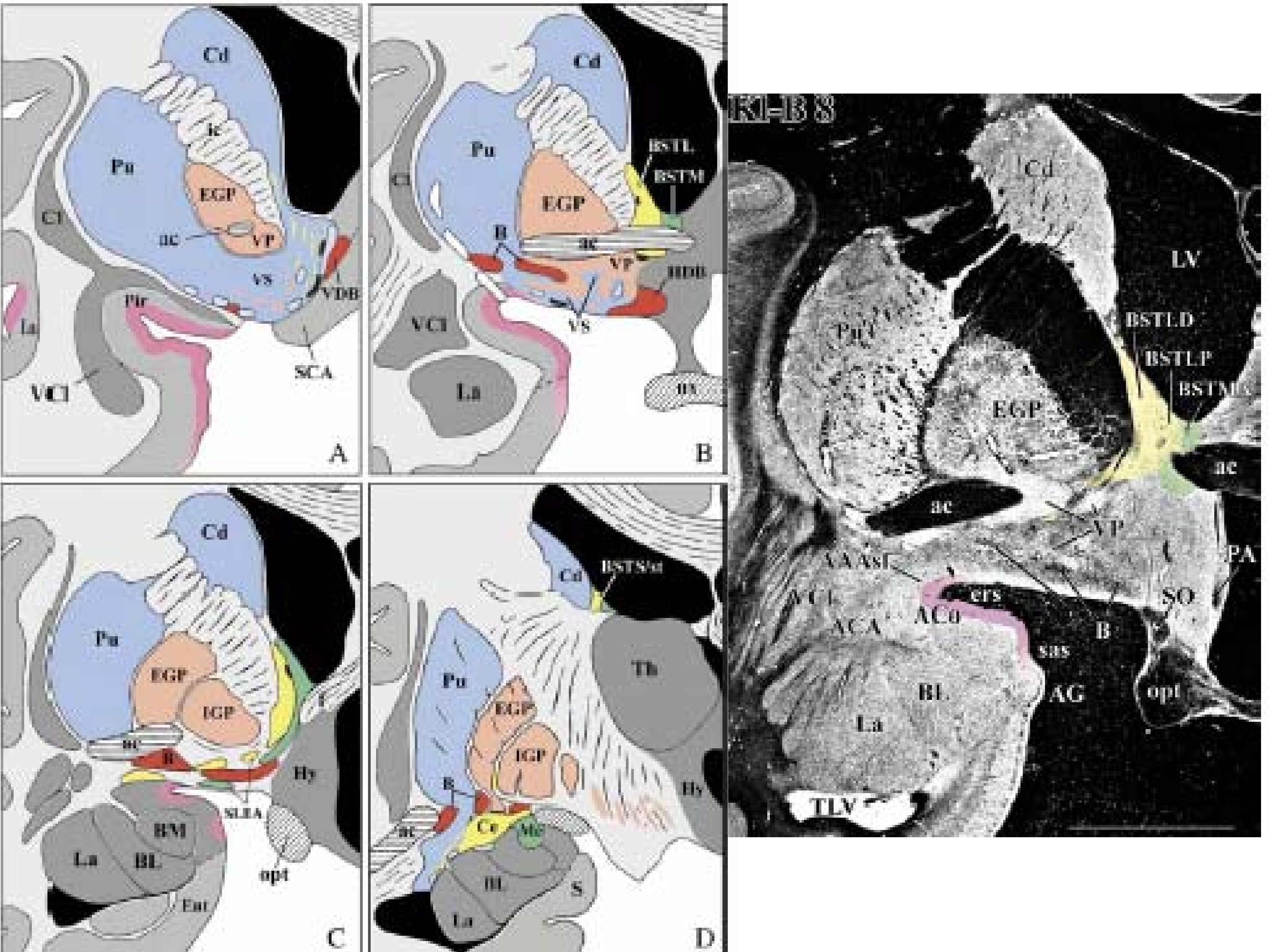
BASAL FOREBRAIN

BASAL FOREBRAIN –FUNCTIONAL ANATOMICAL ‘MACROSYSTEMS’



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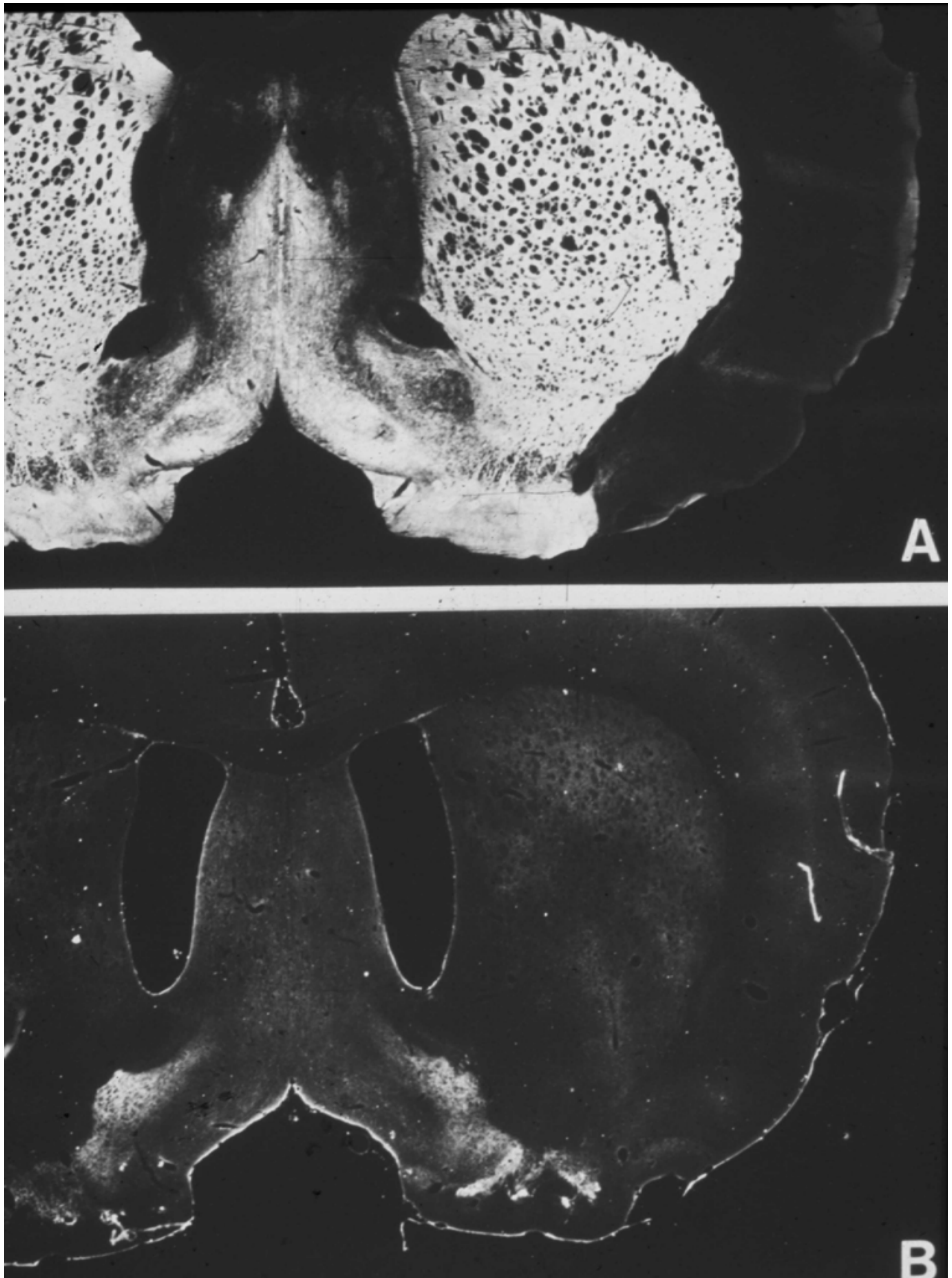
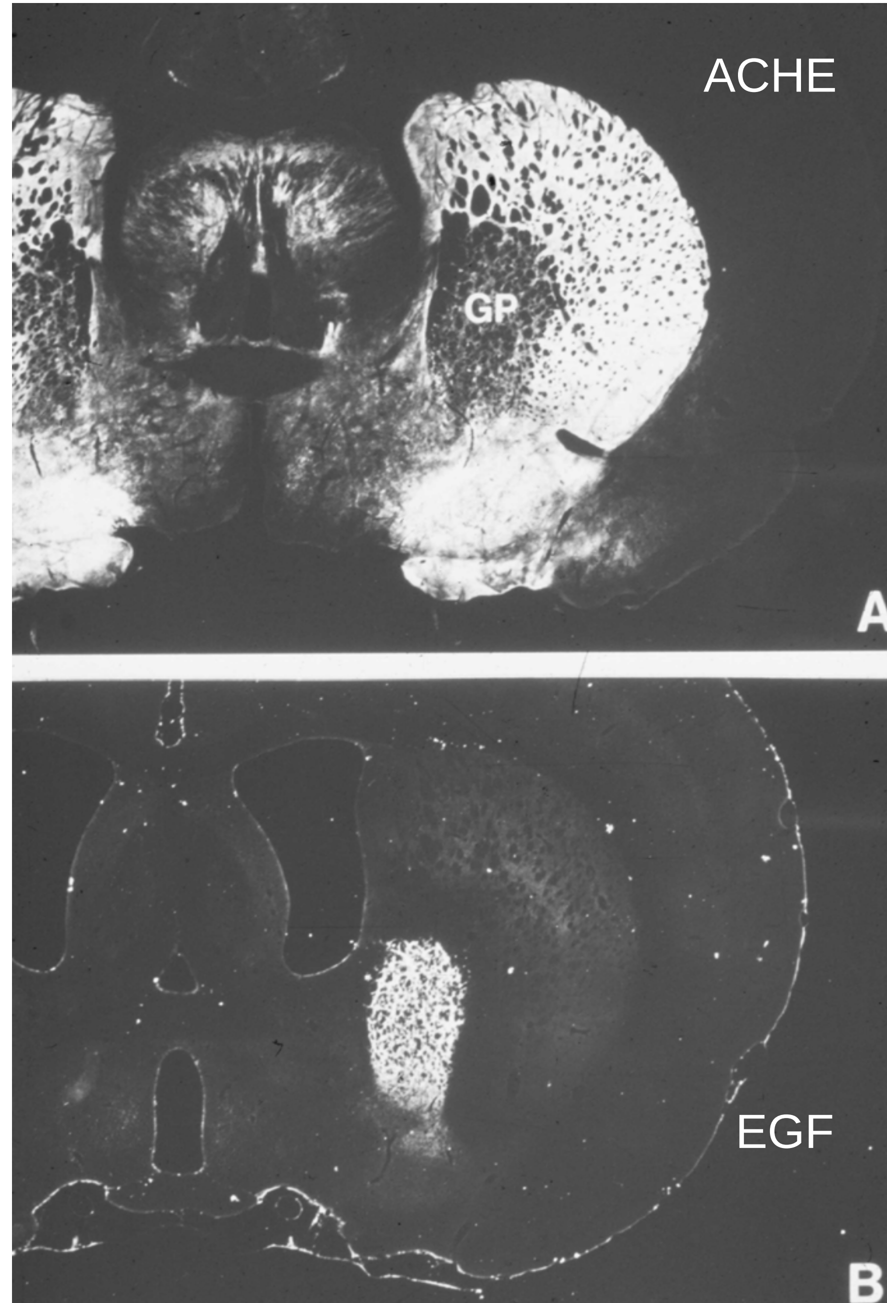
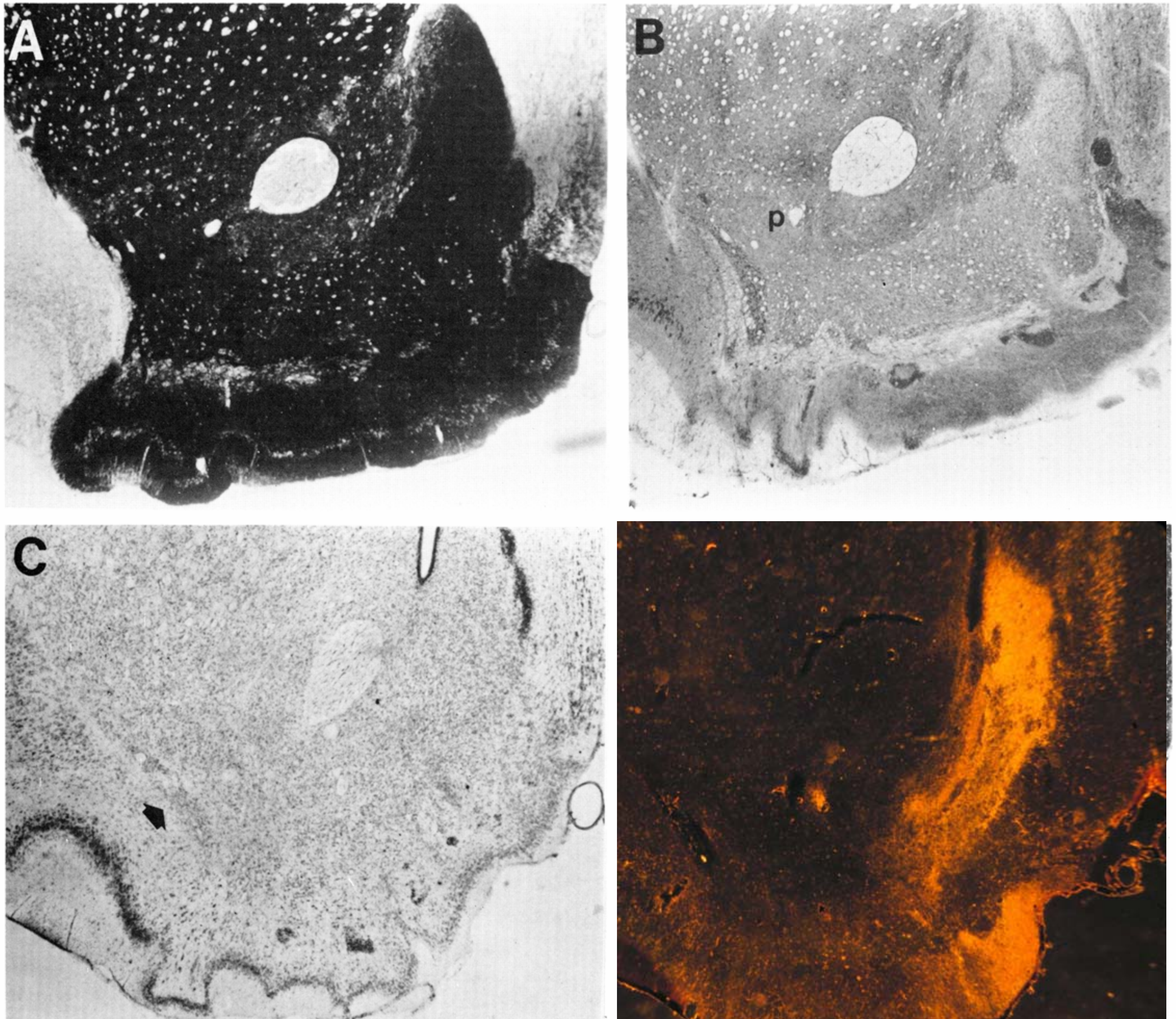
1. VENTRAL STRIATO-PALLIDAL SYSTEM IN RAT

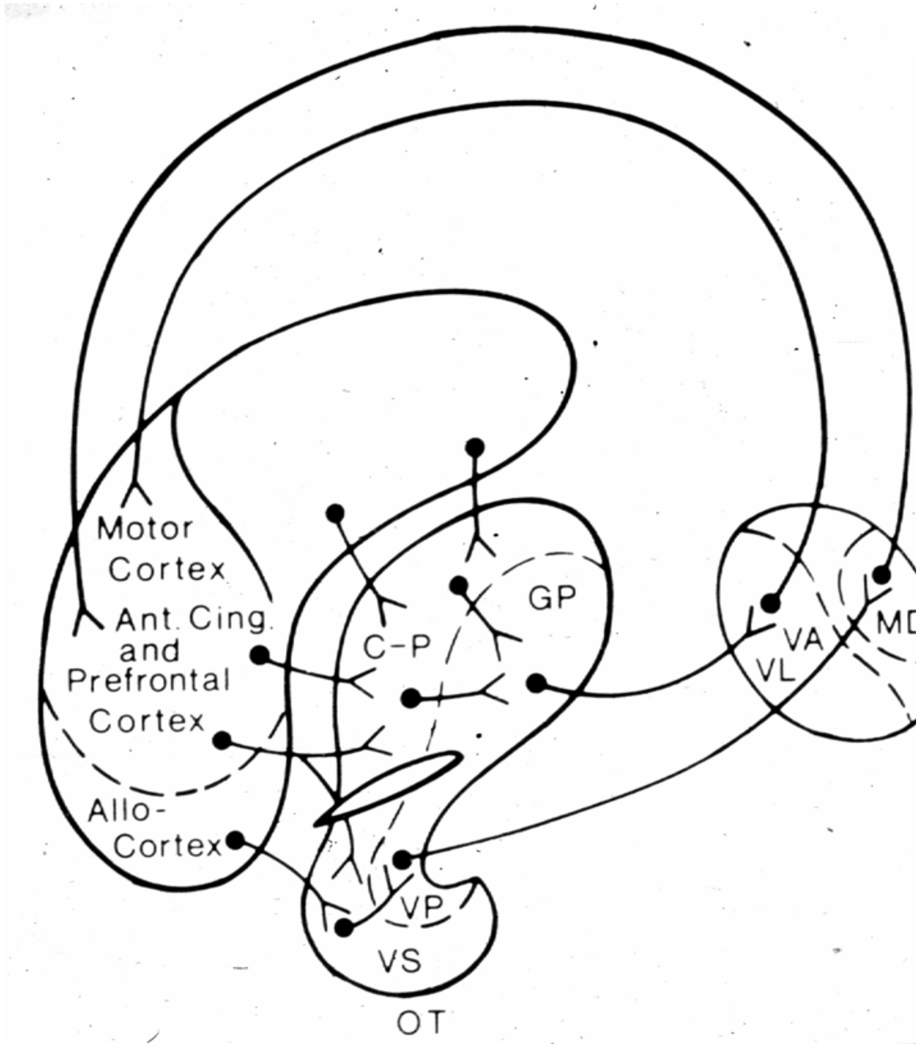


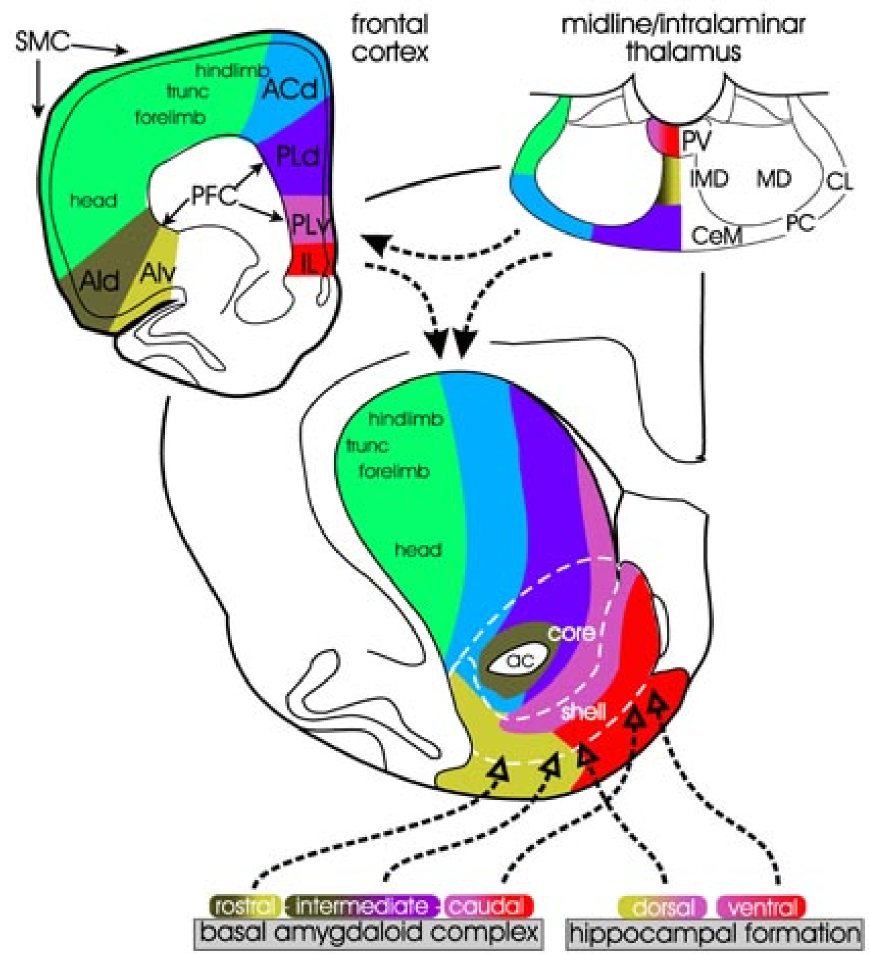


ACCUMBENS: Core and Shell



CIRCUITRIES OF THE VENTRAL STRIATO-PALLIDAL SYTEM



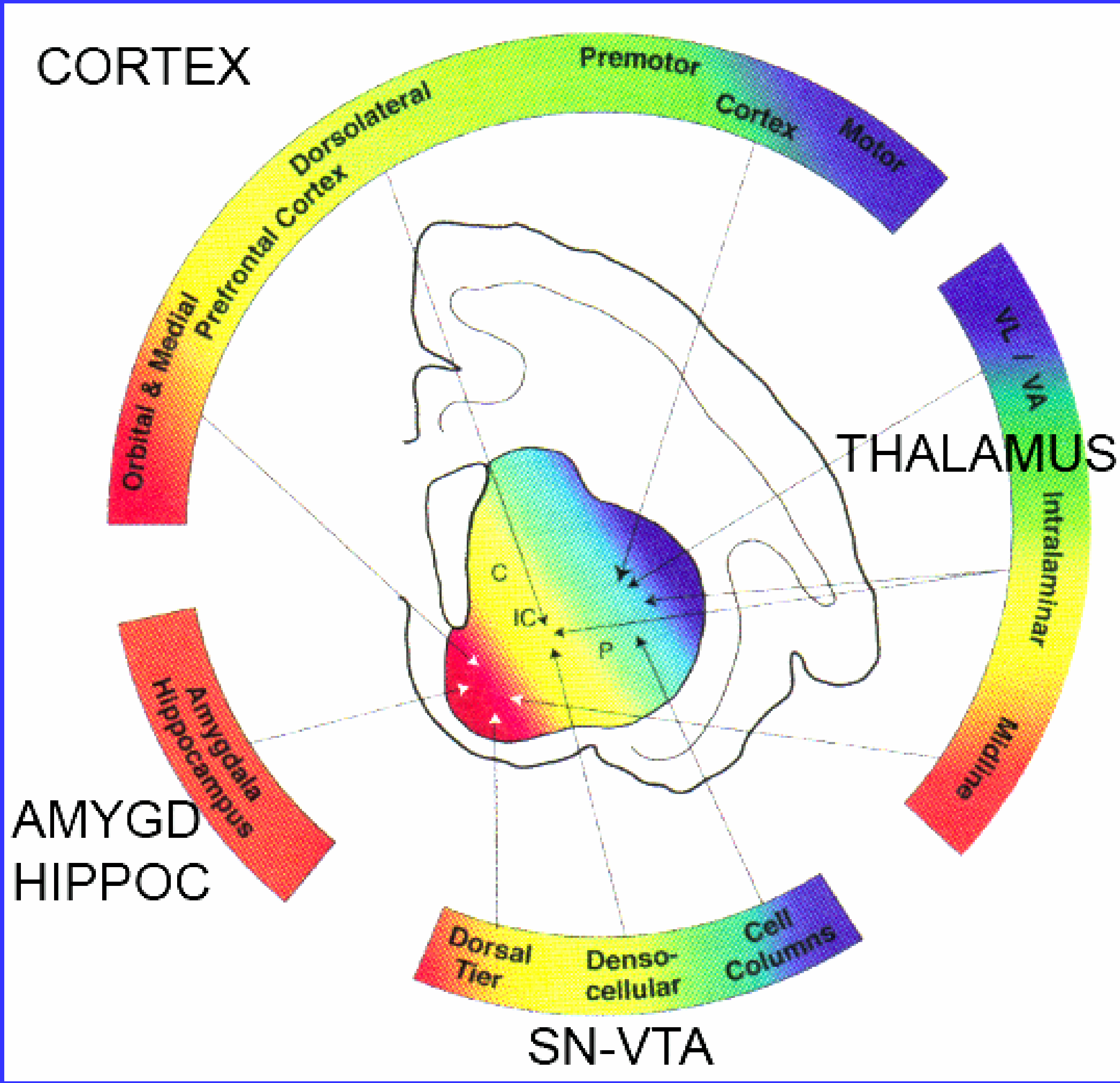


Heimer et al., 1981

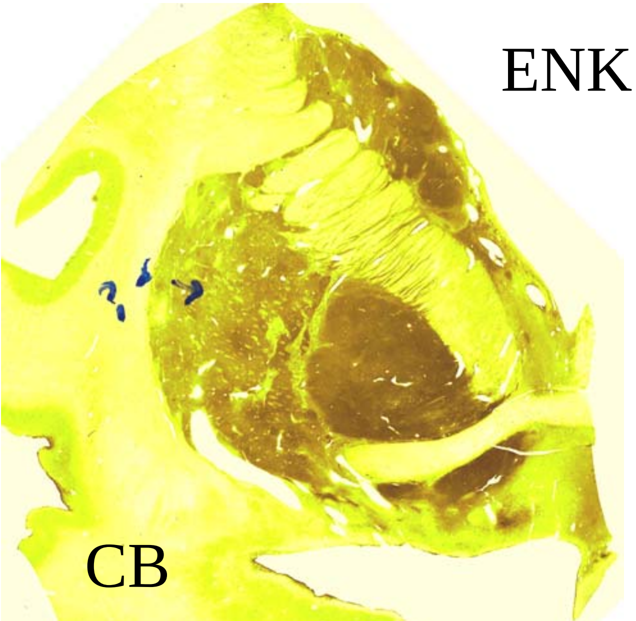
Voorn et al., 2004

CIRCUITRIES OF THE DORSAL AND VENTRAL STRIATUM

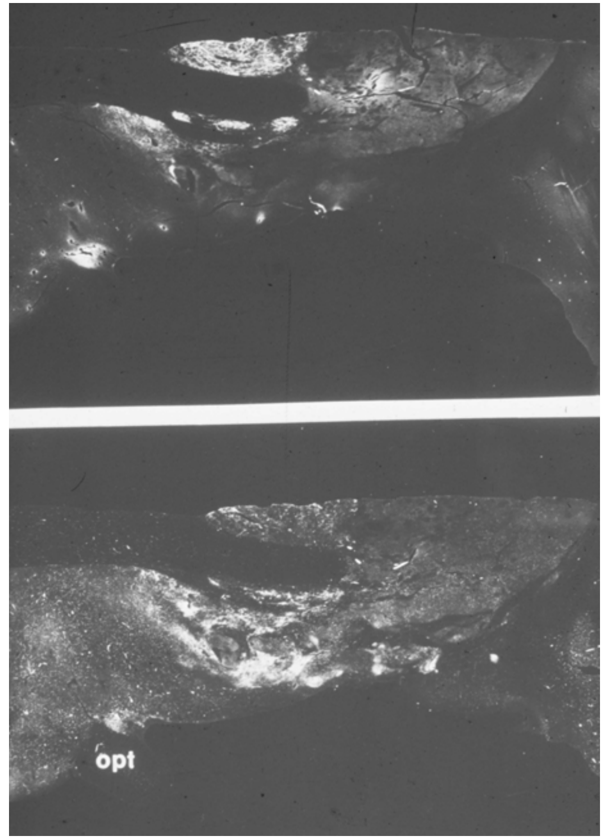
The colors denote functional distinctions. Blue: motor ctx, executive of motor actions; green premotor ctx, planning of movements; yellow dorsal and lateral PFC: cognitive and executive functions; orange: orbital PFC: goal-directed behaviors and motivations, red: mPFC, goal directed behaviors and emotional processing (Haber and Gdowski, 2004)



1. VENTRAL STRIATO-PALLIDAL SYSTEM IN HUMANS



ENK



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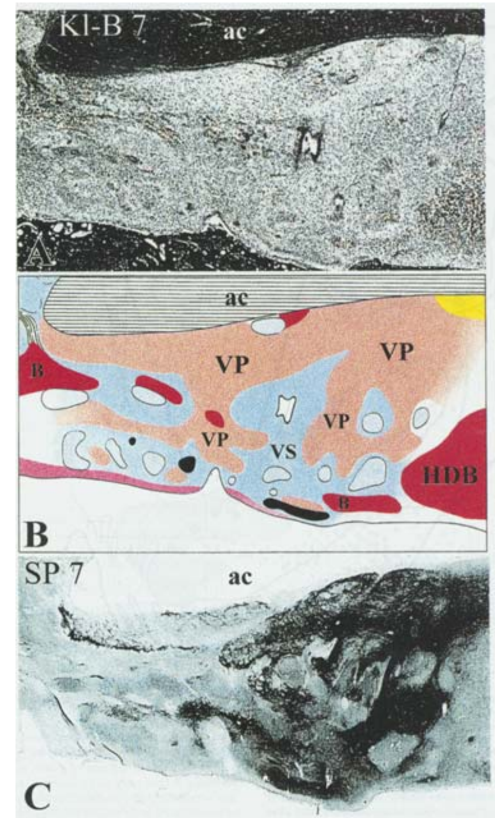
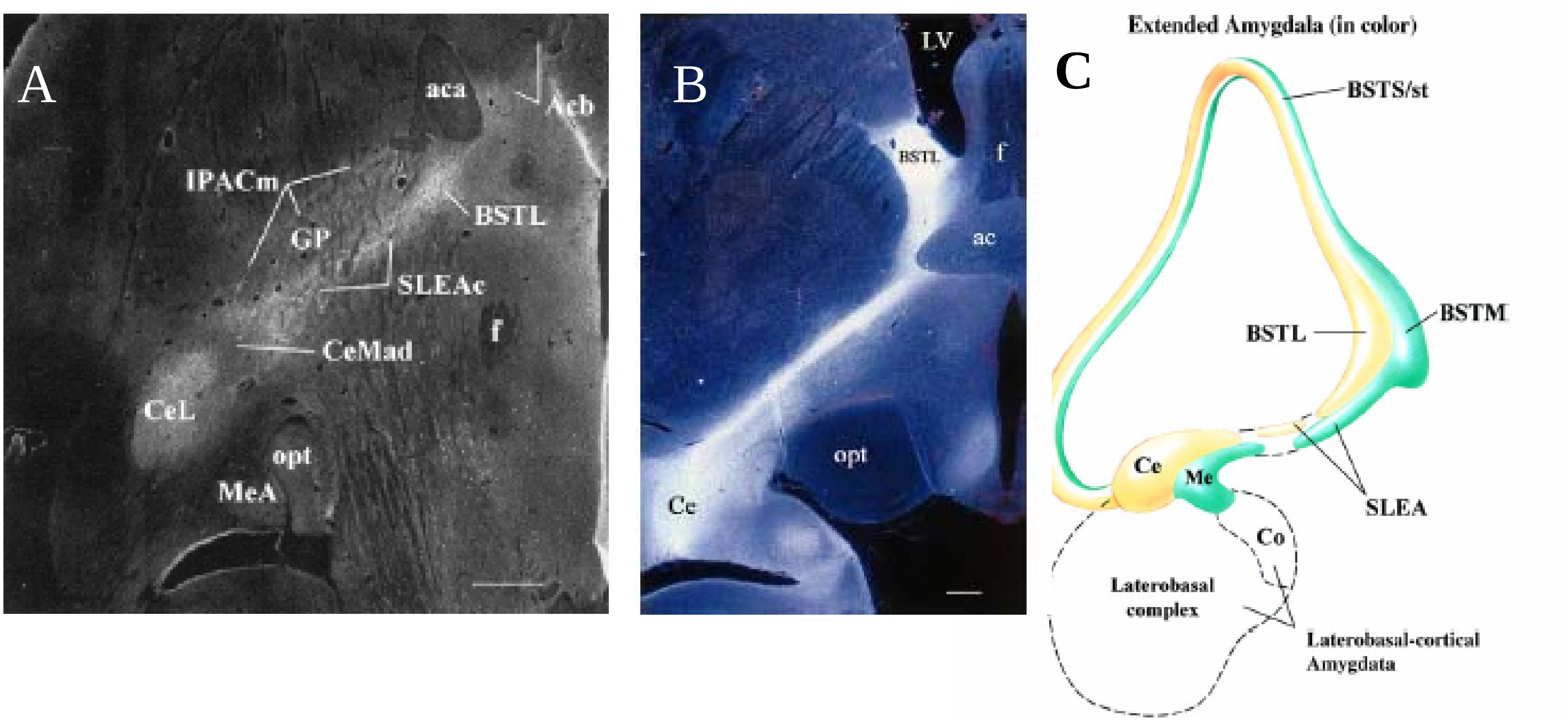
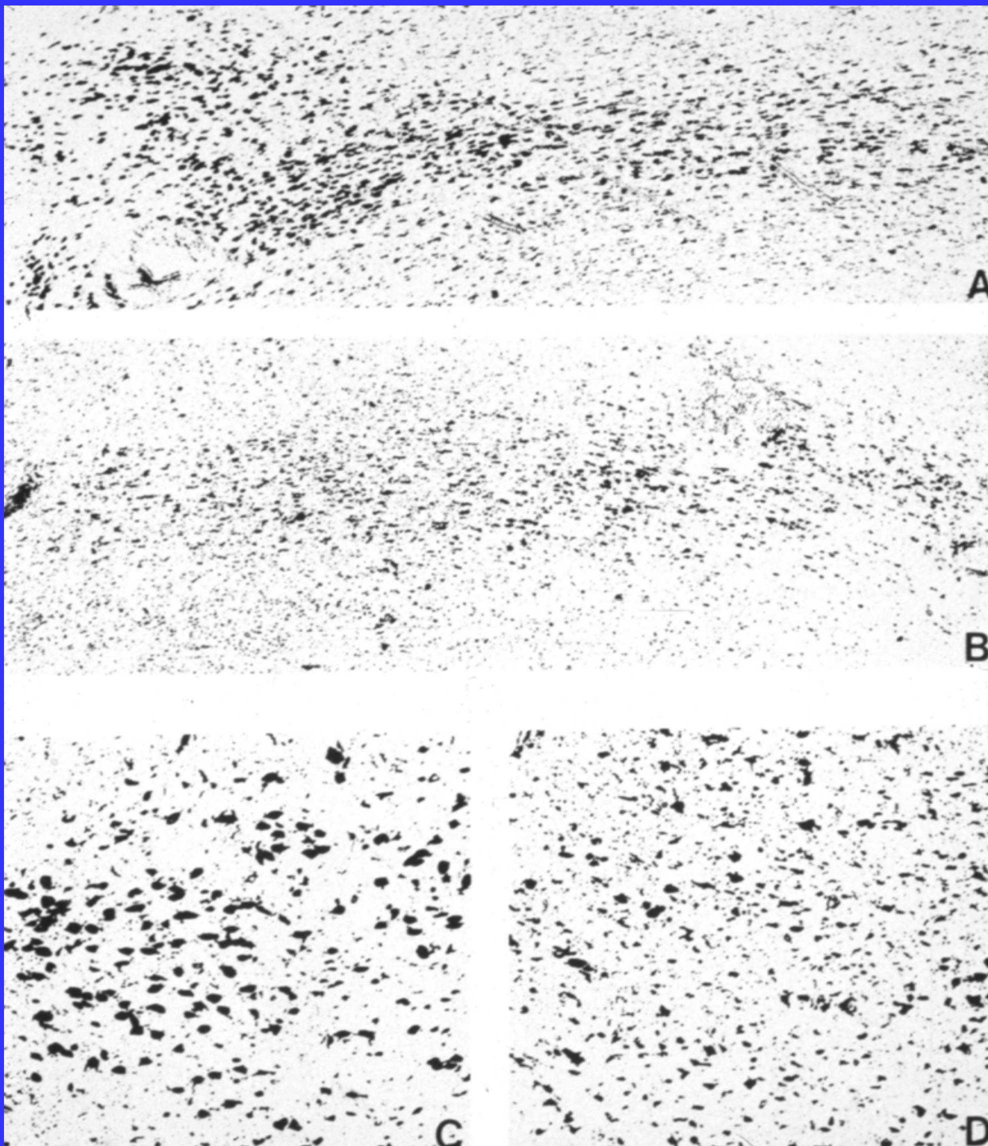


2. EXTENDED AMYGDALA IN RAT AND PRIMATES



A:Dark field image of normal cupric silver staining of the central division of the extended amygdala in rat in horizontal section. **B**: Dark field image of the sublenticular area of the extended amygdala in rhesus monkey following an injection of 3H-amino acid in the region of the central amygdaloid nucleus (Ce). **C**: The extended amygdala shown in isolation from the rest of the brain, with theextension of the Ce and Medial (Me) amygdaloid nuclei within the stria terminalis (st) and through the sublenticular region of the bed nucleus of the stria terminalis (BST). From Heimer and Hoesen (in press)

3. DIAGONAL BAND-NUCLEUS BASALIS MEYNERT



1809: J. C. Reil "unnamed substance"
1861: K. B. Reichert "substantia innominata"
1872: T. Meynert "nucleus basalis"
1896: V. Kolliker "topographical description"
1873-1900 - Golgi and Nissl "staining"
1910-1940: Beccari, Ramon y Cajal, Ayala, Foix and Nicolesco, Kodama and others "cellular description"
1942: Brockhaus "basal nuclei complex"
1949: Moruzzi and Mogoun "energizing system"
Koelle and Friedenwald "AChE"
1960's: Gorry, Leontovitch and Zhukova, Ramon Moliner and Nauta, Lewis and Shute "BF is an extension of the isodendritic core" and "cholinergic system"
1980: Eckenstein and Thoenen "ChAT"
1983: Mesulam "Ch nomenclature"

Cholinergic hypothesis of AD

Bowen et al., 1976; Davies and Maloney, 1976; Whitehouse et al., 1981

Basal forebrain in reward

De Long, 1971; Rolls et al., 1976

Basal forebrain in cortical activation

Detari and Vanderwolf, 1987

Basal forebrain in cortical plasticity

Silito and Kemp, 1983; Sato et al., 1987; Juliano et al, 1989; Weinberger, 1991; Merzenich, 1998

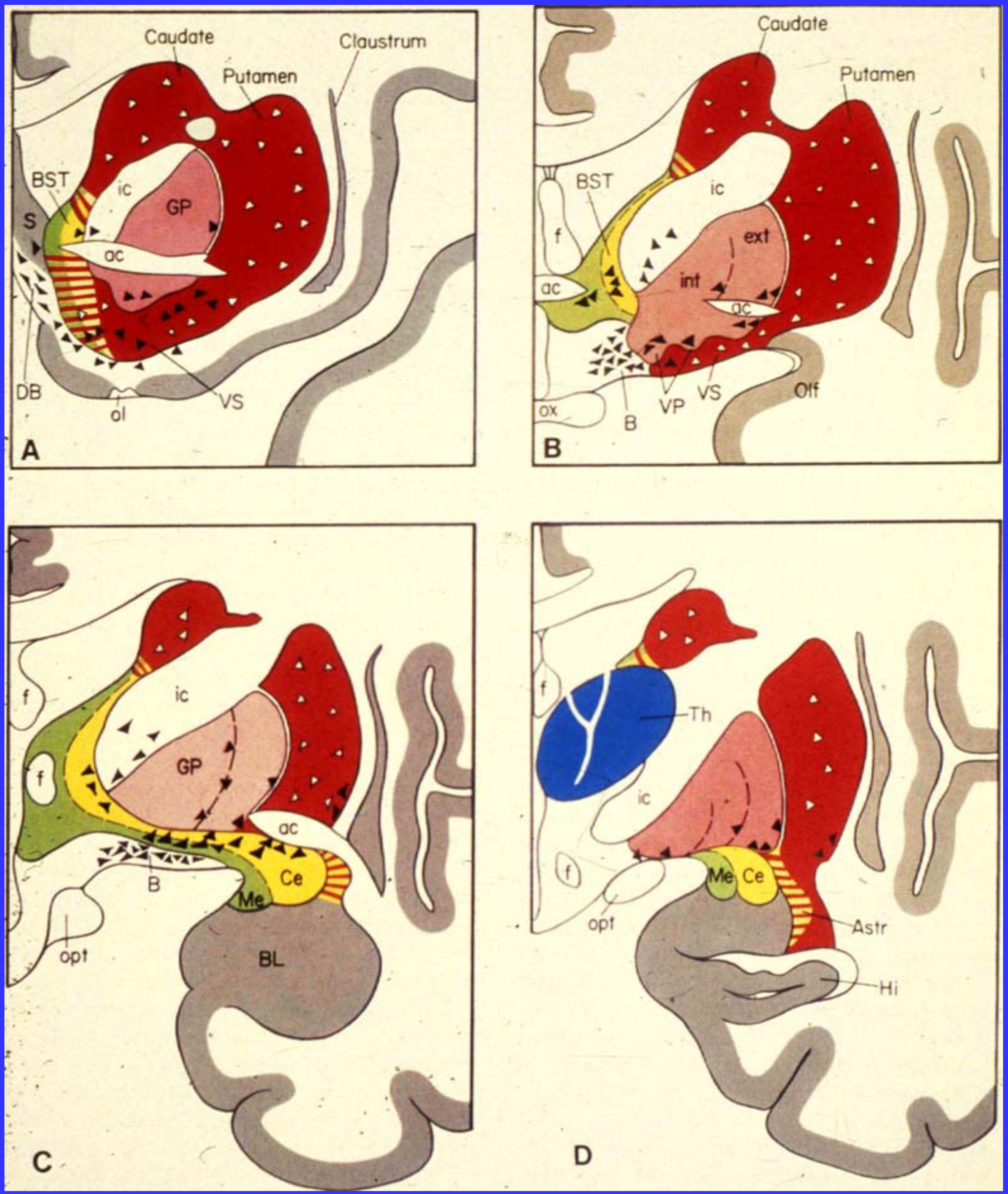
Basal forebrain in learning and memory

Olton, 1991

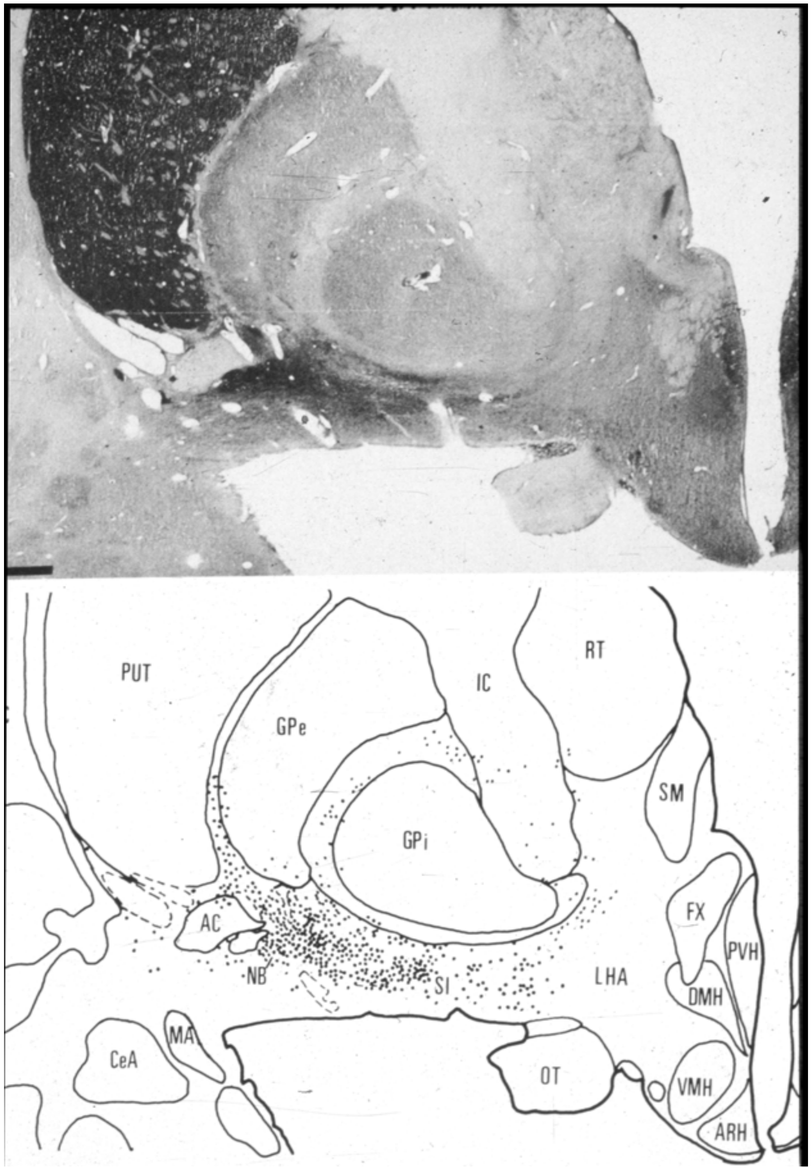
Basal forebrain in attention

Dunnett et al., 1991; Everitt and Robbins, 1997; Gallagher, 1995; Paus et al., 1997; Sarter and Bruno, 1997

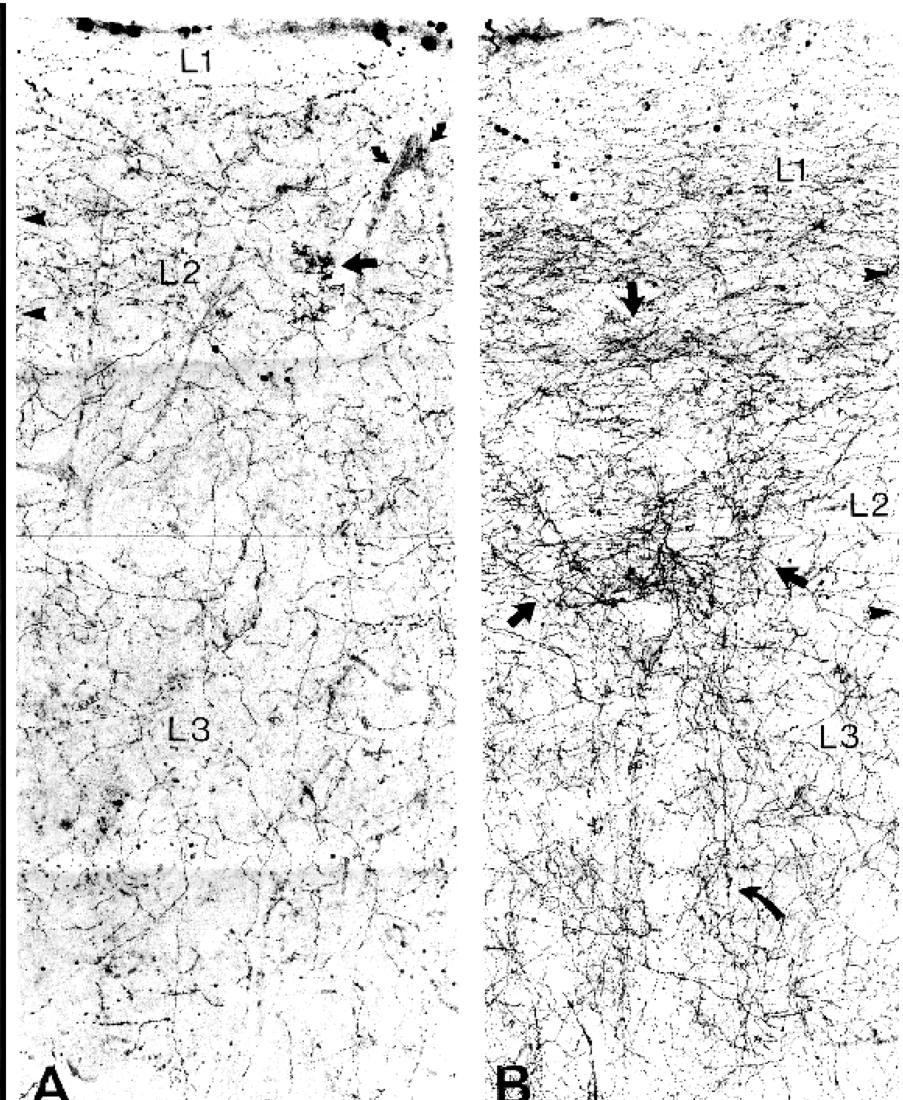
RELATION OF CORTICOPETAL CELLS IN THE BF TO SEPTUM-SUBSTANTIA INNOMINATA-AMYGDALA-BST CONTINUUM



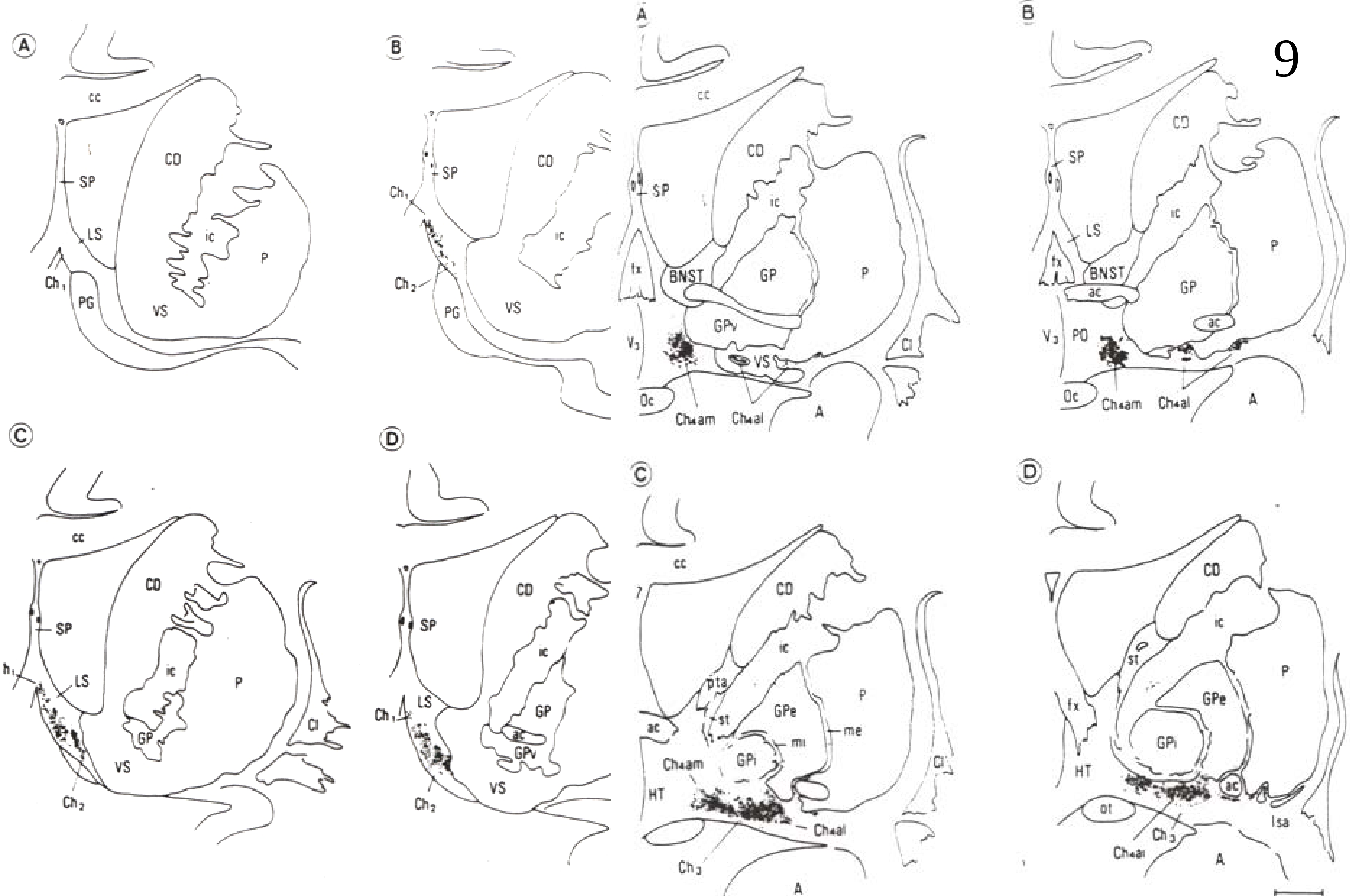
ACHE cell staining (Saper)



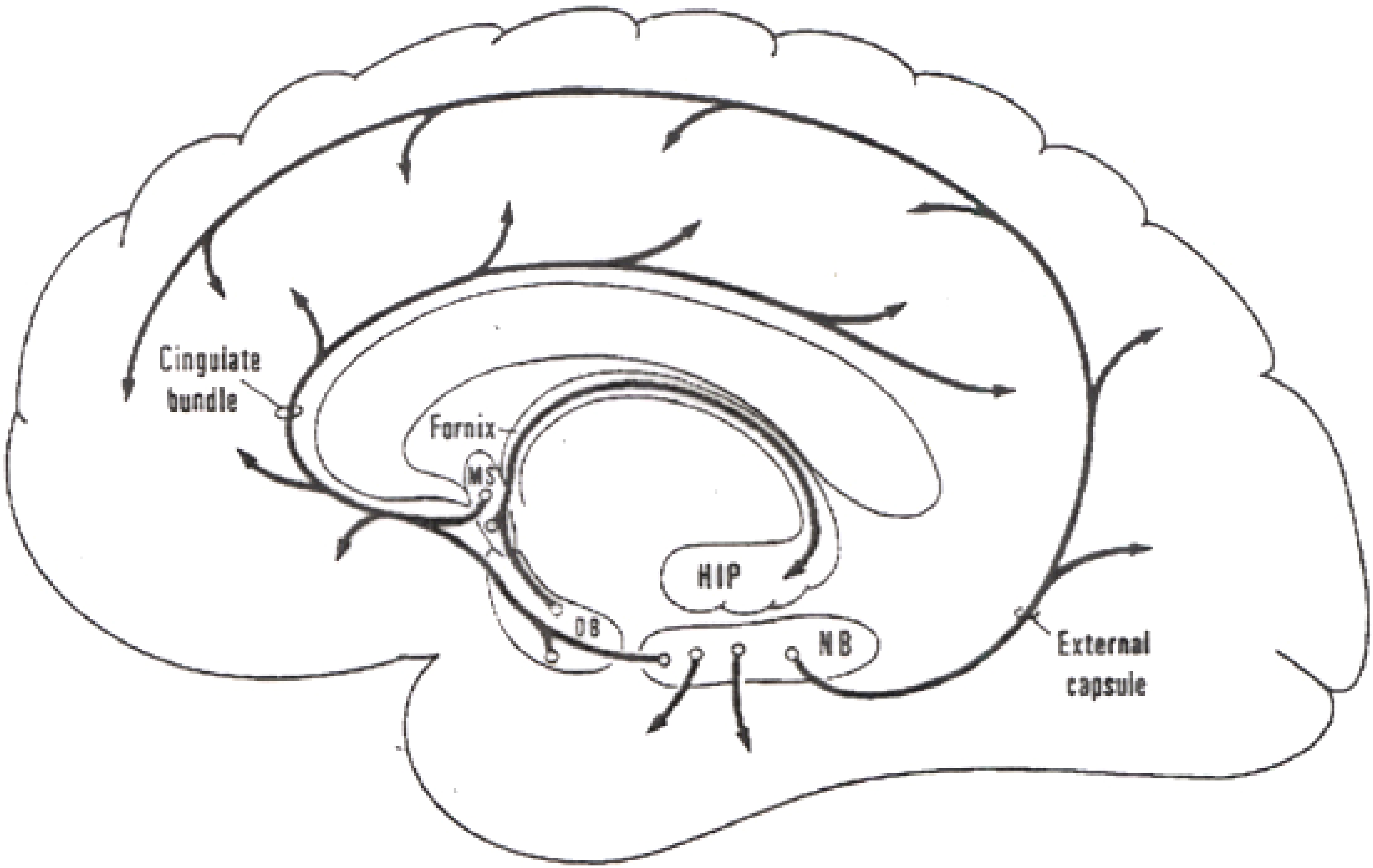
ChAT terminals (Mesulam)



Basal forebrain cholinergic system in human

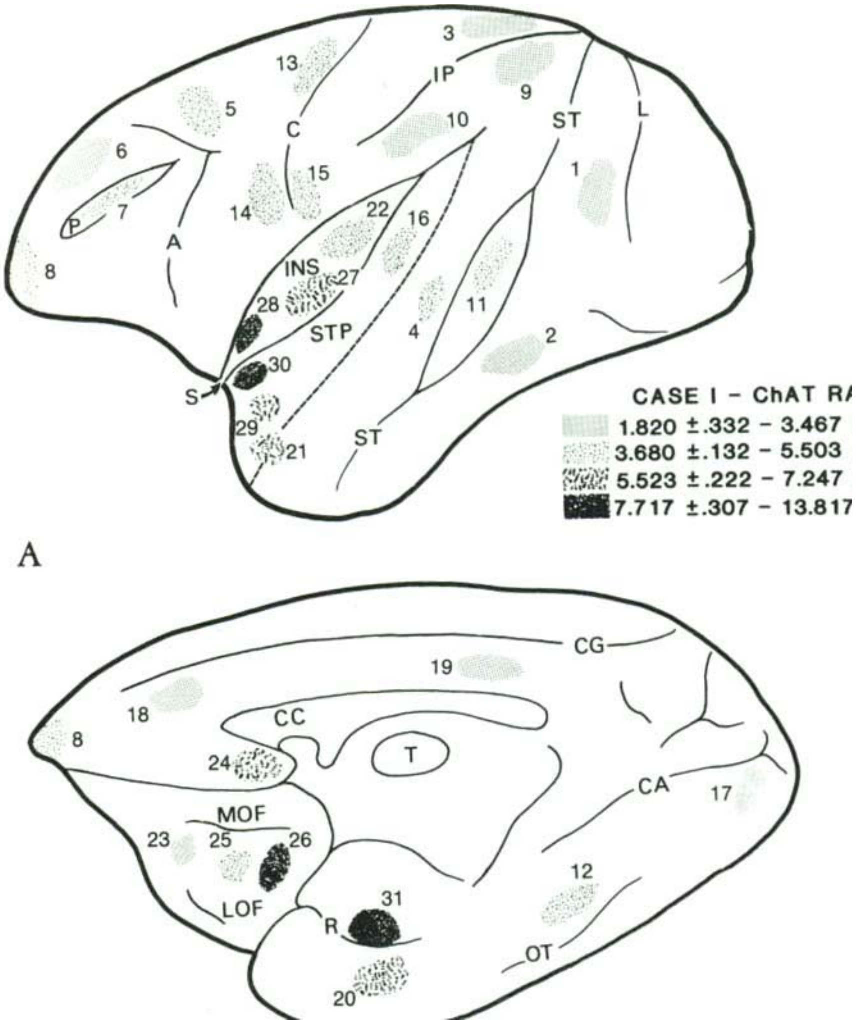


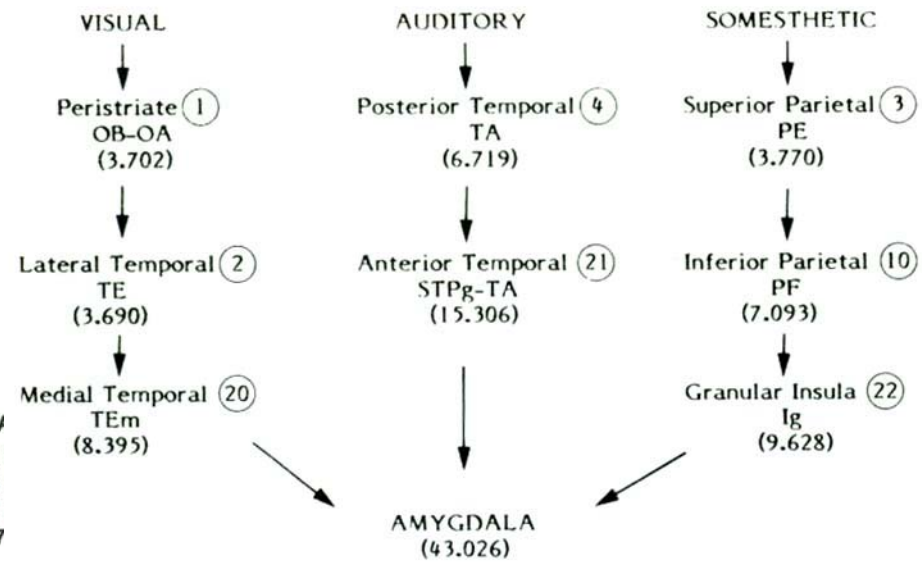
Maps of rostro-caudal cholinergic neurons (stained with the antibodsy against choline acteyltransferase) in serial 40 um coronal sections of the basal forebrain in human. Ch1-Ch4 nomenclature according to Mesulam. From Lehericy et al. 1999



Summary of the major pathways for cholinergic innervation of the cortical mantle by the magnocellular basal complex (Saper, 1990).

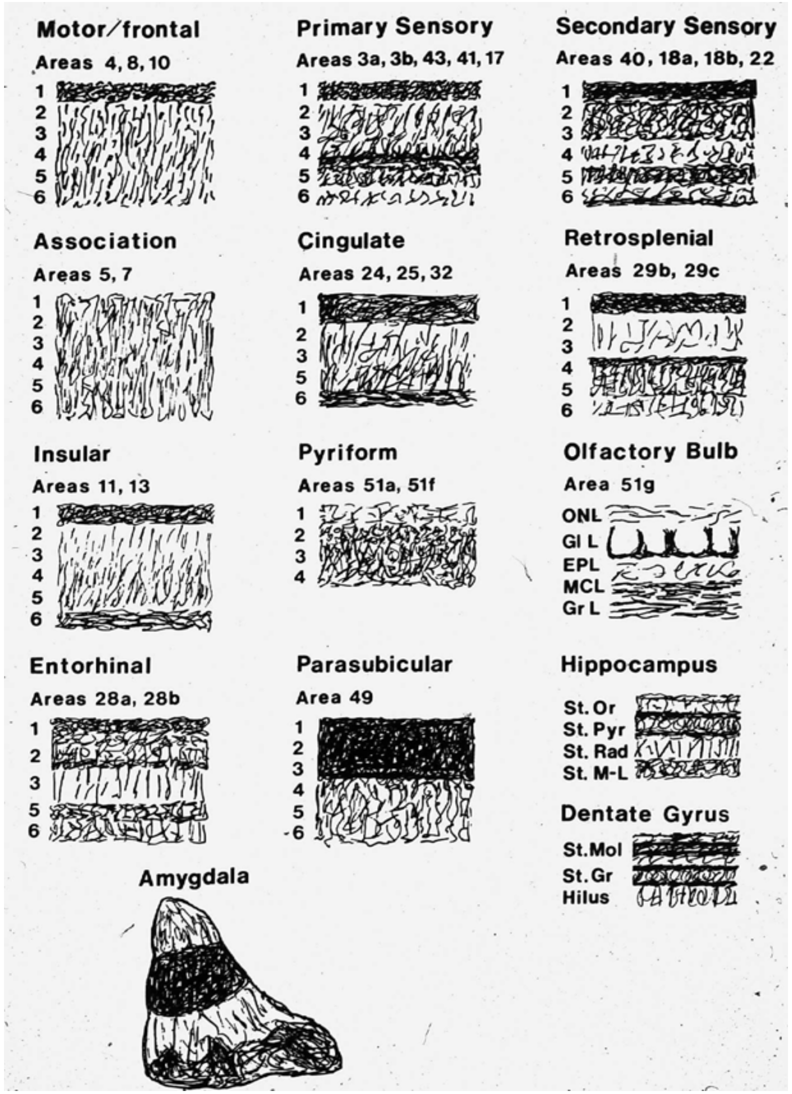
REGIONAL CHAT ACTIVITIES IN RHESUS MONKEY



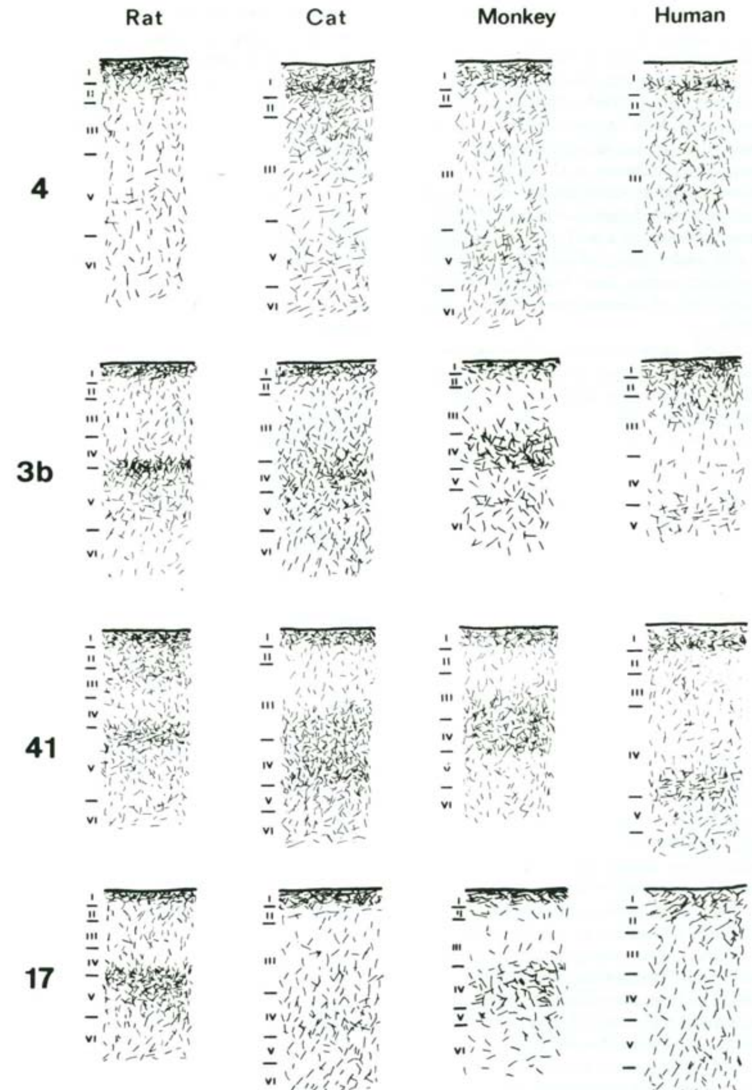


Mesulam et al., 1986

CHOLINERGIC INNERVATION IN VARIOUS CORTICAL AREAS

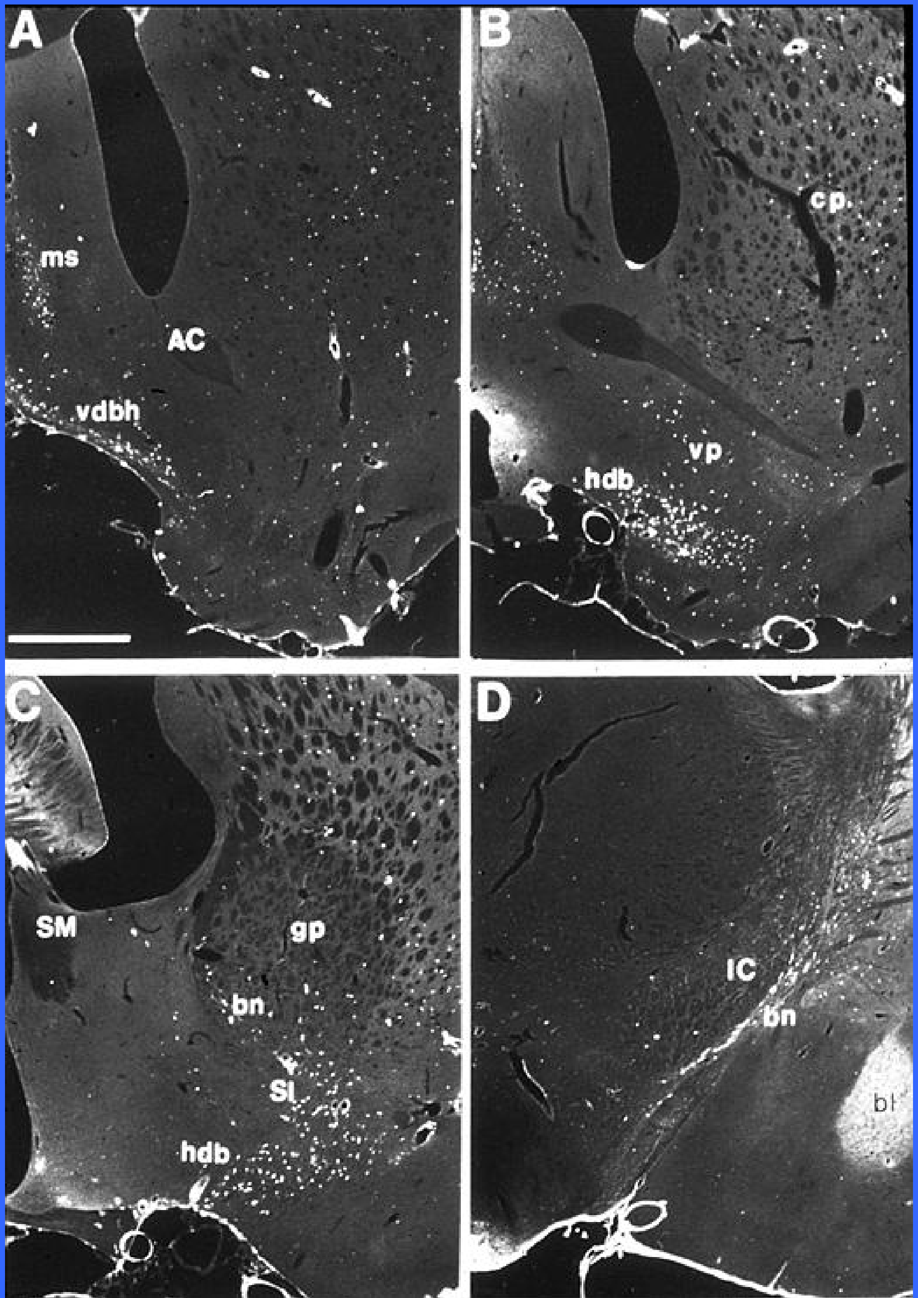


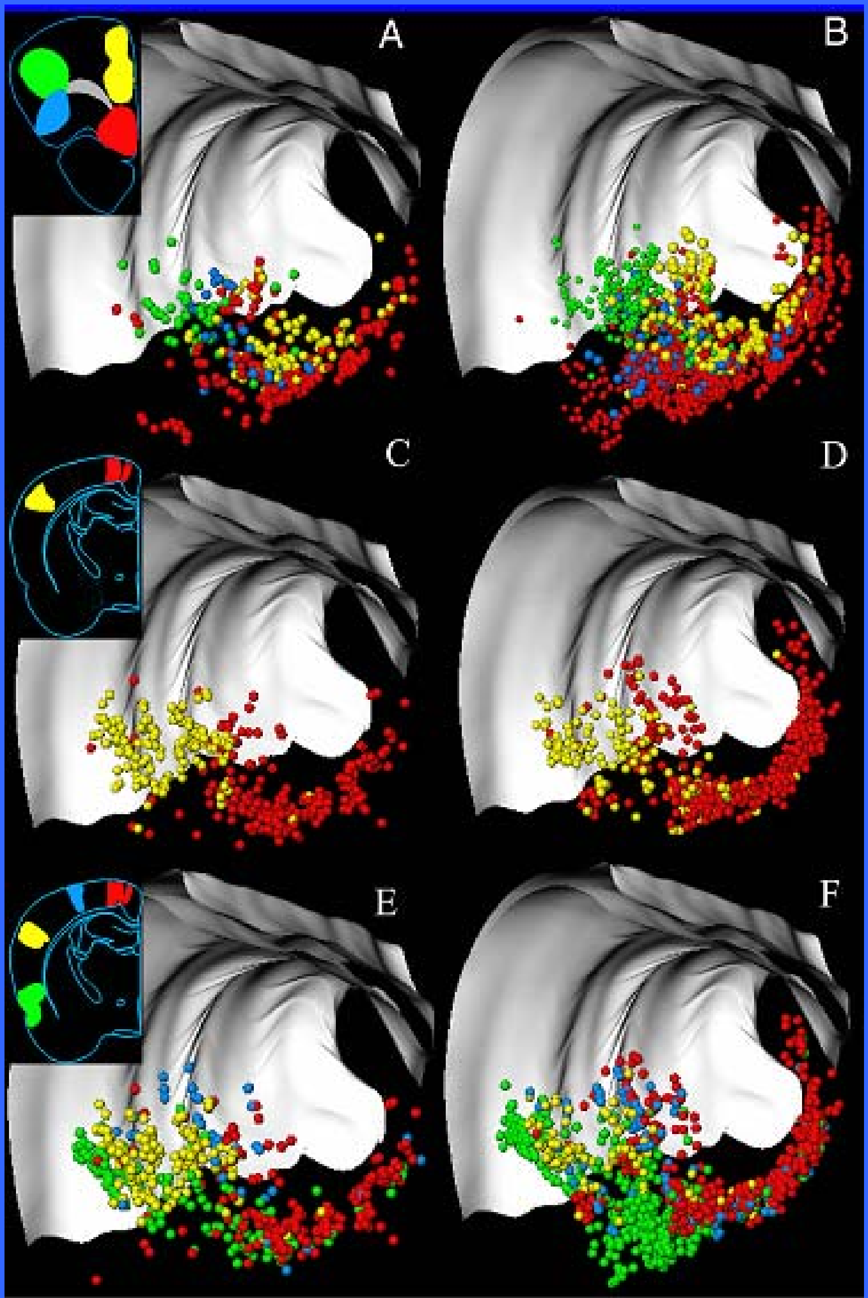
Cholinergic innervation in rat (Lysakowski et al., 1988)

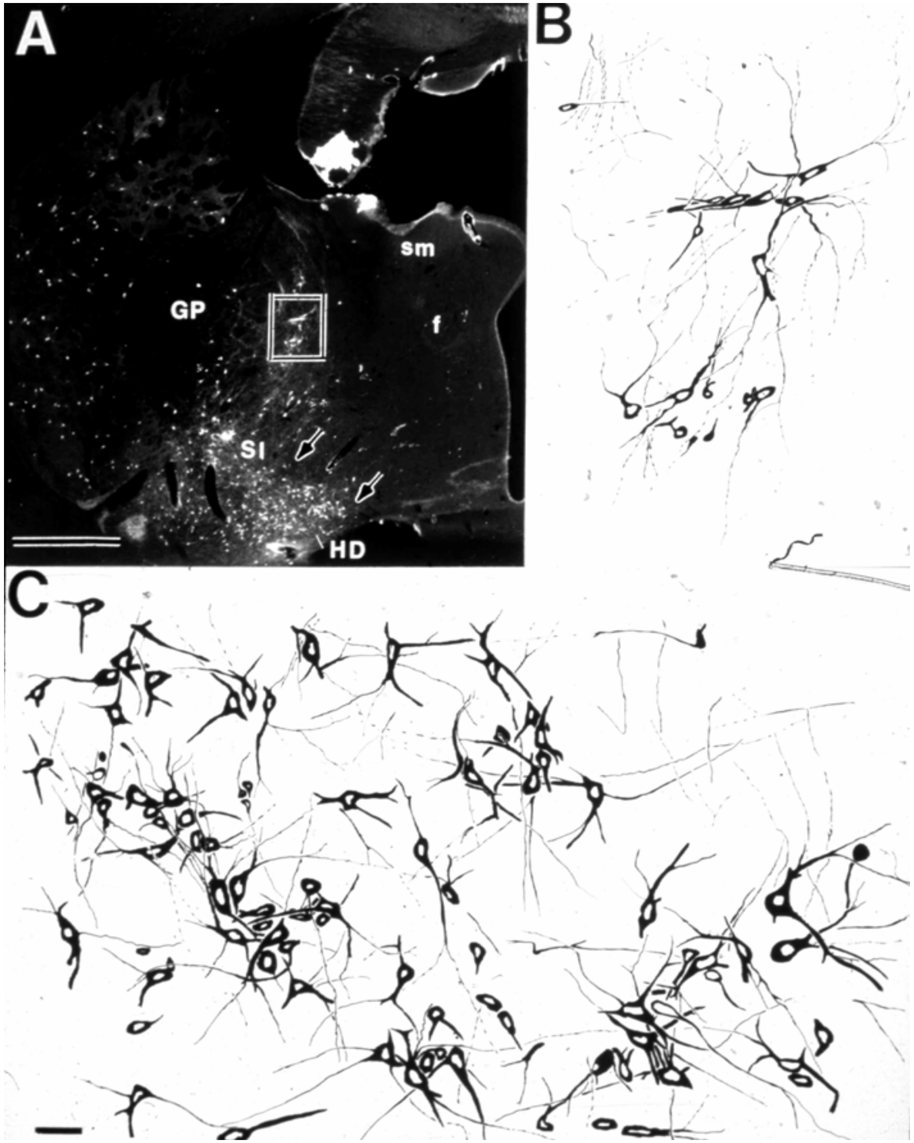


Comparing the ACh innervation of motor (4) and sensory regions of the rat, cat, monkey and human). From Avendano et al.,1996

CORTICOPETAL NEURONS IN THE B. FOREBRAIN OF RATS



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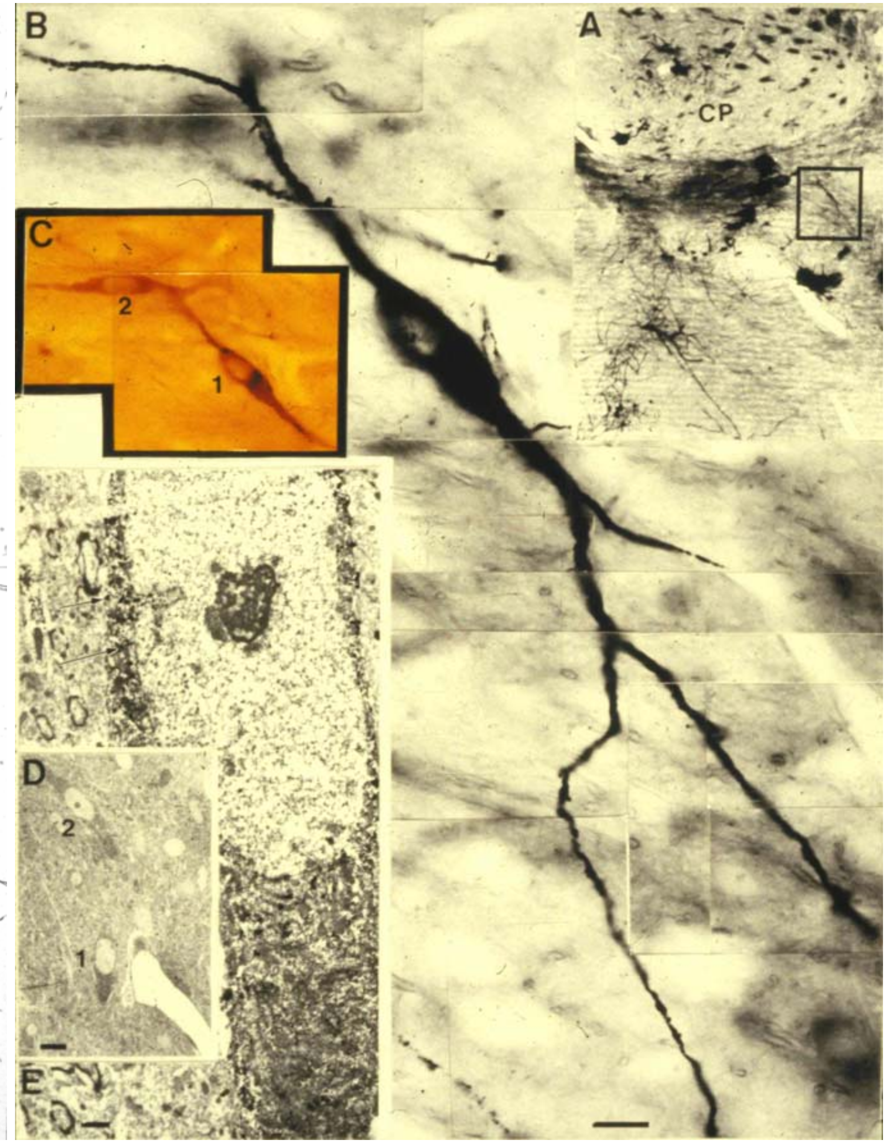
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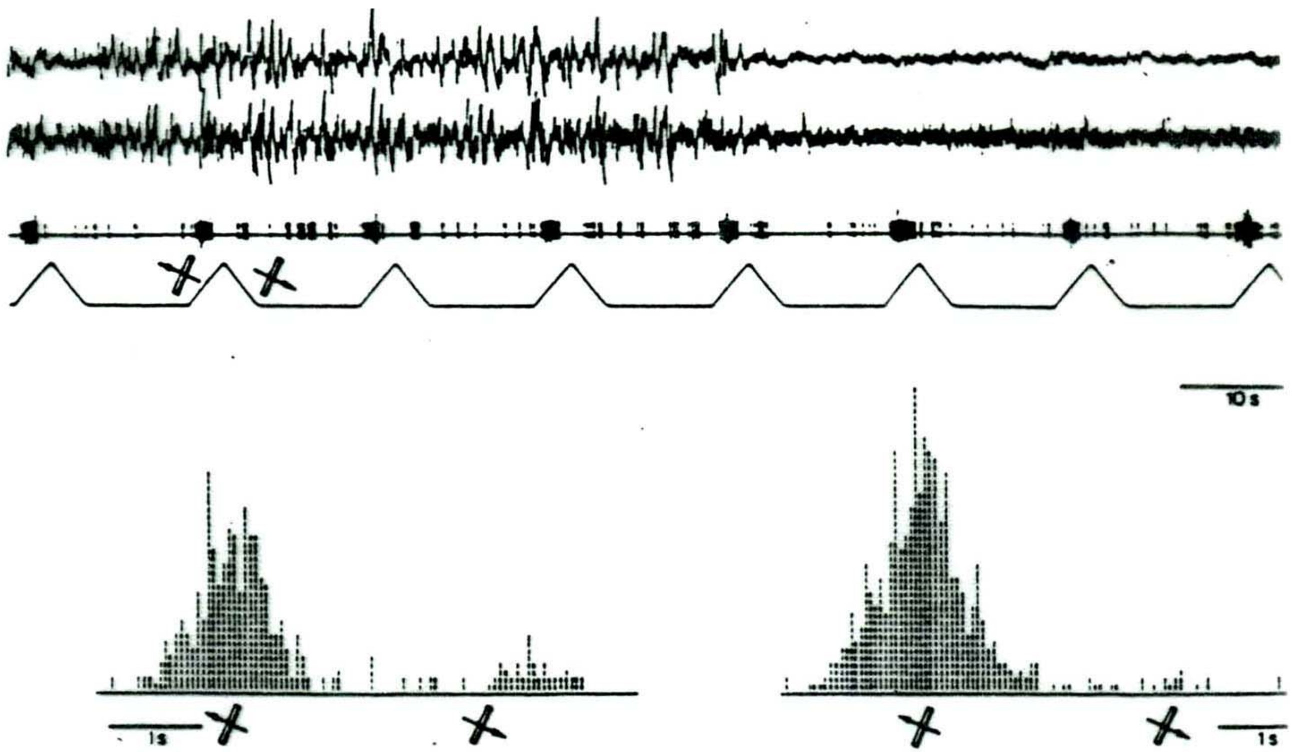
THE BASAL FOREBRAIN IN CORTICAL ACTIVATION AND SENSORY PROCESSING

- AROUSAL CONCEPTS
- FIRING PROPERTIES OF BF NEURONS
- DIFFUSE INPUT TO THE BF FROM ASC. MODULATORY SYSTEMS

- THE BF PROJECTION IS BIASED TOWARD ASSOCIATED CORTICAL AREAS
- FEEDBACK FROM THE PREFRONTAL CORTEX (PFC) TO THE BF
- DISTINCT OPERATION REQUIRES SPECIFIC ORGANIZATION
- WHERE THE BOTTOM UP MEETS WITH THE TOP DOWN?

- HYPOTHESIS: THE BF PARTICIPATE WITH THE PFC IN SELECTIVE AMPLIFICATION OF SENSORY PROCESSES

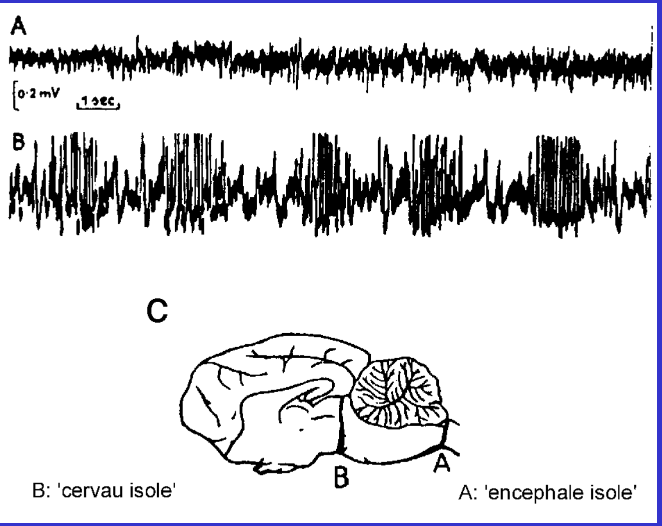
•**Arousal** is a complex state. It is characterized by: 1) switch from slow to fast oscillatory pattern in thalamo-cortical circuits; 2)increased discharge in neurons of the ‘diffuse’ corticopteal’ systems. Arousal is a fundamental change of operation from the storage mode to information-processing mode, including <u>perceptions</u> influenced by external and internal sensory input; capacity of directing <u>attention</u>, accessing <u>memory</u> faithful to recent history; array of <u>motor output;</u> and <u>emotions</u> that are focused to percepts and thoughts.



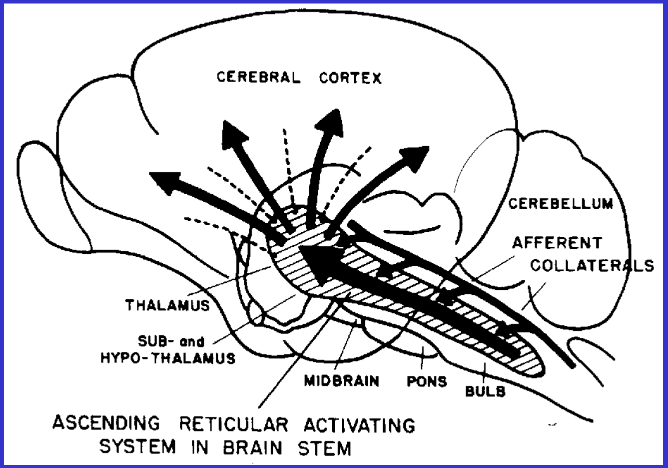
Effects of arousal (noise) from SWS on response selectivity of a cell in LII of the striate cortex. Arousal results in a moderate increase in the response to movement and a virtual elimination of the response to rightward movement (Livingston and Hubel, 1981).

DEVELOPMENT OF AROUSAL CONCEPTS

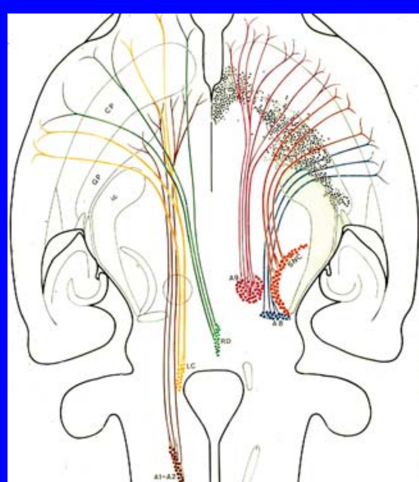
- **1930s**: wakefulness is maintained by afferent input to the brain and sleep ensues when that input is removed, as in the 'cerveau isole' cat, or falls below a certain critical level, as in normal sleeping (Bremer: deafferentation theory)

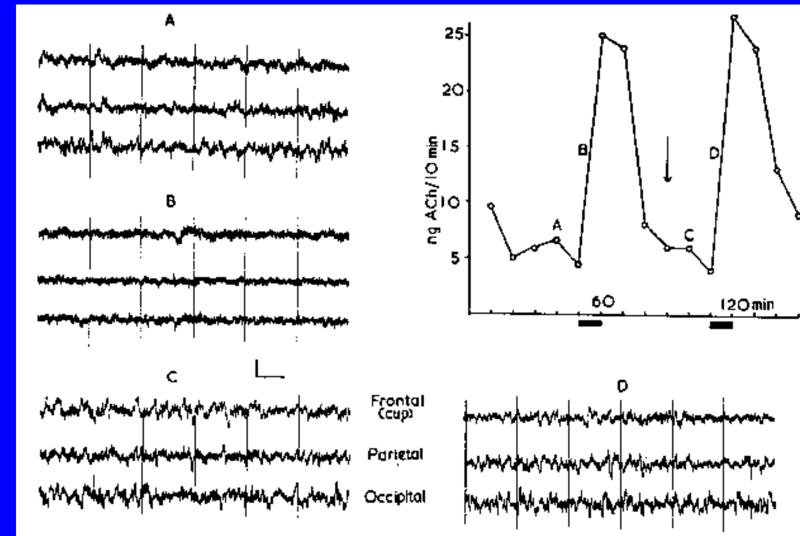


- **1950s**: the brain actively controls its own state by the ascending reticular activating system (Magoun-Moruzzi).

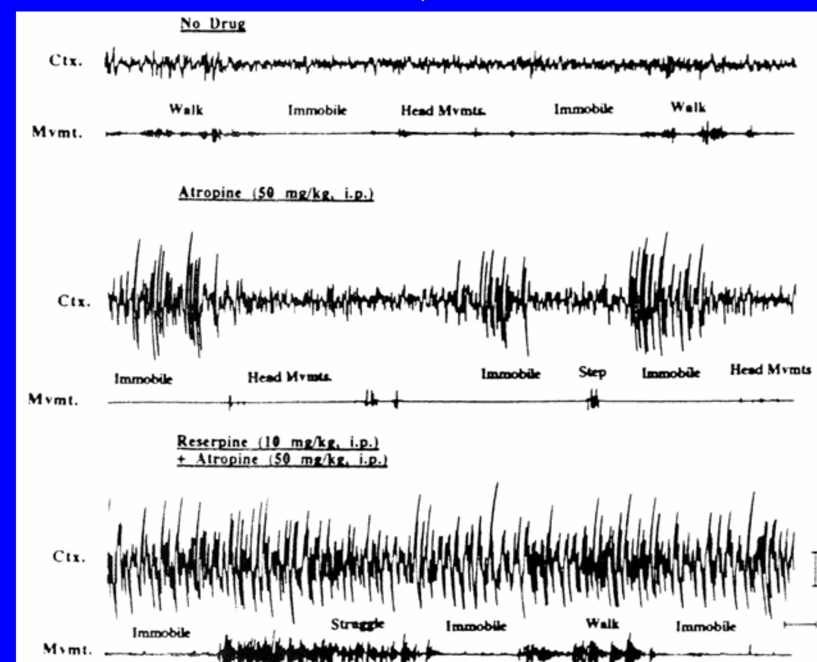


1965s- the concept of an undifferentiated reticular formation is gradually replaced by the description of transmitter-specific cell groups in the brainstem, the basal forebrain and the hypothalamus that send widely branching axons to the cerebral cortex and other parts of the brain. Role of acetylcholine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



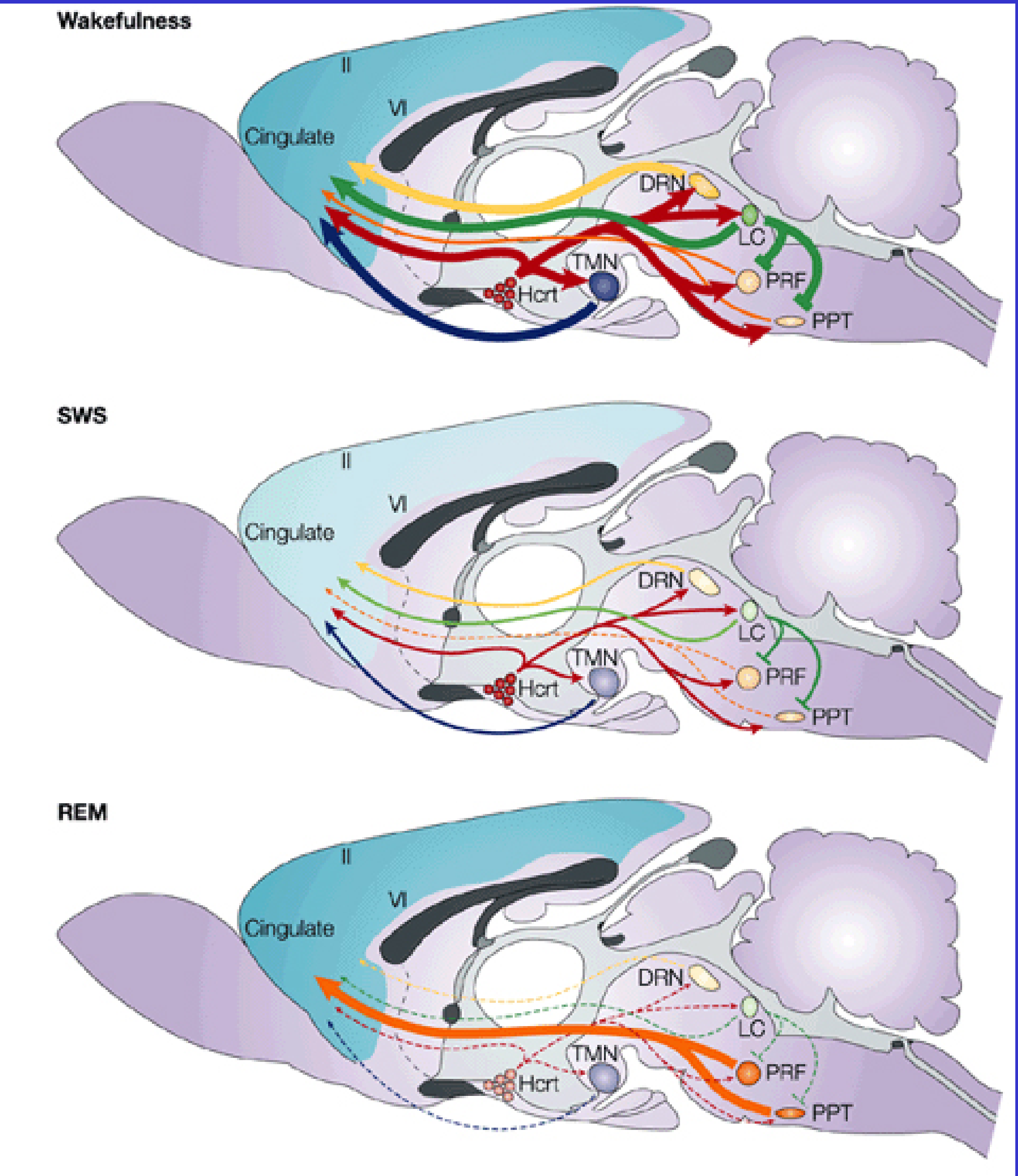


Kanai and Szerb, 1965



Vanderwolf and Dringenberg, 1998

DEVELOPMENTS OF AROUSAL CONCEPTS: Today



•**1990s-** various states can tentatively be linked to the accompanying systematic changes in balance between various neuromodulators.

DRN-5HT (yellow)

LC-NE (green)

PPT-Ach (orange)

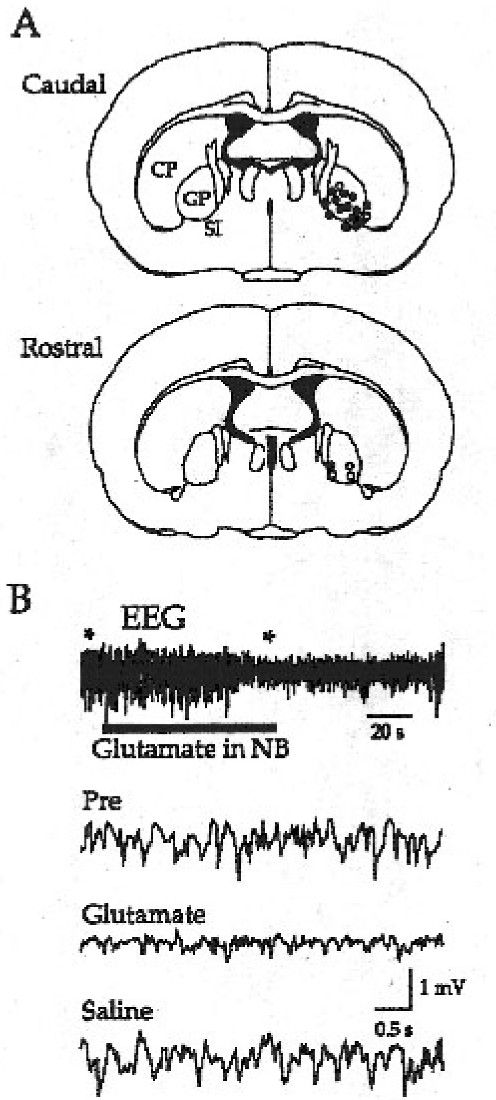
TMN-His

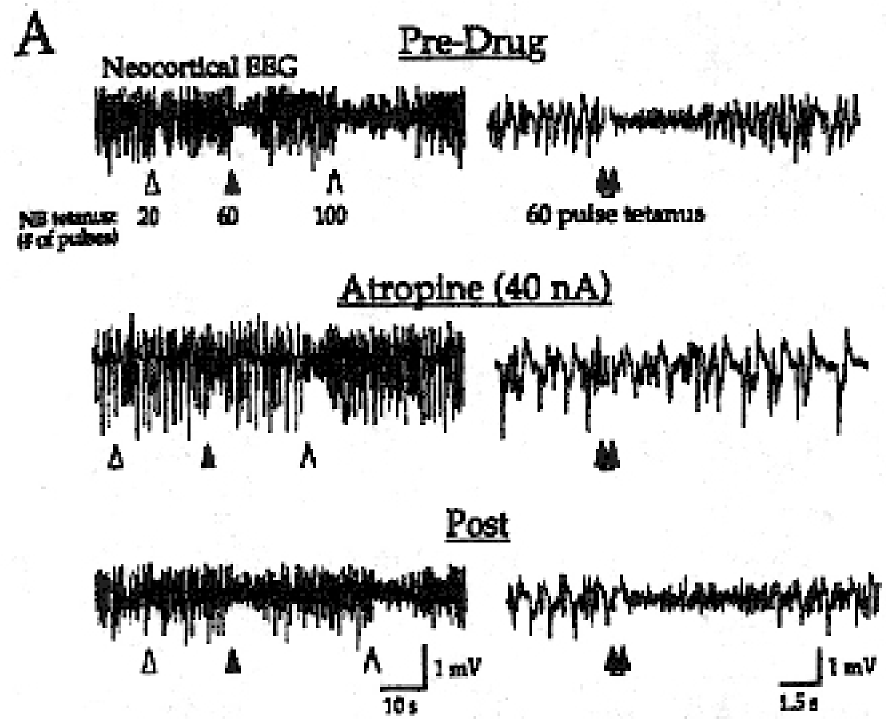
Hcrt/Orexin (red)

Sutcliffe and De Lecea, (2002)

HOW ACTIVITY IN BASAL FOREBRAIN NEURONS RELATE TO CORTICAL ACTIVATION?

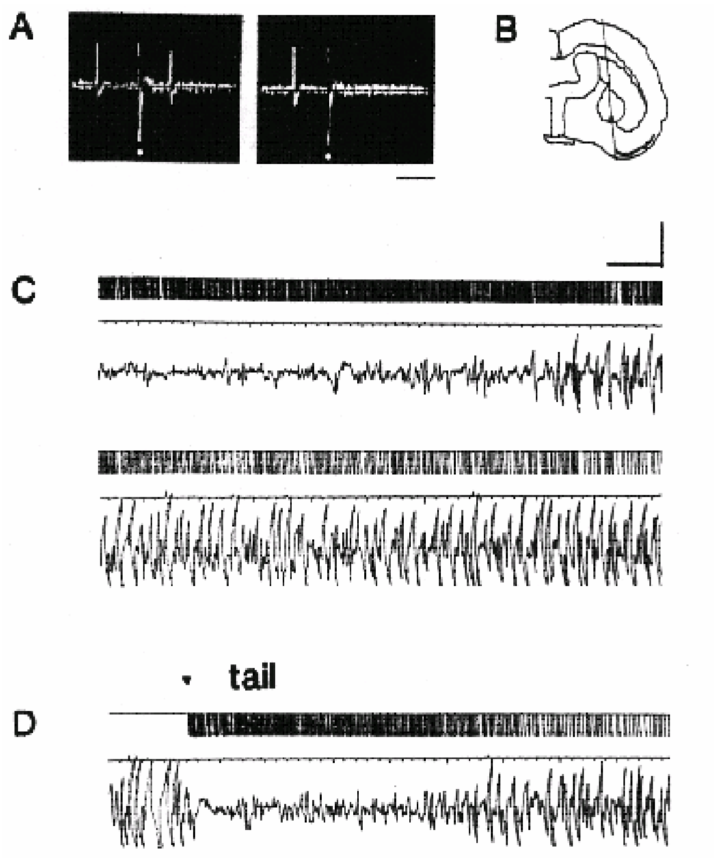
BF stimulation, EEG , Ach action in vitro

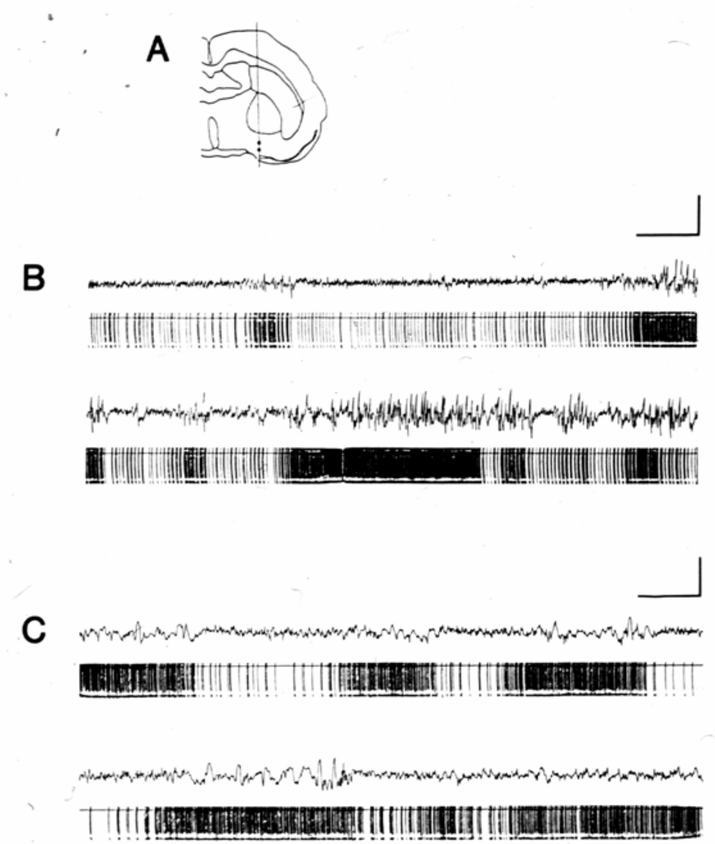




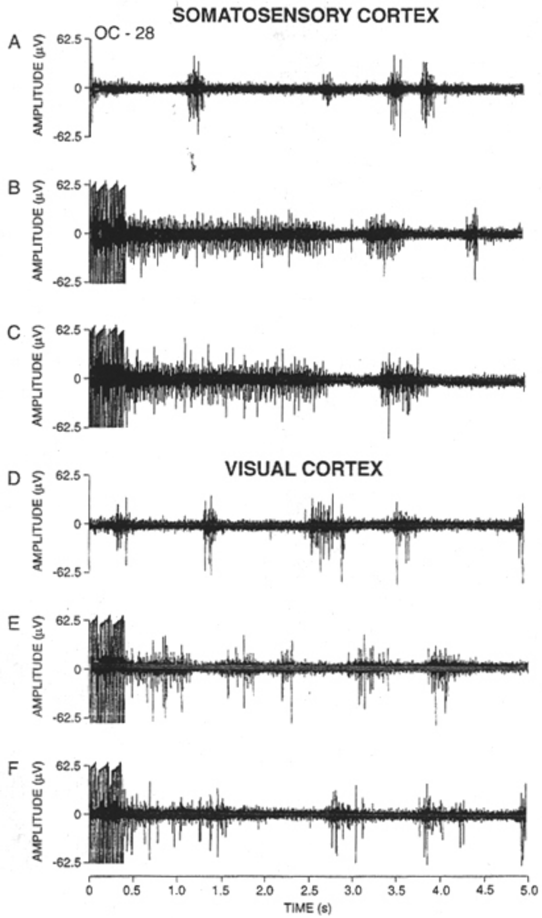
Metherate and Ashe, 1992

BF neurons fire in correlation to various EEG epochs.

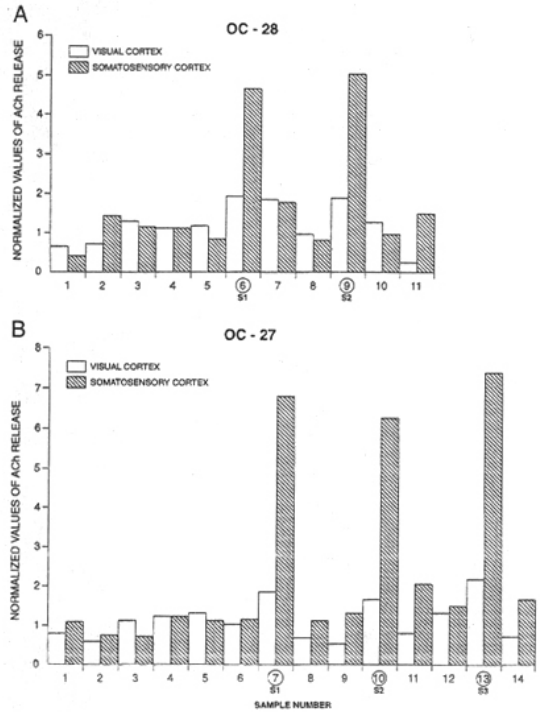




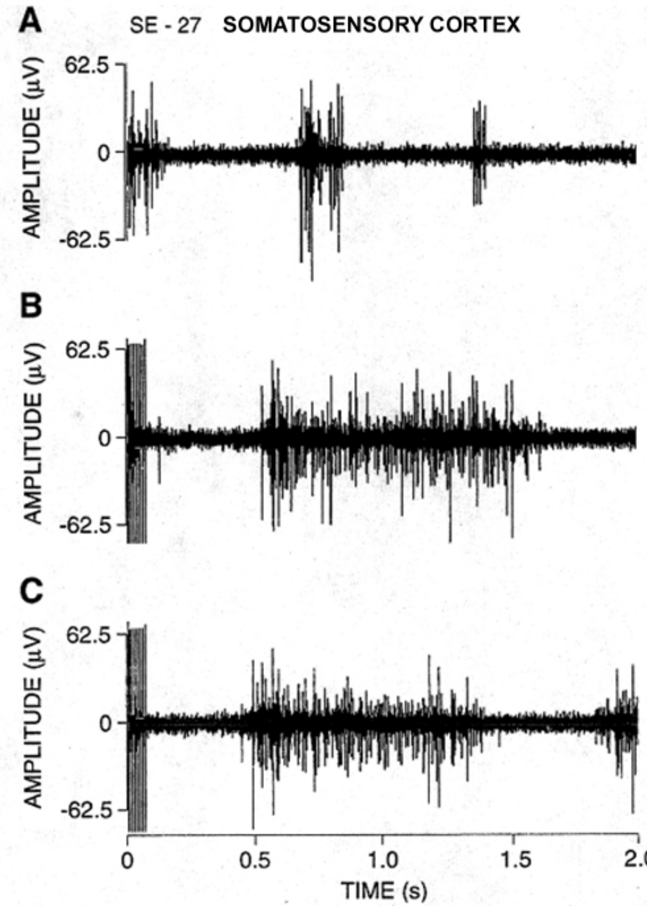
Detari et al., 1987



An example of the effects of BF stimulation on the cerebral cortex elicited from a region of the BF that produced increased ACh release from somatosensory cortex. **A:** Spontaneous activity. **B:** Effect of a 400-ms train of pulses at 100 Hz in the BF. **C:** A second example of the response in the somatosensory cortex. **D:** Spontaneous activity in the visual cortex. **E:** The effect of BF stimulation in the visual cortex from the same site that produced the record in (B). **F:** A second example of the response to BF stimulation in the visual cortex. The release of ACh from the visual cortex was much less than from the somatosensory cortex.

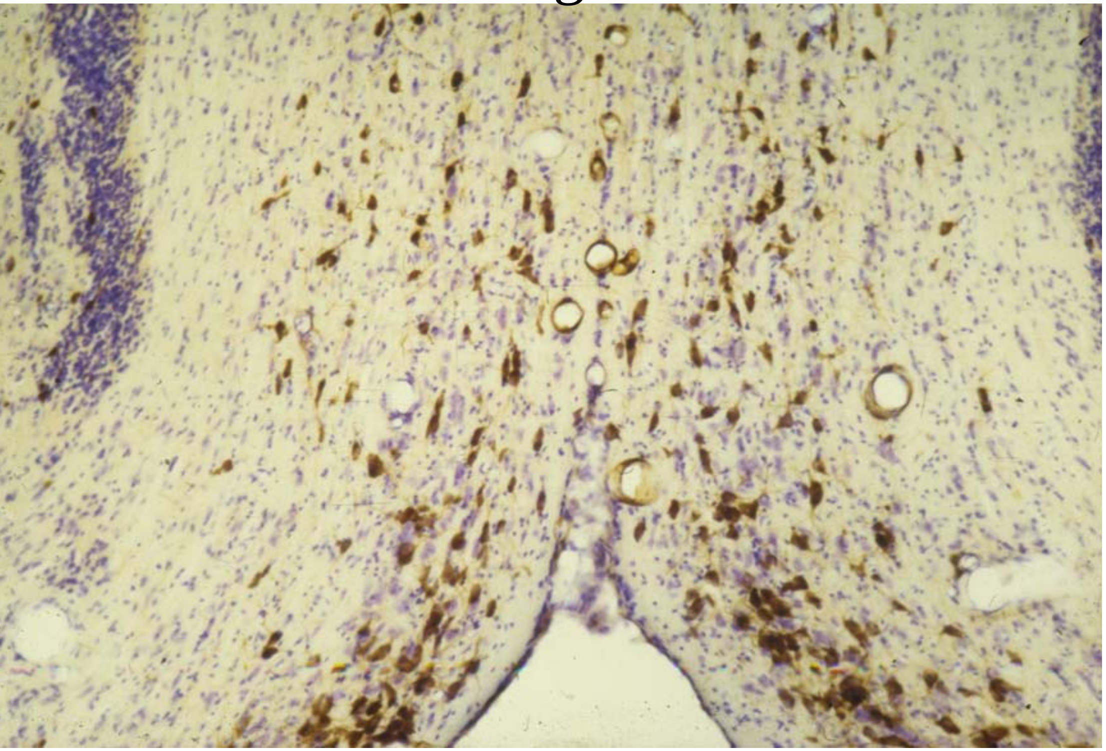


ACh release from sites in the visual and the somatosensory cortex following electrophysiological recordings of the neuronal activity provoked by BF stimulation. **A:** Eleven pairs of 30-minute samples obtained simultaneously from the somatosensory and the visual cortex. The first five pairs provided the baseline levels for both cortical regions. During collection of the sixth pair of samples the BF was stimulated every 4 seconds with a train of 40 pulses at 100 Hz. ACh release increased more in the somatosensory cortex than in the visual cortex. ACh levels returned to normal over the next hour, and the stimulation was repeated during the ninth sampling period. **B:** A second experiment showing the same pattern of differential ACh release following BF stimulation. In this experiment the BF stimulation was performed three times using a train of 50 pulses every 4 seconds for the duration of the 30-minute sampling period (sample pairs 7, 10, and 13). A slight, but significant, increase in ACh occurred in the visual cortex, whereas a 600–700% increase occurred in the somatosensory cortex.

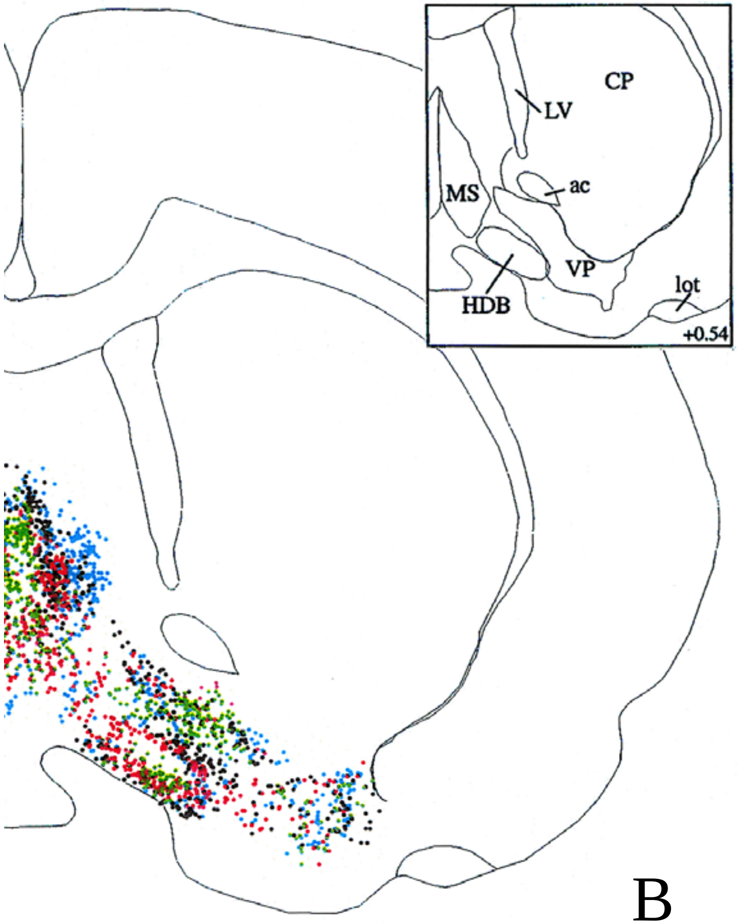


Multiunit recordings from the hindlimb somatosensory cortex showing how BF stimulation could provoke a long suppression of spontaneous activity followed by a large and long increase in neural activity. The several large neurons in this recording were spontaneously active. **A:** A 2-second record of spontaneously active neurons discharging in bursts. **B:** When a 100-ms BF stimulus was administered, all neural activity stopped for about 450 ms after the end of the stimulus; then an intense discharge occurred, lasting for approximately 1.1 second. **C:** A second example of the inhibitory pause produced by BF stimulation.

Basal forebrain corticopetal cholinergic neurons are intermingled with non-cholinergic neurons



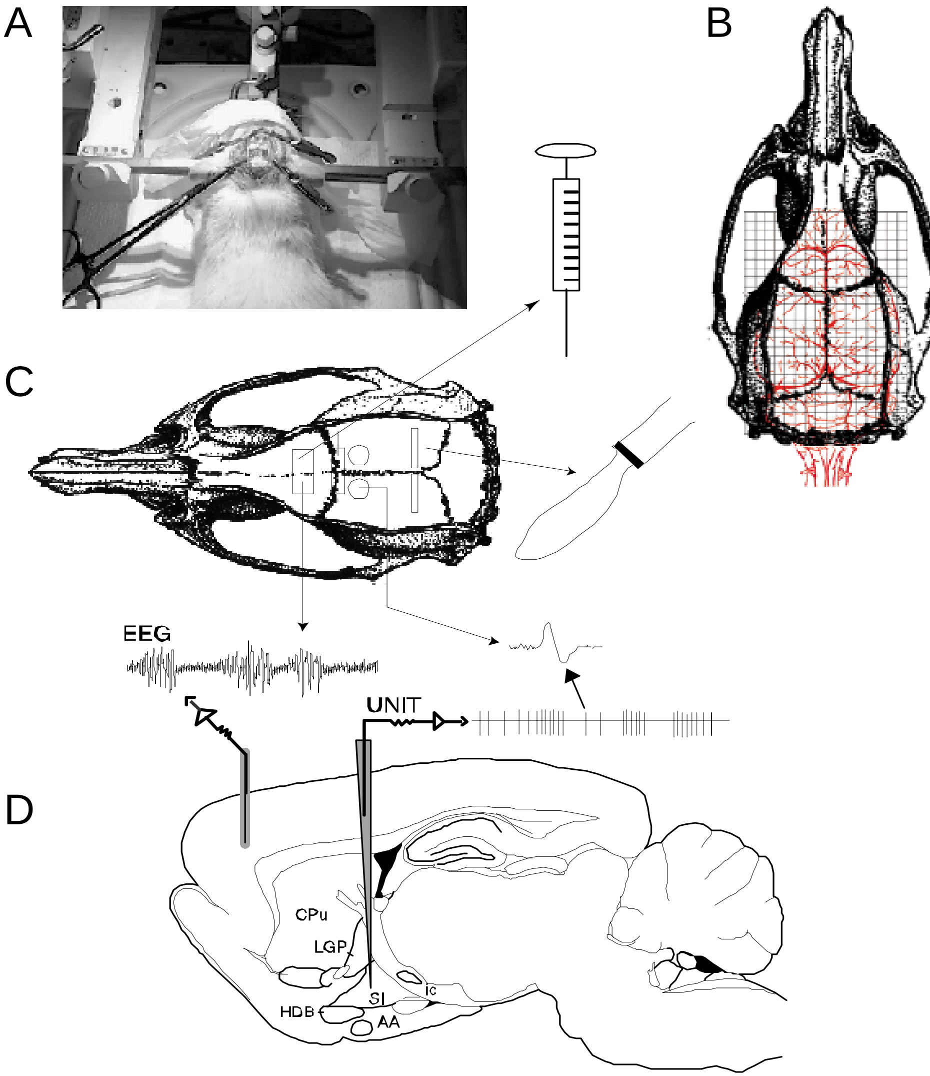
A

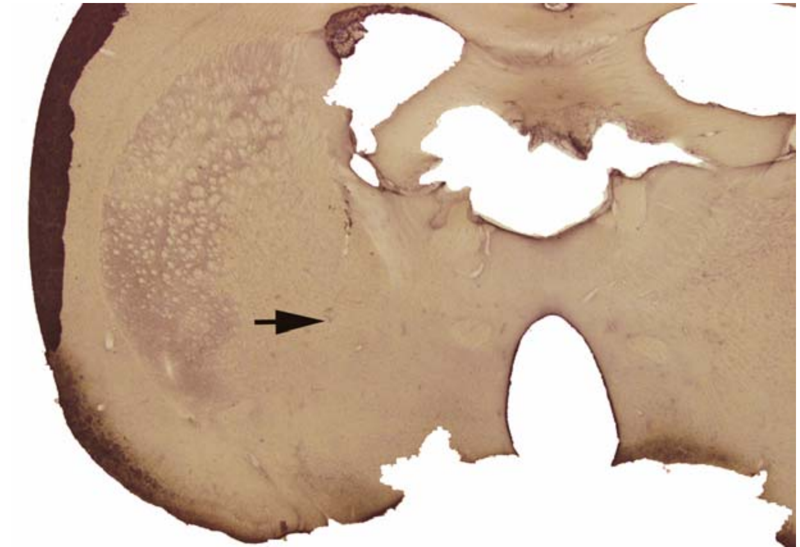


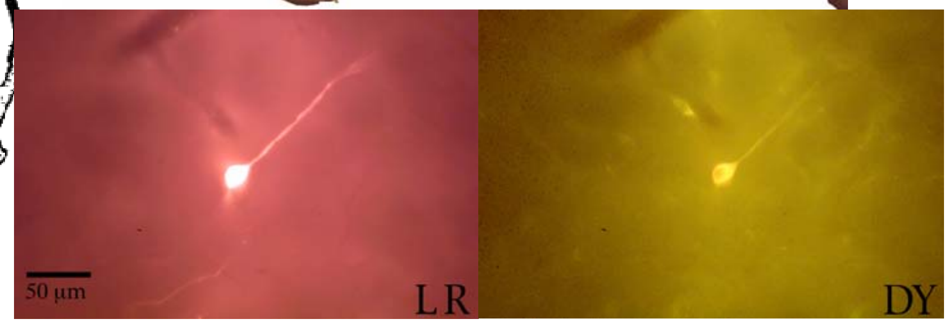
B

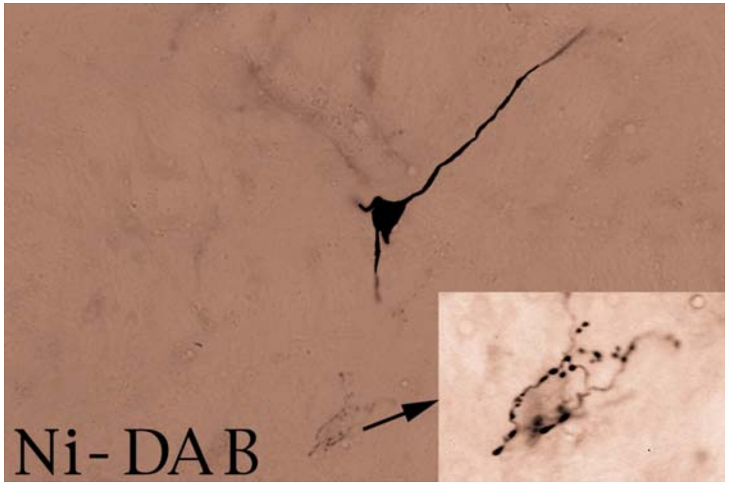
A: Choline acetyltransferase (ChAT) and Nissl-staining. B: cholinergic neurons red) are intermingled with Parvalbumin (green), Calretinin (black) and calbindin (blue) neurons

Juxtacellular filling, transmitter or target identification of the recorded neurons, EEG monitoring. The methods

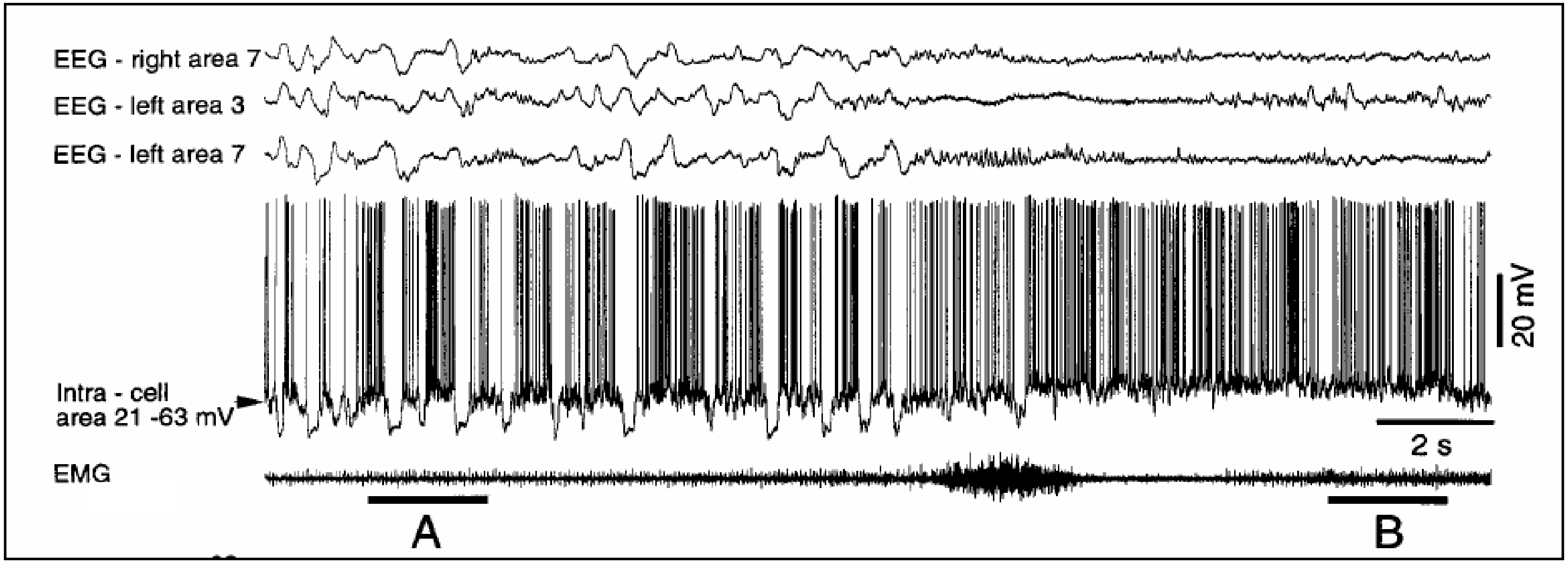


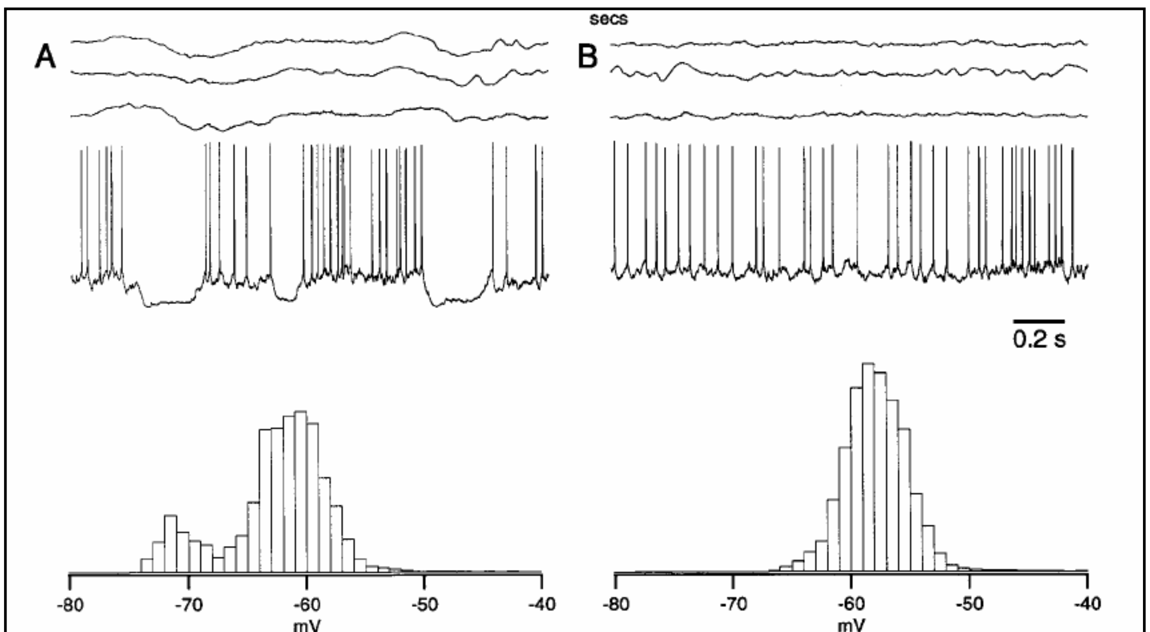






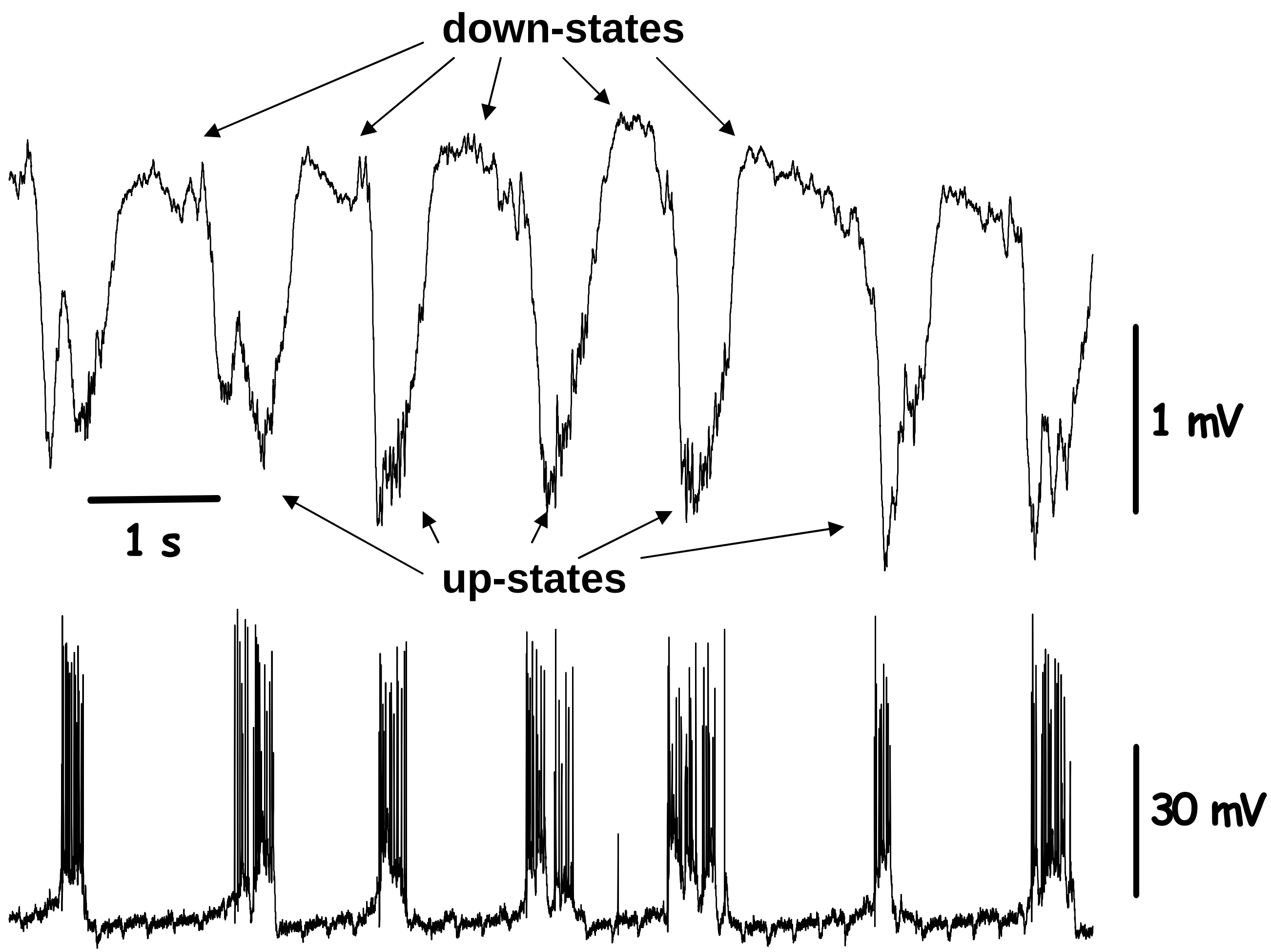
CORTICAL UP AND DOWN STATES





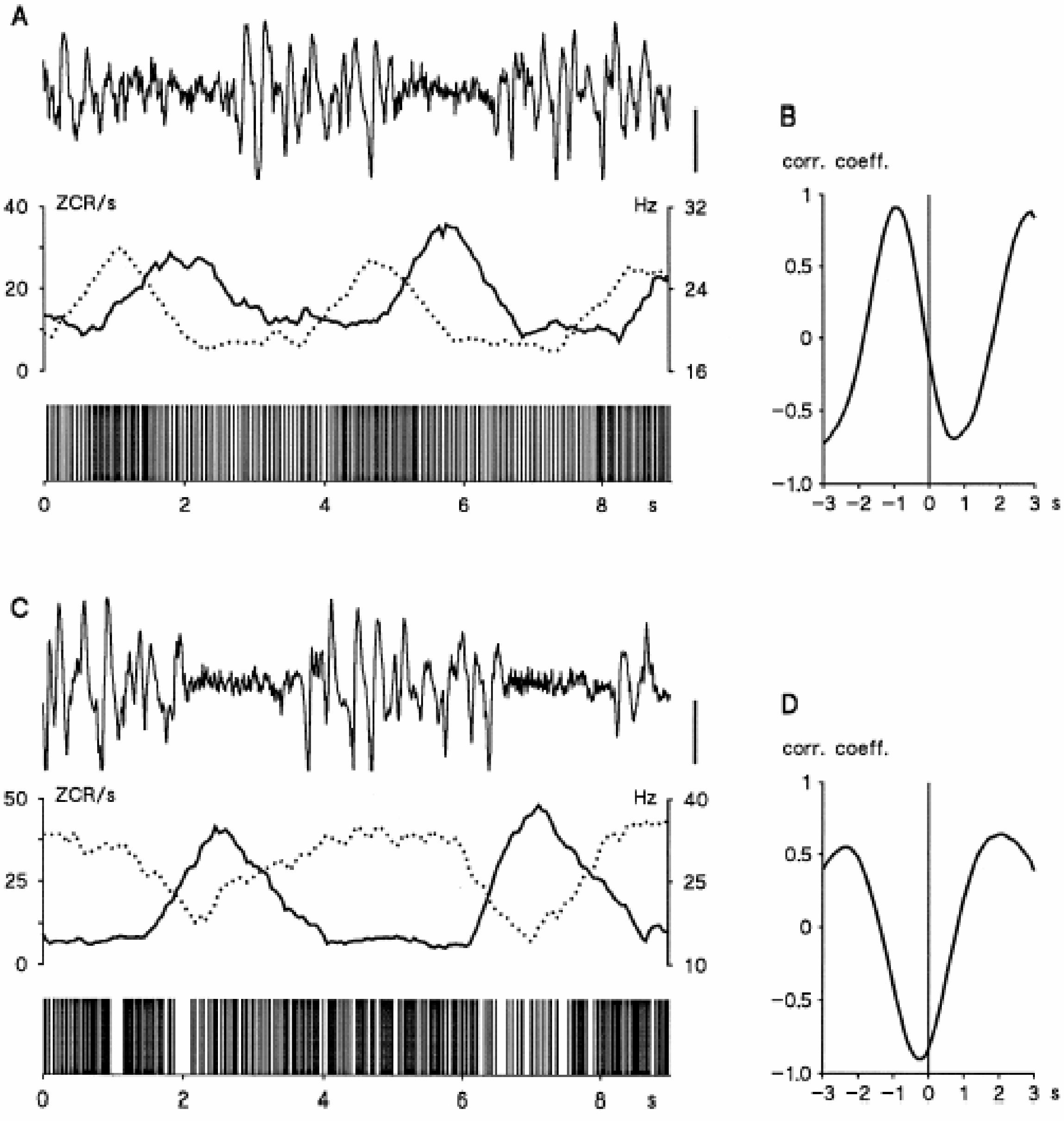
unanesthetized cat
Transitions from SWS to wakefulness. Brief periods of high-frequency firing during SWS are interspersed with silent periods corresponding to the hyperpolarizing phase of the slow oscillation. EEG is characterized by bipolar deflections corresponding to bimodal distribution of membranepotential.

Fig. 9 from Steriade et al., (2001)

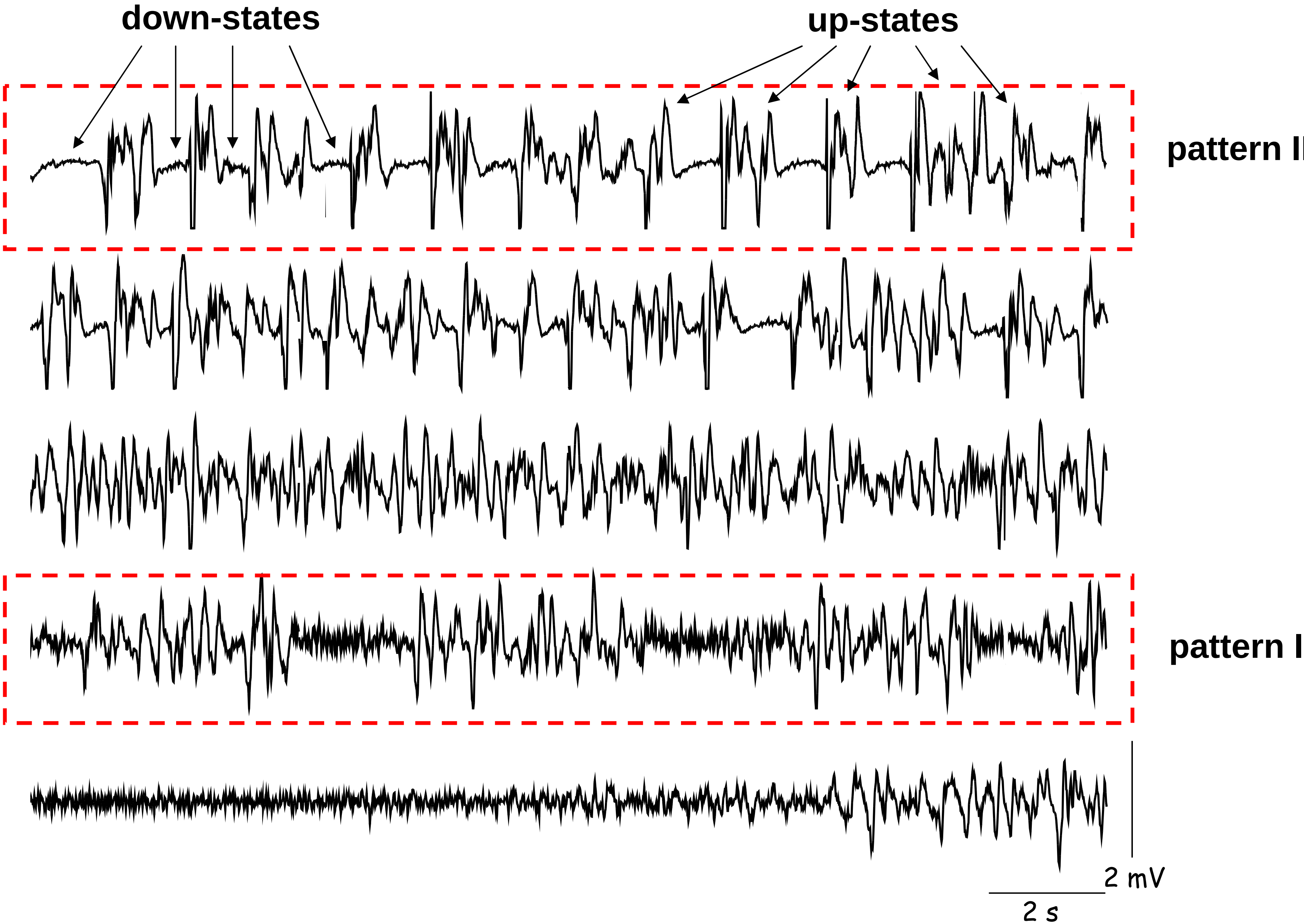


intracellular recording from a pyramidal cell of a urethane-anesthetized rat and the simultaneous EEG recording with transcortical electrodes from the other hemisphere

during the **up-states**, the cell is firing intensively and there are higher frequency waves on the EEG
during **down-states**, EEG is a thin line only and the intracellular recording is noisy and with ECG artefacts (Detari, unpublished observation)

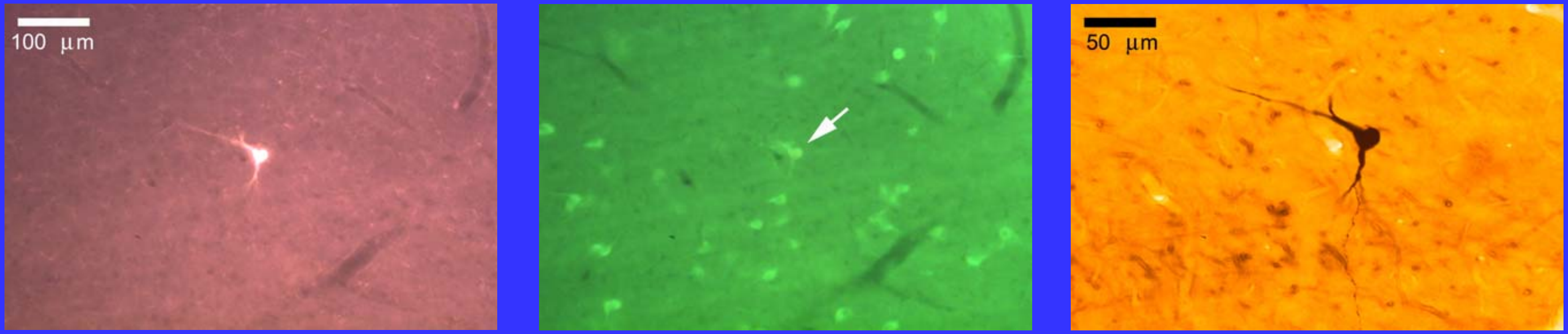


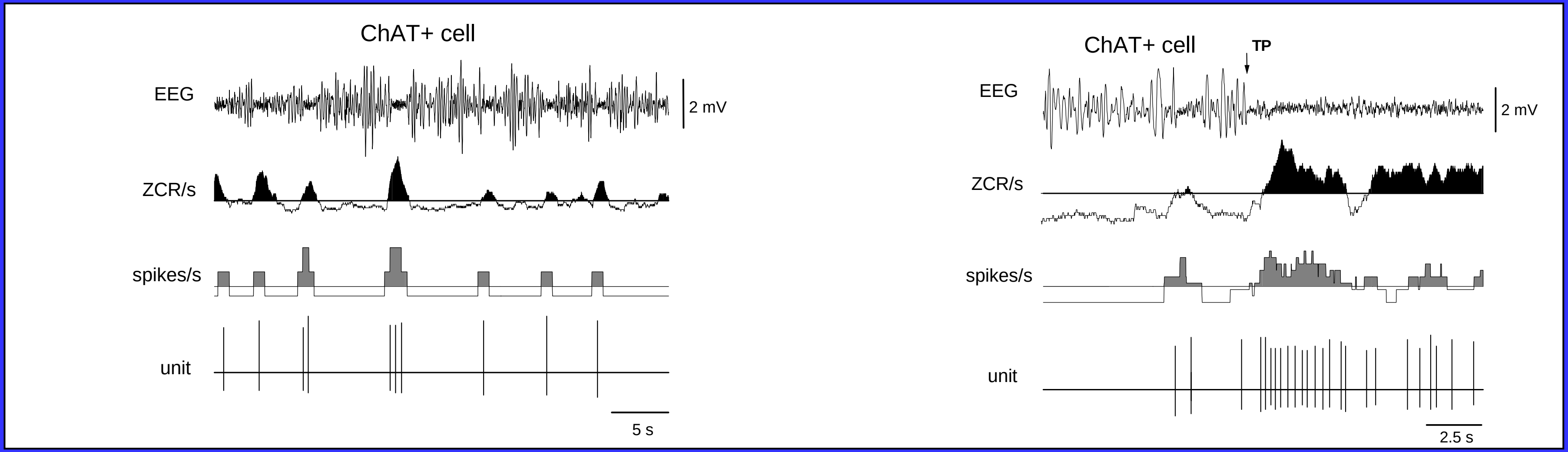
Timing of changes in EEG and neuronal firing rates for an F- (A) and an S-cell C . Top trace: EEG positivity at the deep electrode is upward, calibration 1 mV ; middle traces: frequency of zero-crossings ZCRrs, solid line in EEG and neuronal firing rate dotted line ; bottom trace: computer-generated ticks marking the occurrence of neuronal spikes. The strong positive (A) and negative (C) correlations between ZCR and firing rate can be seen in the correlation coefficients (B and D), peak of 0.91 and y 0.90 at -900 and -200 ms, respectively calculated by shifting the curves in 100 ms steps between -3 and 3 s. (From Detari et al., 1997)



Détári, L., et al., *Brain Res. 759* (1997): 112-121

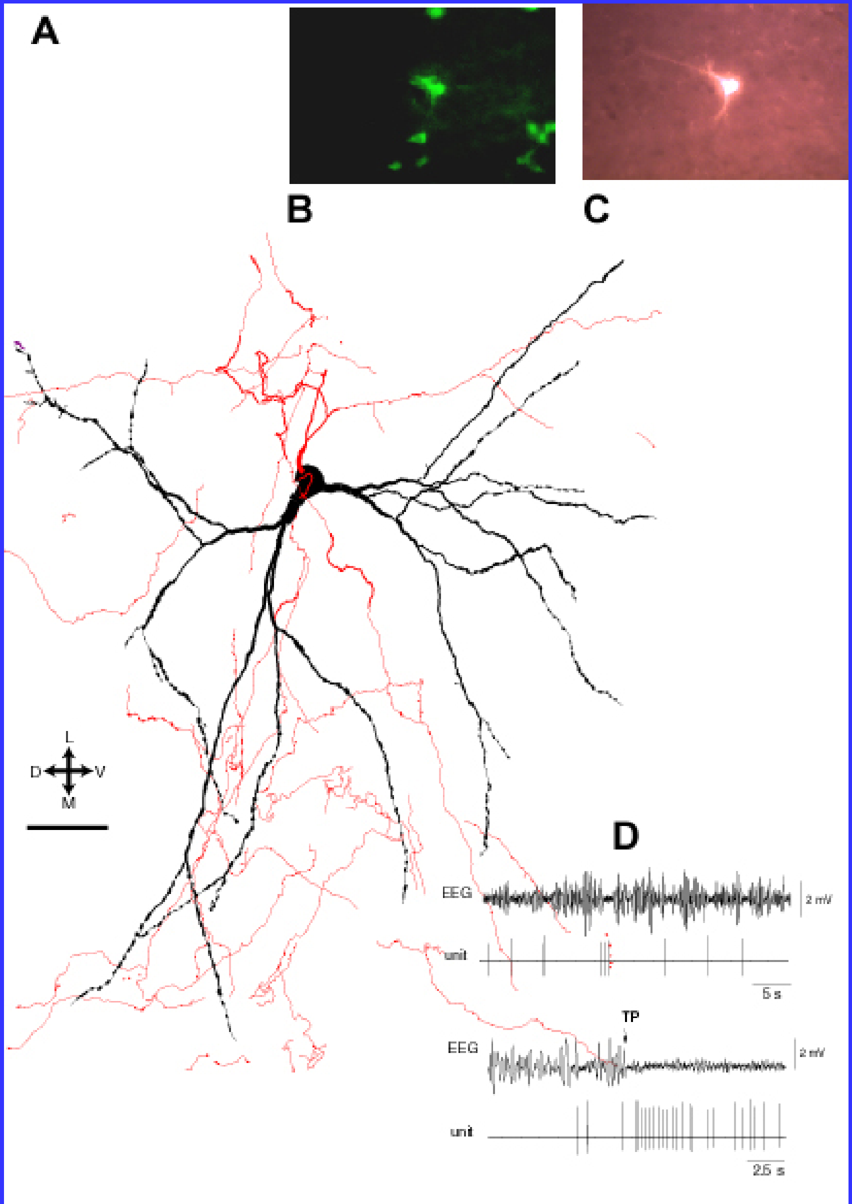
Identified cholinergic cell

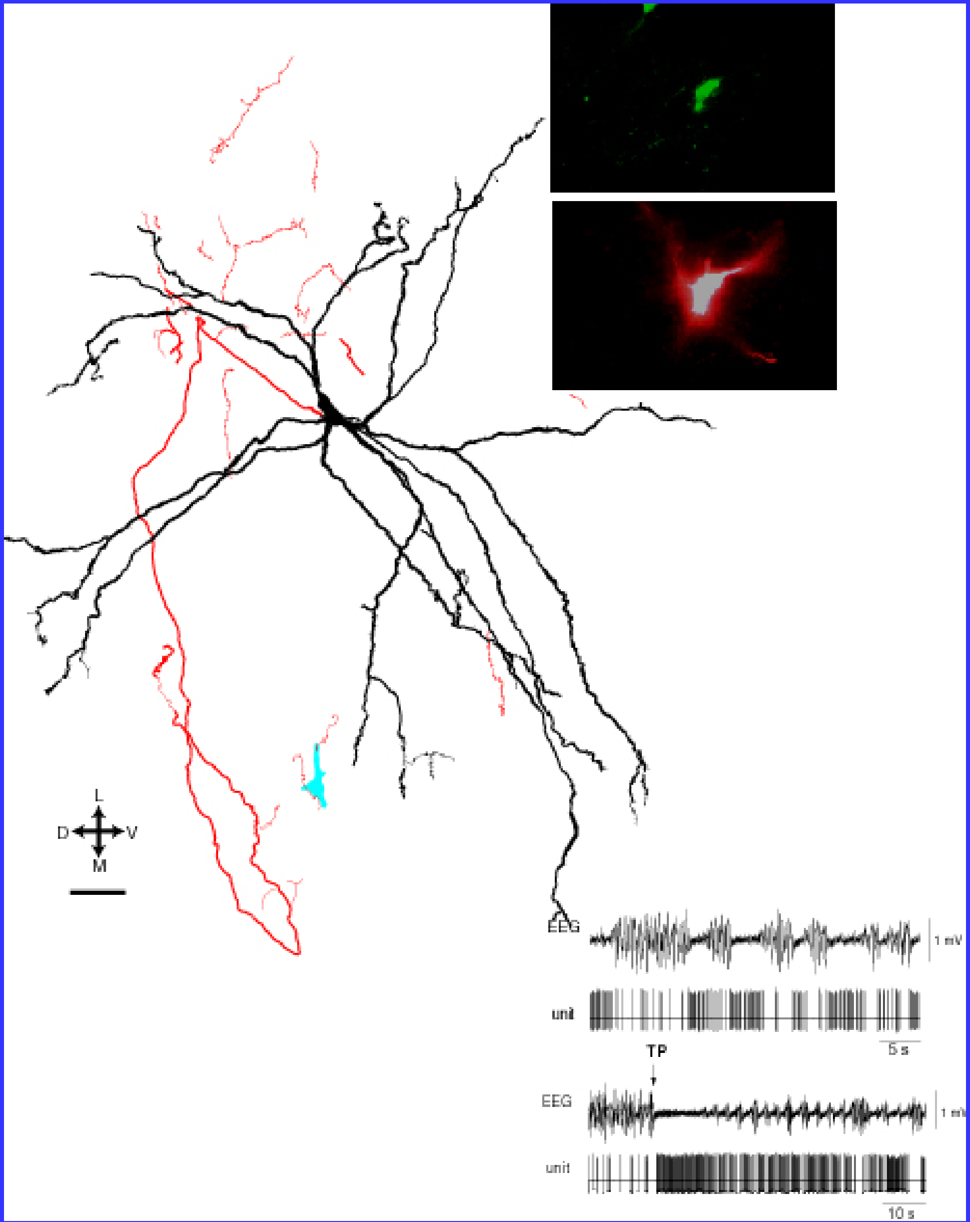




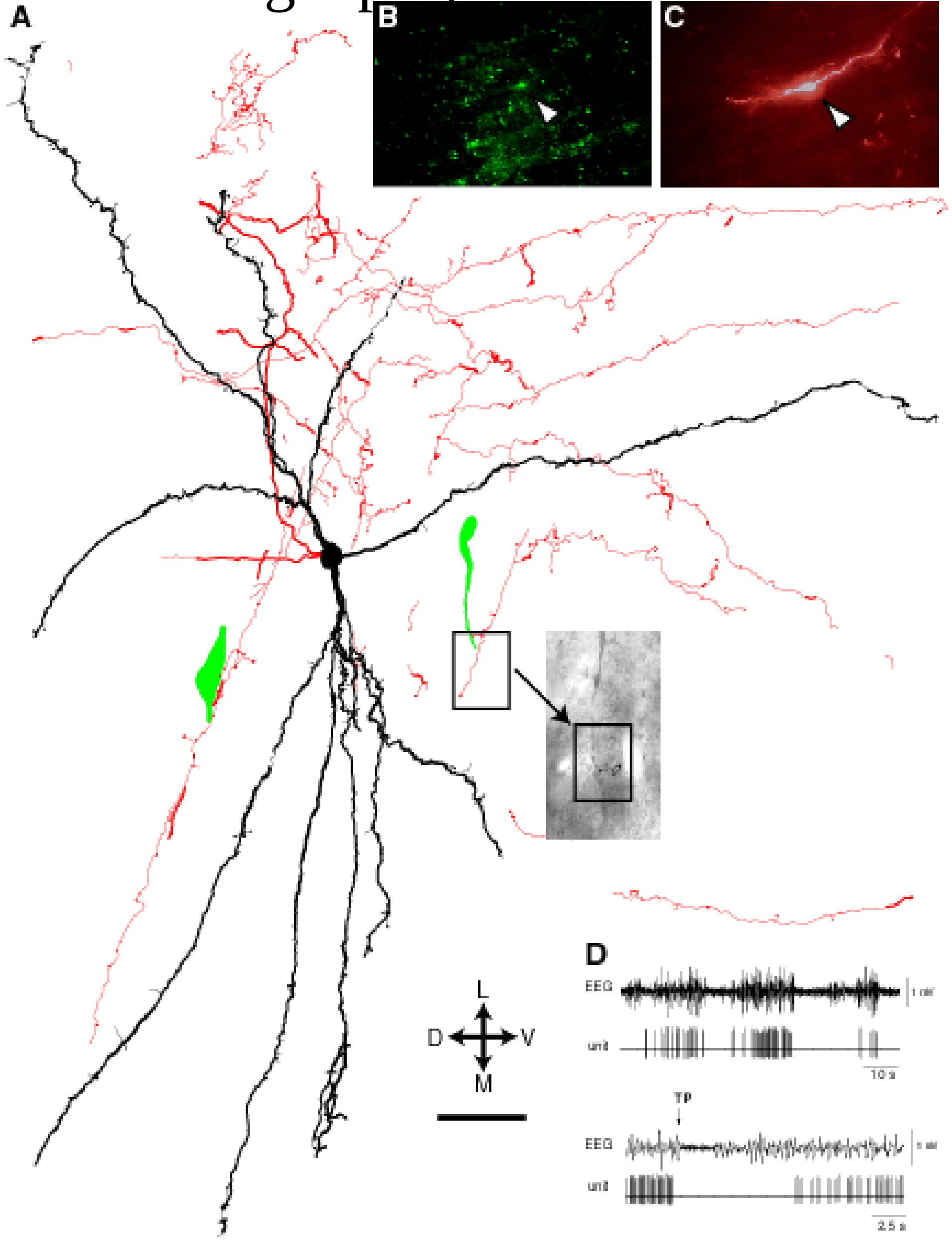
From Duque, Balatoni, Detari, Zaborszky, 2000

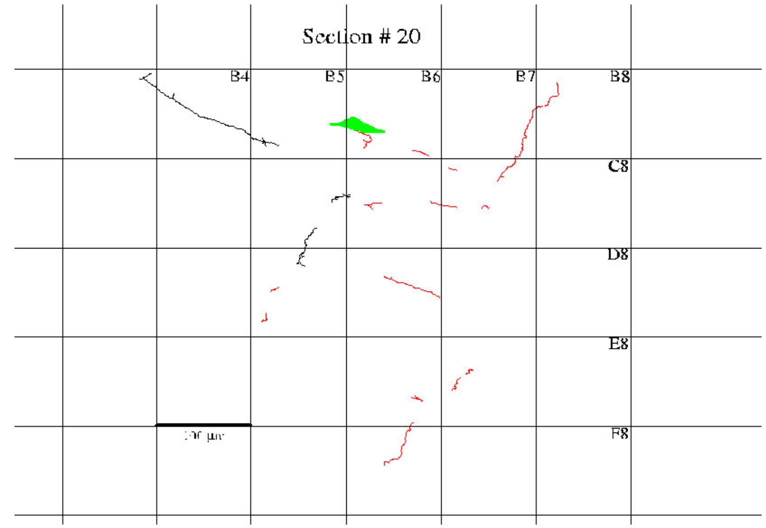
Identified Cholinergic and Parvalbumin (GABA) projection neurons

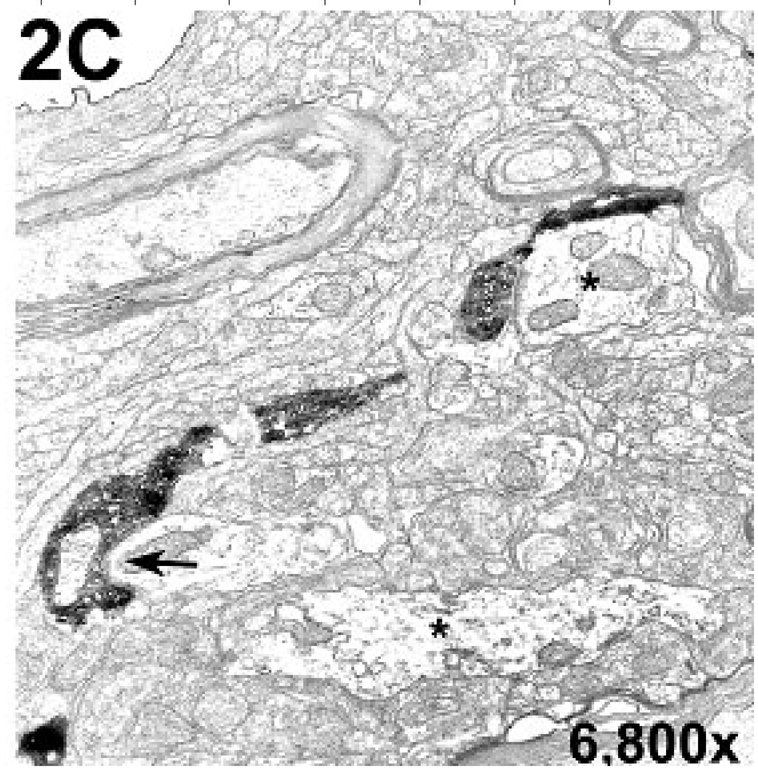




Identified NPY-containing local interneuron and its input to cholinergic projection neurons

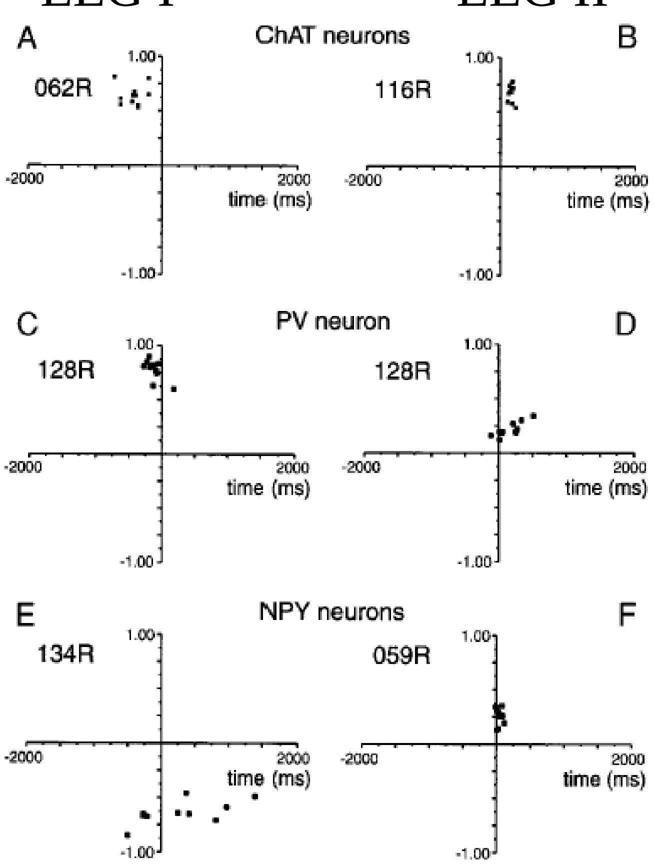




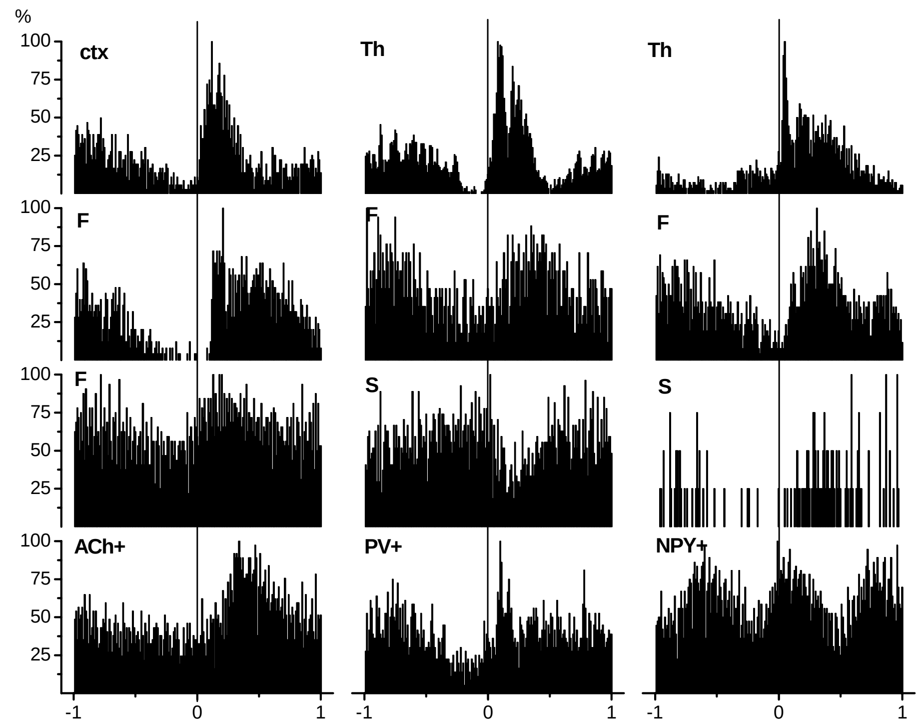


TIMING OF CHANGES IN EEG AND BF UNIT FIRING RATE

EEG I EEG II



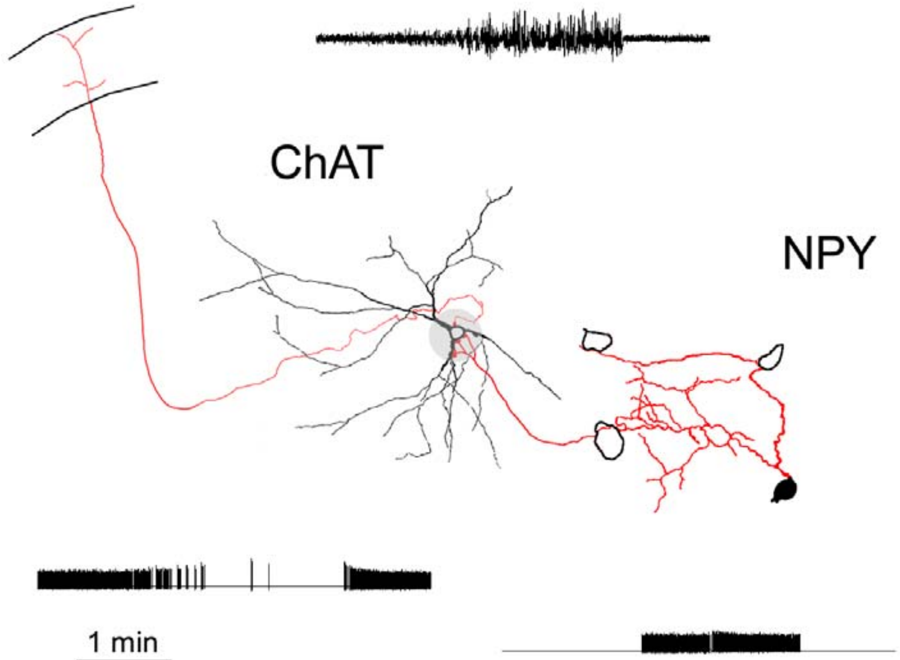
EEG II

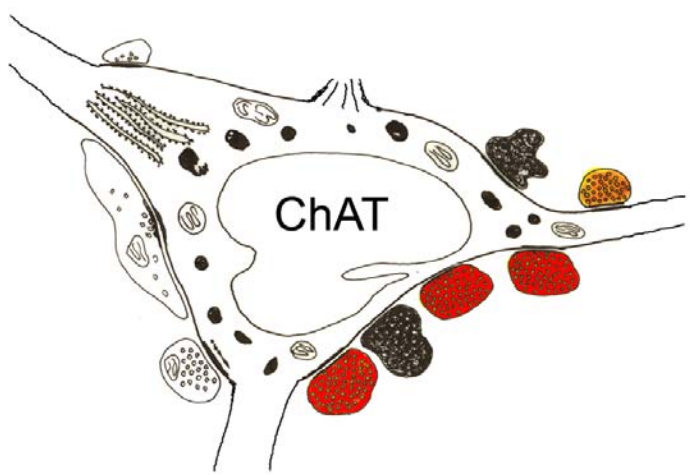


A: change in unit firing precedes the change in EEG pattern (median: **-405** ms). **B**: changes in unit firing follow the EEG changes (median **159** ms). **C:** the correlation indicates that the increased firing precedes (median **-153 ms**) the change in EEG- I (*C*) while it lags (median **210** ms) the EEG- II (*D*). **E** because the points are in both the left and the right side of the lower quadrants, the correlation indicates that the unit activity during EEG pattern I can either precede or lag (median 87 ms) the changes in EEG activity but that in both cases the firing rate is increased during the EEG slow wave activity. **F**: during EEG- II, the NPY cell firing occurs lagging the EEG changes (median **40** ms). Duque et al., 2000

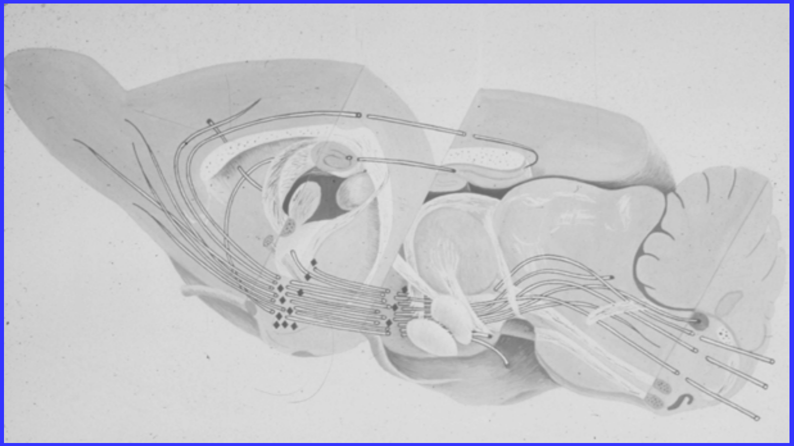
Histograms of neuronal activity around the fast transitions (vertical line; ± 1 s) between the down-, and up-states marked in the cortical EEG. Different number of transitions were averaged, then normalized for the maximal value to construct the histograms. Immediate excitation was obvious in thalamic (Th) and cortical cells (ctx), while the response was usually delayed in both fast-wave-active (F-cell), and slow-wave-active (S-cell) neurons in the BF. Activation in the PV+ and NPY+ neurons (last row) had much sorter latency then the excitation in the ACh+ cell.

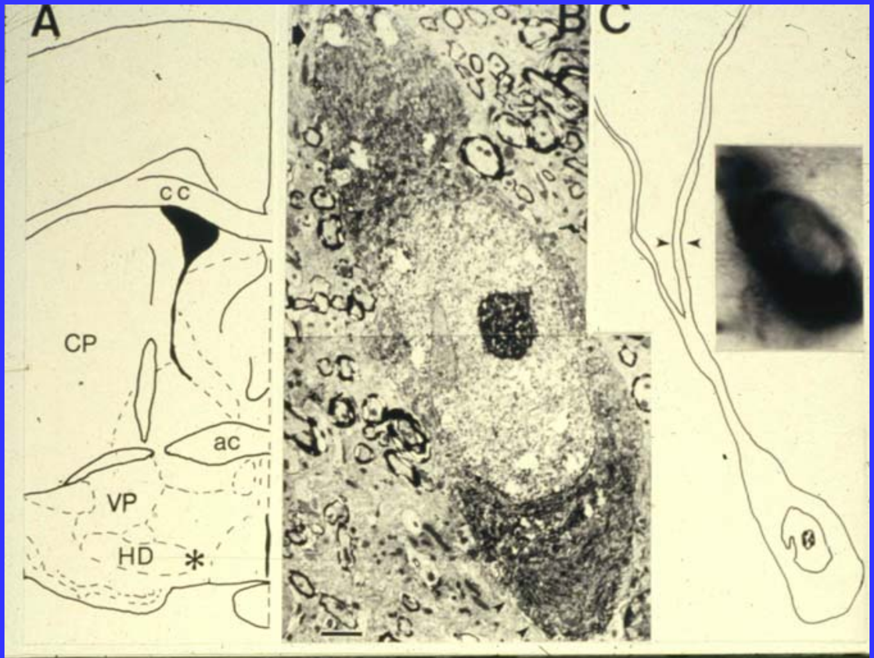
BF CIRCUITRY: A PRELIMINARY IDEA

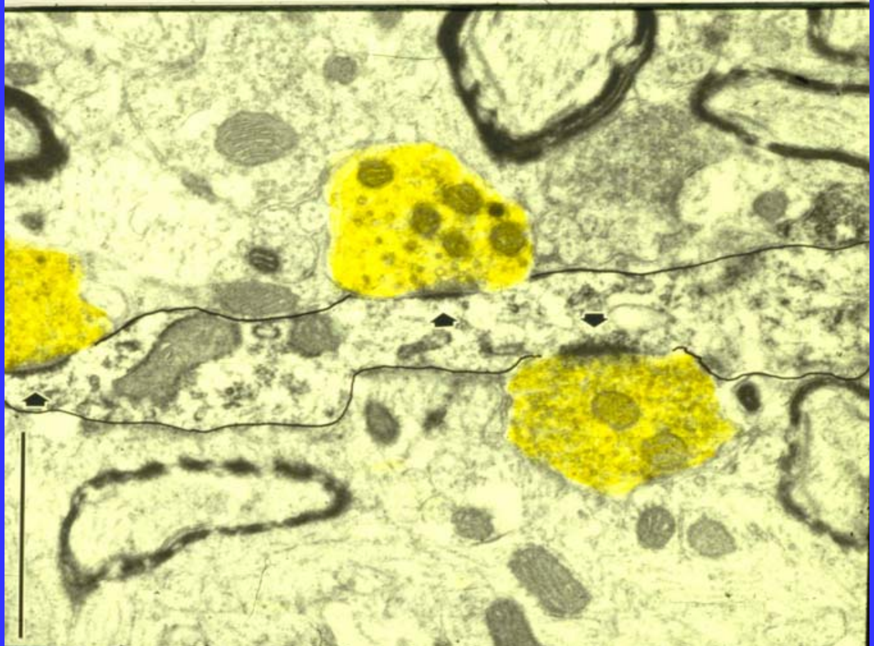




DO CHOLINERGIC OR OTHER BF NEURONS RECEIVE INPUT FROM ASCENDING MODULATORY SYSTEMS?

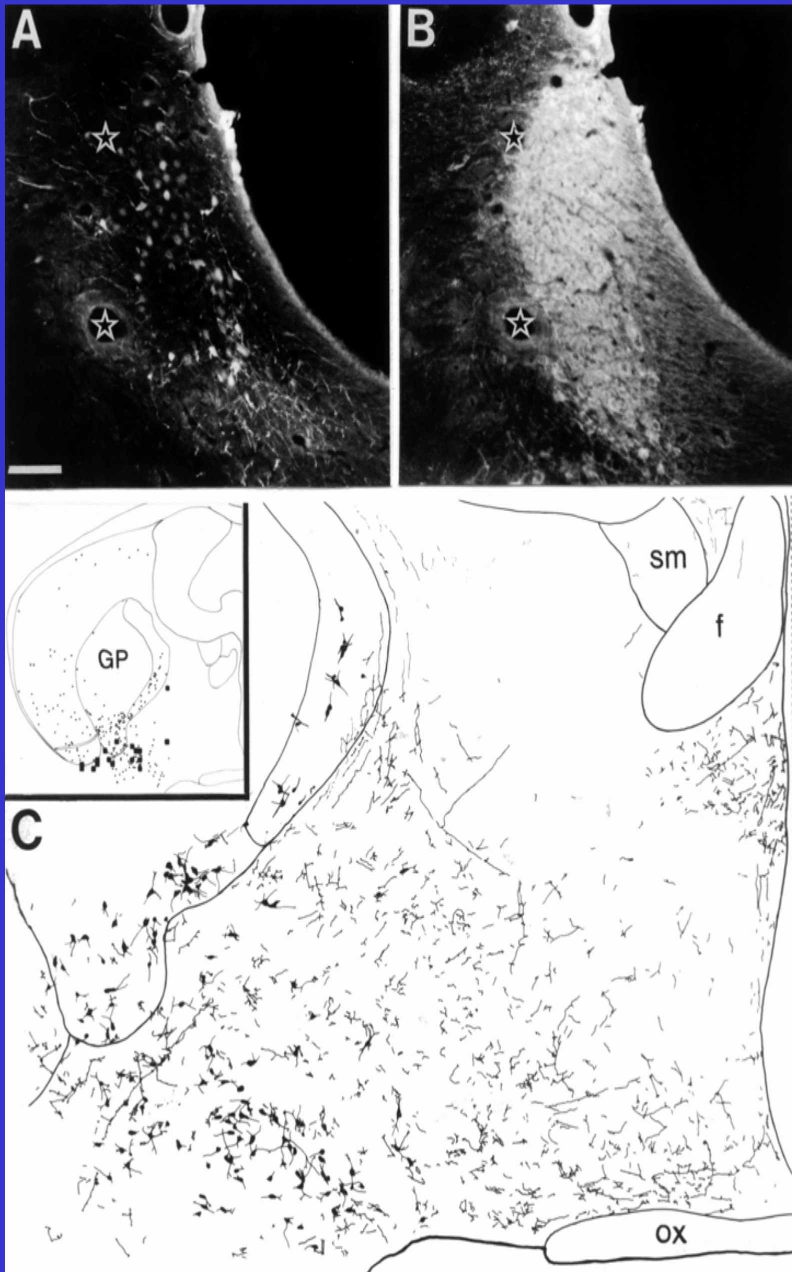


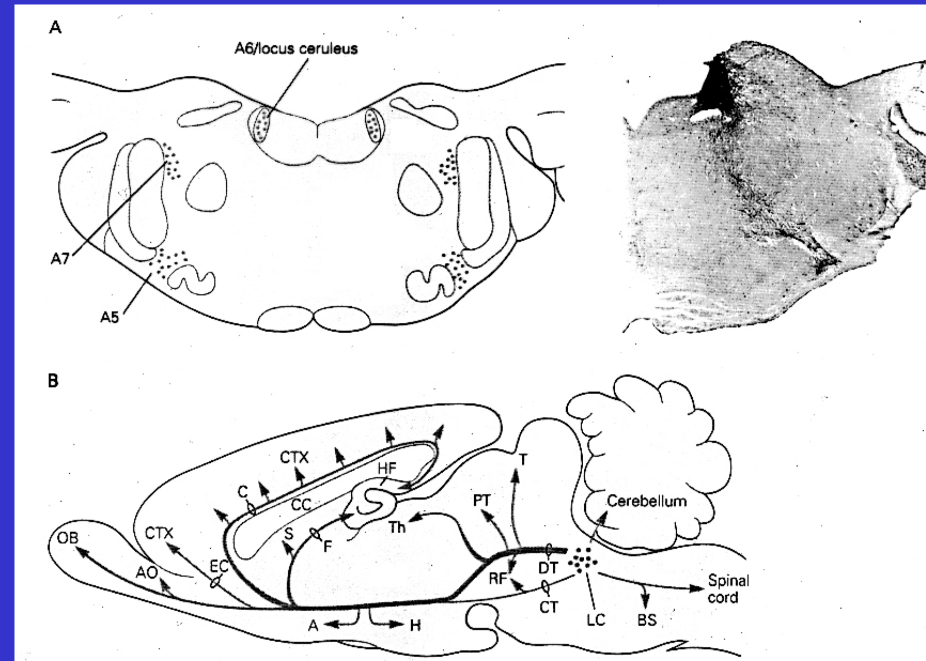


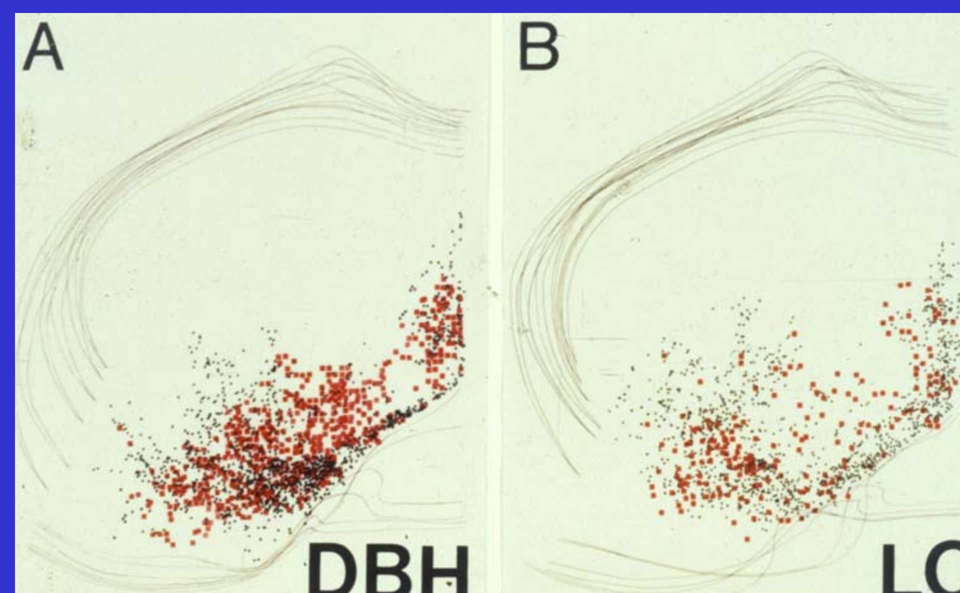


THE NEED FOR EM STUDIES

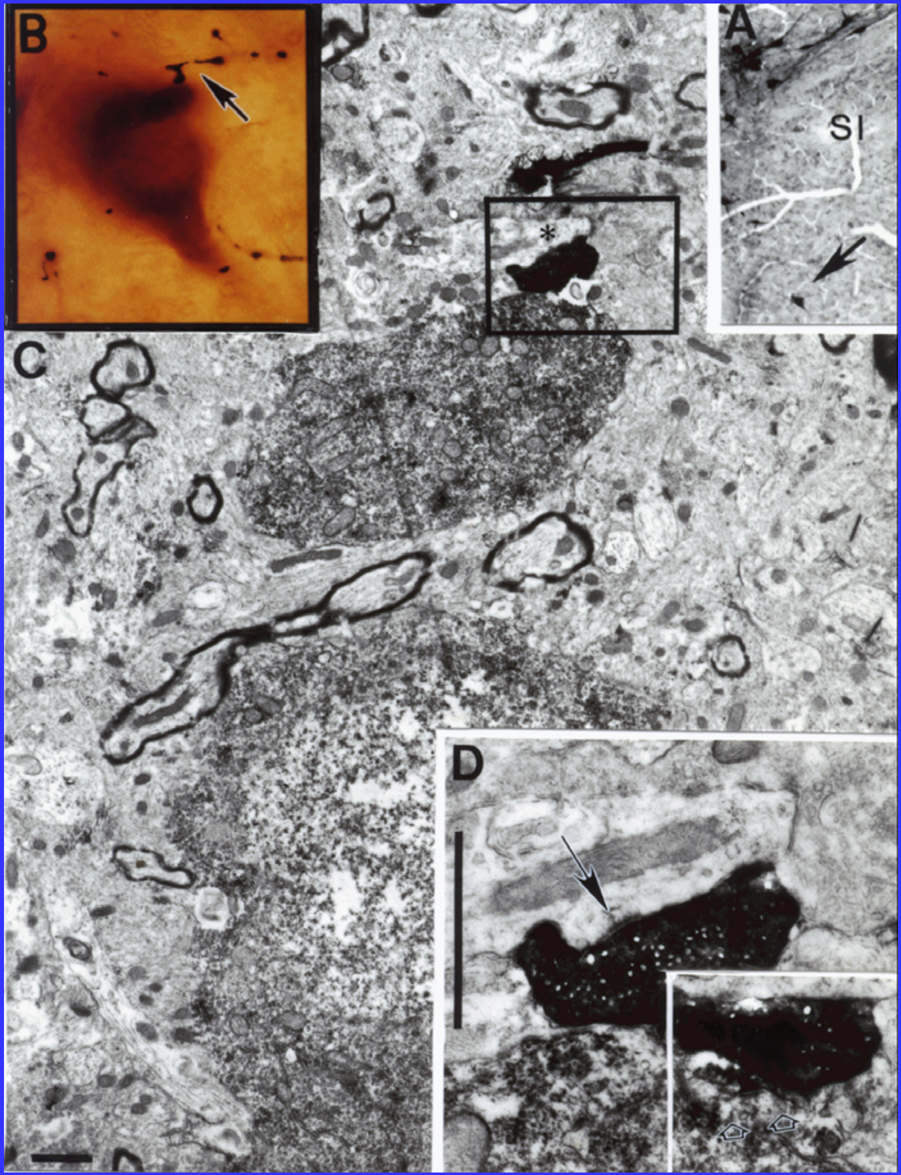
Diffuse input to BF: LC axons

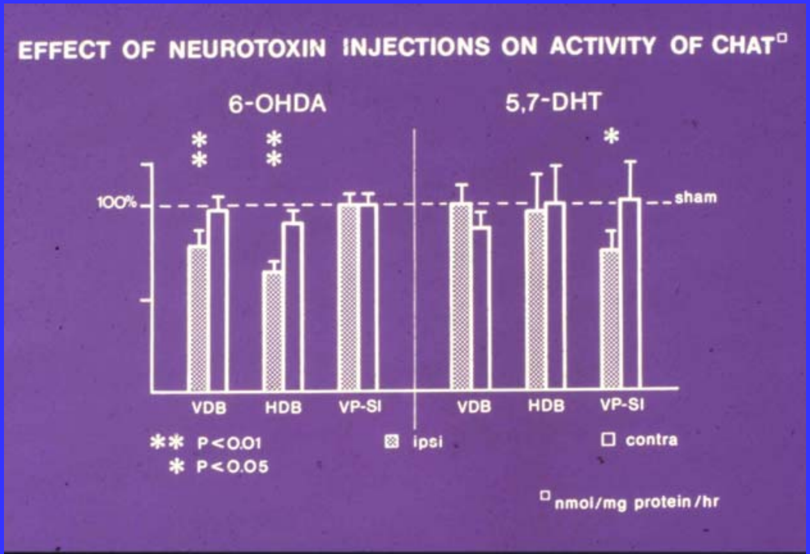


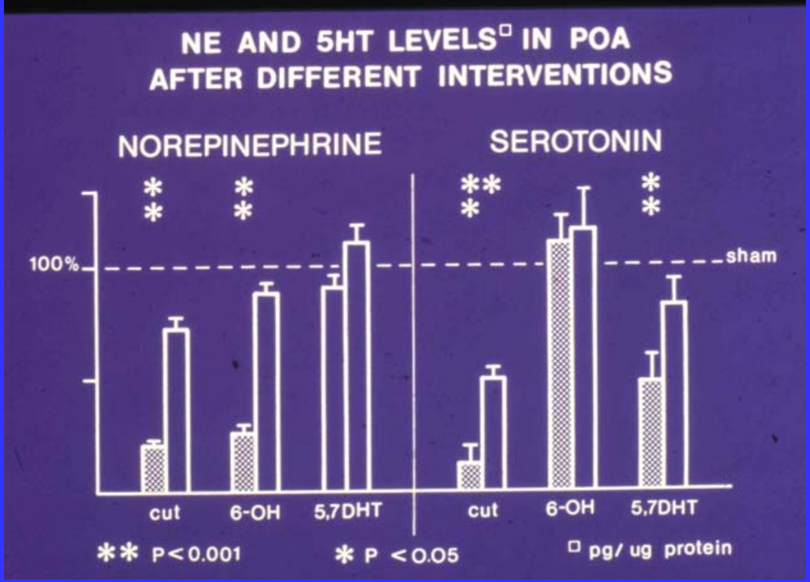




LC axons synapse on cholinergic and non-cholinergic neurons.
Effect of 6-OHDA on forebrain ChAT level

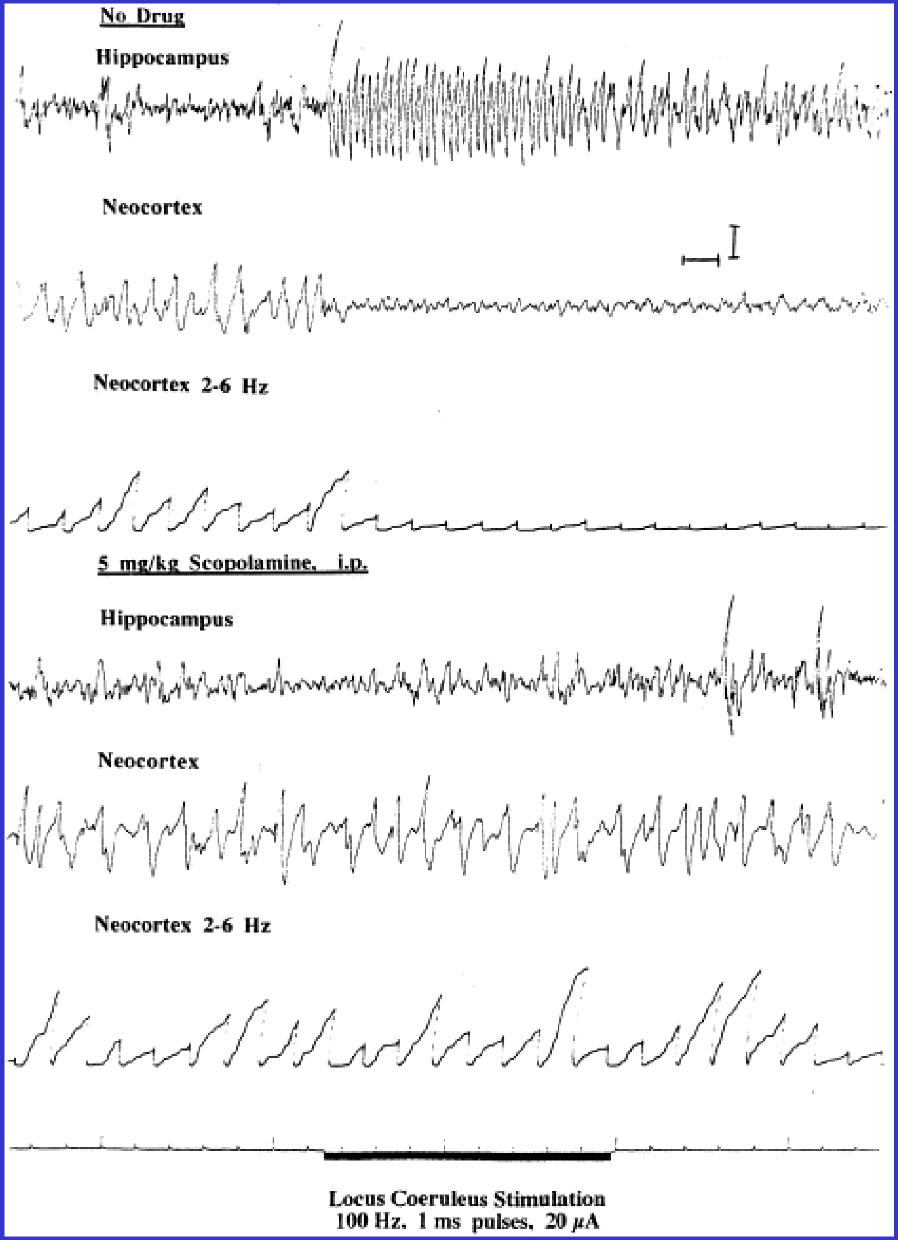


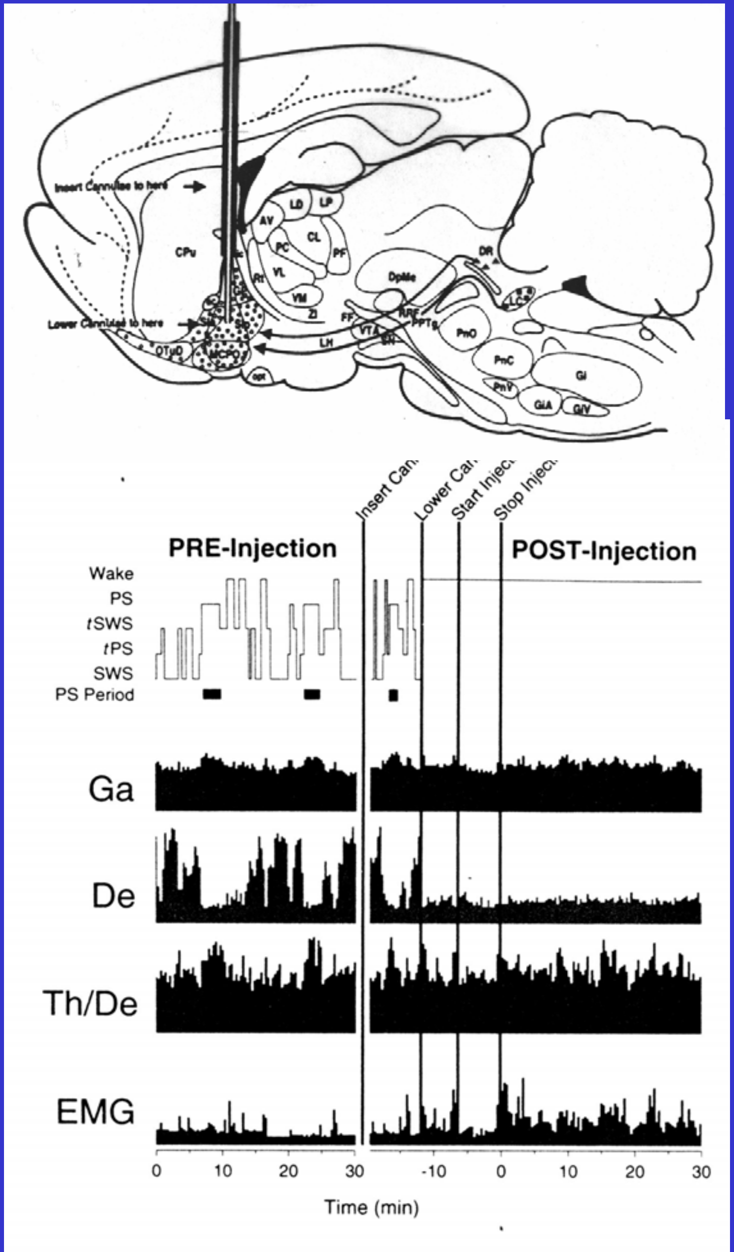




Zaborszky et al., 1993

LC can affect cortical EEG via the BF

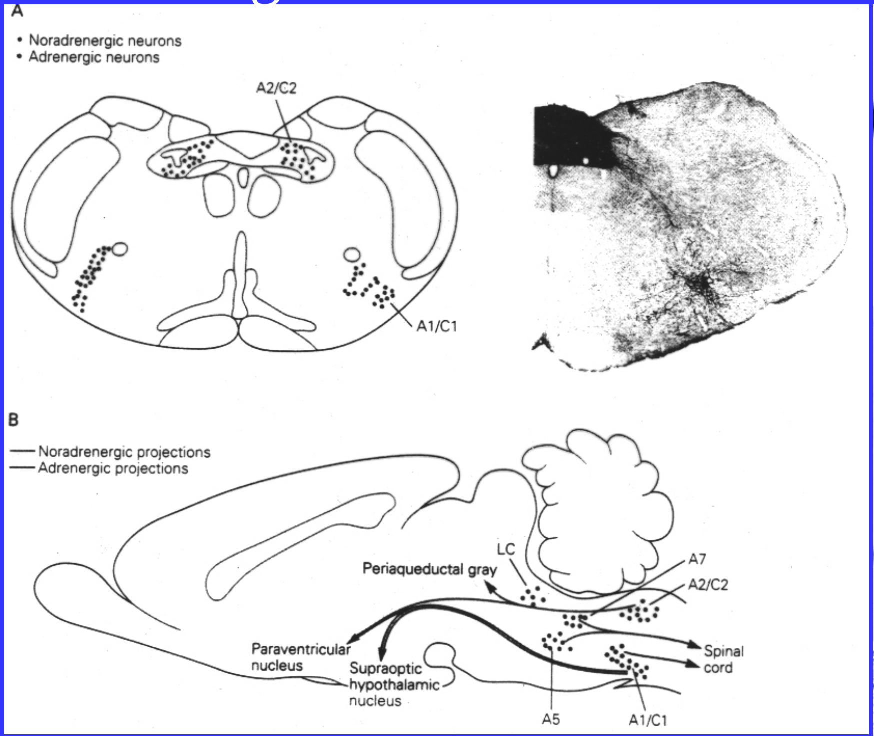


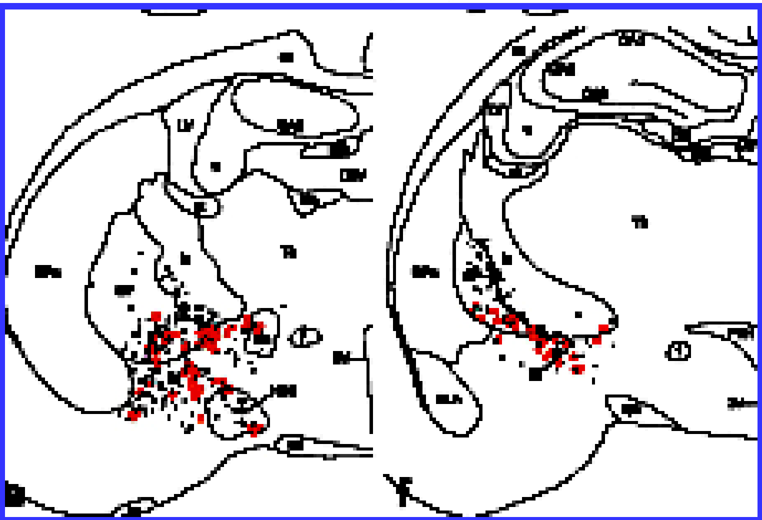


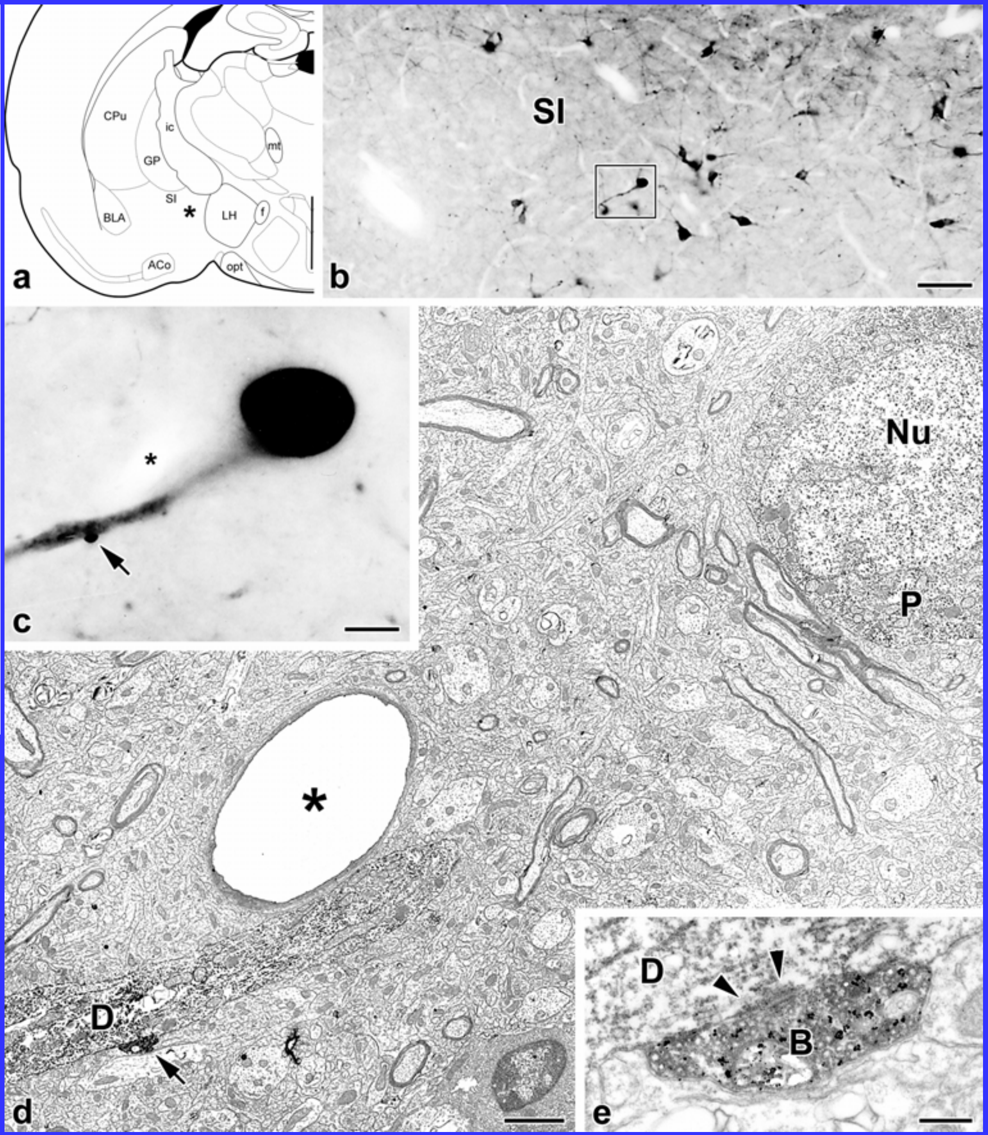
Dringenberg and Vanderwolf, 1998

Cape and Jones, 1998

Diffuse input to cholinergic neurons: PNMT axons synapse with cholinergic neurons

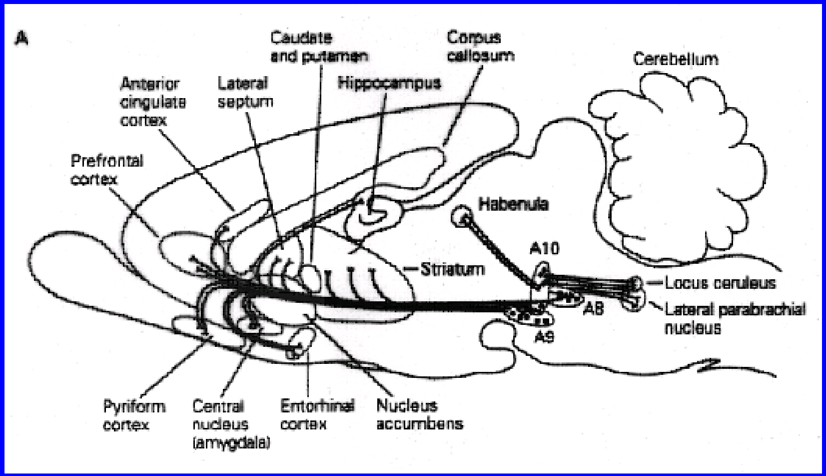


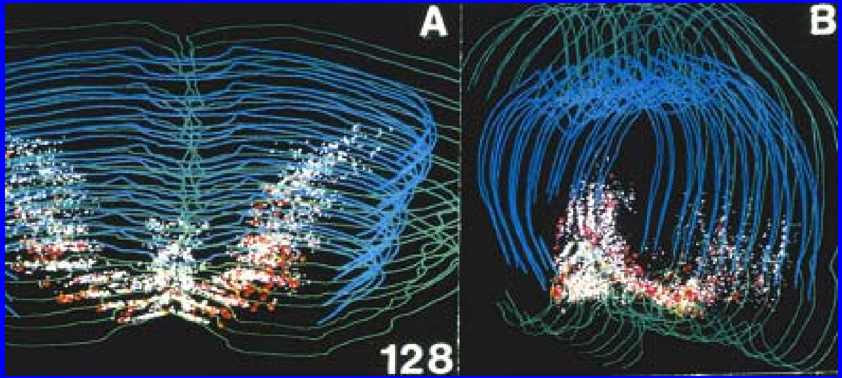


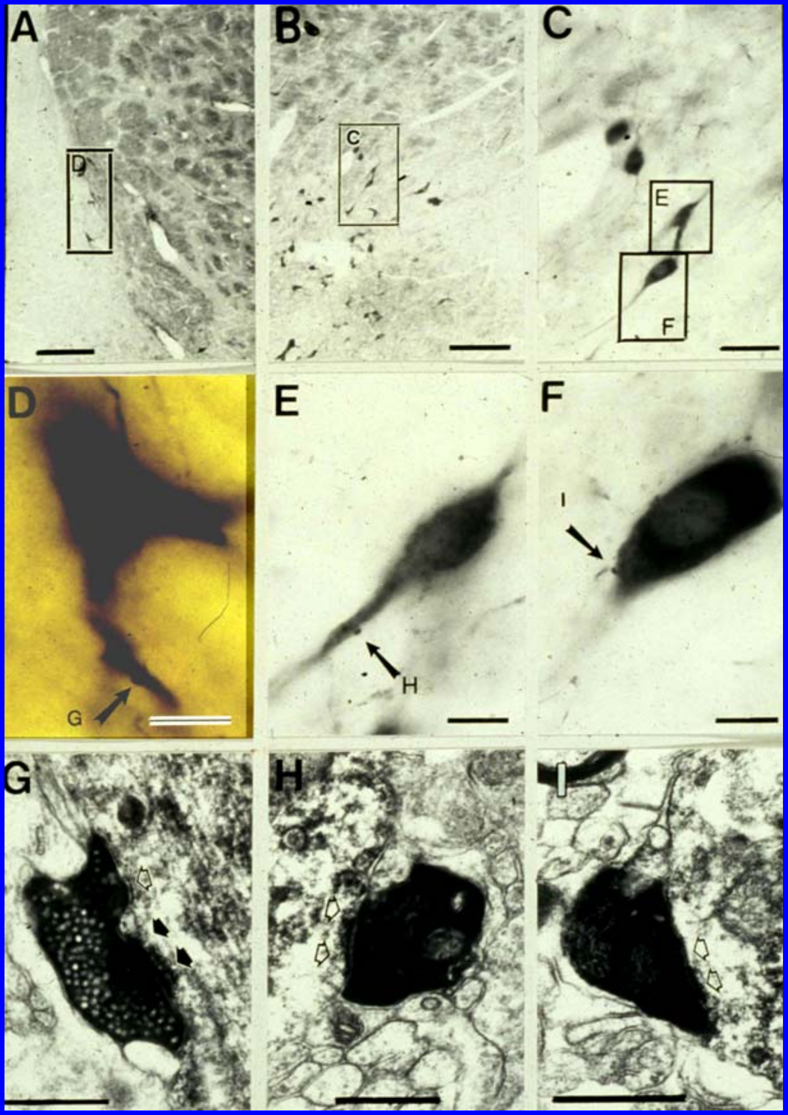


Hajszan and Zaborszky, 2002

CHOLINERGIC NEURONS RECEIVE SYNAPSES FROM THE MIDBRAIN DOPAMINERGIC AREA



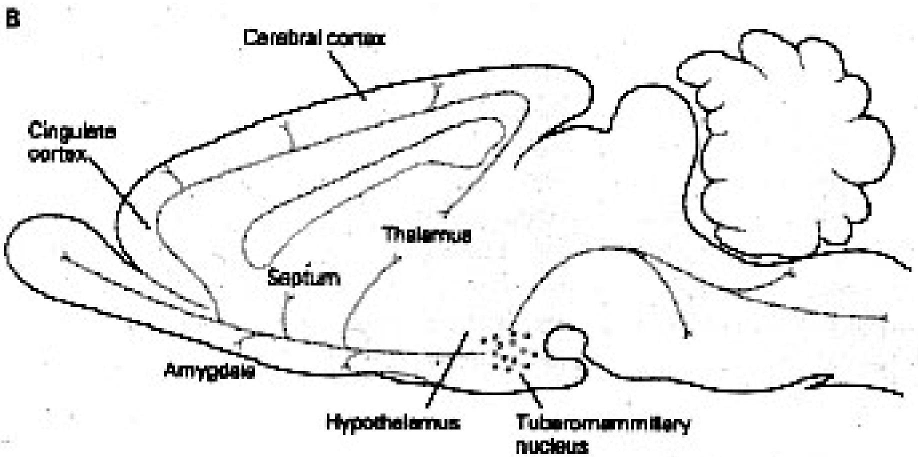


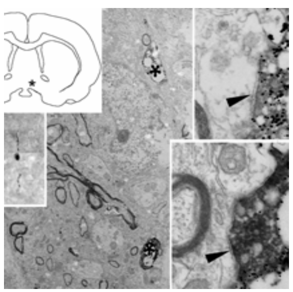


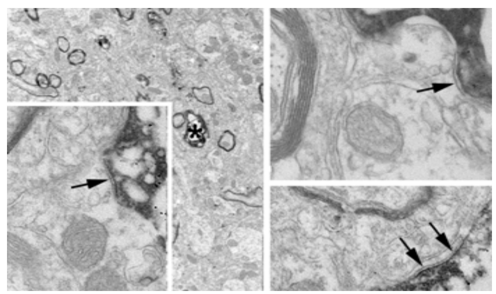
Ventral midbrain axons contact CH (as well as PV) cells in the BF.

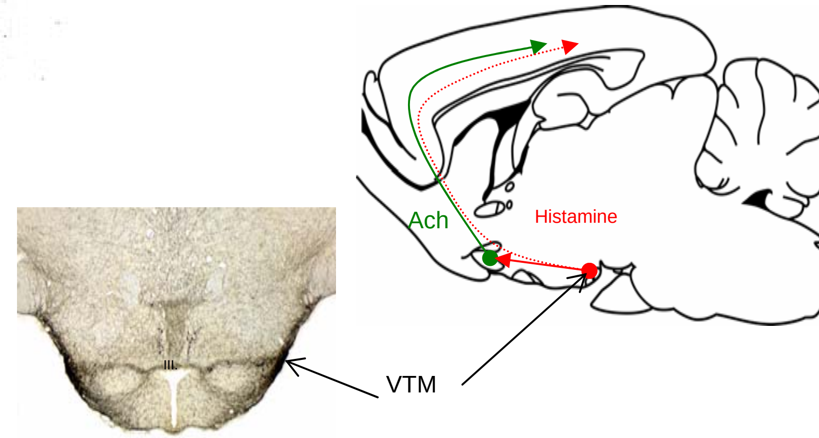
Gaykema and Zaborszky, 1996

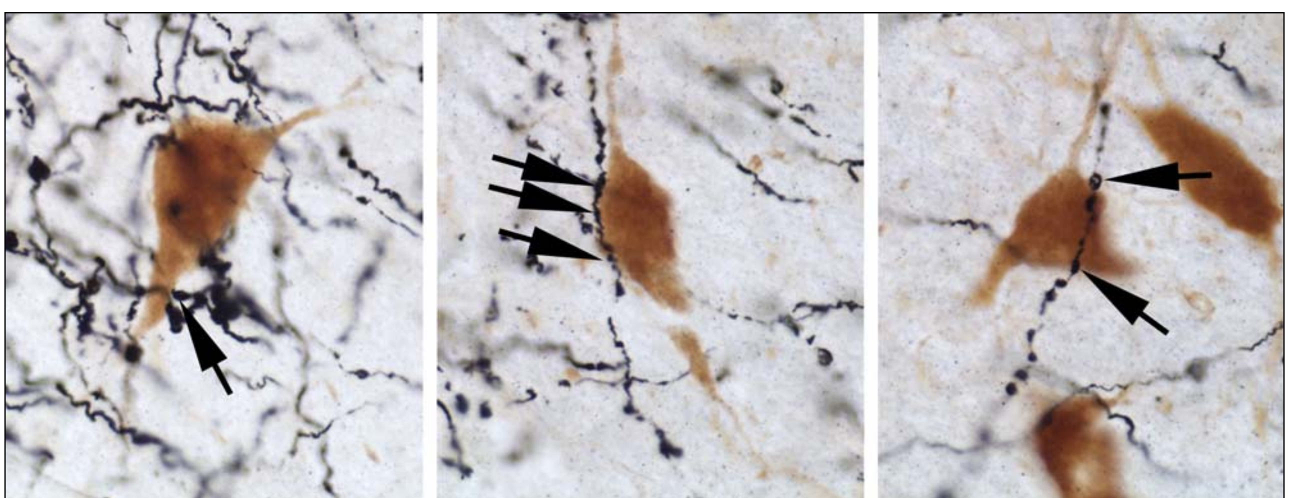
Diffuse input to the BF: histaminergic axons in close proximity to ChAT neurons





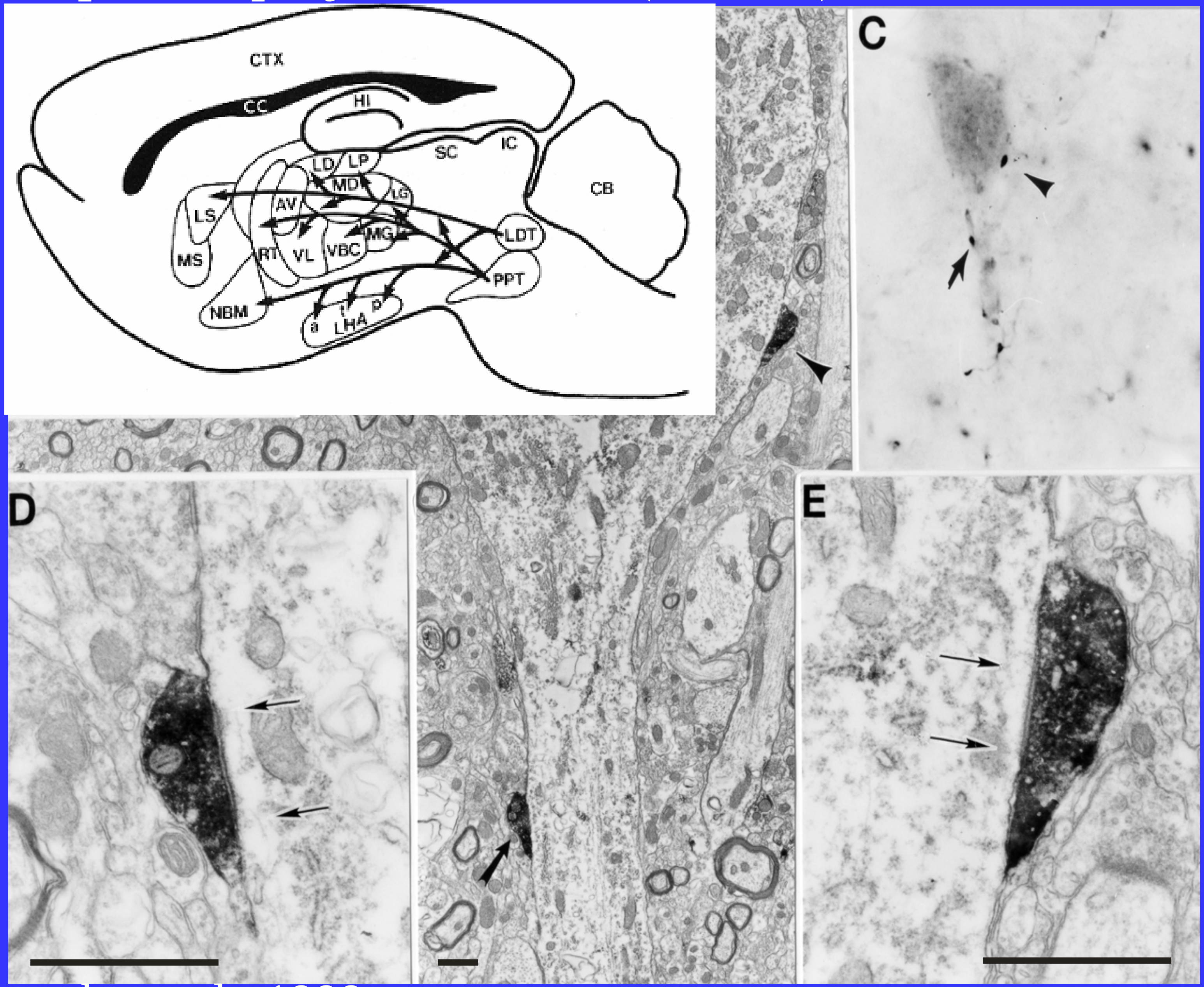






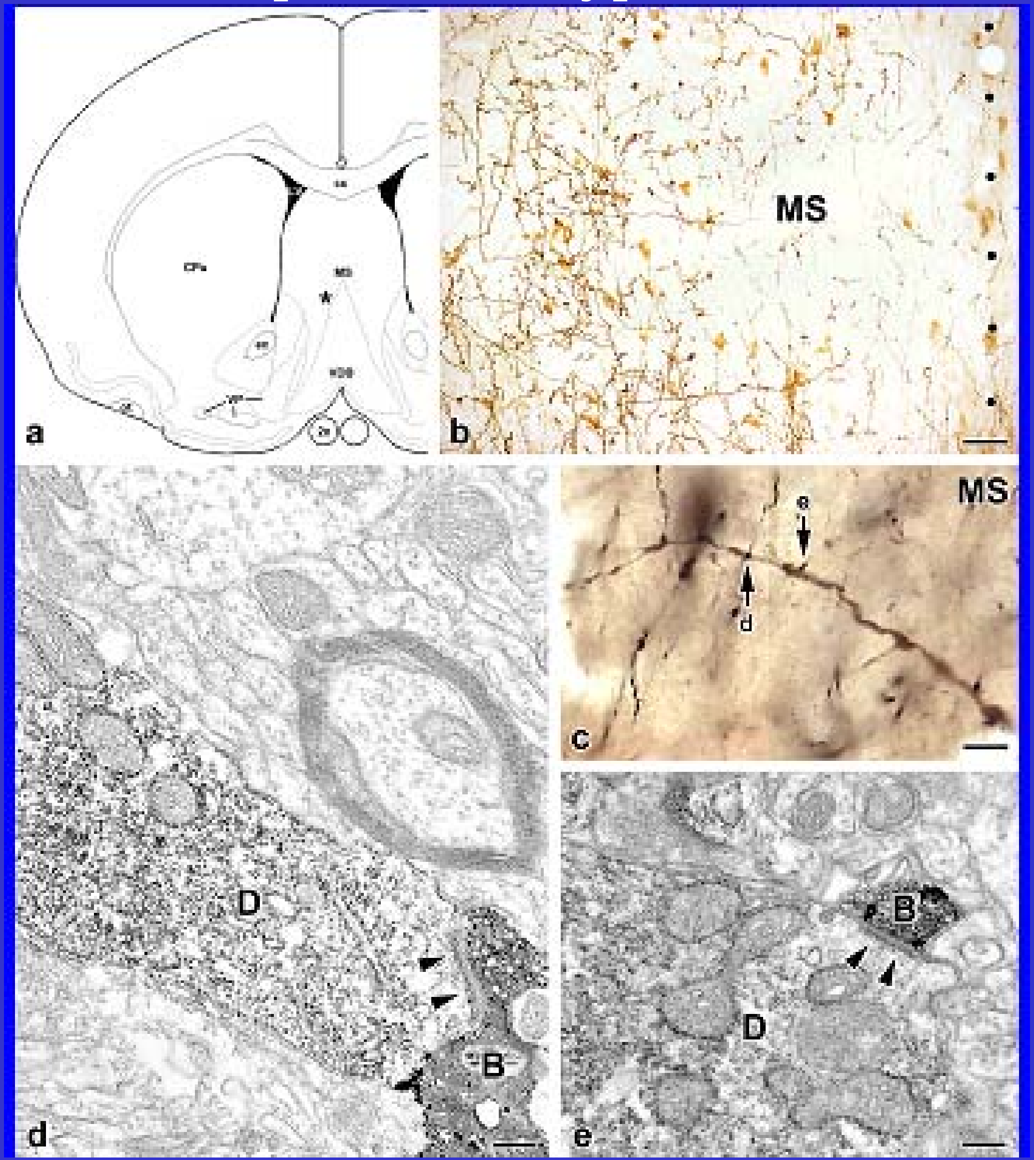
Turi et al.: SFN 2004

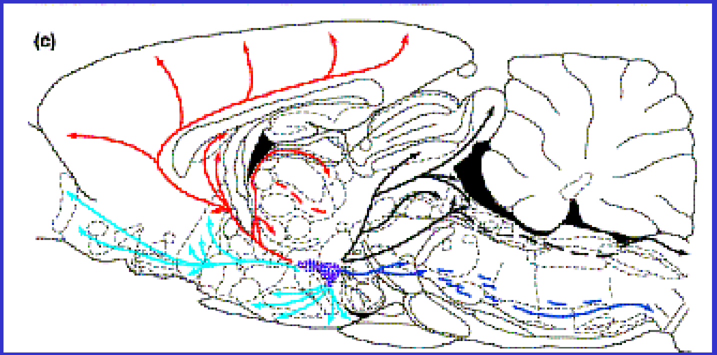
Mesopontine projections to PV (and CH) neurons in the BF

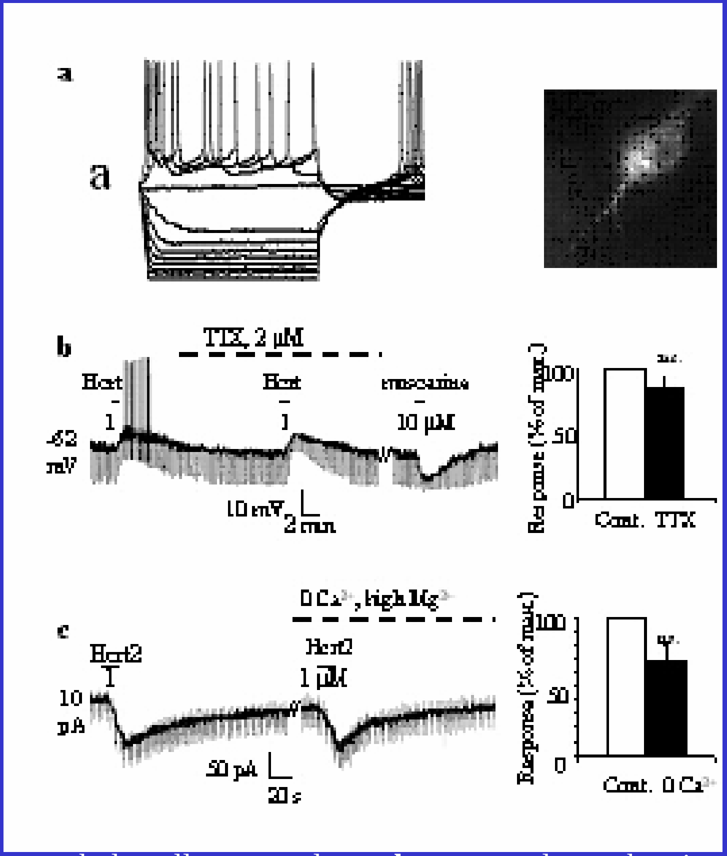


Zaborszky et al., 1999

Diffuse input to BF: hypocretin axons



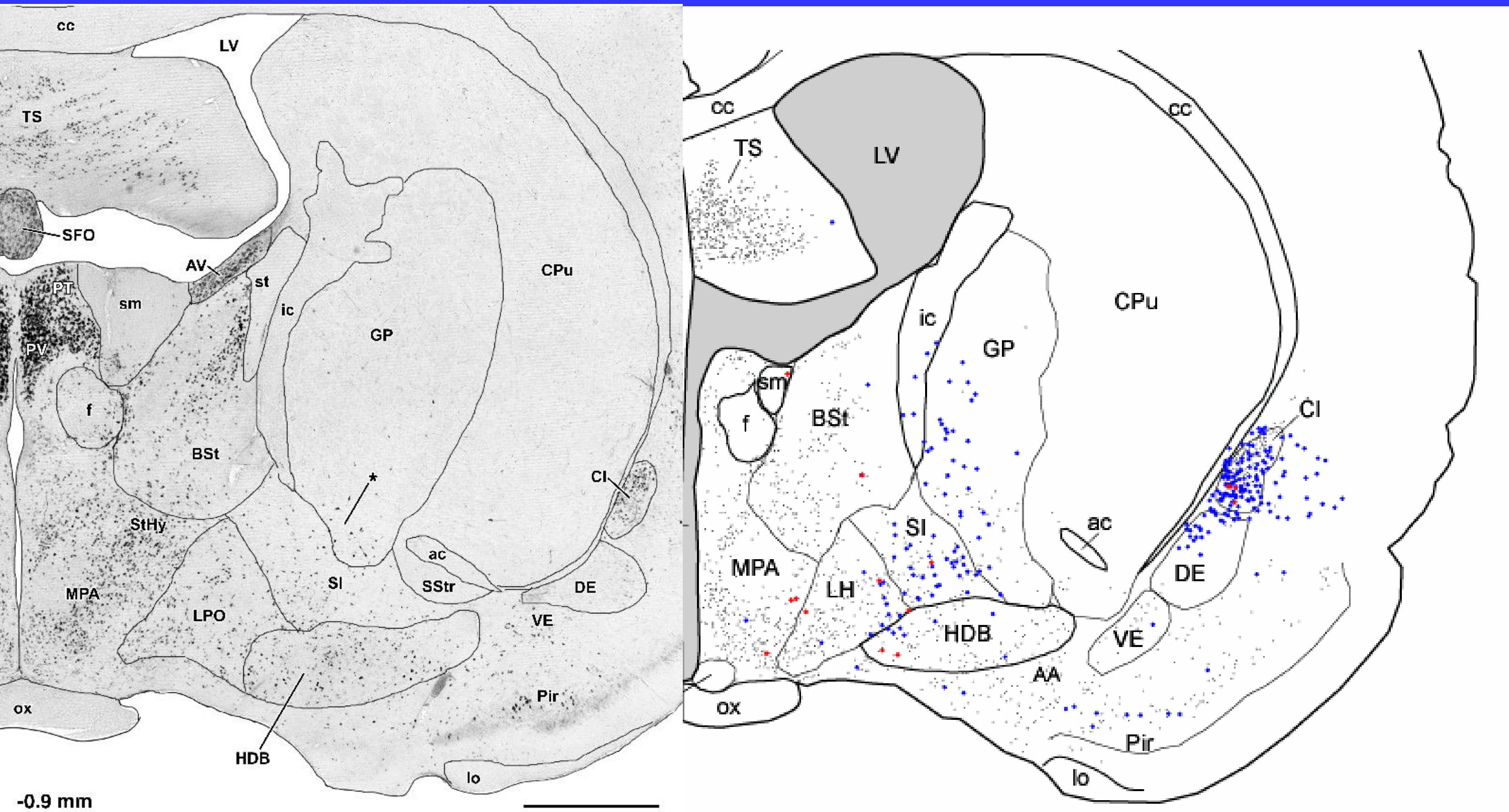




a: whole-cell current clamp; **b**: current clamp showing the depolarizing effect of Hcrt. **c**: voltage clamp (-65 mV) in which Hcrt2 induced an inward current that persisted in zero Ca2+, high Mg2+ ACSF.

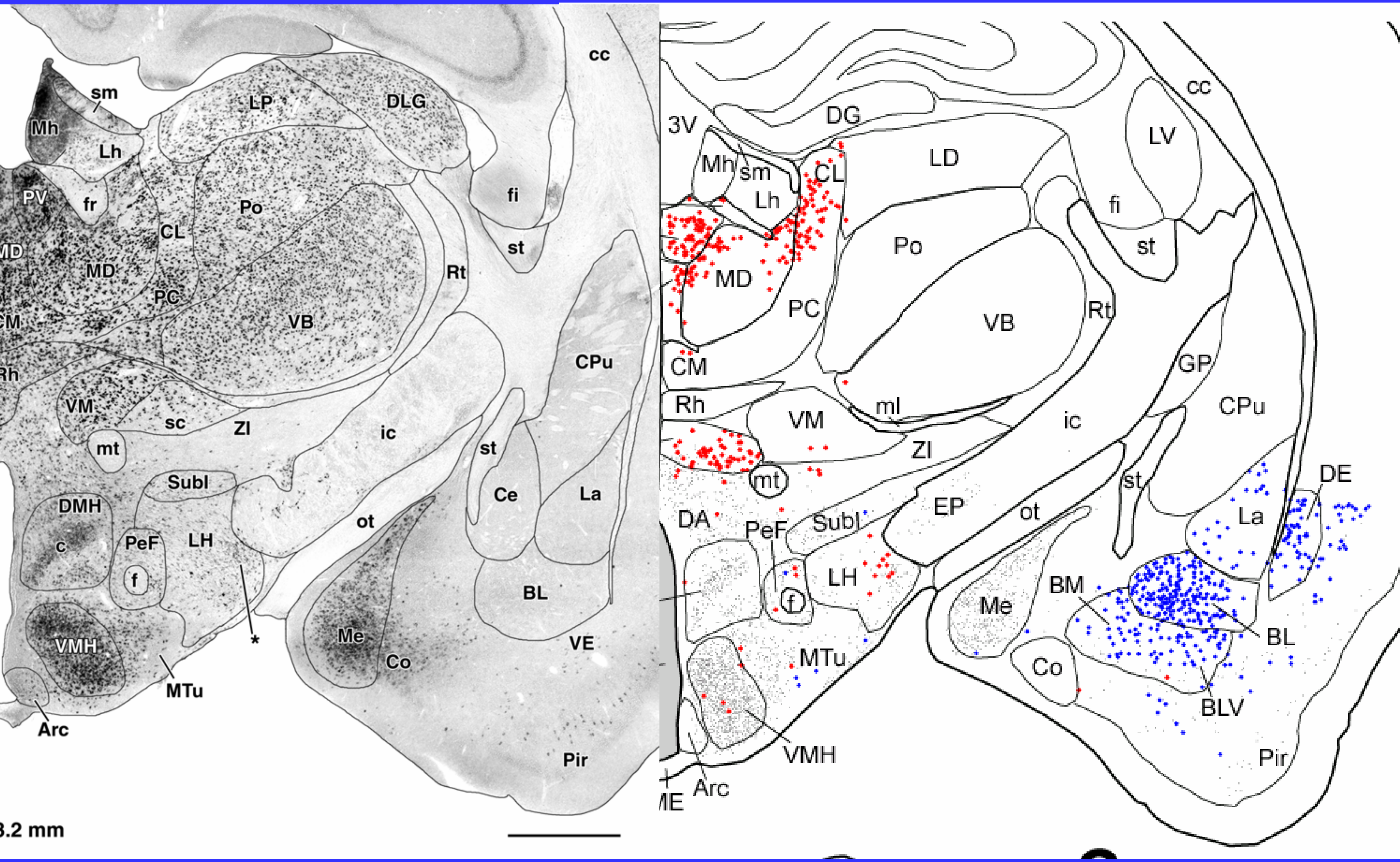
Wu, Zaborszky, et al.: J. Neuroscience, 2004

Glutamatergic (Vglut2) projections to the prefrontal cortex

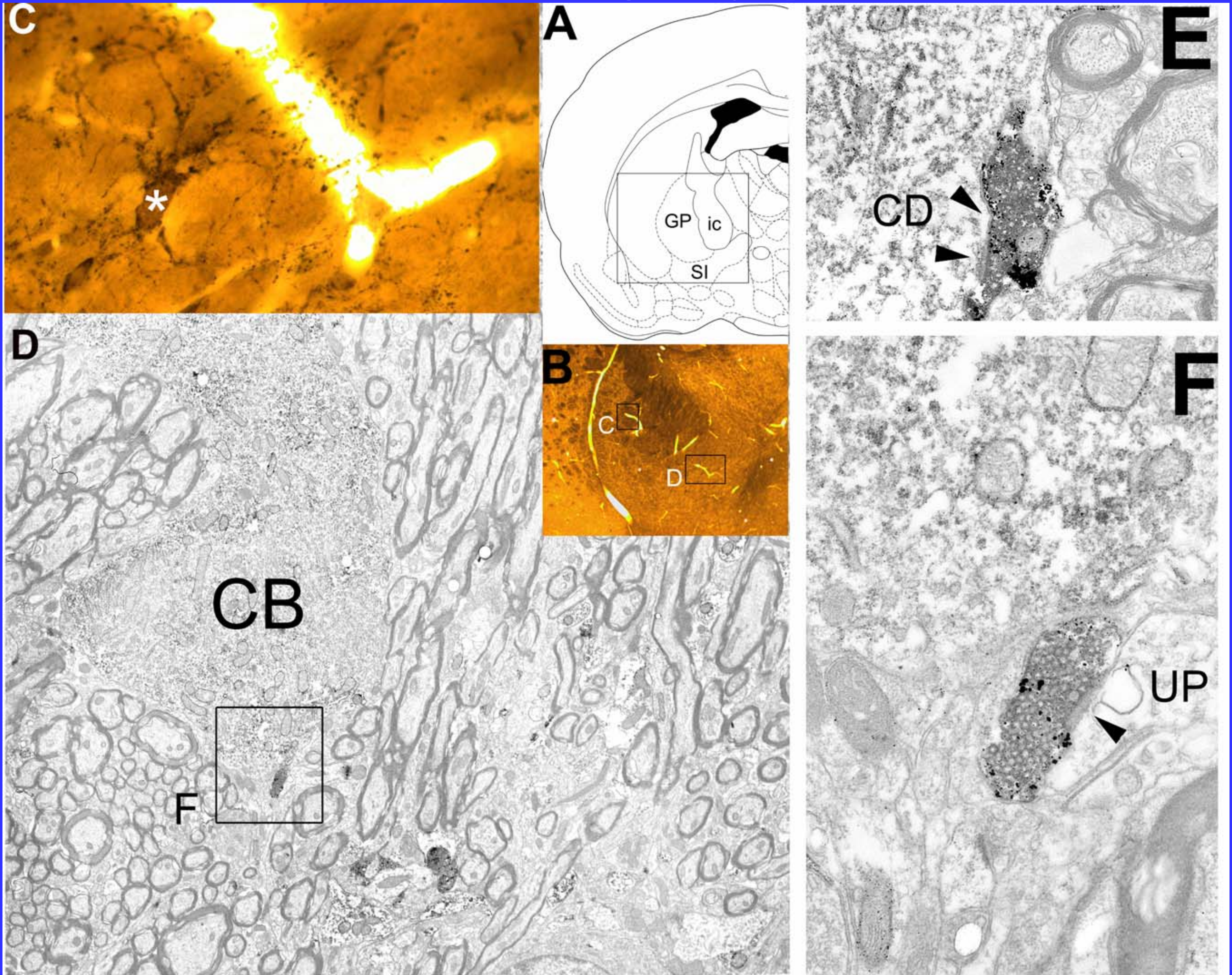


Hur and Zaborszky: J. Comp. Neurol, 2005

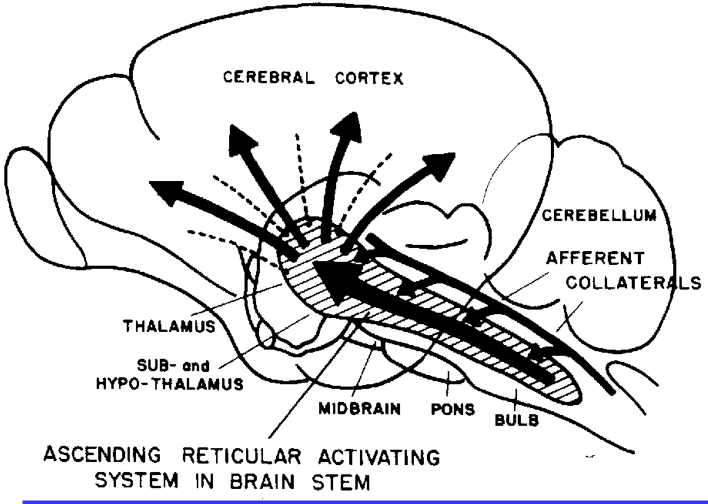
Glutamatergic (Vglut2) projections to the prefrontal cortex

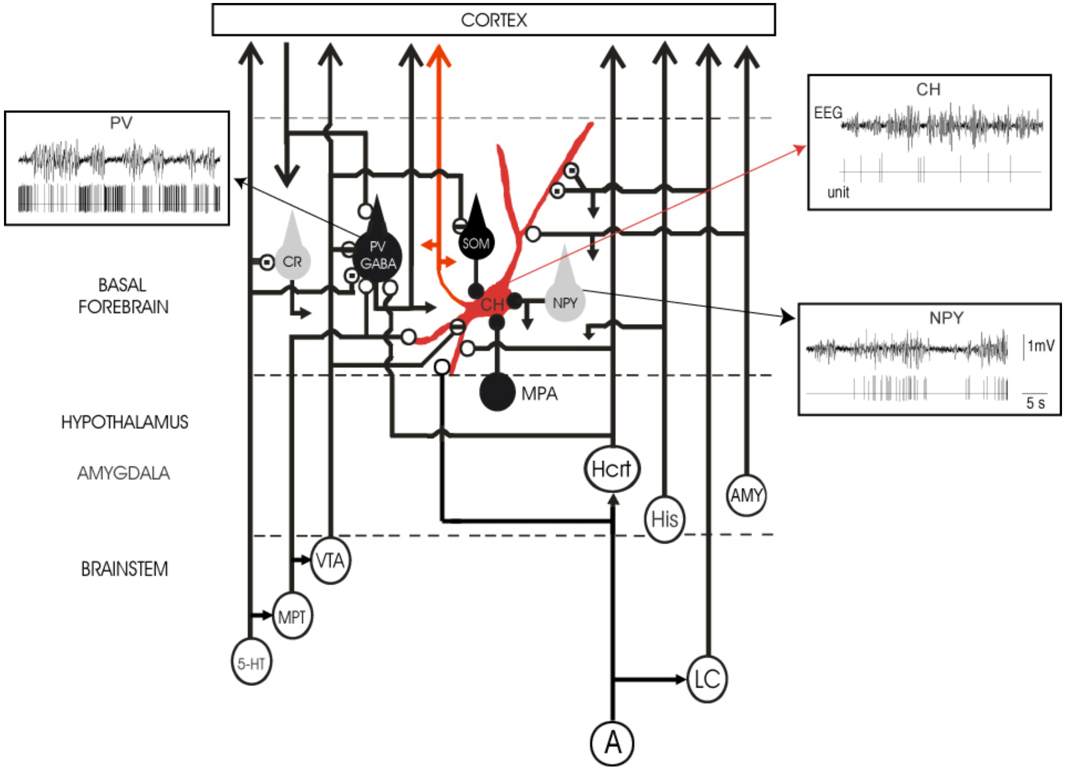


Diffuse input to BF (?): Vglut 2 synapses on CH dendrites



Moruzzi and Magoun, 1951

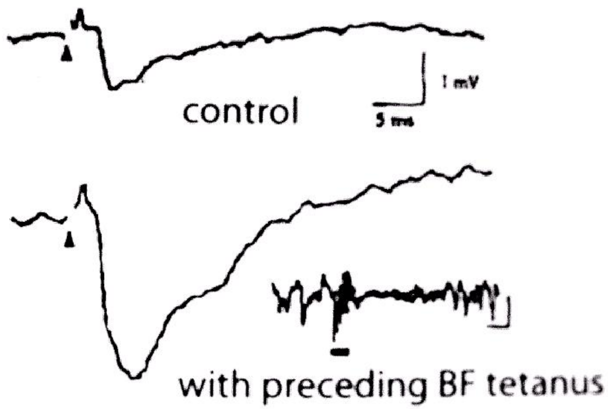




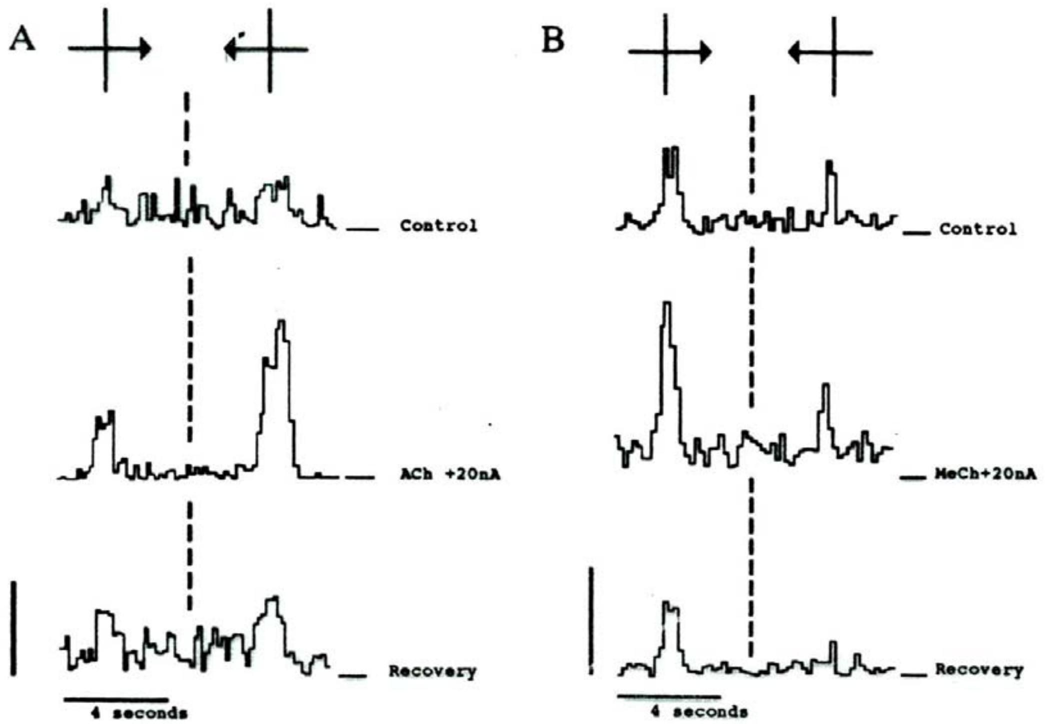
The brainstem can activate neocortical neurons via various neurons in the basal forebrain

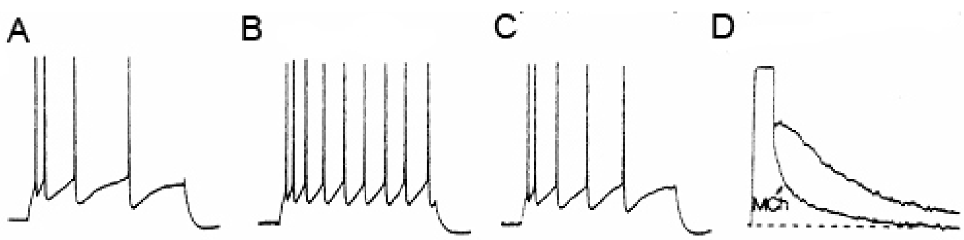
Zaborszky and Duque, 2003

BF stimulation or cortical ACh application enhances sensory evoked responses: Is this part of an arousal reaction or a more selective process (attention)?



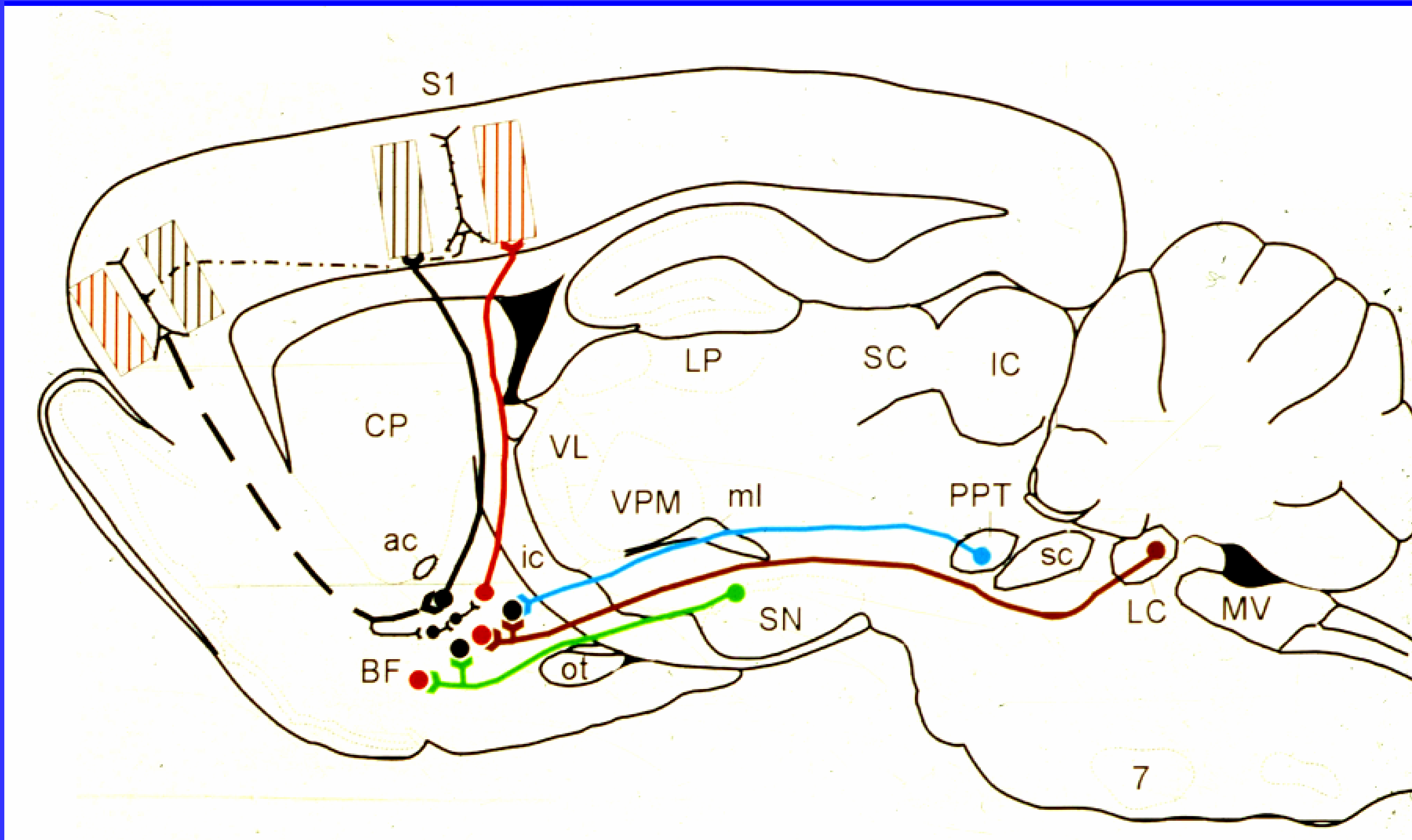
Auditory cortical response to medial geniculate stimulus is modified by preceding (30 msec) basal forebrain stimulation. (Metherate and Ashe, 1991



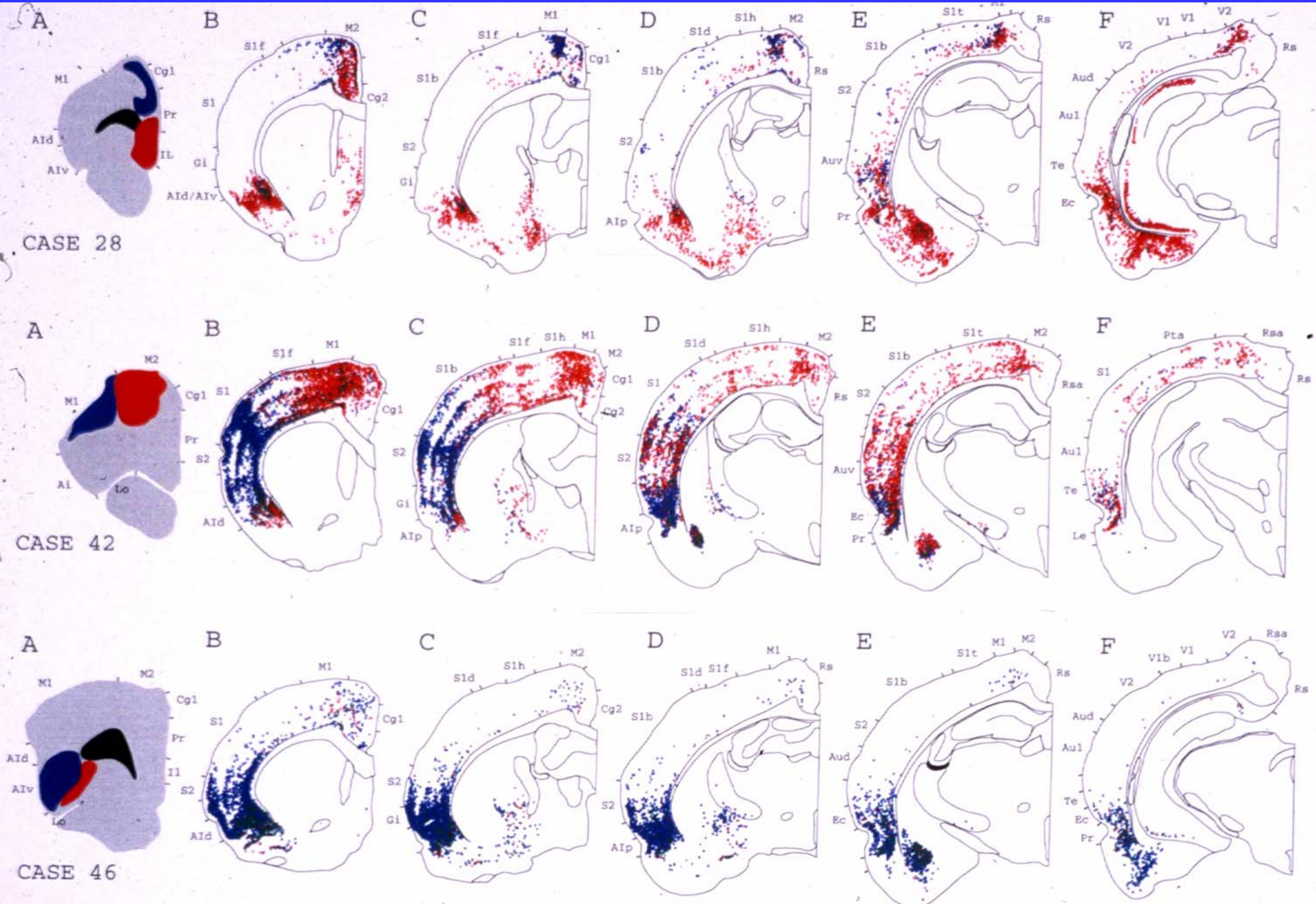


Effect of cholinergic facilitation on the direction selectivity of a LIV simple cell (A) and a LVI complex cell (B). PSTH showing the response of the cells to an optimally oriented bar of light moving forwards and backwards over the receptive field. (Silito, 1993)

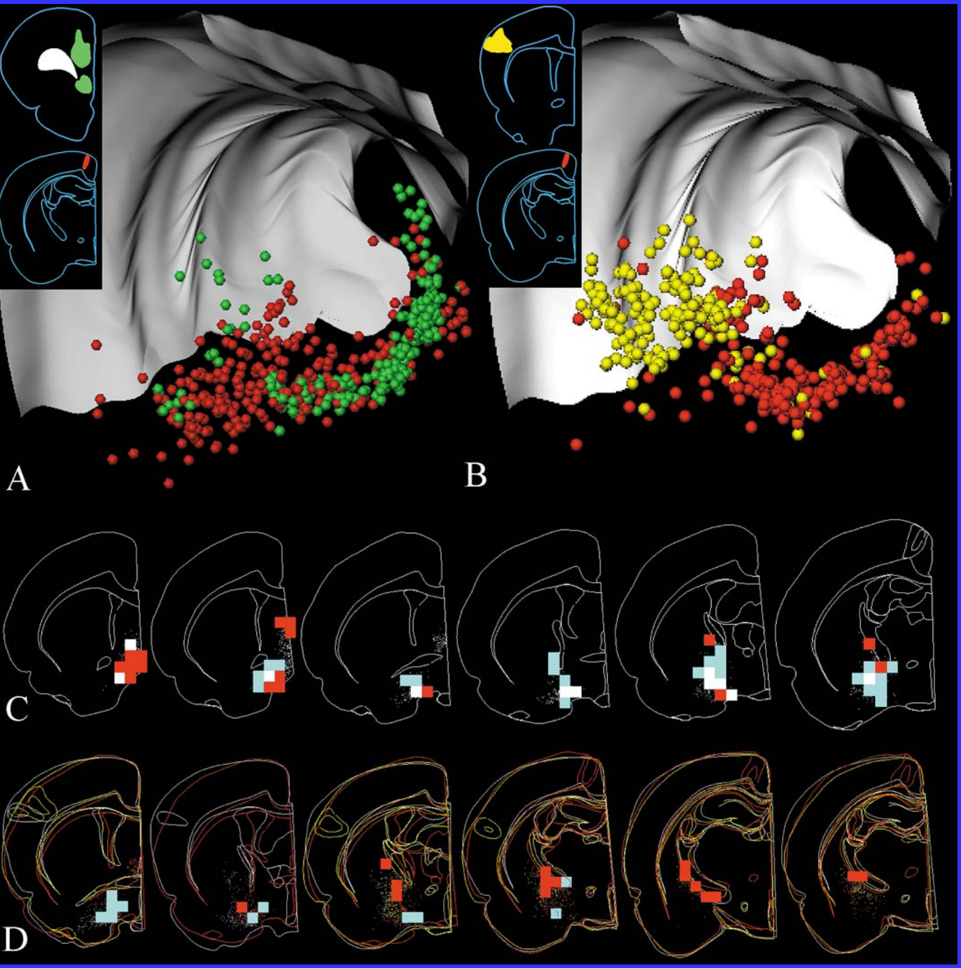
HOW THE BASAL FOREBRAIN ORGANIZATION SUPPORTS A ROLE IN SPECIFIC SENSORY PROCESSING (ATTENTION)?

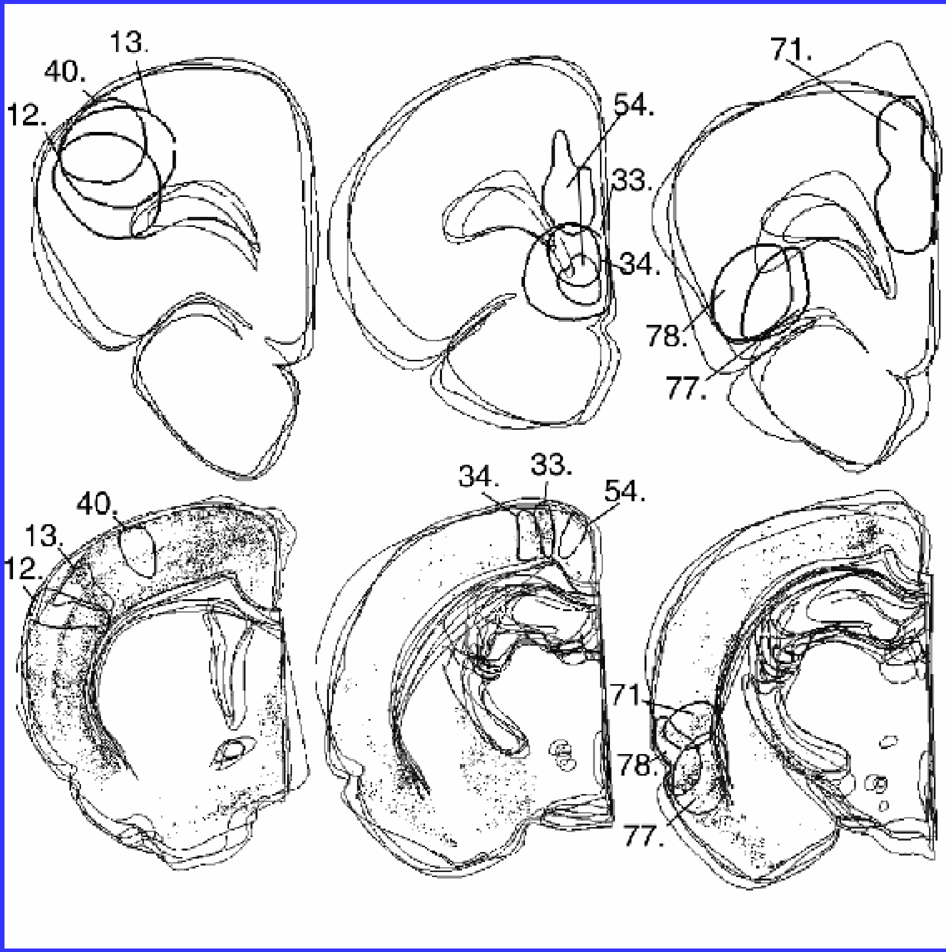


Hierarchical cortical processing

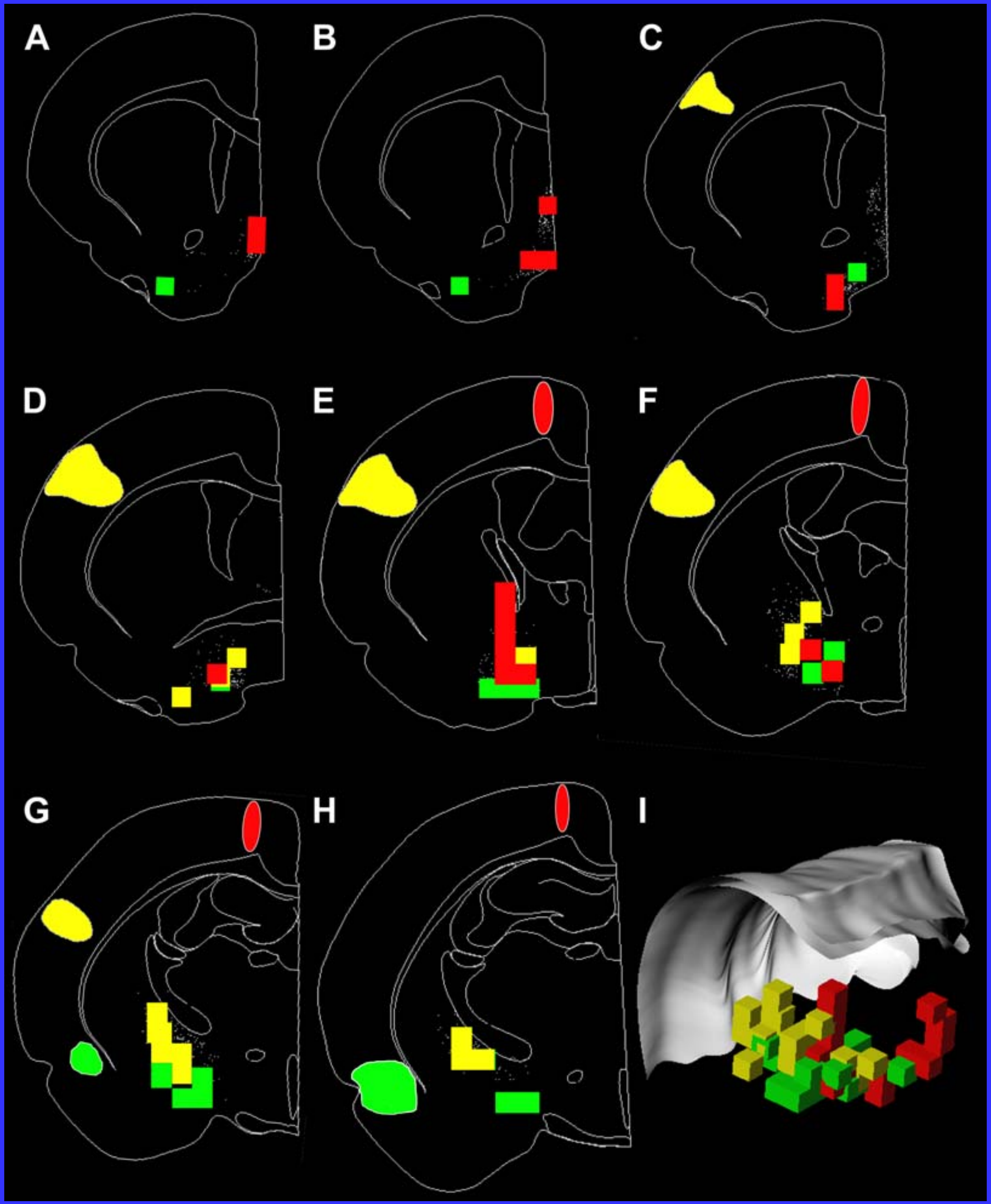


Cortical regions that are in interconenncted receive input from overlapping pool of neurons in the BF. In contrast, cortical regions that are not interconenncted receive their input from segregated pool of BF neurons

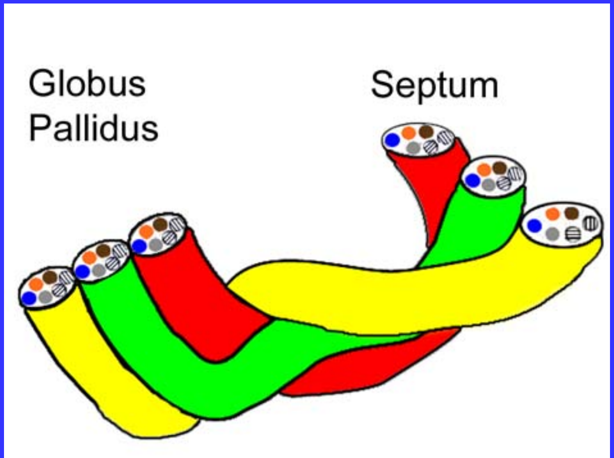




Csordas and Zaborszky, in prep.

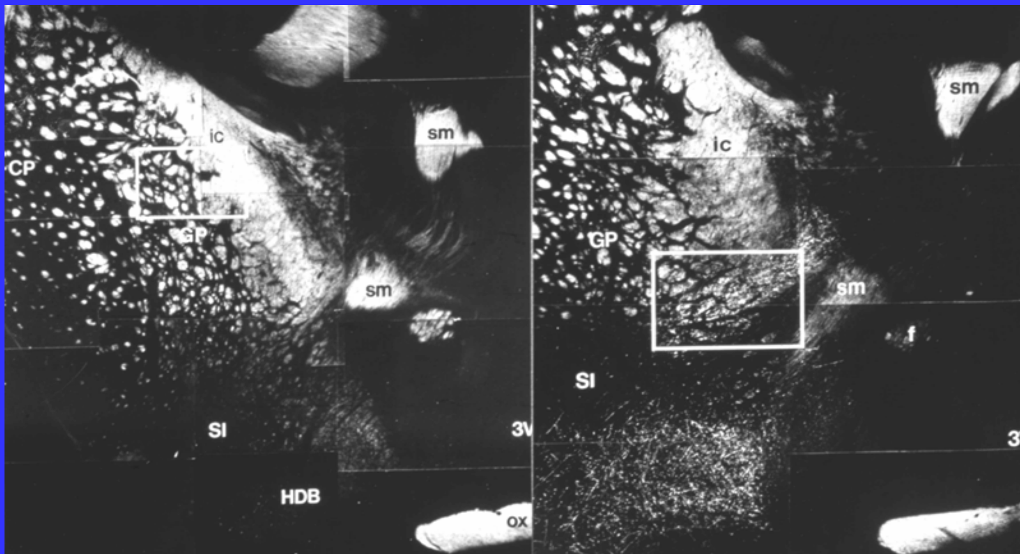


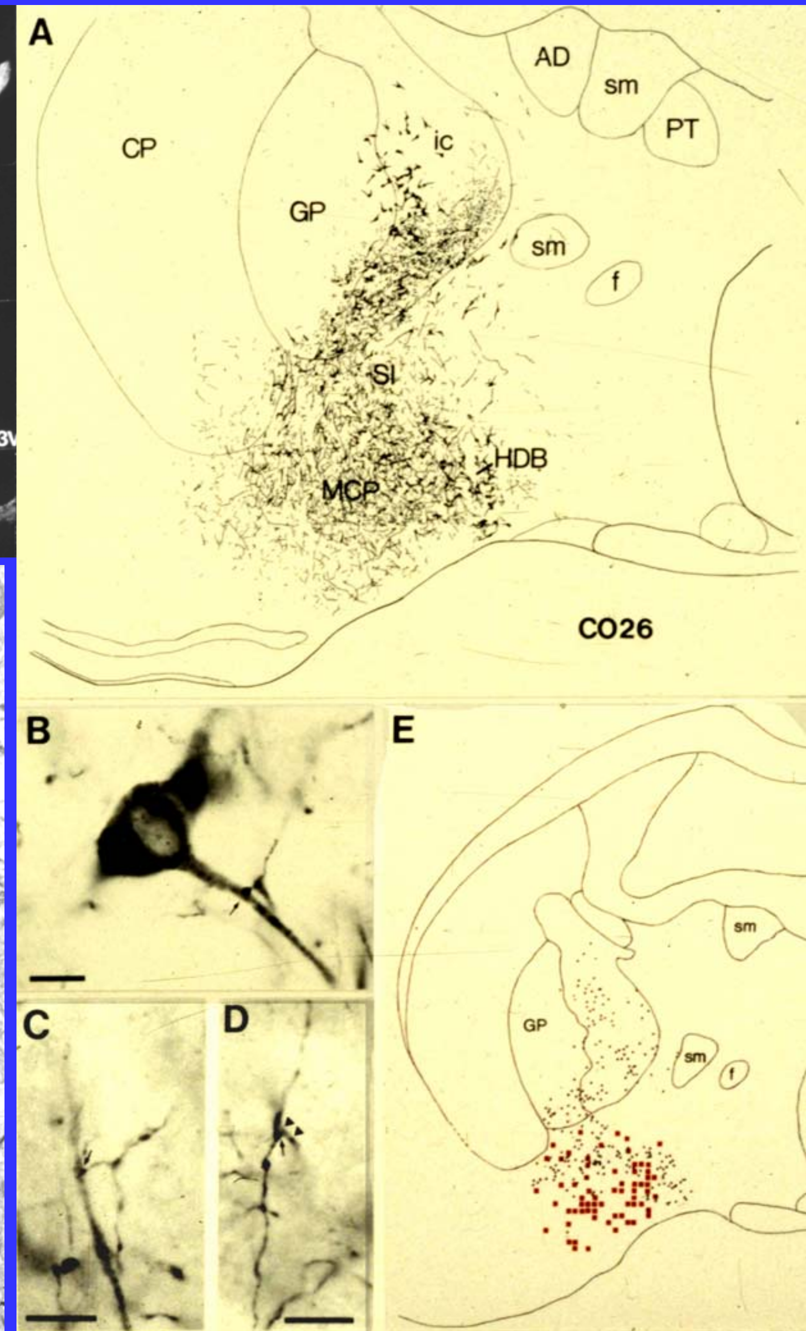
PROJECTIONS FROM BF NEURONS TO DISTINCT CORTICAL ‘MODULES’ ARE SEGREGATED IN THE BASAL FOREBRAIN



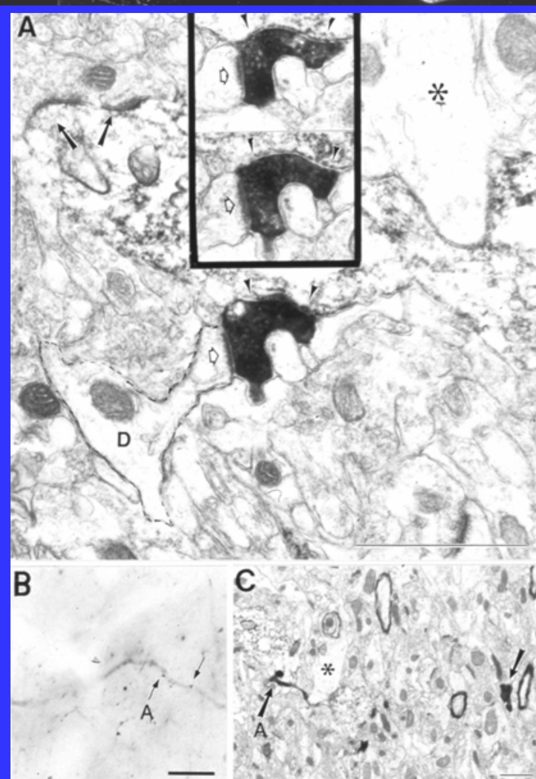
Zaborszky, 2002

CORTICAL FEEDBACK TO BF ORIGINATES IN THE PREFRONTAL CORTEX

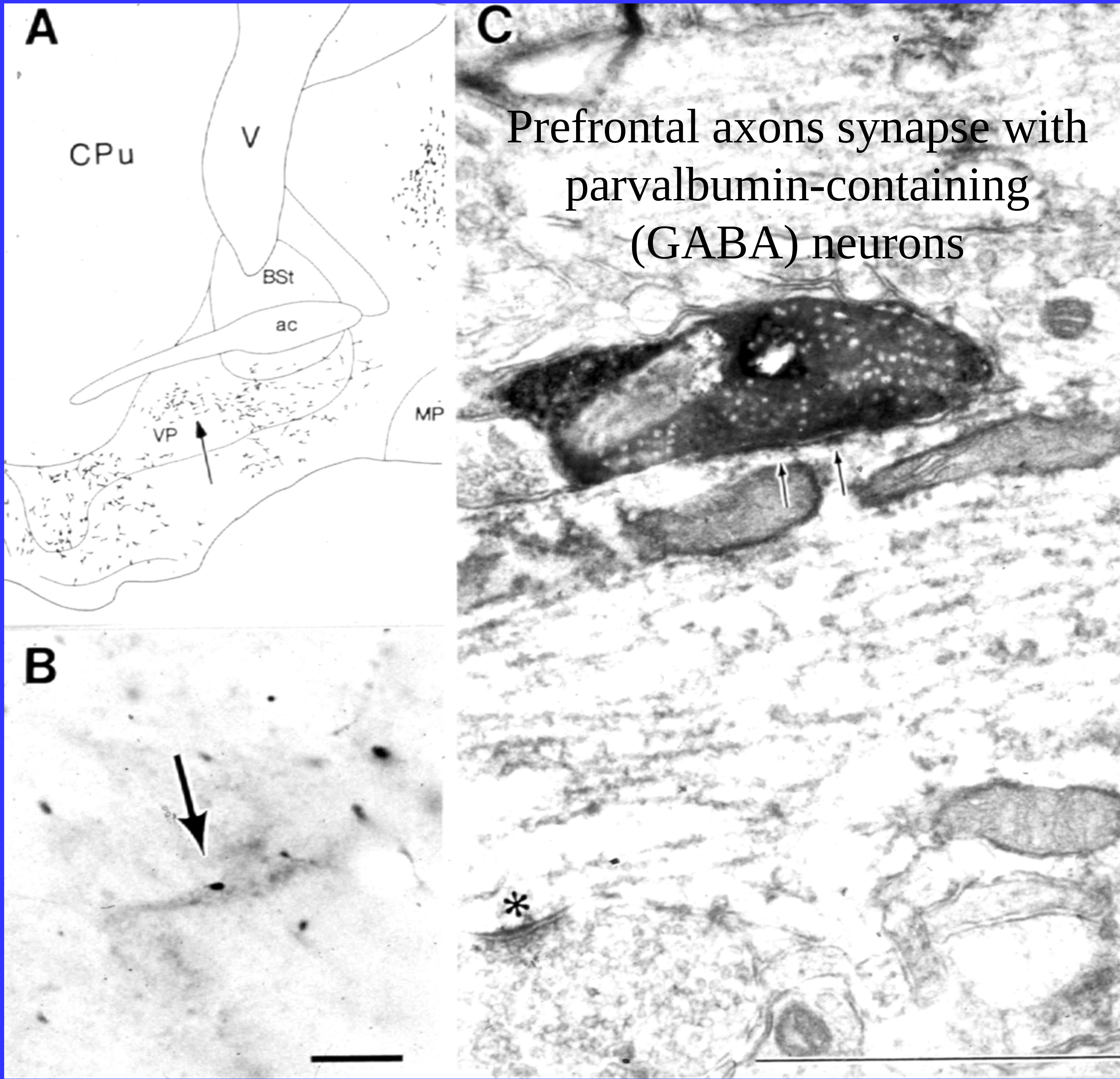


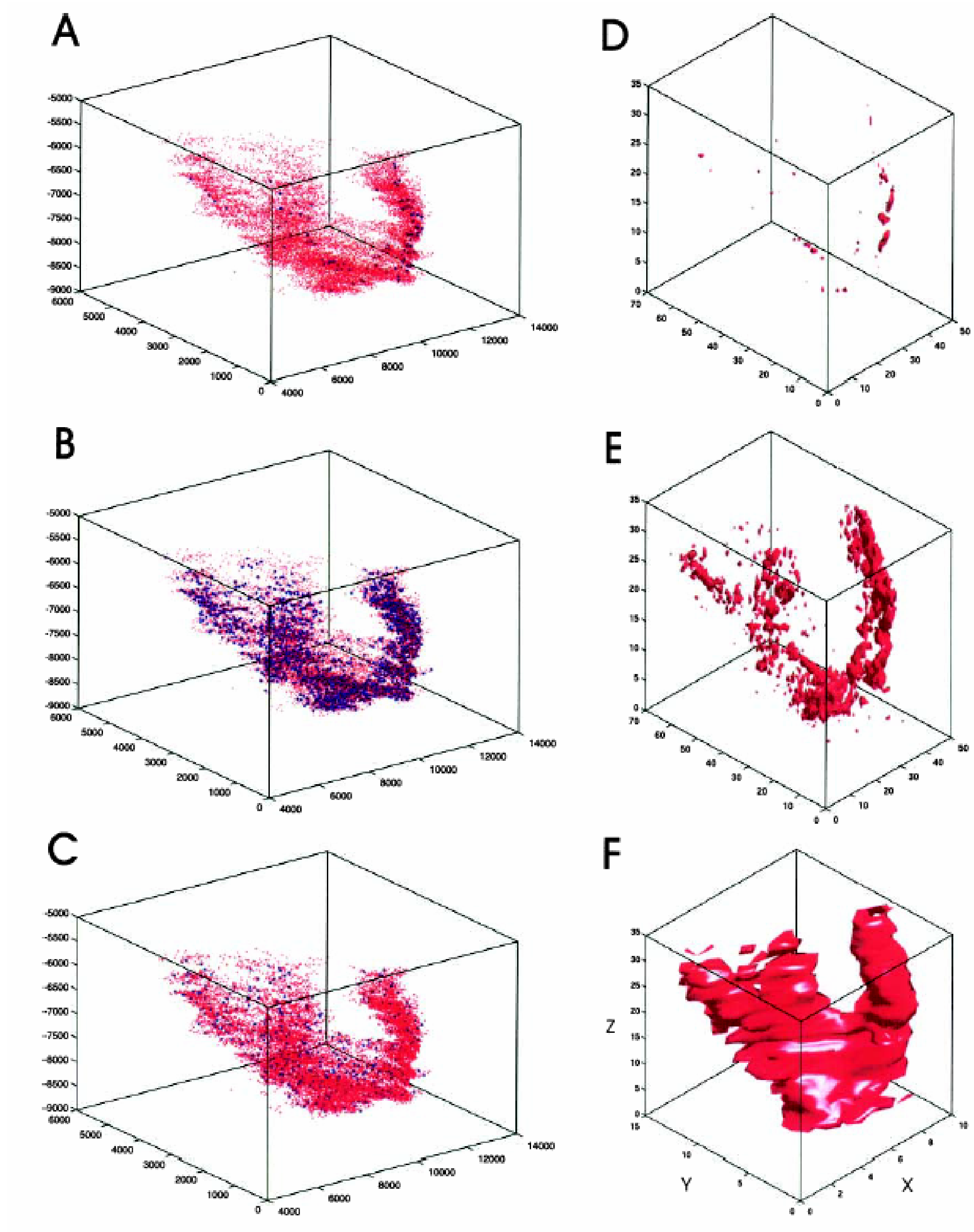


Synapses are on spine heads of non-cholinergic neurons



Zaborszky et al., 1997


A
CPu
V
BSt
ac
VP
MP
B
C
Prefrontal axons synapse with
parvalbumin-containing
(GABA) neurons
*



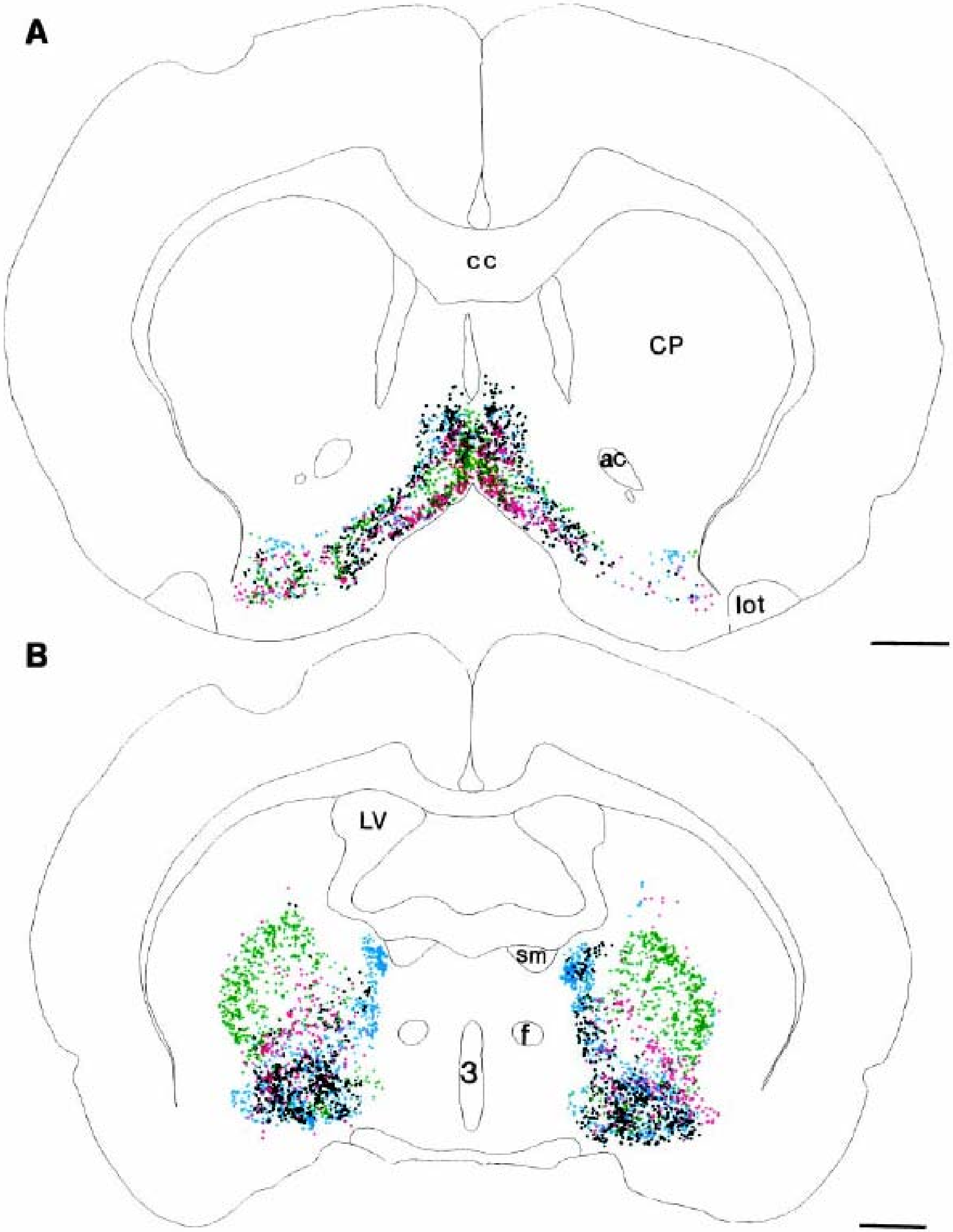
d>8/100x100

d>3/100x100

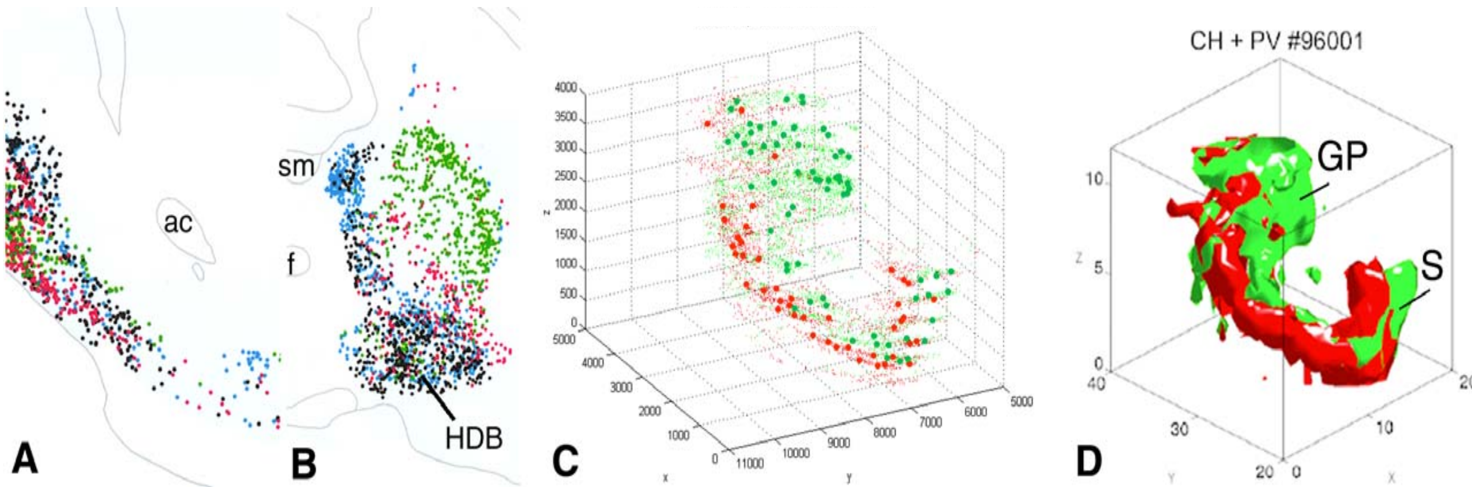
D>8/500x500

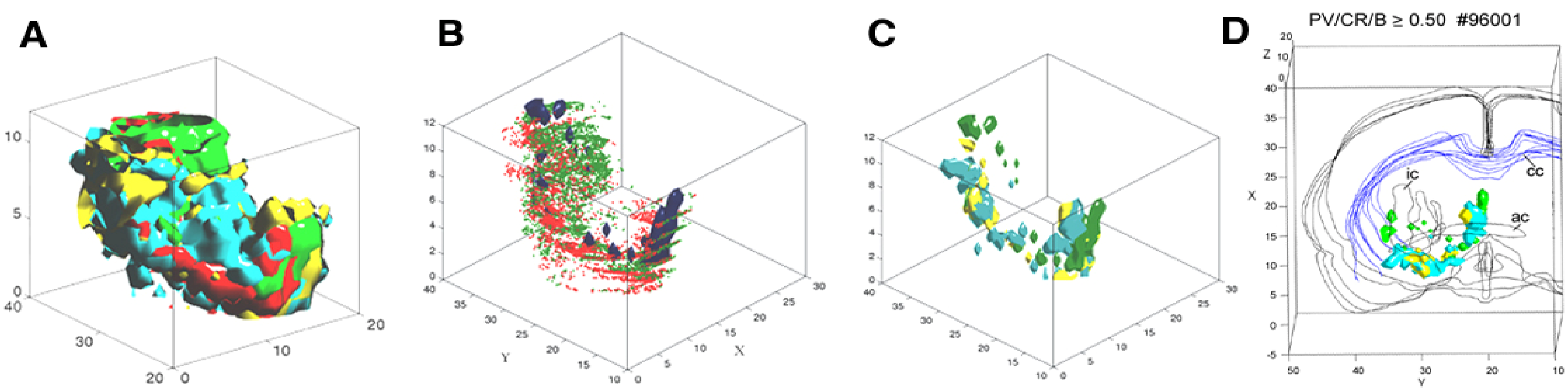
A

B



PRESENCE OF SPATIALLY SPECIFIC 'CLUSTERS' IN THE BF



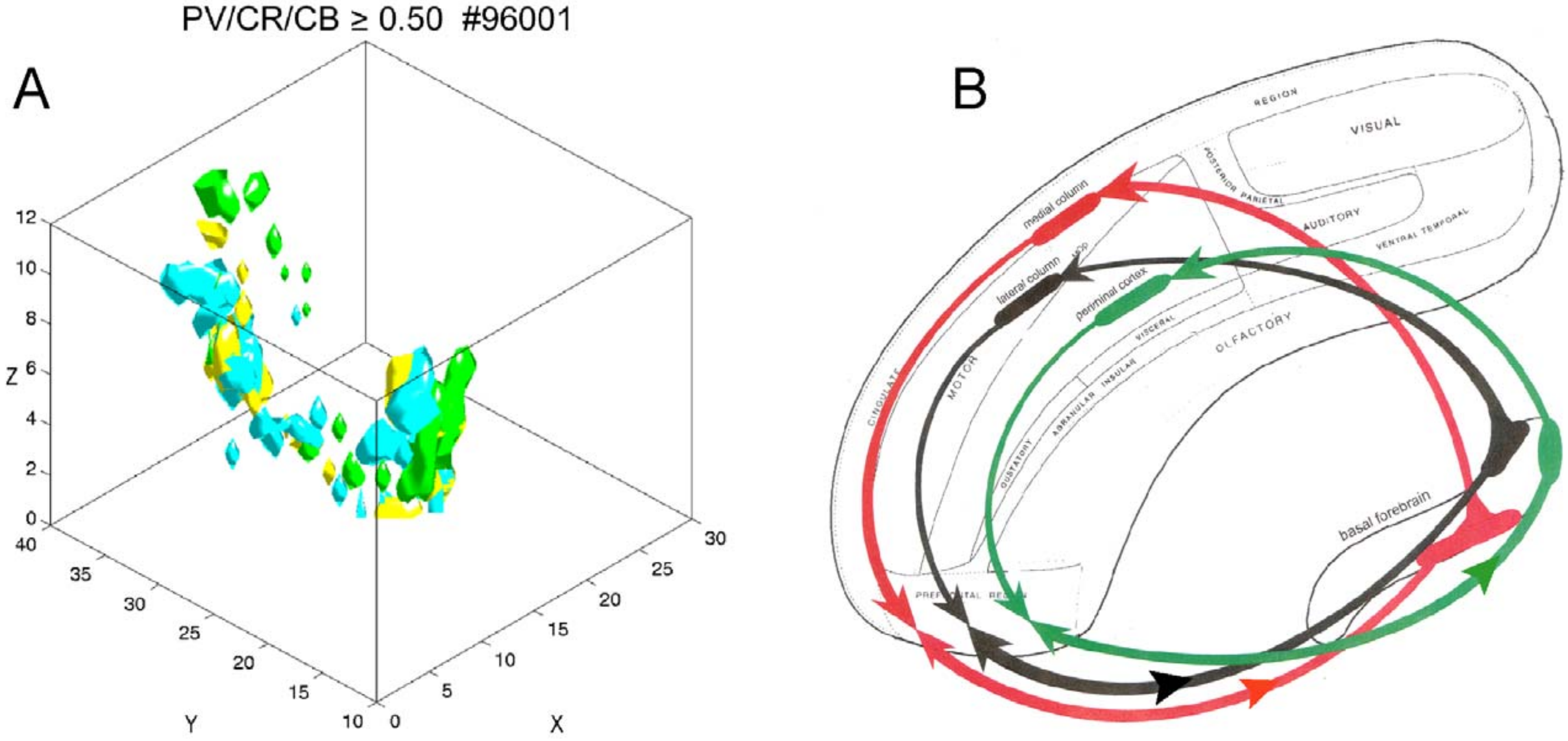


Zaborszky et al., Neuroscience, in press

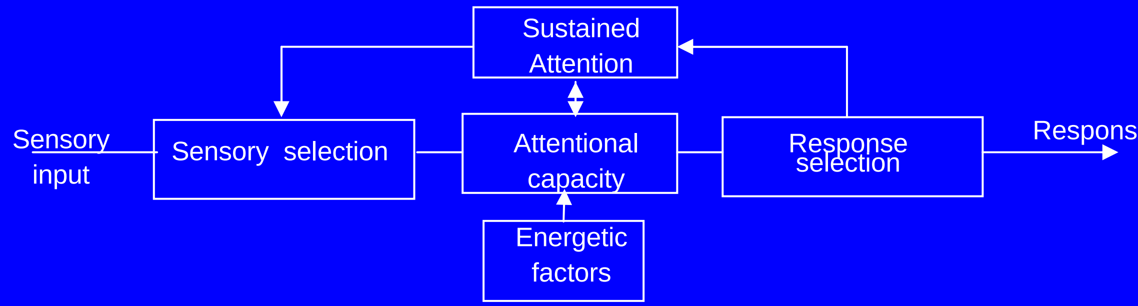
SPECIFIC CELL CLUSTERS IN THE BF TOGETHER WITH SPECIFIC PREFRONTAL AND POSTERIOR ASSOCIATIONAL CELL GROUPS FORM DISTRIBUTED FUNCTIONAL MODULES THAT MAY BE IMPORTANT IN ATTENTIOANL MECHANISMS

(Hypothesis)

C



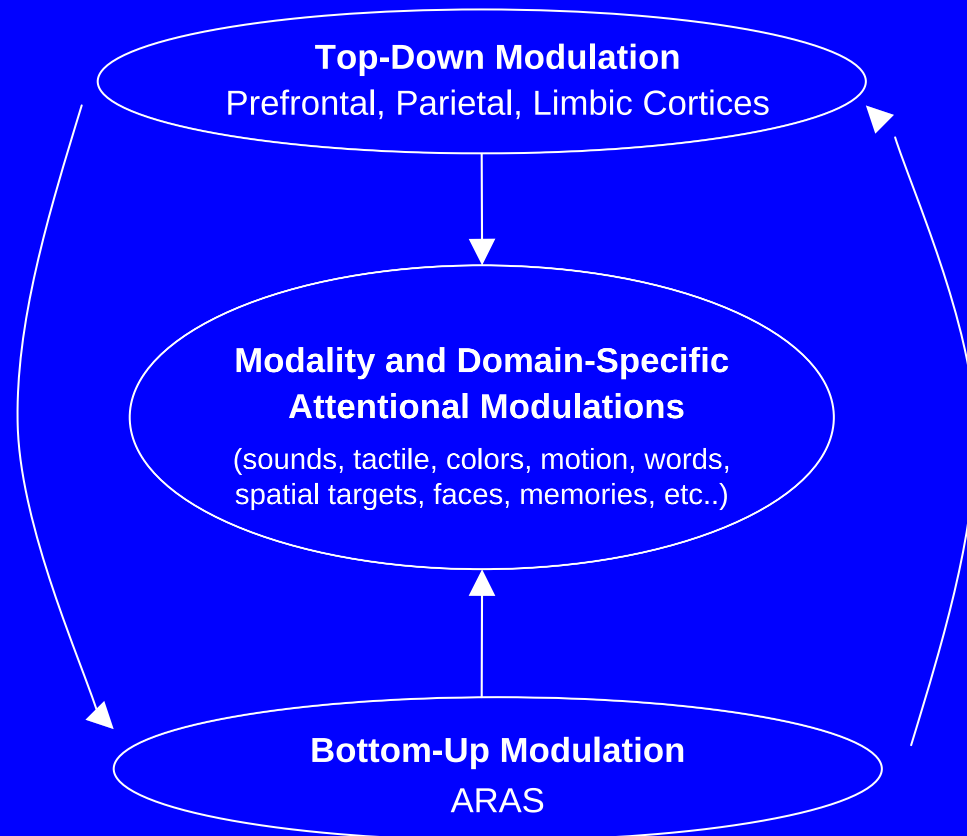
WHERE TH E’BOTTOM UP’ MEETS WITH THE ‘TOP DOWN’?



Cohen, 1993

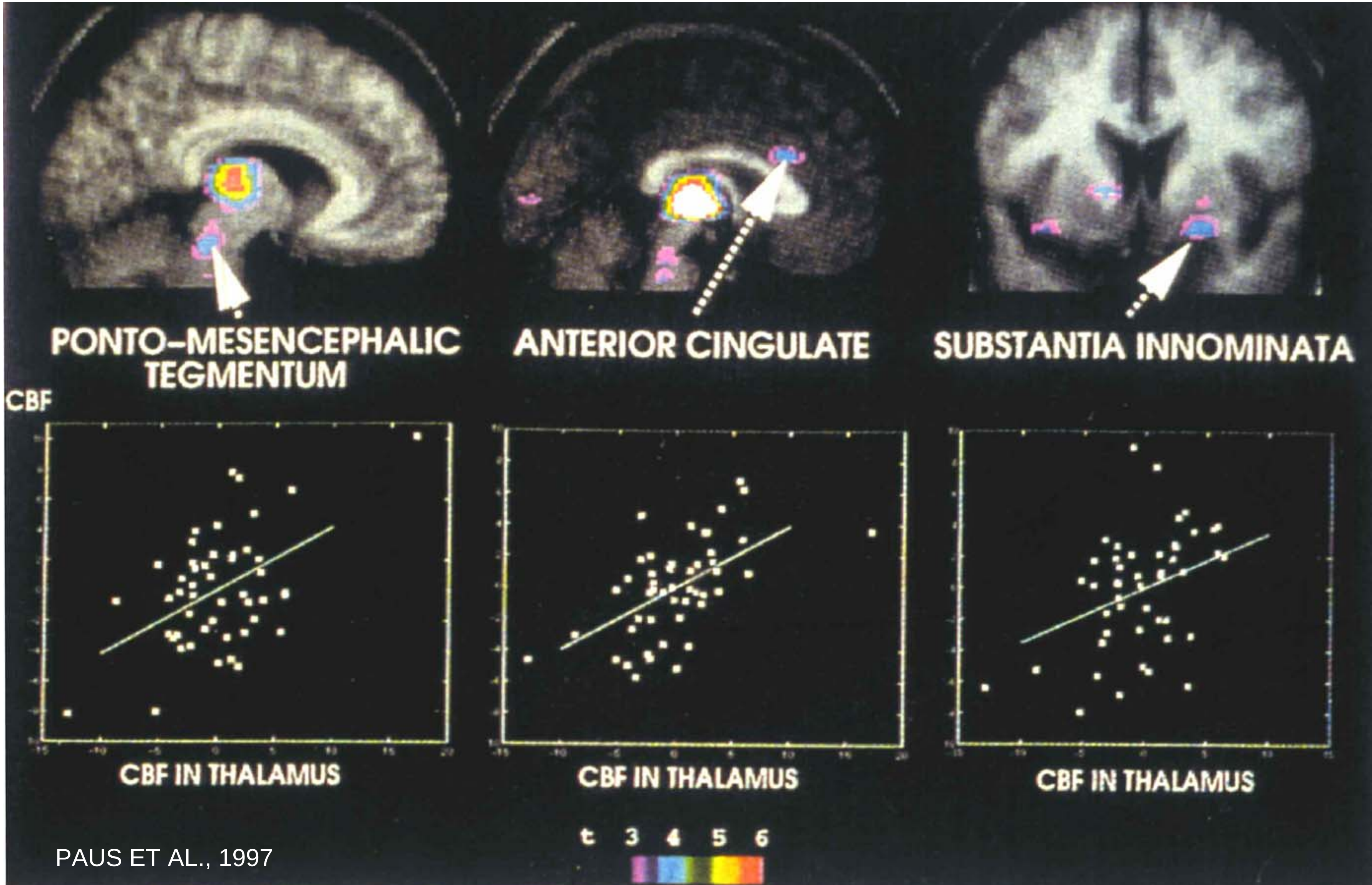
- Attentional mechanisms can act either the input or the output levels of information processing (Broadbent, Treisman, Shiffrin, Shalice, Kahneman, Cohen).

- Attention can be divided into **Bottom-Up**, (filtering of sensory events from a large number of competing stimuli), and T**op-Down processes**, (memory for the significance of stimuli). Top-down processes, are a component of the **prefrontal** mediation of executive functions: they ‘amplify computations within a particular posterior sensory area, by reentering the same area that initially performed the computation’ (Posner and Raichle)

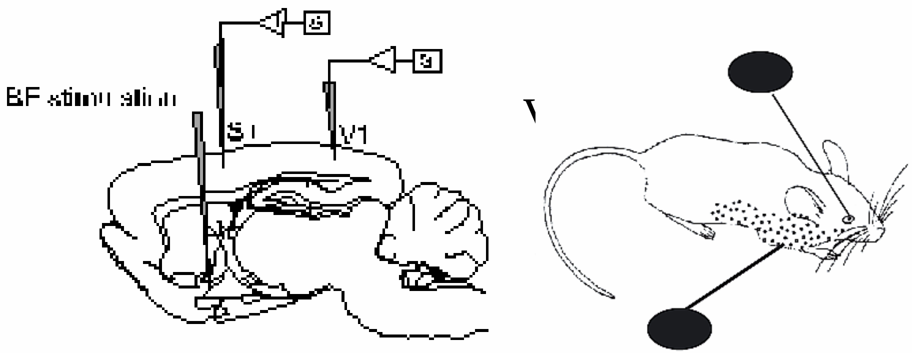


Mesulam, 1990

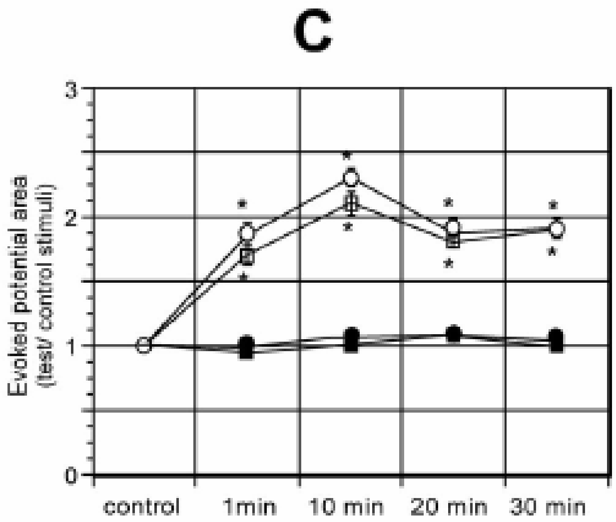
BASAL FOREBRAIN ACTIVATION IN A SUSTAINED ATTENTION TASK (Paus et al., 1997)



CONFIRMATION that BF STIMULATIONS ENHANCES SENSORY-EVOKED POETNTIALS

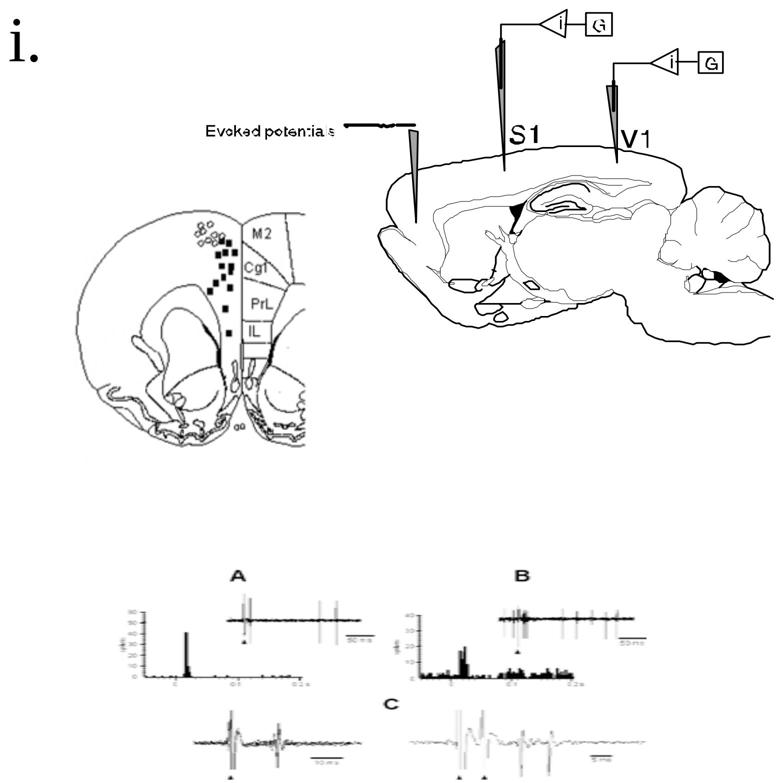


SOMATOSENSORY VISUAL

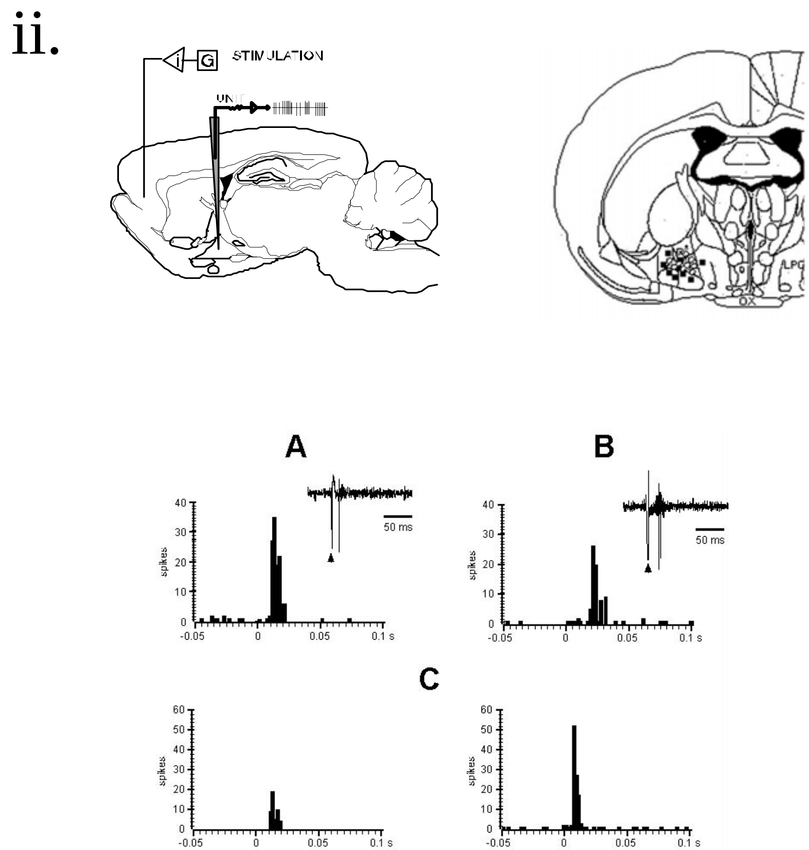


Golmayo, Nunez, Zaborszky, 2003

FUNCTIONAL CIRCUITR from POSTERIOR SENSORYAREAS to PFC (i) and hence to BF (ii)

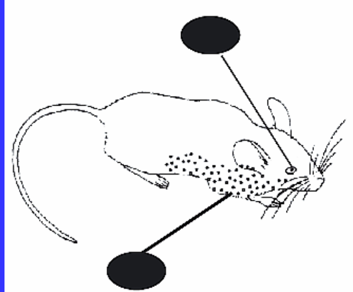


Orthodromic activation of PFC neurons from the somatosensory (A), and from the visual cortex (B).

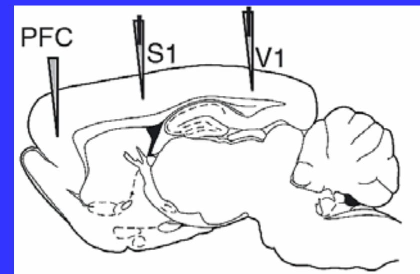


Orthodromic activation of BF neurons by PFC stimulation in the visually responsive area (A) and from the somatosensory-responsive area (B). PTSH of a BF neuron during stimulation of the visual (left) and somatosensory (right) PFC areas

Golmayo, Nunez, Zaborszky, 2003

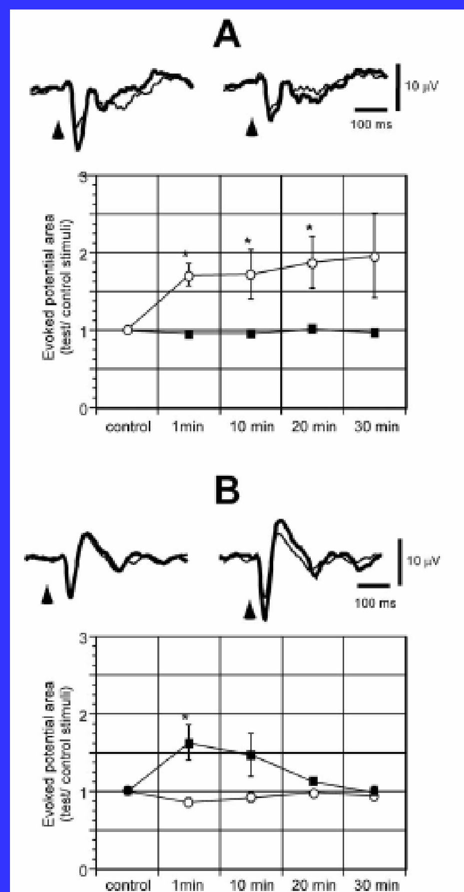


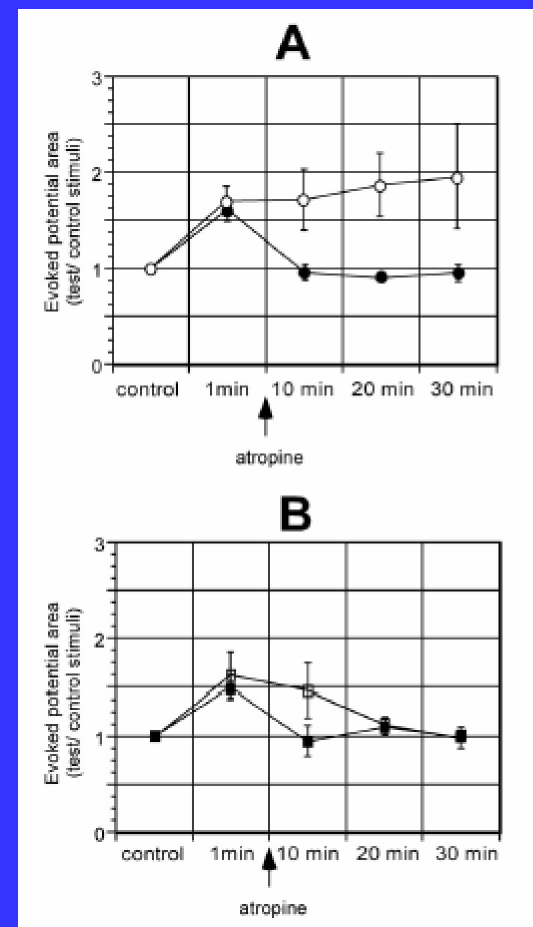
PFC STIMULATIONS SELECTIVELY MODIFY EVOKED RESPONSES in SOMATOSENSORY or VISUAL CORTICES. THESE SENSORY RESPONSES ARE ATROPINE-SENSITIVE



A: Stimulation of the <u>somatosensory-responsive</u> PFC area facilitates SS evoked potentials (open circles and left) but does not modify the visual-evoked potentials (solid squares).

Stimulation of the <u>visual-responsive</u> PFC area slightly decreases SS evoked potentials (open circles) and induces a short-lasting facilitation of the visual-evoked potentails (solid squares and right)





SUMMARY

- Specific BF neurons posses distinct temporal relationship to different EEG patterns. There may be a **dynamic interplay between brainstem-BF and cortical circuitries**
- **Corticopetal neurons** in the BF are uniquely positioned **to integrate** the constant flow of cellular and homeostatic ‘states’ derived from the **ascending modulatory systems and to channel** this momentarily changing neural pattern to the cortical mantle to **modulate alertness**.
- Against the relatively ‘diffuse’ termination of the ascending axons, the **restricted input from the prefrontal cortex to BF** projection neurons and through local processing might be instrumental in communicating state-related changes to specific posterior sensory areas to **modulate sensory plasticity and attention**.

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