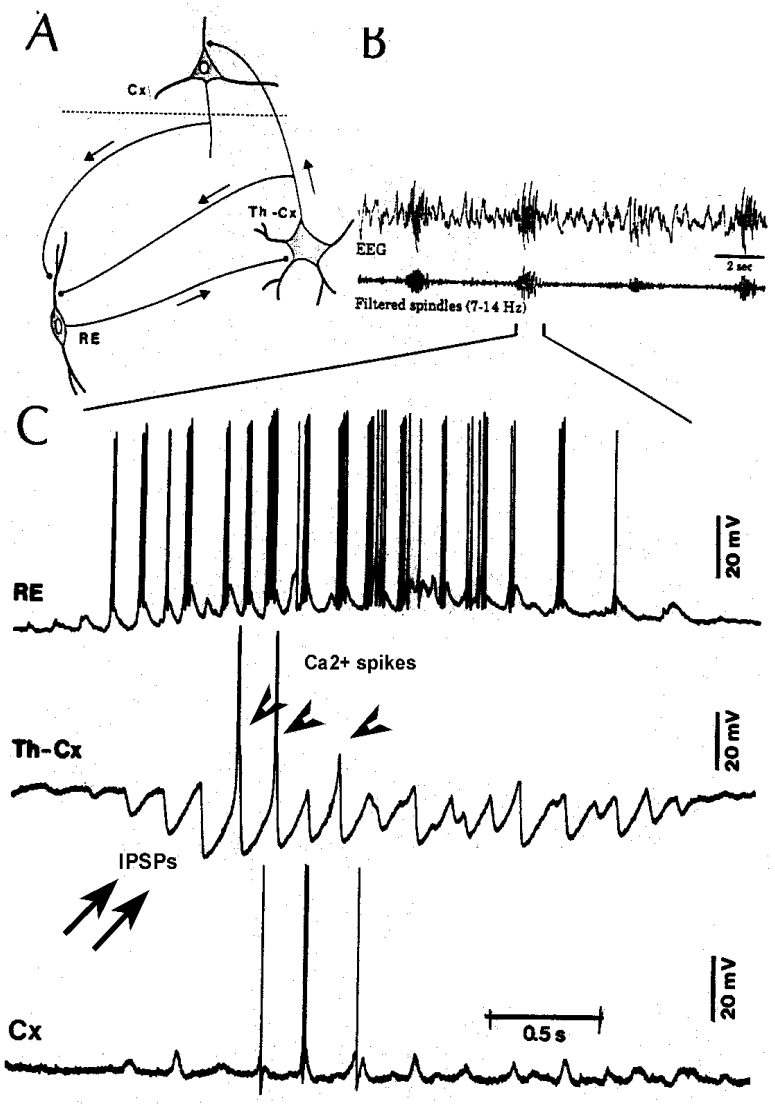
intracellular traces showing the cortical slow oscillation (0.3 Hz), the spindles in the thalamic RE neuron (7 Hz) and the intrinsic clock-like delta rhythm of TC neuron (1.5Hz) Note the different time calibrations. (Steriade, 2000).

Coherence of cortical and thalamic spindles



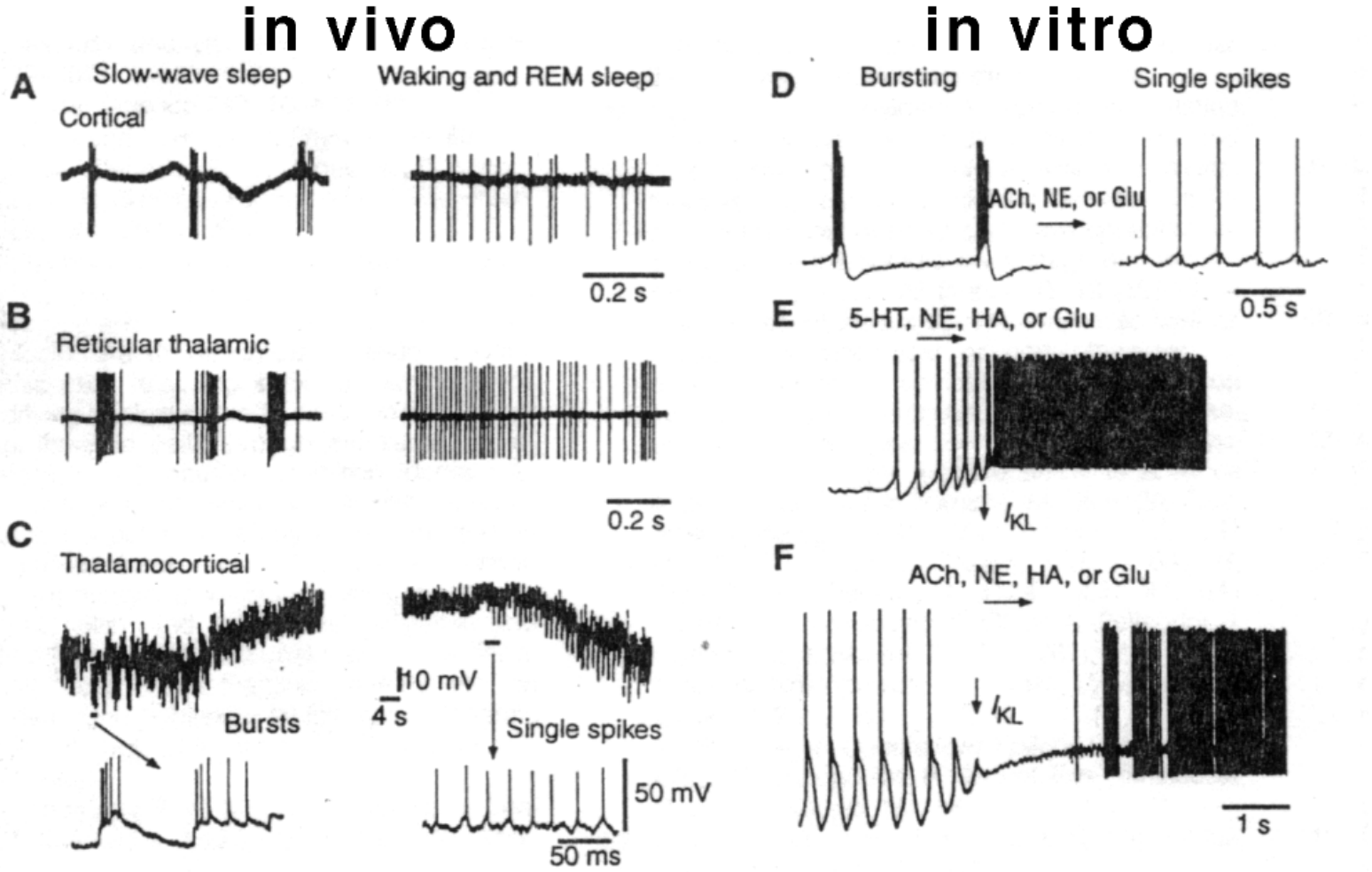
Cortical spindle sequences occur nearly simultaneously during natural sleep of humans and cats but decorticaltion disorganizes the widespread coherence of thalamic spindles. Averaged correlations shows rhythmicity at 14 Hz and central peak values between 0.7-09. After decortication, recordings from virtually same thalamic sites showed disorganization of spindle simultaneity (Steriade, 2000).

Intracellular aspects of spindling in the thalamocortical system



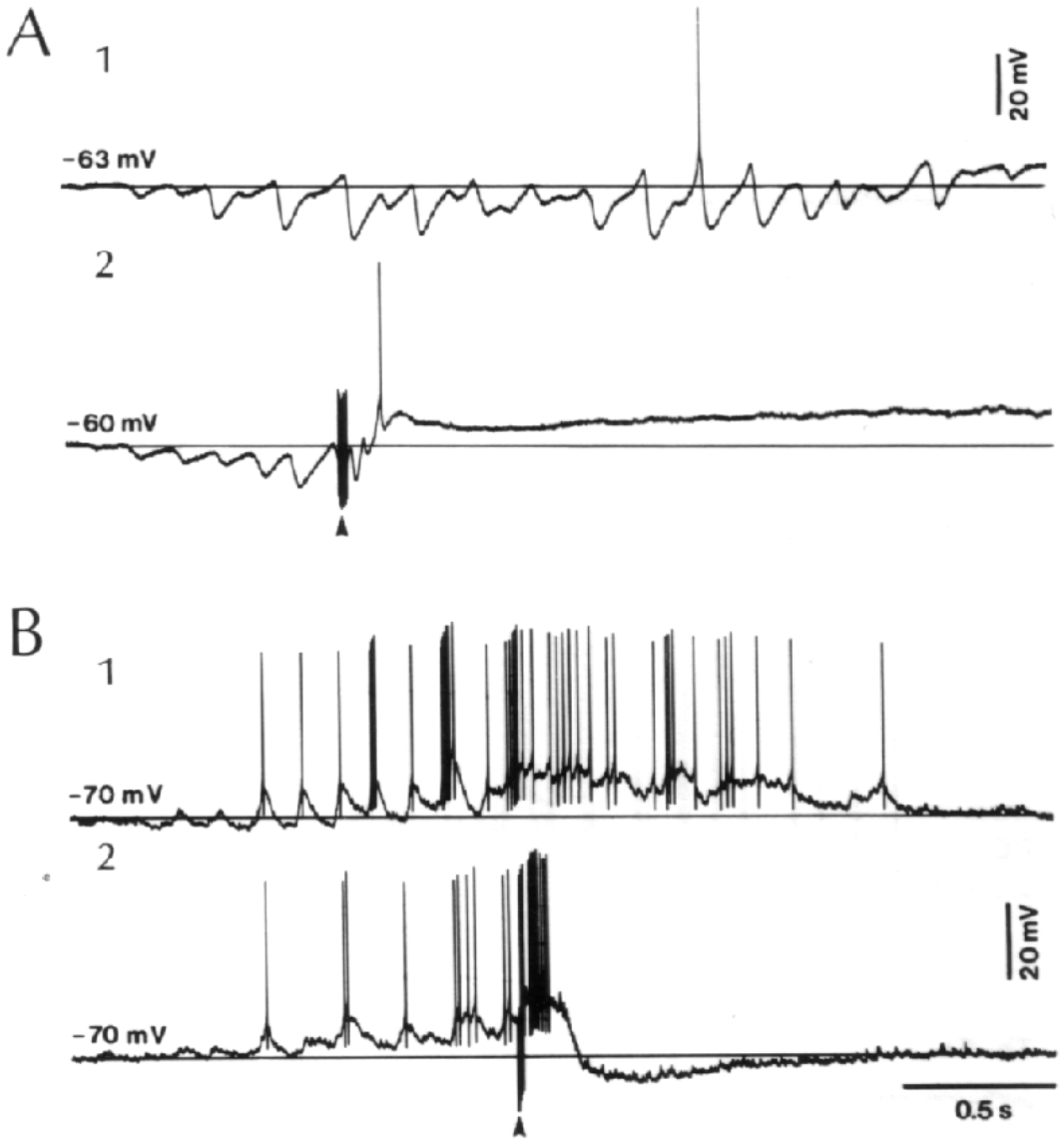
Spindle oscillations in reticular (RE), thalamocortical(Th-Cx, VL) and cortical (Cx, motor) neurons. **A**: Circuit of 3 neurons. **B**: Two rhythms (7-14 Hz and 0.1-0.2 Hz) of spindle oscillations in cortical EEG. **C**: Intracellular recording in cats under barbiturate anesthesia. Note rhythmic spike-bursts of RE neuron during a spindle sequence and concomitant IPSPs leading to post-inhibitory rebound bursts in Th-Cx and Cx neurons. (Steriade, 2002)

State-dependent activities in cortical and thalamic neurons



Neurons in the cerebral cortex (A), thalamic reticular nucleus (B) and thalamic relay nuclei (C) change their activities in vivo from periodic and rhythmic spike bursts during natural, SWS to tonic firing of trains of single spikes during waking and REM-sleep in behaving cats with chronic implants (D-F). Similar changes in firing pattern occur in vitro in these neurons in response to various neurotransmitters released by brainstem modulatory systems (Steriade et al., 1993).

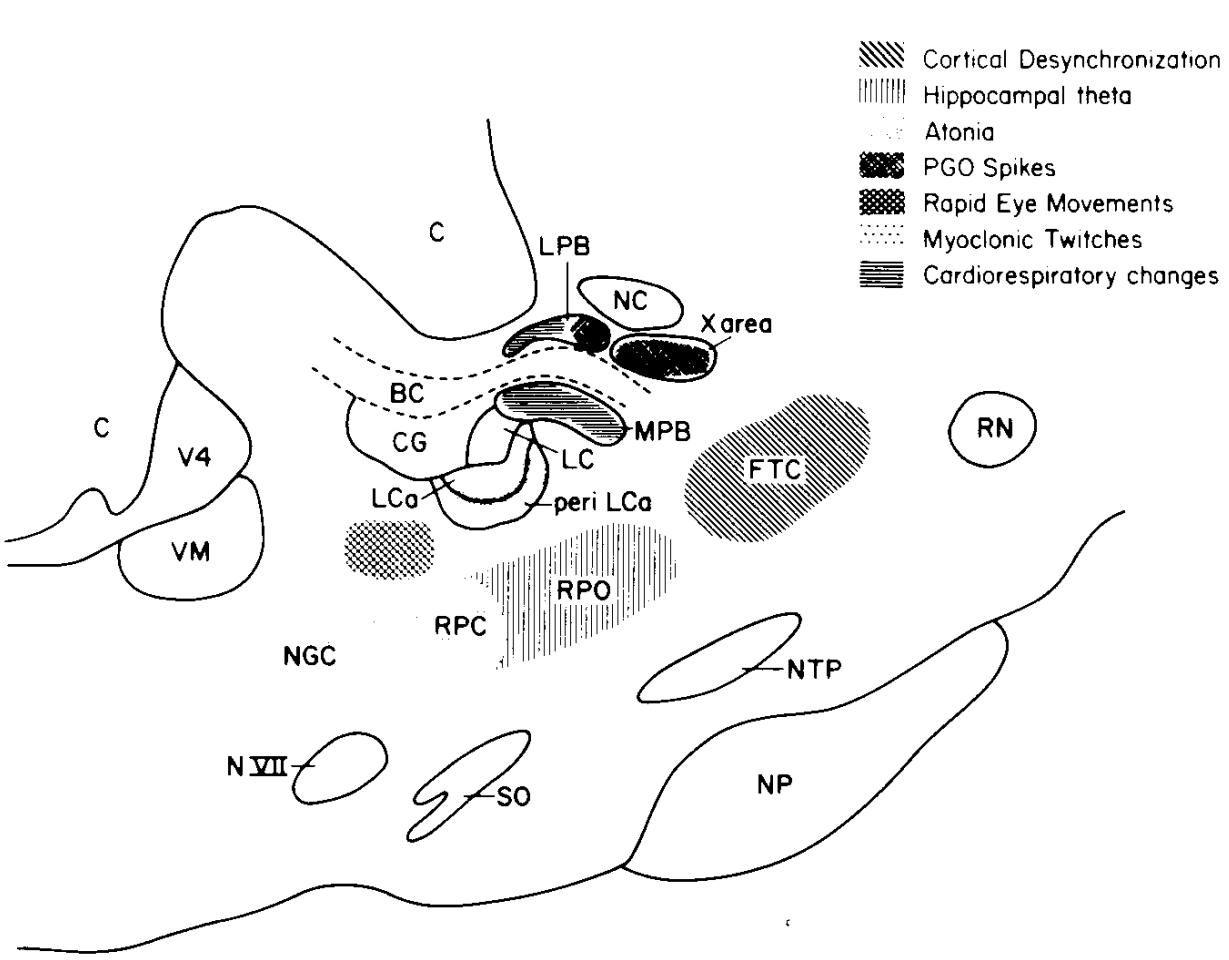
Blockage of thalamic spindle oscillation by peribrachial stimulation

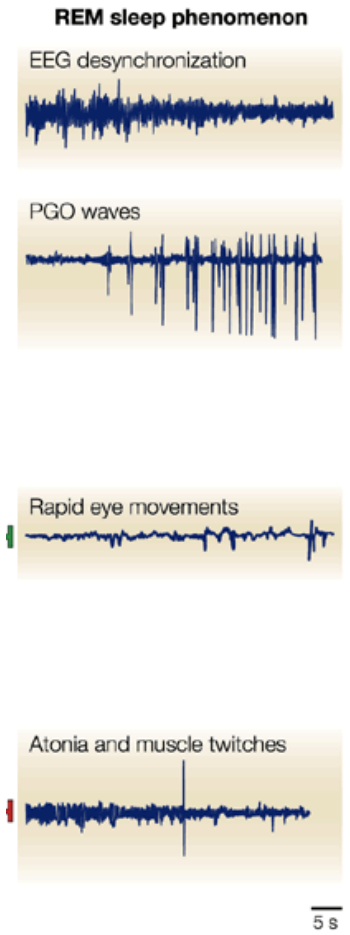


Blockage of spindle oscillations in intracellularly recorded

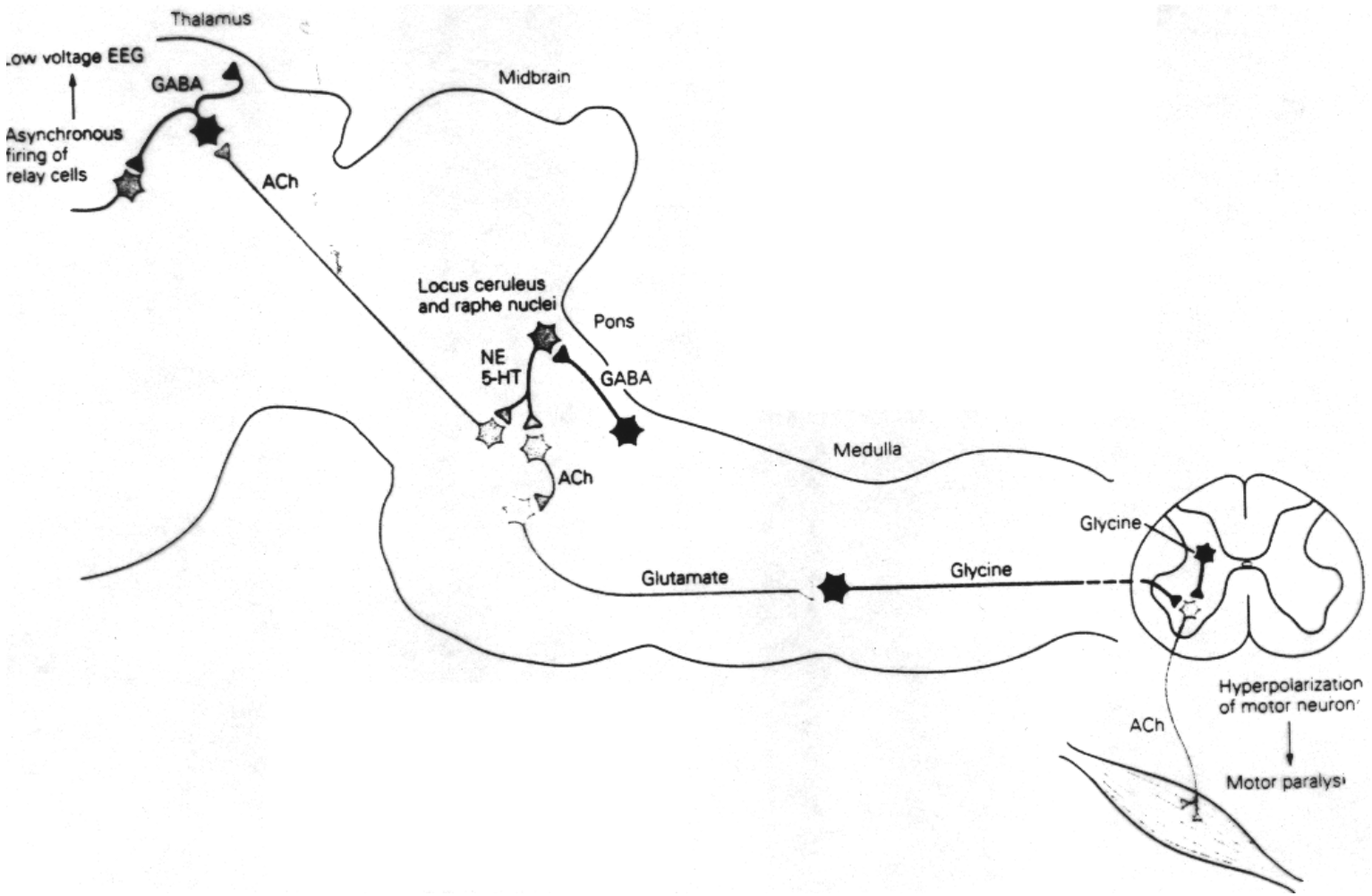
thalamocortical and reticular thalamic (RE) neurons of unanasthetized encephale isole cats with deafferentation of trigeminothalamic pain pathways. **A**: an Lateral geniculate relay neuron.**B**: a neuron recorded in the perigeniculate sector of the RE. Arrowhead: brainstem mesopontine cholinergic (peribrachial) area stimulation. The disruption of spindles occurein thhe RE where sleep oscillation is generated (Hu, Steriade, Deschenes, 1989).

REM sleep phenomenon I.

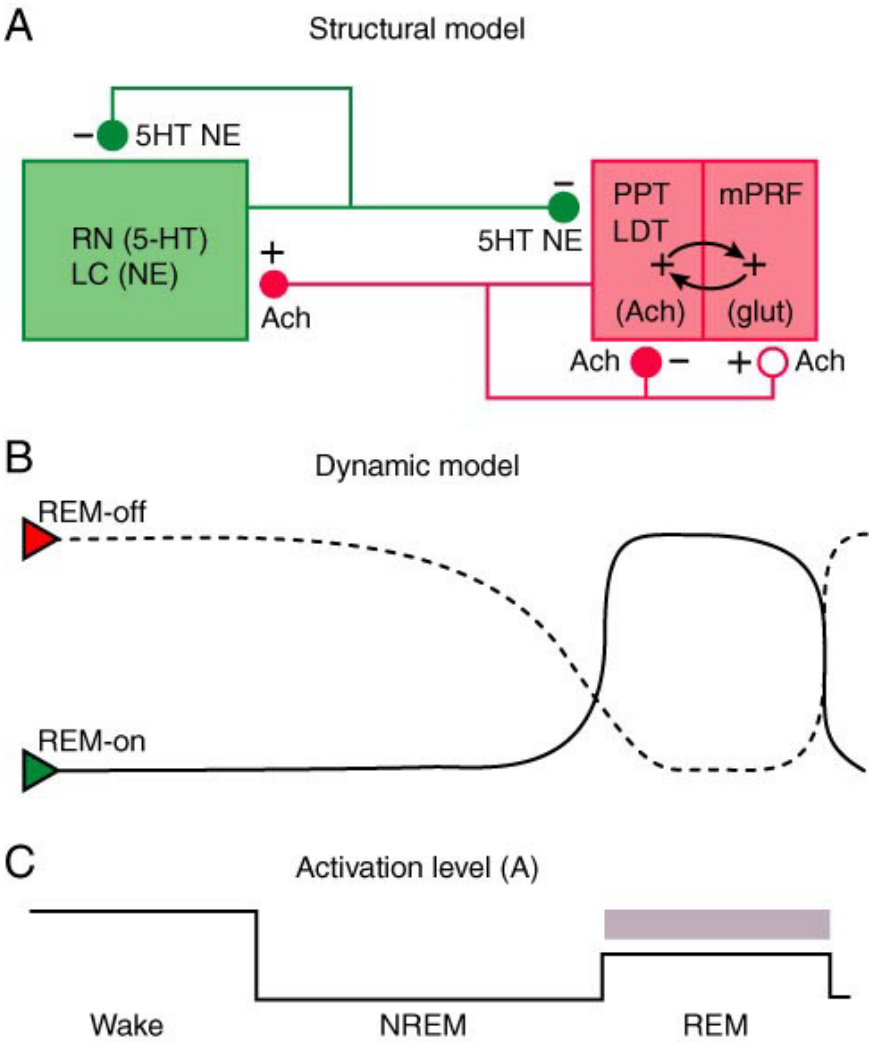




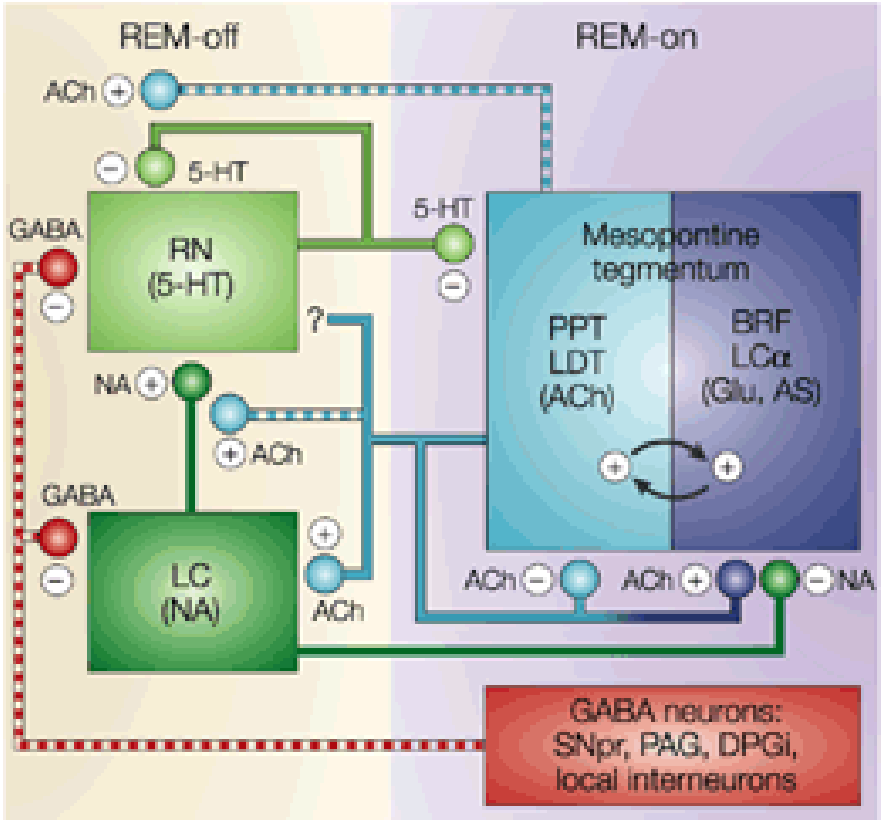
REM phenomenon II.



REM –NonREM oscillation I

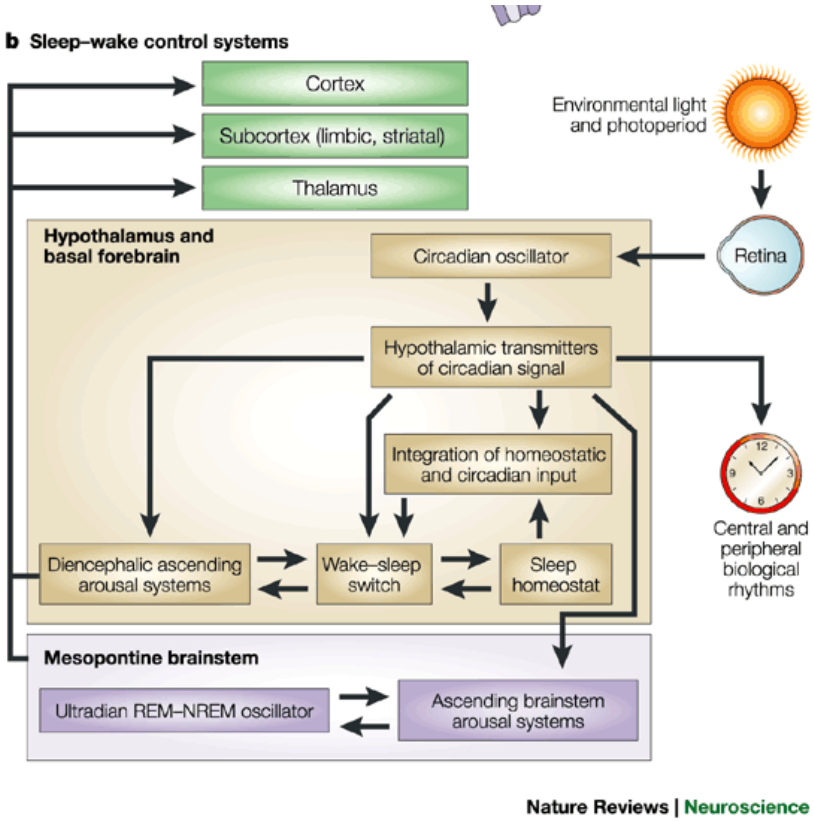


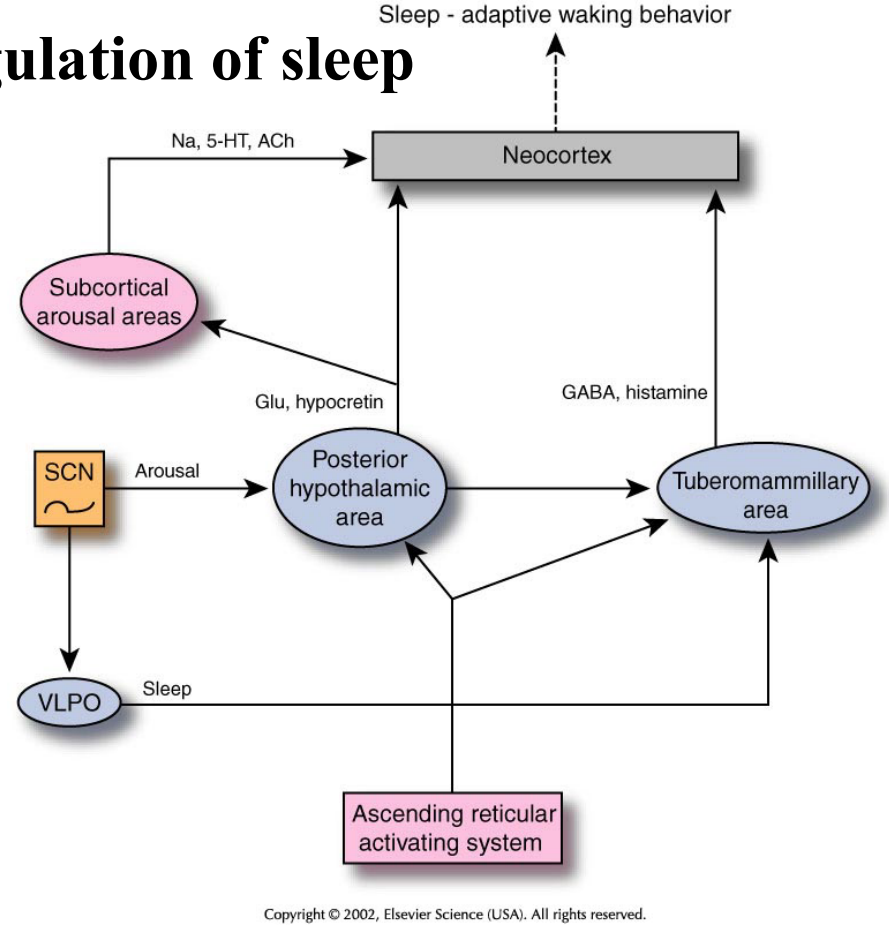
REM-nonREM oscillation I I

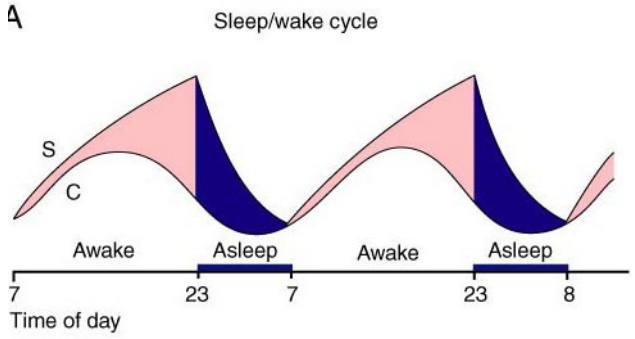


The reciprocal-interaction model of REM-NREM alternation. **REM-on cells** are the cholinergic cells in the PPT/LDT area, GABAergic local or projection neurons neurons in the ponto-medullar reticular formation (DPGi), periaqueductal gray (PAG), and in the substantia nigra pars reticularis. There are also putative glutamatergic REM-on neurons in the reticular formation. **REM-off** cells are the noradrenergic locus coeruleus (LC) and the serotoninergic (5-HT) raphe (RN) neurons. Note that there are self-inhibitory cholinergic autoreceptors in the mesopontine cholinergic nuclei. Also, the noradrenergic (NA) and 5-HT fibers inhibit the wake-REM-on neurons (Pace-Schott and Hobson, 2002).

The circadian regulation of sleep



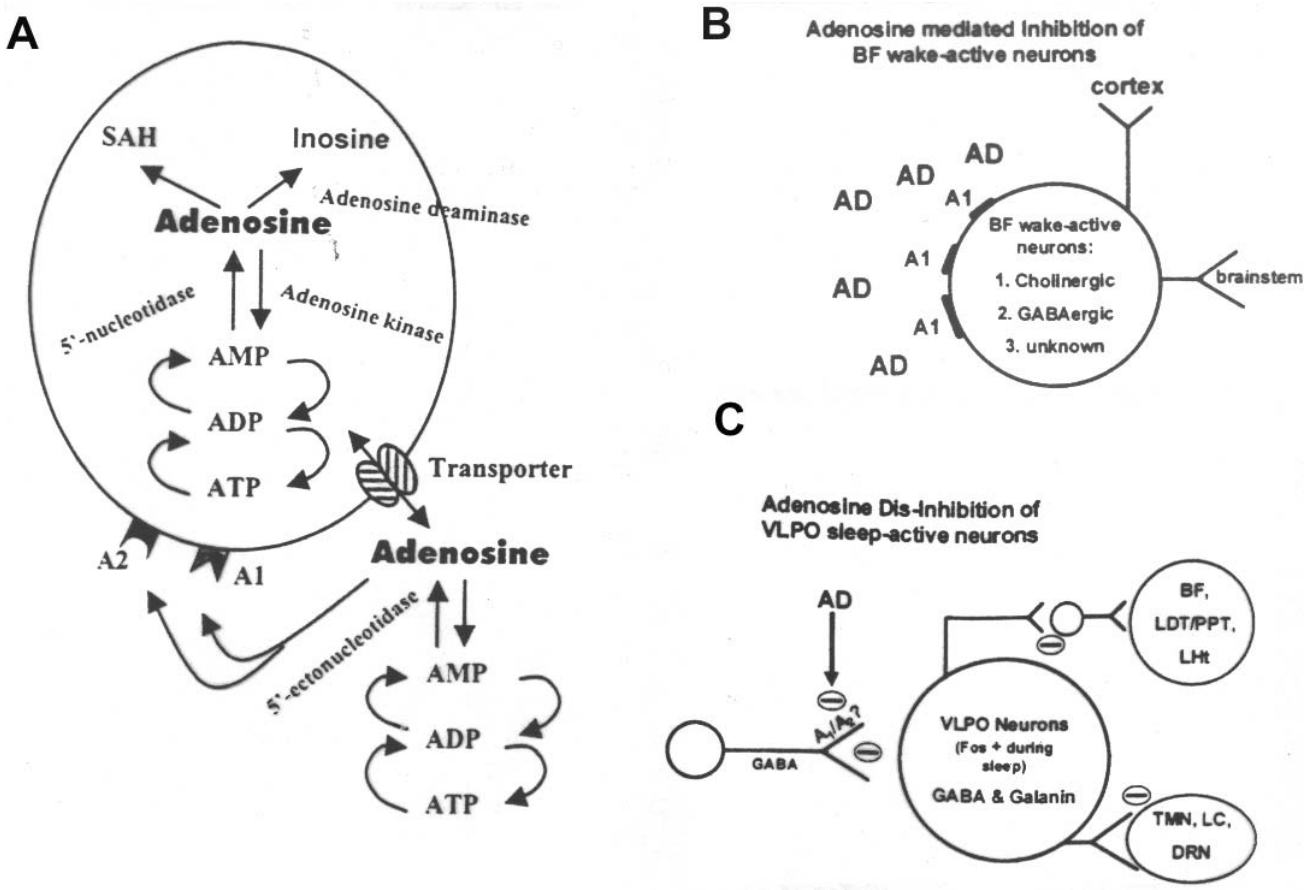




The SCN project to the VLPO, an area mediating sleep. VLPO inhibits the arousal activity of the tuberomammillary histaminergic (and other monoaminergic cell groups in the brainstem during sleep. The SCN provides an arousal promoting input to the hypocretin/orexin neurons of the posterior-lateral hypothalamic area, that are projecting to the cortex and promotes arousal (Moore, 2002)

The S (metabolic) and circadian process of sleep (Dunn and Borbely)

The homeostatic process of sleep-wake control



A: Schematic of the main intra- and extracellular metabolic pathways of adenosine. A1, A2 adenosine receptor subtypes. **B**: The BF region contains numerous cholinergic and non-cholinergic wake-active neurons that project to the cortex and thalamus and whose activity is thought to promote cortical activation. Adenosine is proposed to inhibit the activity of these neurons possibly via A1 receptor mediated hyperpolarization.

C: The hypothalamic preoptic area (POA/VLPO) contains sleep-active neurons and send inhibitory projections directly to all major monoaminergic cell groups and indirectly to the cholinergic (PPT,LDT,BF) and lateral hypothalamic neurons. AD can activate neurons in the POA via an inhibition of presynaptic GABA reelase onto the putative sleep-active neurons.Functionally, these two mechanisms are complementary, ie. Increased AD levels in either area is predicted to reduce W and promote the transition to sleep (Strecker et al., 2000).

Brain activation and deactivation in REM/ waking