

Brain Rhythms

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Objectives

- Understand the basis of cellular rhythmicity
- Describe the principles of intrinsic cellular resonance
- Describe how groups of neurons may synchronize their activity
- Understand the role of two ionic currents that synchronize brain activity
 - brain “pacemaker circuits”
 - role of inhibition



Disclosure

- In the last two years, I have had no financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.



Brain Oscillations: correlate to differing behavioural states

•EEG

•ALPHA

•Alpha waves are those between 7.5 and thirteen(13) waves per second (Hz). Alpha is usually best seen in the posterior regions of the head on each side, being higher in amplitude on the dominant side. It is brought out by closing the eyes and by relaxation, and abolished by eye opening or alerting by any mechanism (thinking, calculating). It is the major rhythm seen in normal relaxed adults - it is present during most of life especially beyond the thirteenth year when it dominates the resting tracing

•Delta

•Delta activity is 3 Hz or below. It tends to be the highest in amplitude and the slowest waves. It is quite normal and is the dominant rhythm in infants up to one year and in stages 3 and 4 of sleep. It may occur focally with subcortical lesions and in general distribution with diffuse lesions, metabolic encephalopathy hydrocephalus or deep midline lesions.

•Beta

•Beta activity is 'fast' activity. It has a frequency of 14 and greater Hz. It is usually seen on both sides in symmetrical distribution and is most evident frontally. It is accentuated by sedative-hypnotic drugs especially the benzodiazepines and the barbiturates. It may be absent or reduced in areas of cortical damage. It is generally regarded as a normal rhythm. It is the dominant rhythm in patients who are alert or anxious or who have their eyes open.

•Theta

•Theta activity has a frequency of 3.5 to 7.5 Hz and is classed as "slow" activity. It is abnormal in awake adults but is perfectly normal in children upto 13 years and in sleep. It can be seen as a focal disturbance in focal subcortical lesions; it can be seen in generalized distribution in diffuse in diffuse disorder or metabolic encephalopathy or deep midline disorders or some instances of hydrocephalus

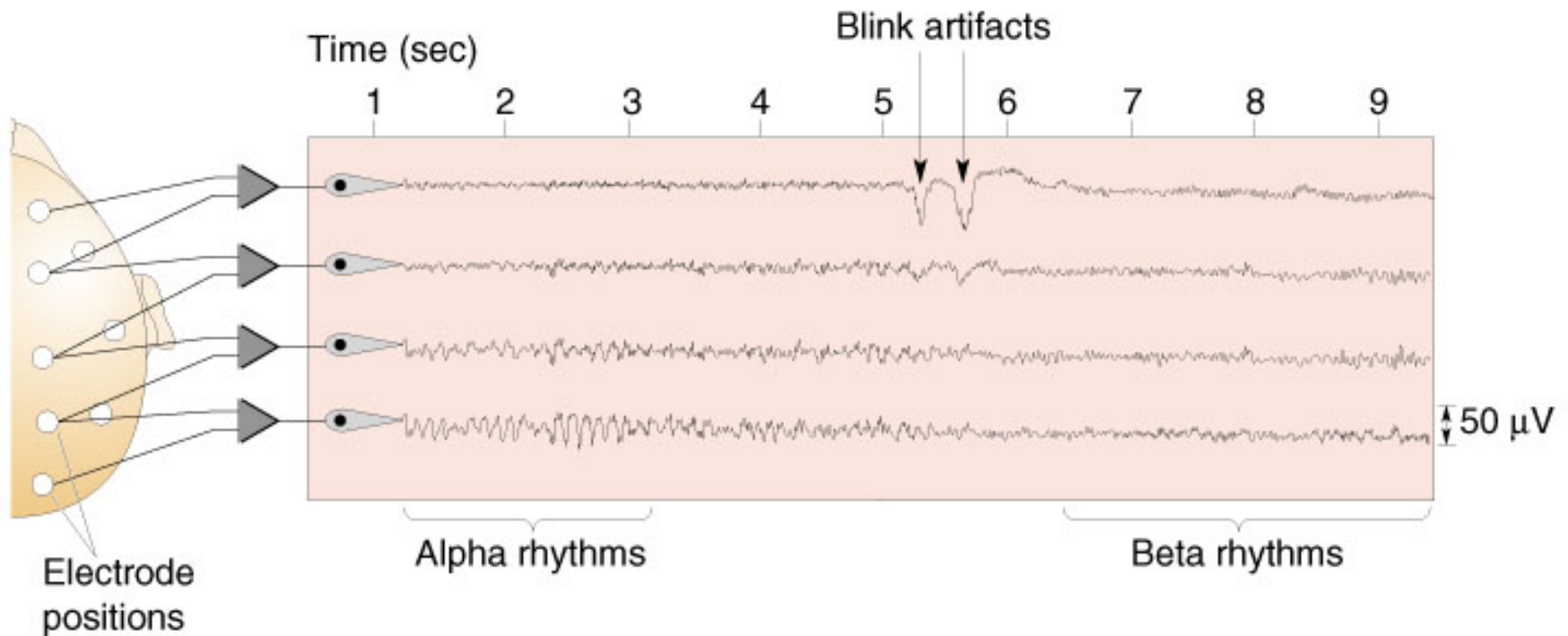
•Gamma

•Gamma activity 40- 80 Hz is present in waking individuals and is thought to be the learning rhythm. Fixing one's attention on something typically illicit gamma rhythm in many area including cortex, hippocampus.

The Normal EEG

Figure 19.5

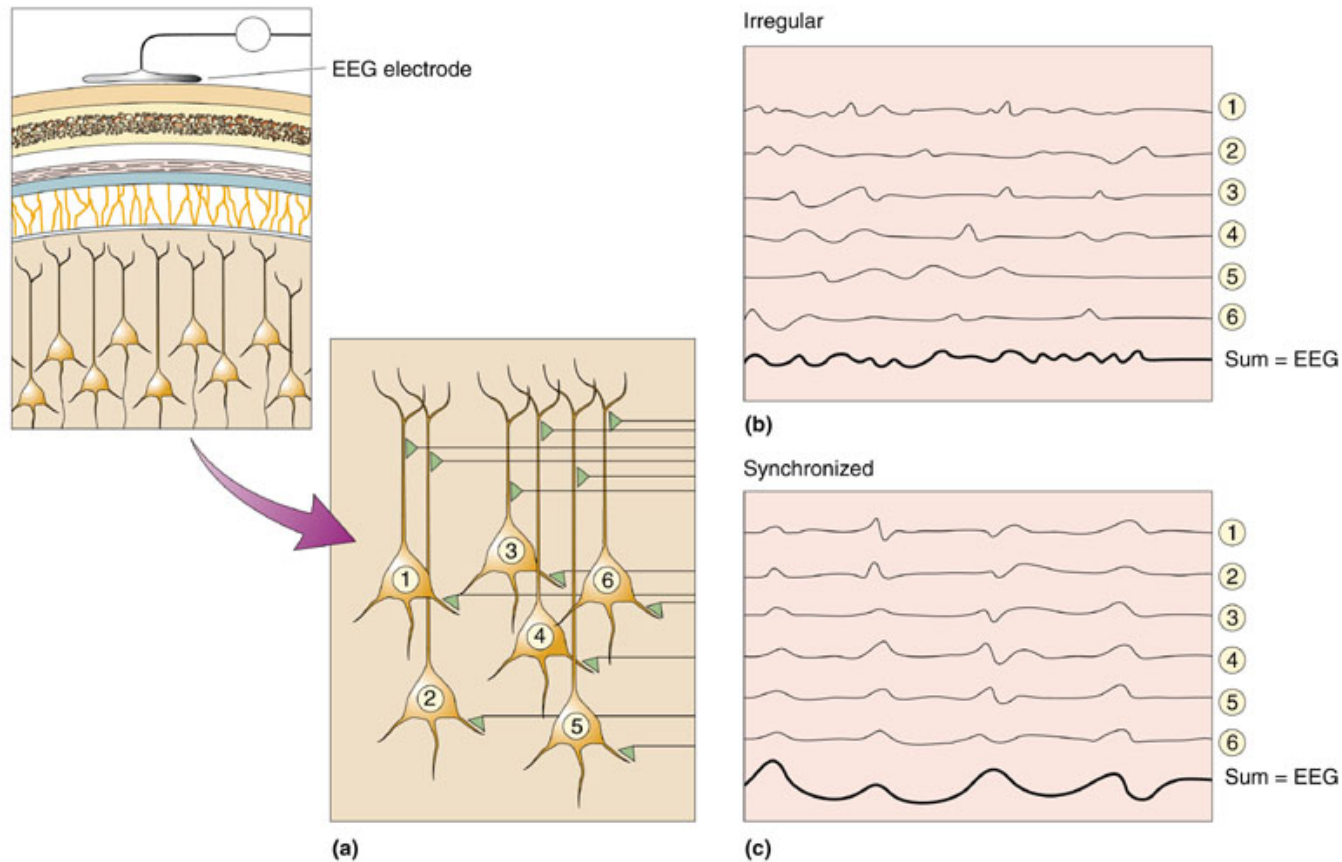
A normal EEG. The subject is awake and quiet, and recording sites are indicated at the left. The first few seconds show normal alpha activity, which has frequencies of 8–13 Hz and is largest in the occipital regions. About halfway through the recording, the subject opened his eyes, signaled by the large blink artifacts on the top traces (arrows), and alpha rhythms were suppressed.



EEG requires neural synchrony

Figure 19.4

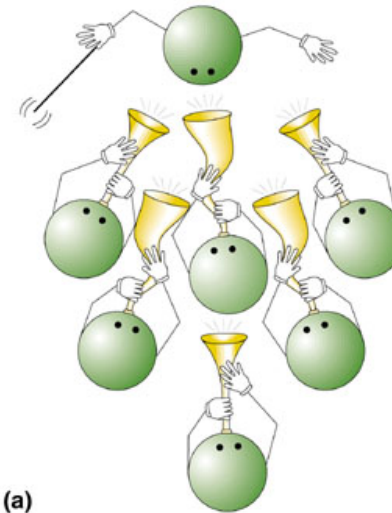
The generation of large EEG signals by synchronous activity. (a) In a population of pyramidal cells under an EEG electrode, each neuron receives many synaptic inputs. (b) If the inputs fire at irregular intervals, the pyramidal cell responses are not synchronized, and the summed activity detected by the electrode has small amplitude. (c) If the same number of inputs fire within a narrow time window so that the pyramidal cell responses are synchronized, the resulting EEG sum is much larger.



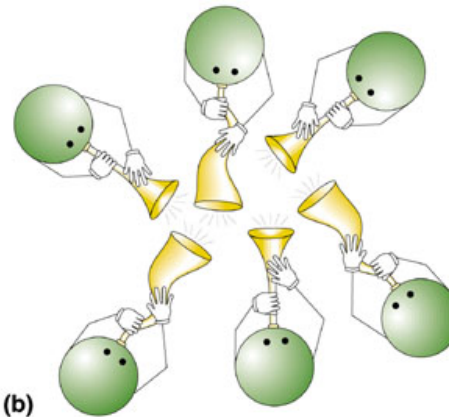
•How does synchrony arise ?
a conductor
or
well rehearsed ensemble

Figure 19.6

Two mechanisms of synchronous rhythms. Synchronous rhythms may (a) be led by a pacemaker or (b) arise from the collective behavior of all participants.



(a)



(b)

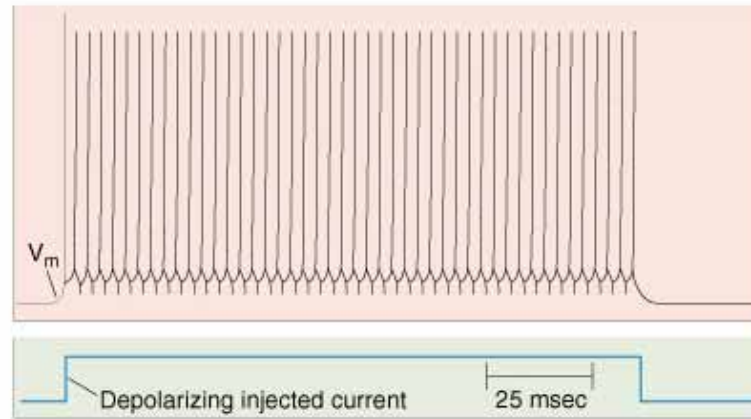
Cellular and circuit properties that determine brain rhythms

- Cellular Basis of rhythmicity
 - Intrinsic rhythmicity in single neurons
 - What is neuronal resonance?
- Rhythmic Currents and synaptic connections
 - I_h – pacemaker current
 - Inhibitory neurotransmission – so much more than action potential truncation

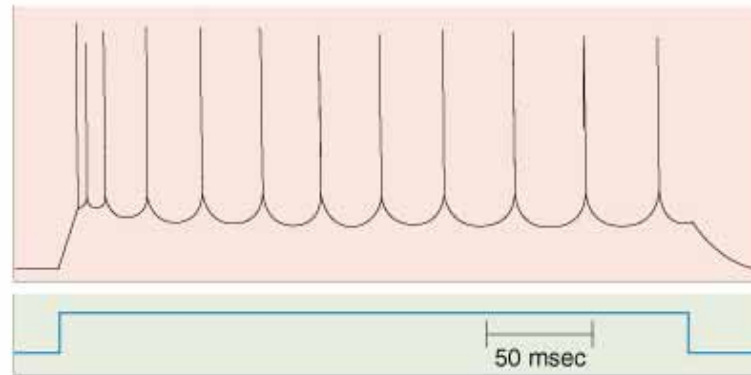


Action potential firing patterns are not constant and may vary tremendously

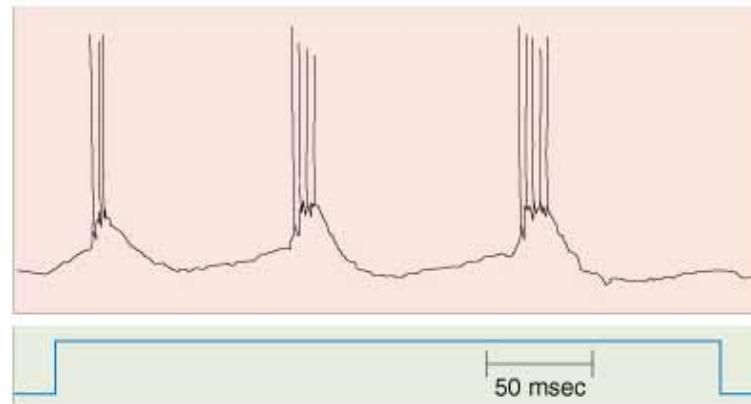
These firing patterns are created by combining the activity of potassium and calcium channels which all are activated by voltage, in and in a time dependent manner



(a)



(b)

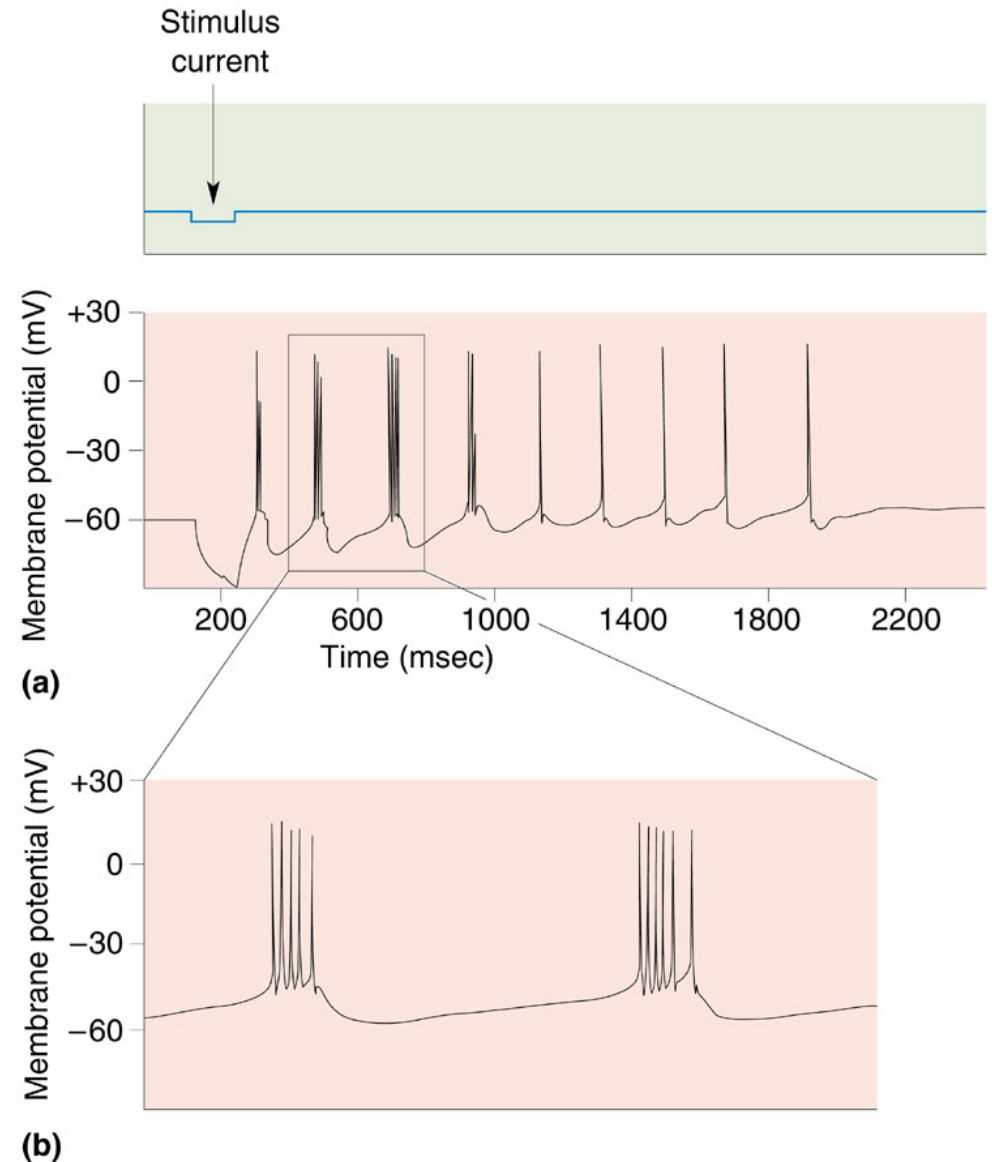


(c)

Cells have “natural” oscillatory behaviour

Figure 19.8

A one-neuron oscillator. At times during sleep states, thalamic neurons fire in rhythmic patterns that do not reflect their input. Shown here are intracellular recordings of membrane voltage in such a case. (a) A short pulse (less than 0.1 second) of stimulus current was applied, and the cell responded with almost 2 seconds of rhythmic firing, first with bursts at about 5 Hz and then with single spikes. (b) Two of the bursts expanded in time; each burst is a cluster of five or six action potentials. (Source: Adapted from Bal and McCormick, 1993, Fig. 2.)



Some rhythmically burst due to constant stimulus

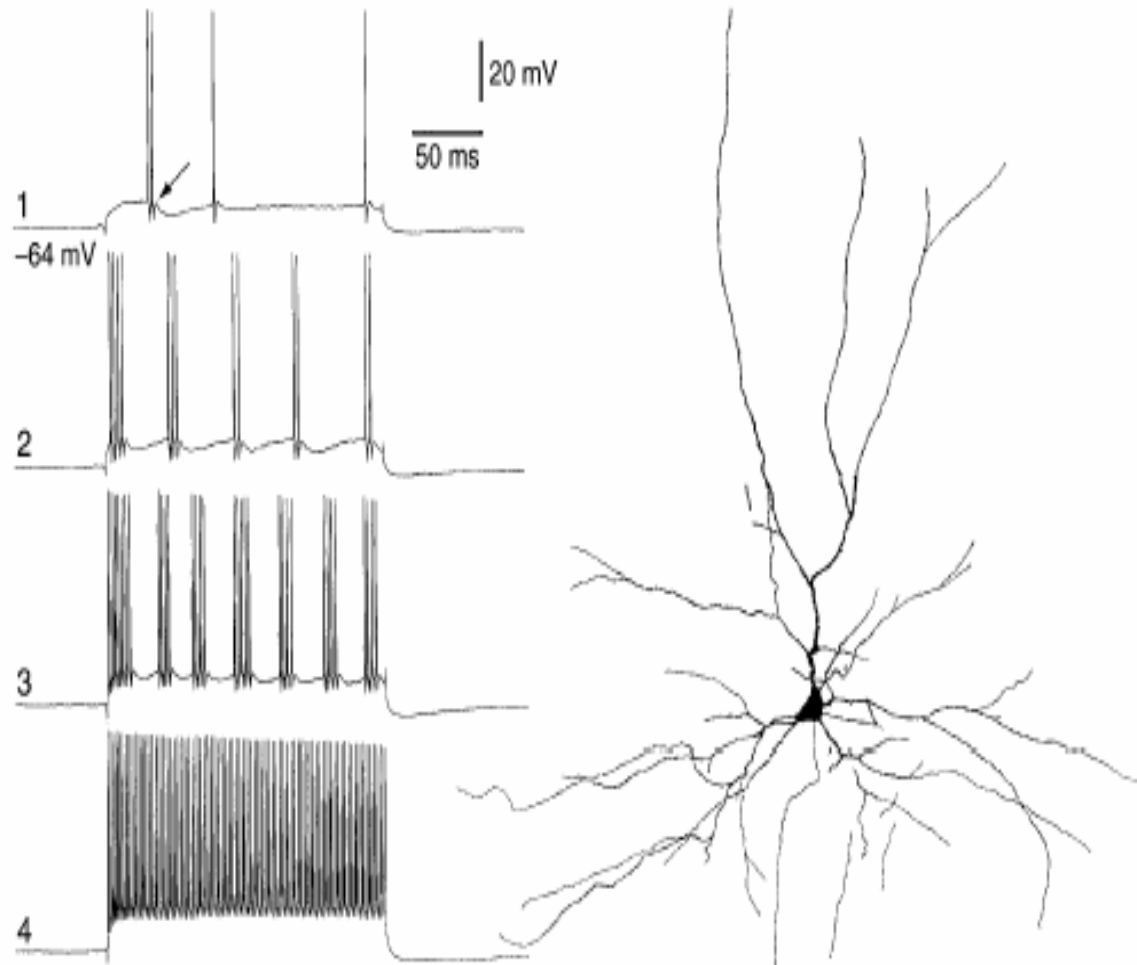


Fig. 2. *Dynamic properties of fast-rhythmic-bursting neocortical neurons.* Intracellular recording of corticothalamic neuron from the cat association suprasylvian gyrus, which has been antidromically activated by stimulating the thalamic lateral posterior nucleus (see antidromic identification procedure in corticothalamic neuron depicted in Fig. 1). Depolarizing current pulses with different intensities [0.3 nA in (1), 0.7 nA in (2), 0.9 nA, in (3) and 1.2 nA in (4)] elicited changing firing patterns, from single action potentials (1) to rhythmic spike-bursts at ~25 Hz (2) and ~35 Hz (3), and further to fast firing (~400 Hz) without frequency adaptation (4). On the right, a corticothalamic neuron from layer VI is shown that has been stained intracellularly using Neurobiotin. Such neurons display fast-rhythmic-bursting patterns, which develop into fast-spiking patterns, such as those shown on the left. The arrow points to the depolarizing afterpotential that generates an increased number of spikes. Modified, with permission, from Ref. 14.

Are neurons intrinsically rhythmic?

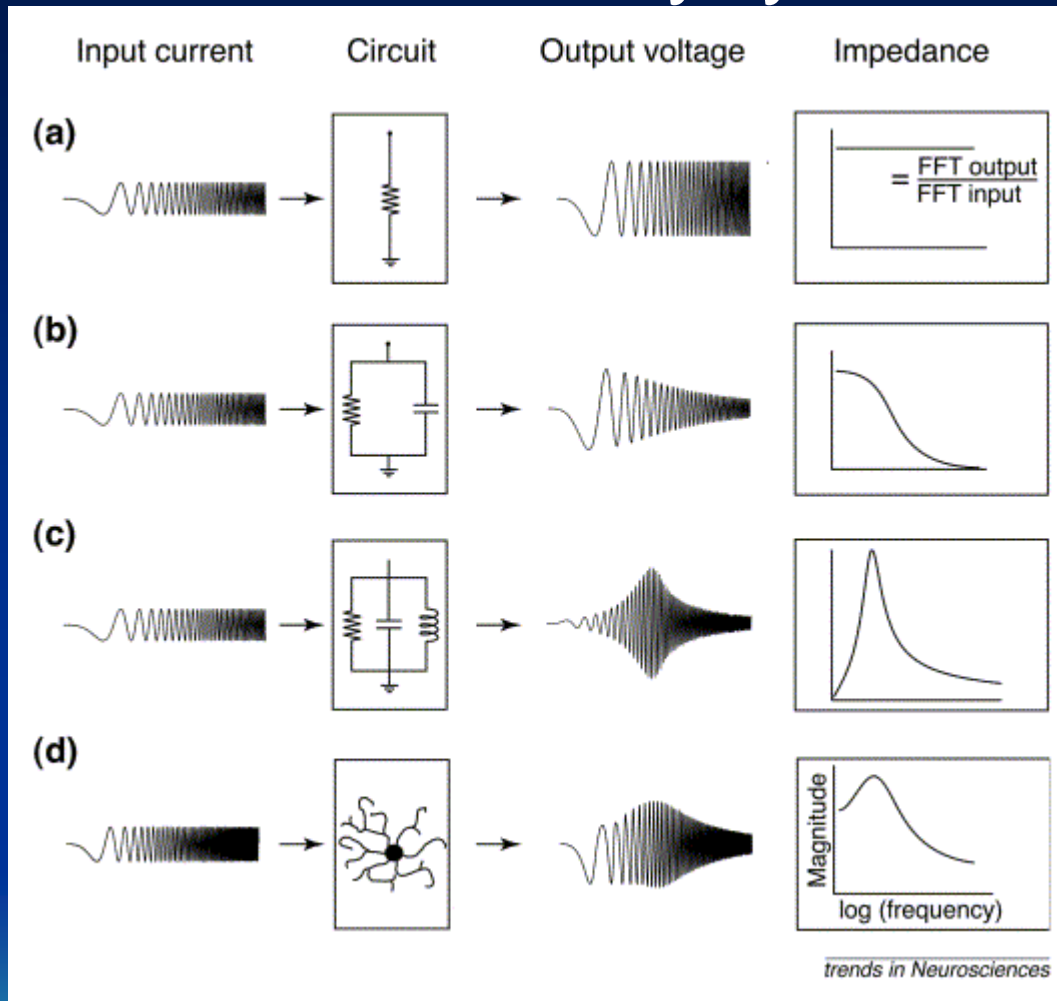
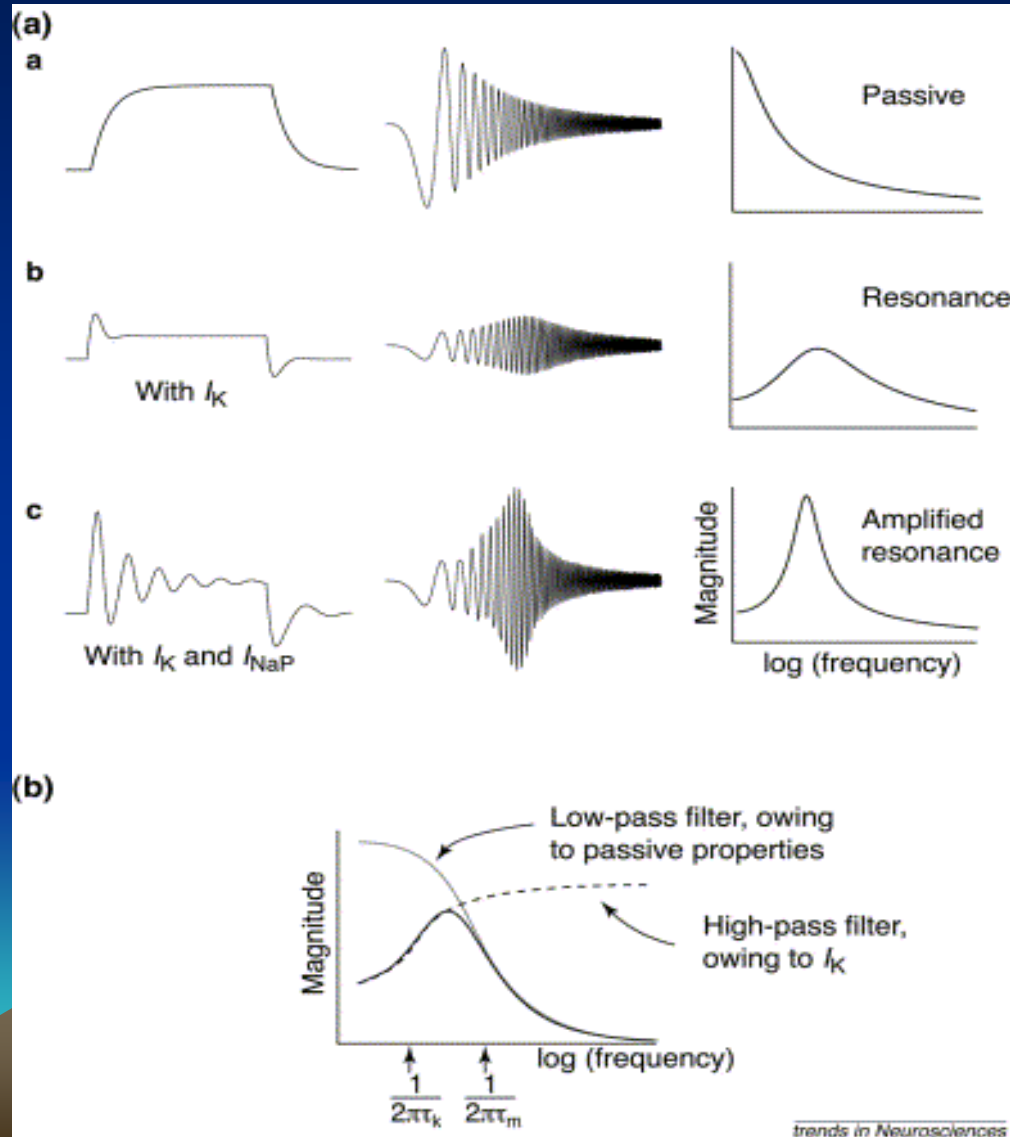
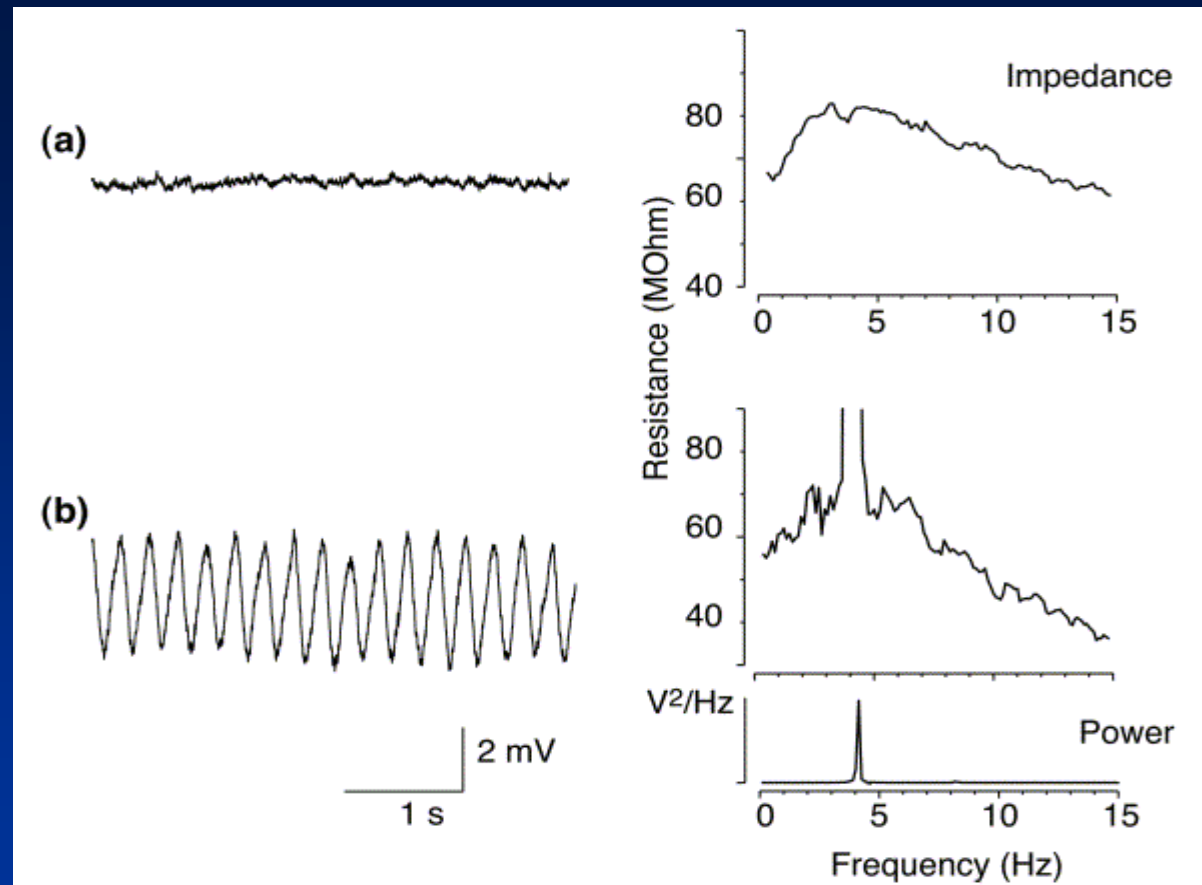


Fig. 1. **Frequency-dependent properties of electronic circuits and neurons: detection and analysis.** The relationship between the current input (first column) and the voltage output (third column) of electrical circuits or neurons (second column) enables the calculation of the impedance as a function of frequency (fourth column). The use of a ZAP input function concentrates the analysis within a specific range of frequencies

Intrinsic Rythmicity is due to an interaction between passive and active electrical components



Membrane Resonance in a real neuron



Neurons of the inferior olive have an intrinsically determined frequency preference that is reflected in their network behaviour. **(a)** A whole-cell recording of an olivary neuron *in vitro* shows that it has a stable resting potential (left). The impedance profile of the same neuron (right) reveals a resonance at 4 Hz. The resonance is generated by the low-threshold Ca^{2+} current, I_T . **(b)** In a different olivary neuron, the membrane potential (left) oscillates steadily at 4 Hz as shown by the power spectrum (lower right). The impedance of this neuron also exhibits a resonance with a peak at the same frequency as the oscillations (the large truncated peak centered on the top of the resonance is due to the spontaneous oscillations). Oscillations in these neurons are partly intrinsic and partly caused by electrical coupling with other olivary neurons. Although the existence of oscillation is controlled by the strength of coupling and other modulatory factors such as the leak conductance, the frequency of the oscillations is determined by the resonance in the individual cells.

Resonance tunes neurons to differing inputs

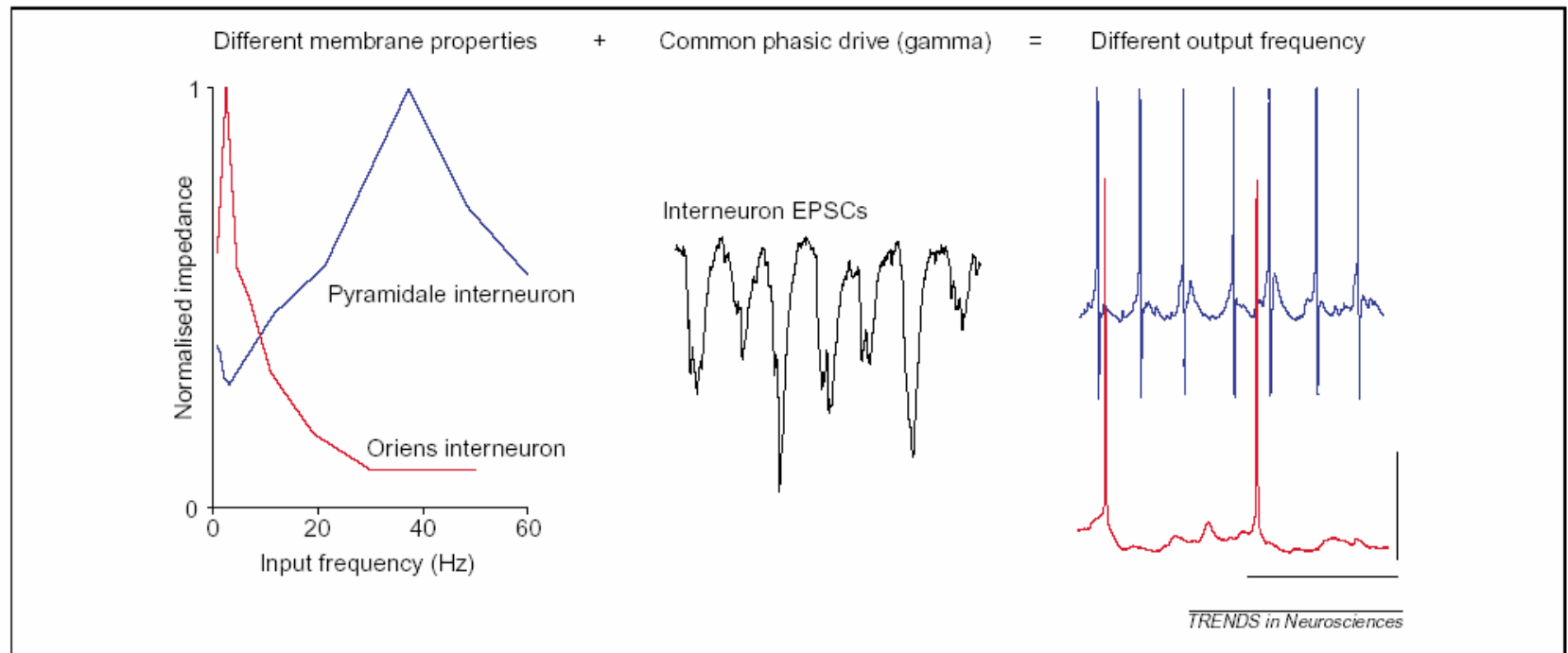
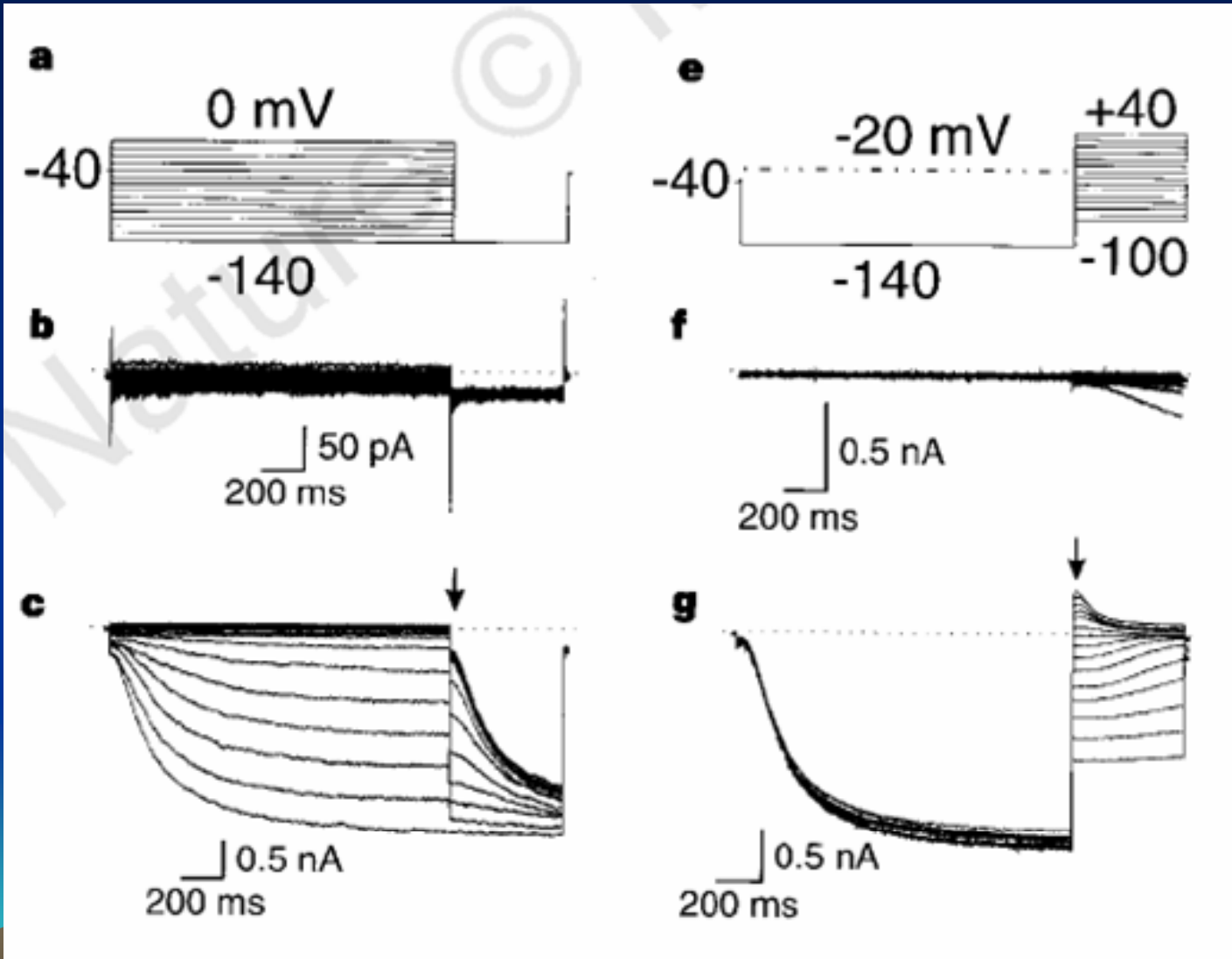


Figure 2. Different intrinsic membrane properties of interneurons generate different outputs from a common excitatory synaptic network drive. Impedance profiles from basket cells and stratum oriens interneurons (blue and red, respectively, to match Figure 1) reveal strong frequency dependence. Fast-spiking interneurons such as basket cells have a peak impedance for inputs at gamma frequencies, whereas slow-spiking oriens interneurons have a peak impedance for inputs at theta frequencies. During kainate-induced field gamma oscillations *in vitro*, different interneuron subclasses receive remarkably similar rhythmic excitatory postsynaptic currents (EPSCs, here illustrated from a holding potential of -70 mV). The interaction between the common network input and the specific intrinsic properties of fast-spiking and slow-spiking interneurons leads to a different frequency of interneuron output, closely correlated with the frequency of peak impedance. Voltage traces are shown at -58 mV (pyramidal layer interneuron) and -55 mV (stratum oriens interneuron). Thus, a single frequency mode of principal cell output can generate multiple frequencies of feedback inhibitory input. Impedance graph reproduced, with permission, from Ref. [13].

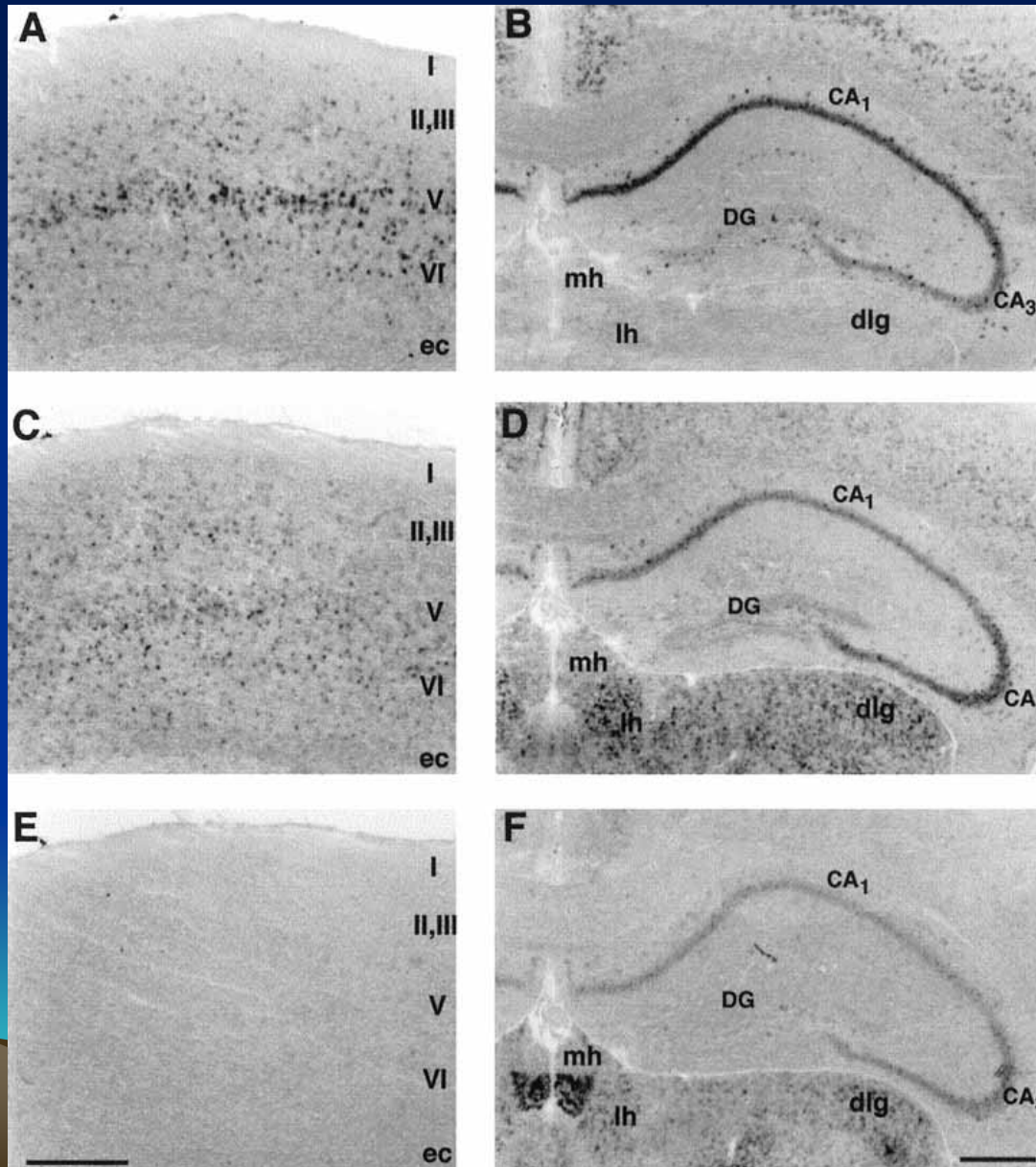
I_h

- Activated by hyperpolarization of the neuron
- Reverse potential is positive to RMP
- Slowly shuts off
- Modulated by drugs that increase cAMP
- Cloned called Hyperpolarizing cAMP Channel (HCN)- potential therapeutic target for control of epilepsy

Characteristics of I_h behaviour

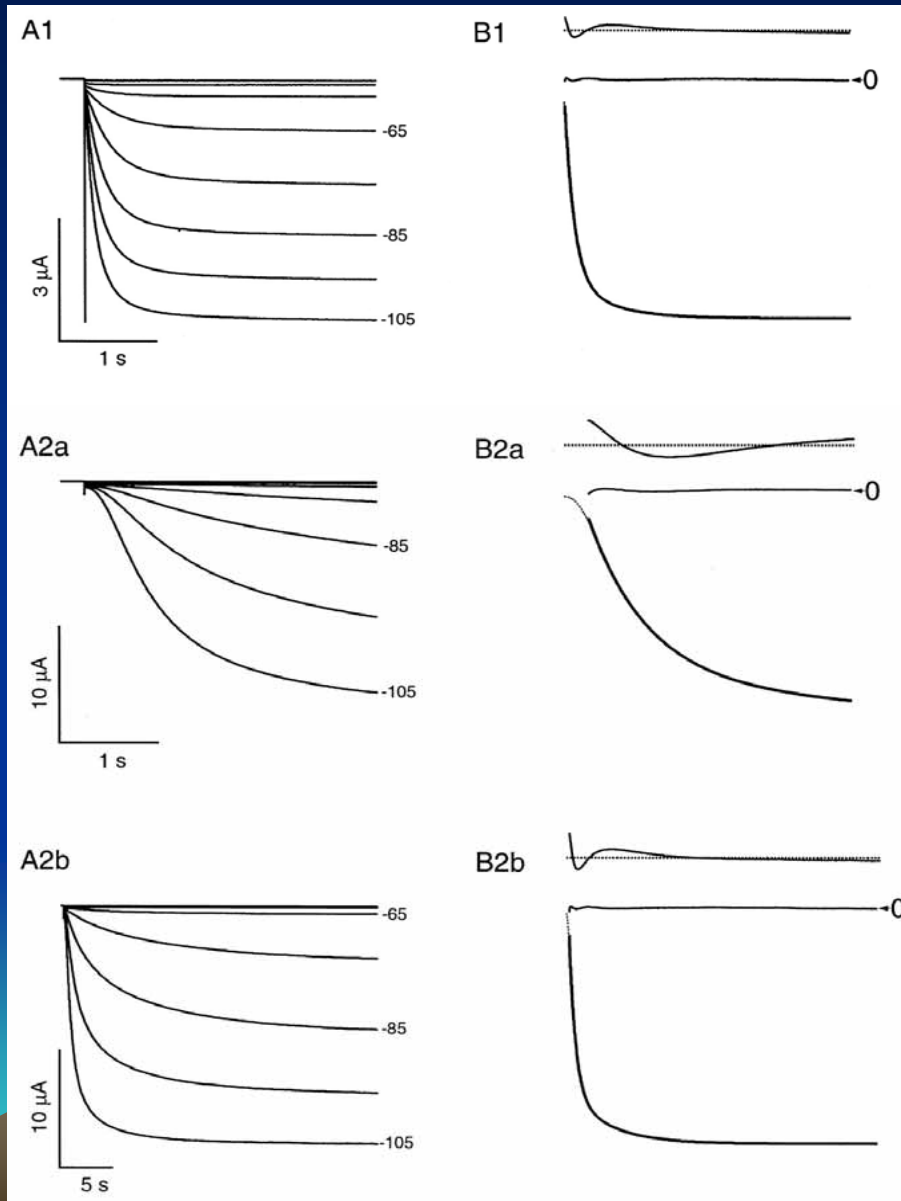


Distribution of HCN transcripts is not uniform



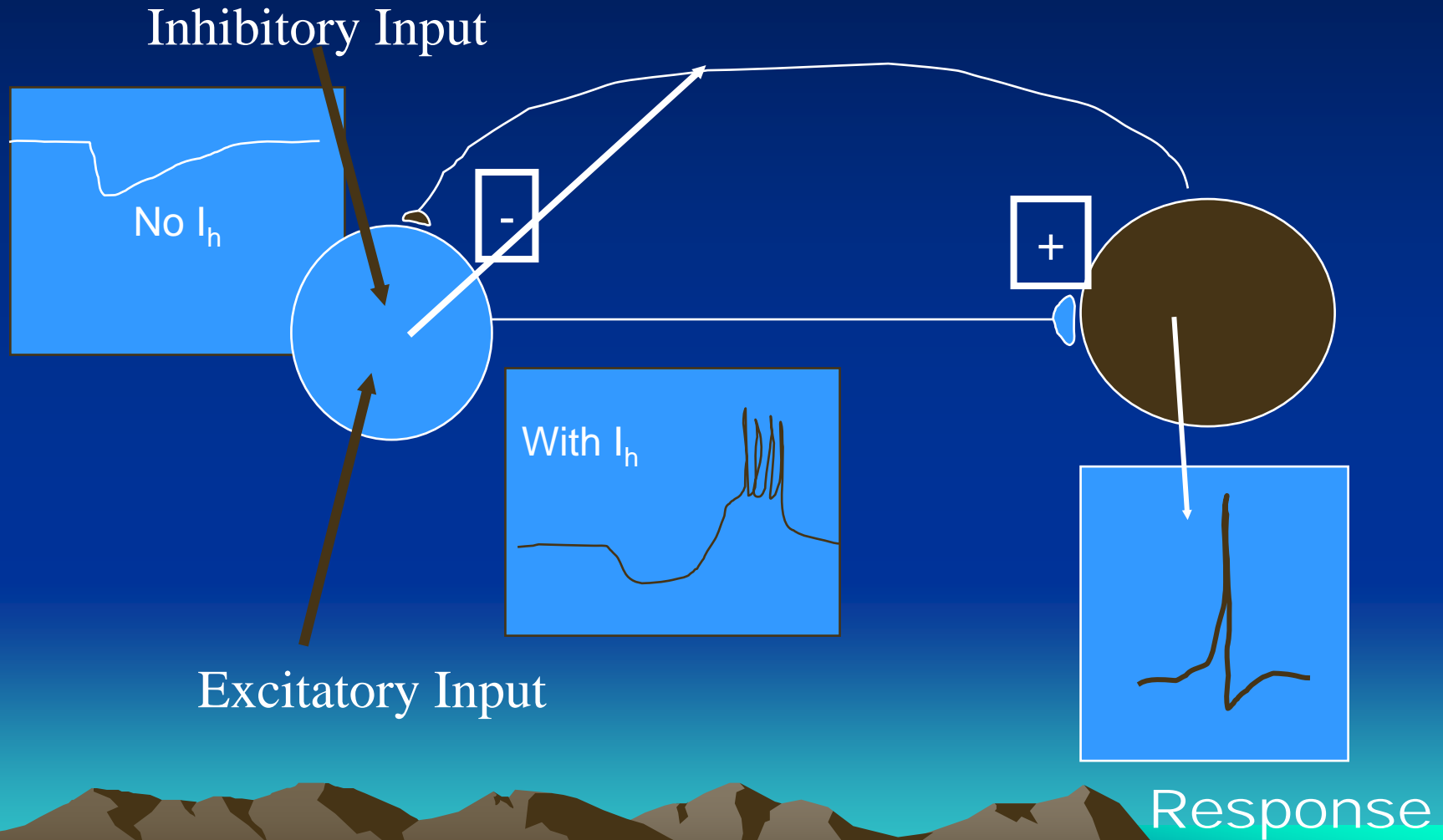
Differential distribution of mHCN1, mHCN2, and mHCN4 in the mouse cerebral and hippocampal cortex. *A*, Coronal section (bregma, +0.74) showing mHCN1 labeling in the motor cortex. *B*, Coronal section (bregma, 2.06) showing mHCN1 labeling in the hippocampus. *C*, mHCN2 labeling in the motor cortex. *D*, mHCN2 labeling in the hippocampus, lateral habenula, and dorsal lateral geniculate nucleus. *E*, mHCN4 labeling is absent in the motor cortex. *F*, mHCN4 labeling in the hippocampus, medial and lateral habenula, and dorsal lateral geniculate nucleus. *ec*, External capsule; *mh*, medial habenula; *lh*, lateral habenula; *dlg*, dorsal lateral geniculate nucleus; *DG*, dentate gyrus; *CA₁*, *CA₃*, cornu ammonis fields *CA₁* and *CA₃*. Scale bars, 500 μm .

Differing HCN activate at different rates



Distinct functional properties of I_h currents generated by mHCN1 and mHCN2. *A*, Currents generated in response to hyperpolarizing voltage steps in *Xenopus* oocytes expressing mHCN1 (*A1*) or mHCN2 (*A2*), respectively. *A1*, mHCN1 currents shown during 3-sec-long hyperpolarizing voltage steps. *A2a,b*, mHCN2 currents shown during initial 3 sec (*A2a*) and entire 30 sec time course (*A2b*) in response to hyperpolarizing voltage steps. For both *A1* and *A2*, membrane held at 30 mV and stepped from 35 to 105 mV in 10 mV increments (selected voltages indicated to right of current traces). *B*, Two exponential components are required to adequately fit activation time course of mHCN currents. Time and current scales as in corresponding panels in *A*. For *B1* and *B2*, bottom traces show current during hyperpolarizing step to 105 mV with superimposed fit using two exponential components. The middle and top traces show the residuals of difference between the recorded current and the fitted single (top trace) or double (middle trace) exponential functions. Zero current is indicated by the arrowhead (labeled 0). The residuals from the single exponential fits are displaced from zero for clarity; zero current for these traces is indicated by the dashed line. To facilitate comparison between mHCN1 and mHCN2, the first 3 sec of the mHCN2 activation time course and fits to this are shown on an expanded time scale in *B2a*.

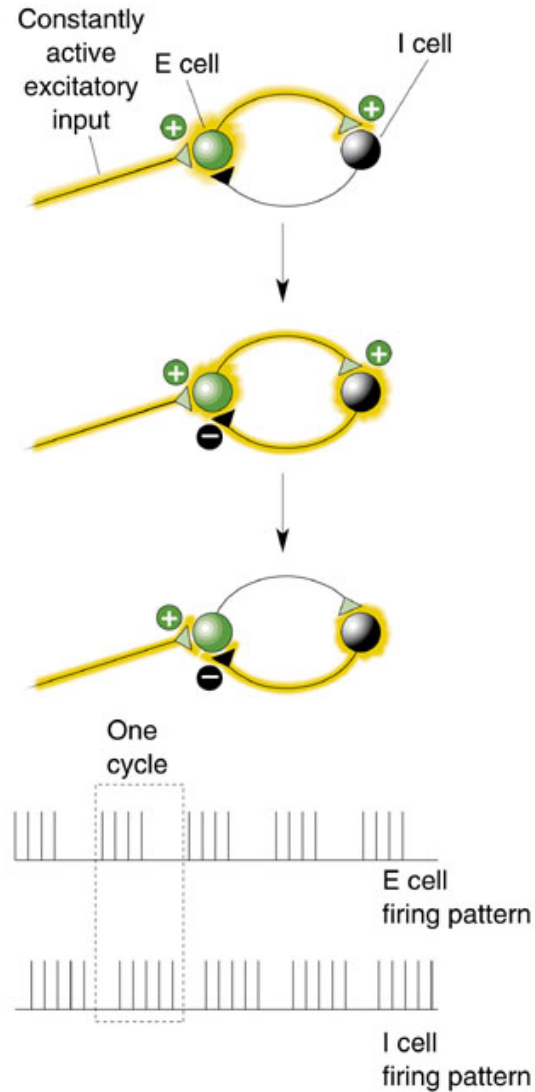
HCN drive network Oscillations



Synaptic connections create oscillatory behaviour

Figure 19.7

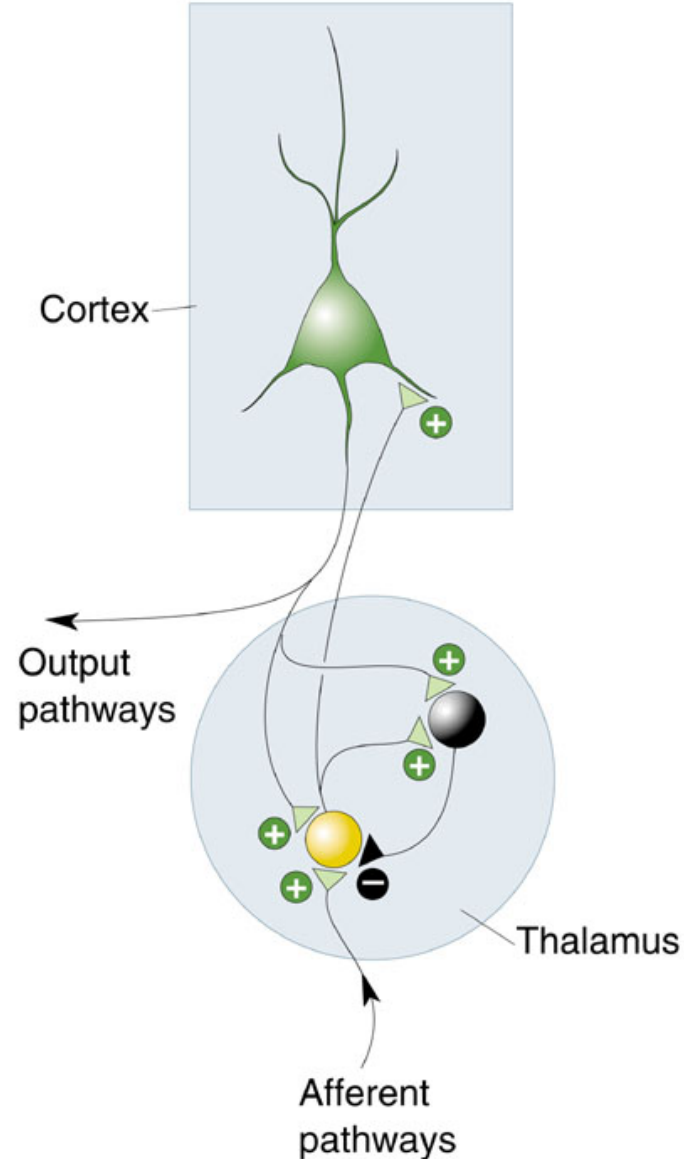
A two-neuron oscillator. One excitatory cell (E cell) and one inhibitory cell (I cell) synapse upon each other. As long as there is a constant excitatory drive, which does not have to be rhythmic, onto the E cell, activity tends to trade back and forth between the two neurons. One activity cycle through the network generates the pattern of firing shown in the box.



Brain
connectivity
provides a
way of
promoting
oscillatory
behaviour

Figure 19.9

Rhythms in the thalamus drive rhythms in the cerebral cortex. The thalamus can generate rhythmic activity because of the intrinsic properties of its neurons and because of its synaptic interconnections. Yellow indicates a population of excitatory neurons, and black indicates a population of inhibitory neurons.



Summary of I_h activity

- slow activation and inactivation
- provides prolonged rebound excitation that drives neural circuit synchrony
- modifiable by drug therapy, although it has not been done
- may be implicated in epilepsy, increased expression of HCN 1 in seizure circuits, block may be viable antiseizure compound



GABA_A Receptors in the CNS

major inhibitory neurotransmitter (usually)

chloride ion channels mediating fast synaptic inhibition



Clinical Uses

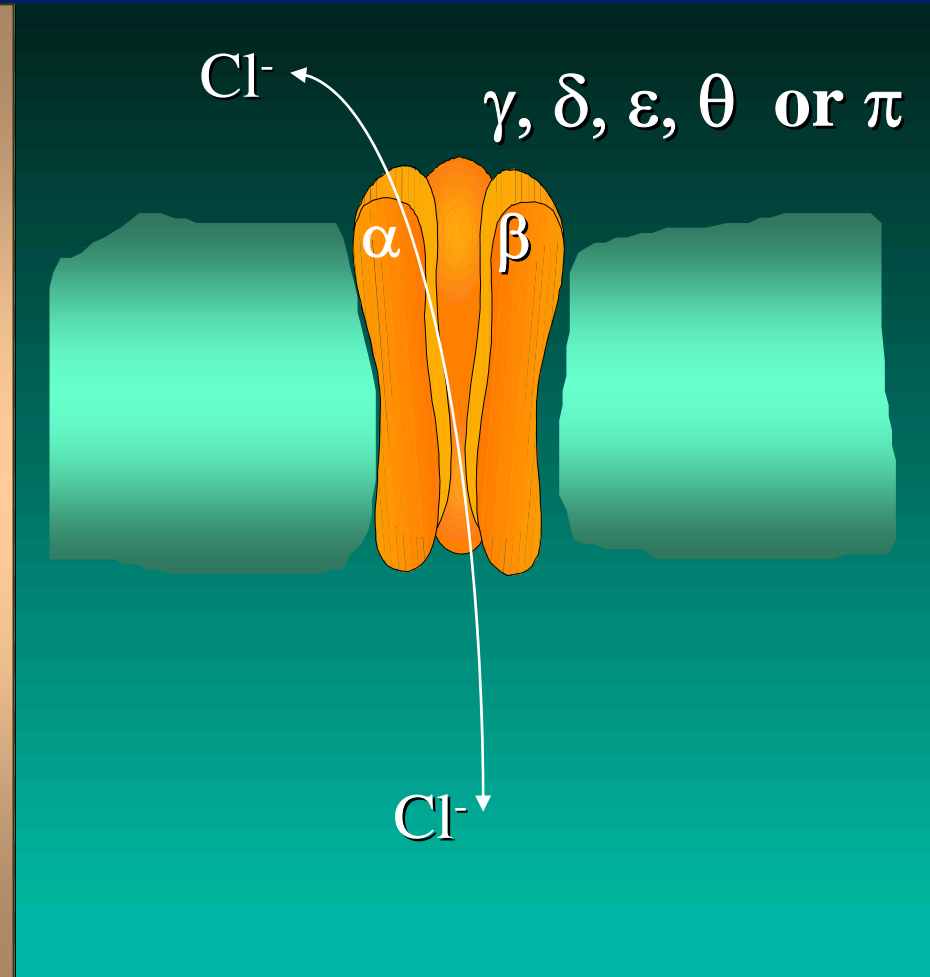
- 20% of the “neuro” drug market are GABAergics
- this includes:
 - anxiolytics e.g.. zolipidem
 - anesthesia induction and maintenance e.g.. propofol, halothane
 - sleep disorders e.g.. pentobarbital
 - acute treatment of seizures e.g. diazepam
 - seizure prevention e.g. colbazam. Vigabitrim

Are they modifiers of rythmicity ?



GABA_A Receptor Structure

- Pentameric multi subunit complex (2 α : 2 β : & γ , δ , ϵ , π or θ)
- Each subunit has 4 transmembrane spanning regions
- Predominant subunit combination $\alpha\beta\gamma$
- More regionalised expression of $\alpha\beta\delta$ & $\alpha\beta\epsilon$



GABA_A Receptor Structure/Function

Seven families of subunits

6 α : GABA and BDZ affinity, kinetics

4 β : GABA binding site

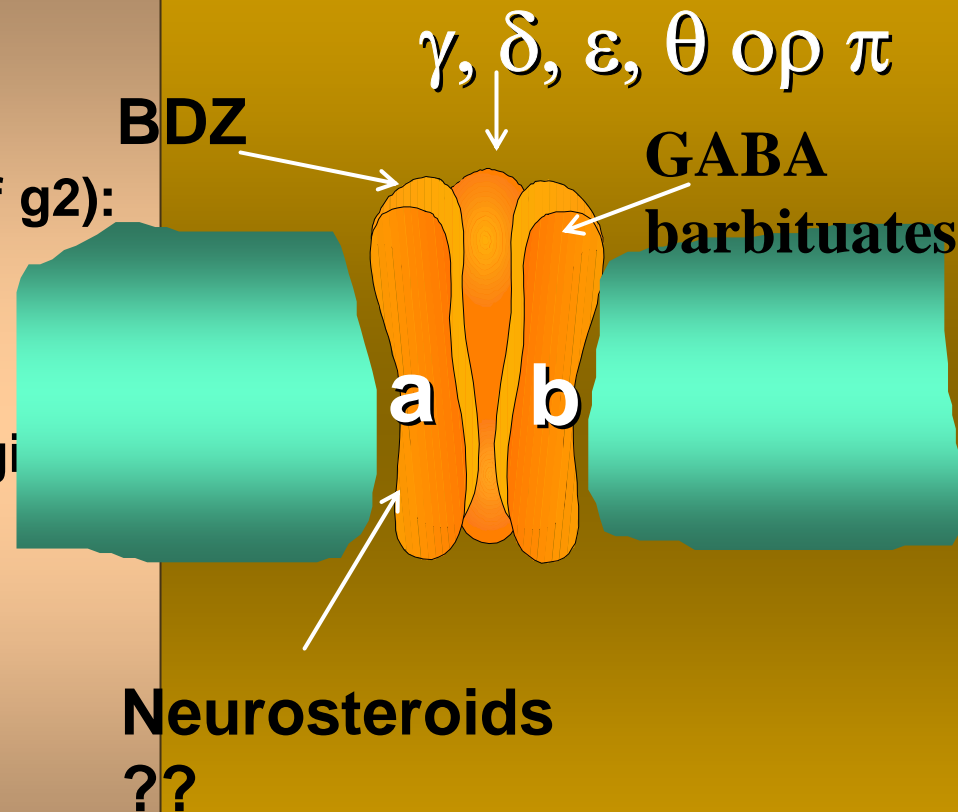
4 γ (includes splice variant of $\gamma 2$): kinetics, conductance, BDZ modulation

δ : modulatory as well

ϵ : abolishes all pharmacological properties (??)

π : human only, unknown function

θ : reduces affinity for GABA



Distribution of the major GABA_A receptor subunits in the rat brain

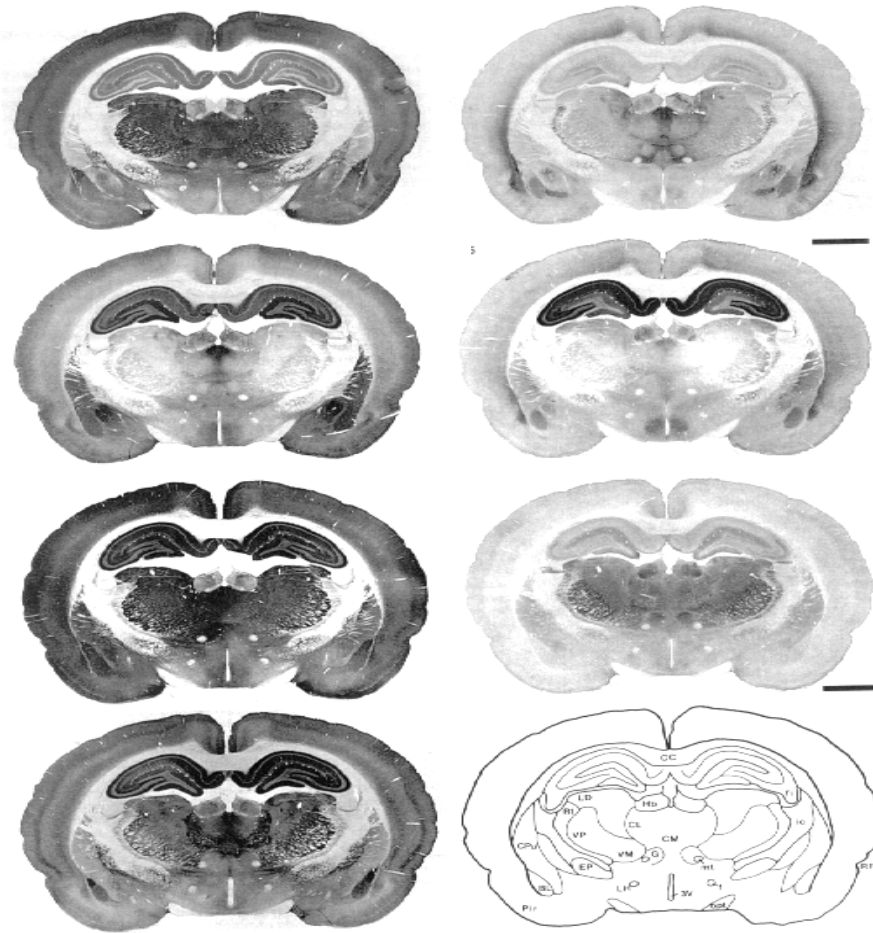
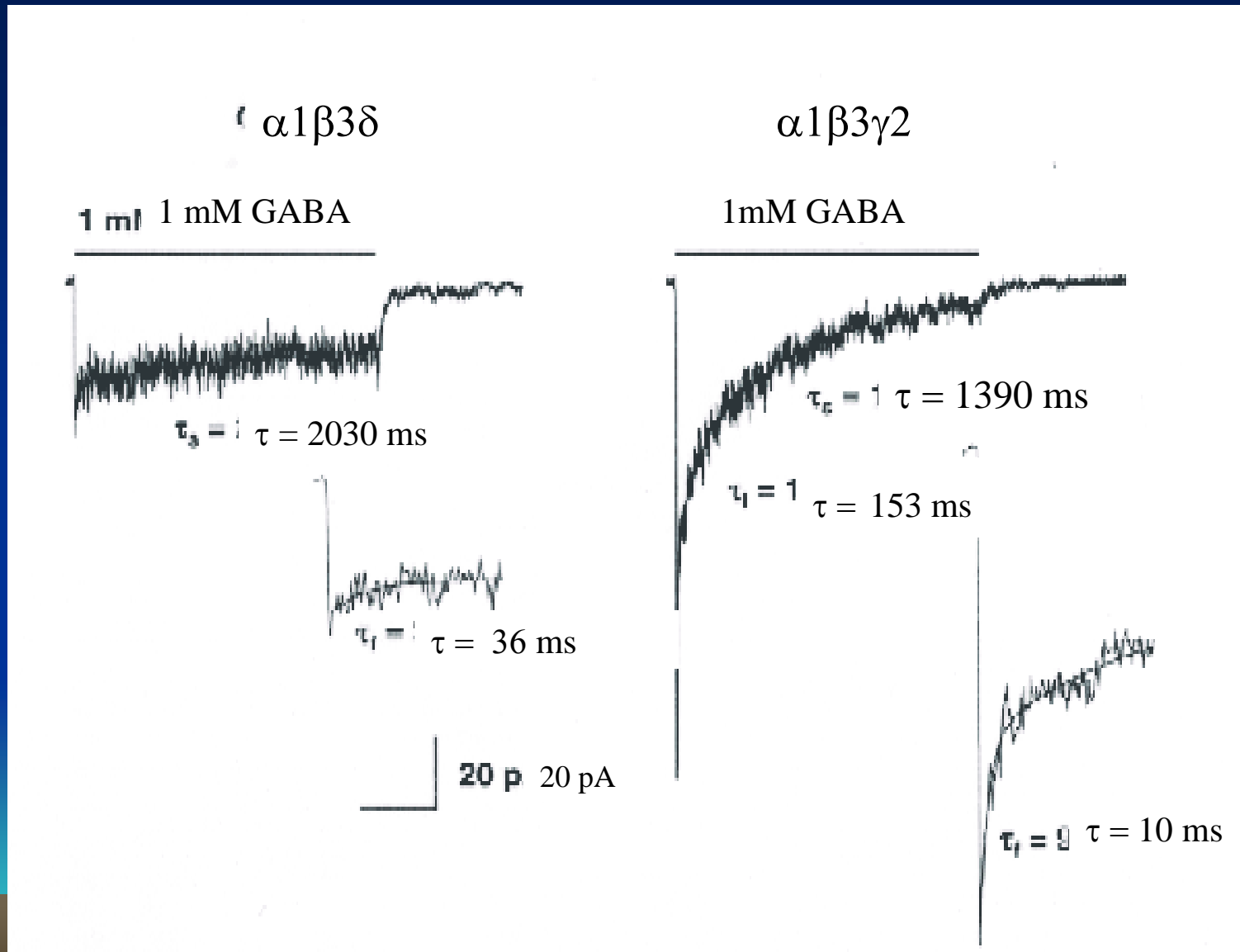
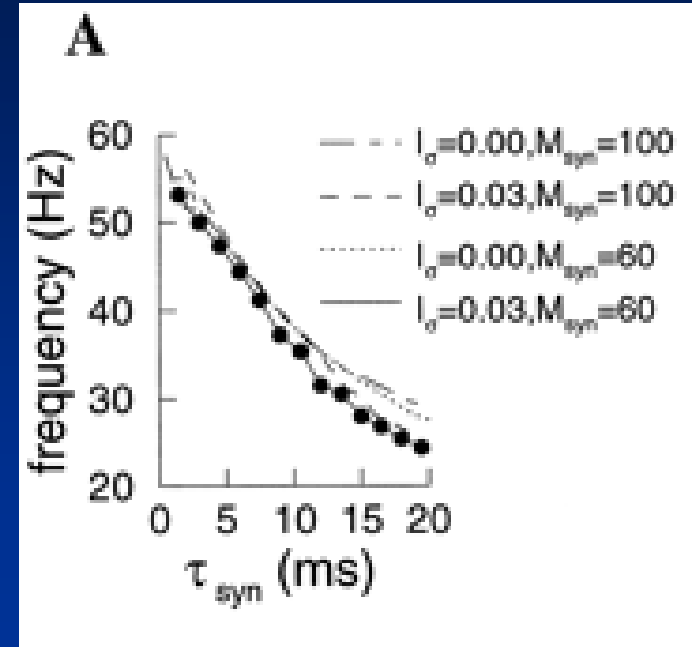
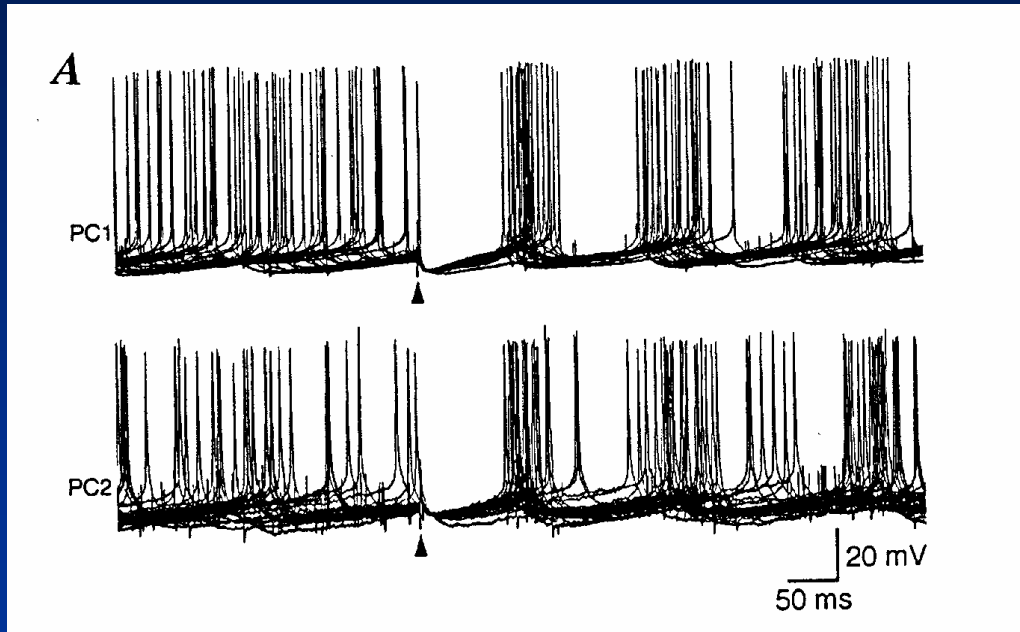


Figure 5

Altering structure alters timing behaviour



GABA_A receptor mediated neural network synchronisation and oscillations



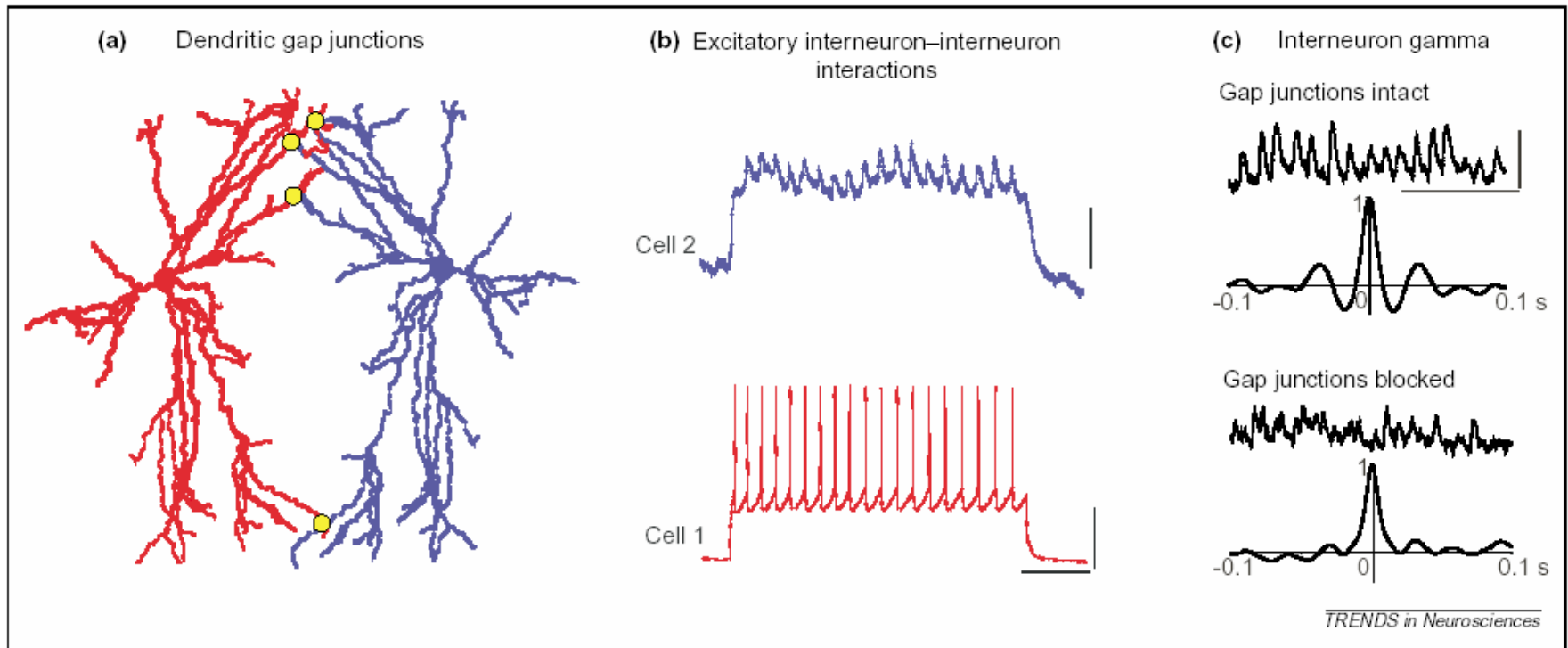


Figure 5. Gap junctions between interneurons stabilize interneuron network gamma oscillations. **(a)** The putative organization of dendro-dendritic gap junctions between fast-spiking interneurons. The dendritic field of a basket cell is used to show representative gap junctions between distal dendritic compartments (yellow circles). **(b)** Electrical coupling between interneurons using dendritic gap junctions allows excitatory interneuron interactions, whereby tonic depolarization is shared between cells and a low-pass-filtered correlate of action potentials in an active interneuron can be seen in the coupled interneuron. Reproduced, with permission, from Ref. [28]. Such a pattern of propagation of membrane potential changes in one interneuron to coupled neighbours can solve the heterogeneity problem of rhythm generation in isolated interneuron networks. Unless drive to each interneuron in a network is nearly identical to the drive presented to other interneurons in the network, only a ragged population rhythm can be observed. Gap-junction coupling provides a mechanism by which changes in membrane potential can be passed throughout the interneuron network, thus 'smoothing' the postsynaptic effects of any input heterogeneity. Scale bars: 2 mV, 40 mV and 100 ms. **(c)** Using pyramidal cell recordings to sample the output from interneurons [as inhibitory postsynaptic current (IPSC) trains with holding potential -30 mV] during interneuron-network gamma rhythms reveals a strong dependence on patent gap-junction coupling. The upper trace shows a gamma-frequency IPSC train in response to glutamate pressure ejection with fast excitatory synaptic transmission blocked. The lower trace shows the response in the same cell with gap-junction conductance reduced by 0.2 mM carbenoxolone. Graphs show autocorrelations to illustrate changes in rhythmicity and local temporal coherence. Scale bars, 0.3 nA and 200 ms. Using data from Ref. [43].