Background I – Neurodynamics: The Neuron and its electrical language .

Aims and Objectives

To understand information transfer and information processing in the brain.

Intended learning outcomes

By the end of the lecture you should know the basics of:
- membrane potentials
- how the membrane potential is generated
- what ion channels are
- different types of ion channels
- an action potential
- dendrites
- axon hillocks
- axons and axon terminals
- synapses
- spike trains
- Peri-Stimulus Time Histograms

Today's reading reference:

Kandel, E.R., Schwartz, J.H., Jessell, T.M. (2000) Principles of Neural Science, 4th Edition,

McGraw-Hill, Chapter 6-14

One of the crucial questions in Neuroscience was (and still is) how information is processed in the central nervous system. In today's lecture we will try to understand the basics of this information processing and transfer in the brain. The information processing units in the central nervous system are ***Neurons,*** which are highly specialised cell types**.** Neurons communicate by means of electrical and chemical signals. Like all other cells, neurons are built from molecules and macromolecules; these form biological structures (e.g. membranes);

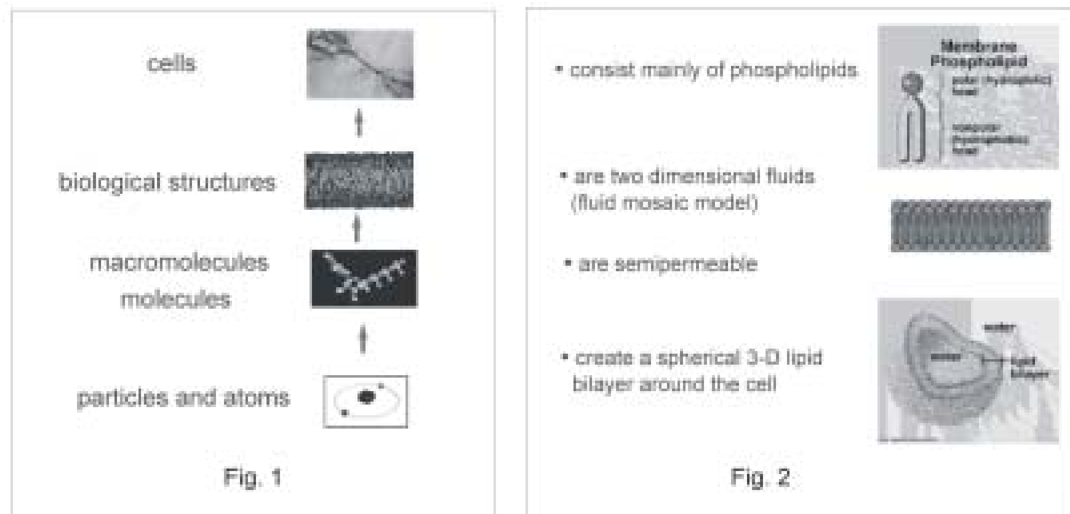

Fig. 1 Fig. 2

and the enormously complex sum of all these constitutes the cell (fig. 1).

An important structure of all cells is their membrane. Membranes are borders between the cell in- and outside (or between cell organelles and the rest of the cell). They can be highly specialized and have a variety of functions. Biological membranes, in conjunction with membrane-associated proteins, have certain electrical properties that enable them to translate chemical into electrical signals (and vice versa).

Membranes are built mainly from phospholipds. Phospholipids are polar molecules, i.e. one end of the molecule is attracted by water (due to electrical charge asymmetries) while the other end is not. Due to their polar structure phospholipds will spontaneously form a ***lipid bilayer***, when brought into an aqueous environment (see fig. 2, graph 2). In water the non-polar 'fork like' ends will face each other, while the polar heads will face the aqueous environment. Individual phospholipids (and embedded proteins) can move horizontally in the lipid bilayer (the membrane), therefore it is also called the ***fluid mosaic model***. The bilayer has one particular important characteristic: it allows certain substances to cross, while holding others back -- it is ***semi-permeable***. This semi-permeability allows cells to build up a gradient (i.e. an unequal distribution of substances between the cell's in- and outside). Of importance in today's lecture is the ability to separate ions across the membrane.

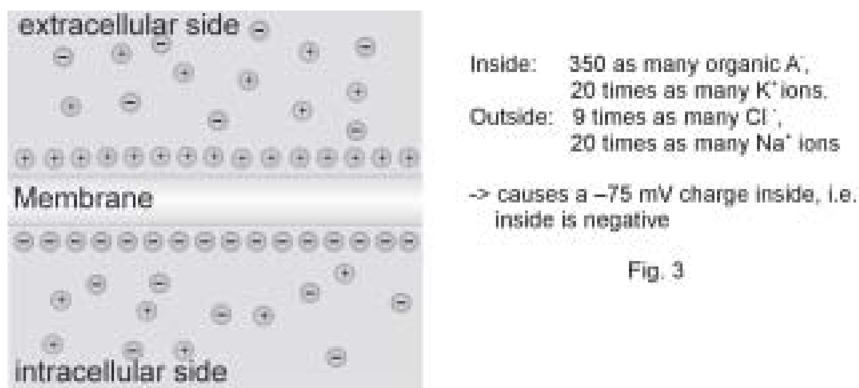

Fig. 3

Figure 3 shows the distribution of some important ions across the cell membrane of a neuron. Organic Anions (negatively charged proteins!) are highly concentrated on the inside. They are mainly responsible for the negative ***resting potential*** of neurons. Other ions, such as K^+, Na^+, and Cl^- are also asymmetrically distributed across the membrane (see details in figure 3). Due to the asymmetrical distribution of ions the cell is electrically and chemically charged. This electrical charge is highly useful, it can be exploited to integrate and generate electrical signals.

Electrical cell signals: Electrical signals are generated by means of ***ion channels***. Ion channels are membrane-spanning proteins. They consist of a few (similar or identical) *subunits*. These are arranged in a circular manner, thereby forming the *central pore* (see fig.4). Ion channel are generally selective for just one or two different ions. This can be exemplified by looking at the Na^+- channel. The Na^+- channel will allow Na^+- ions to pass through the pore, however, it is impermeable to K^+ - ions (fig. 5, right channel). Many different ion channels have been identified so far.Most ion channel exist in a variety of different models. Some form simple tunnels across the membrane and are open all the time

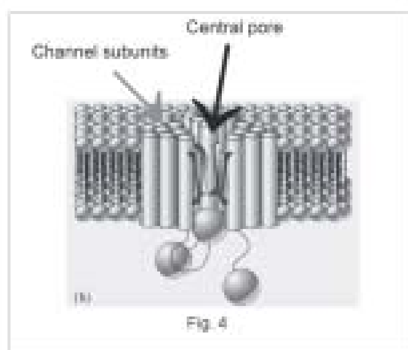

Fig. 4

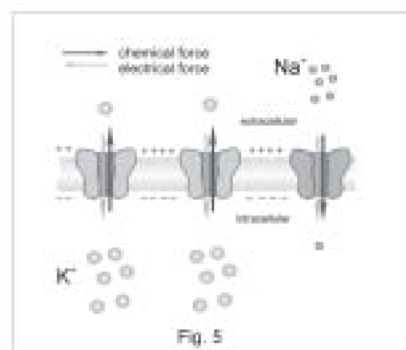

Fig. 5

(the ion which they are selective for can pass through the pore at all times). These channel types are called ***resting channel***, they are leaky (fig. 5). These leaks bring about a particular problem. If ions can freely cross the membrane, how is the unequal distribution of ions and the resting potential maintained? This is achieved by specialized proteins, which allow them to selectively pump certain substances across the membrane. The ***Na/K-ATPase*** is such a specialized pump. During every cycle it transports 3 Na^+ out of the cell, and takes 2 K^+ ions into the cell. The energy is obtained by hydrolysis of an ATP molecule into and ADP + P. The action of this protein allows to counteract any Na^+ and K^+ flow across the membrane. Before we proceed, two definitions have to be made: (1) Whenever a cell's membrane potential becomes more positive (by Na^+, or Ca^{++} influx) the cell ***depolarises***; depolarisation is also called ***excitation***. (2) Whenever the cell becomes more negatively charged (by outflow of K^+ ions or inflow of Cl^- ions) it is called ***hyperpolarisation*** or ***inhibition***. The change of electrical charge due to ion flow across the membrane can be used to integrate and transfer information. In addition to resting channels (which are open all the time) more specialised channels exist. These specialised channels allow a *controlled and rapid flow* of selected ions across the membrane. The most common mechanisms to allow such controlled and rapid flow of ions across the membrane are:

1. Mechanically activated channels
2. Receptor/ligand activated channels
3. Voltage gated channels

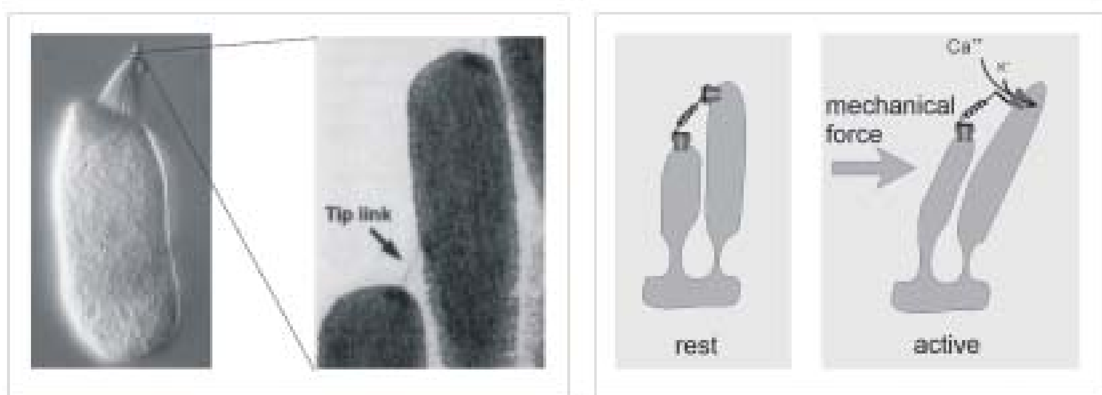

Fig. 6

Mechanically activated channels open their pores if mechanical force is applied to the cell membrane. A fascinating example of a mechanically selective channel system is realized

in our inner ear. When sound waves impound onto our ear drum, these waves are transferred into the inner ear, where they cause a deflection of a structure called *basilar membrane*. This deflection causes the extensions of so called *hair cells* to be sheared (the name *hair cells* is due to the little hair like extensions at the top of the cell, see fig. 6 left). The individual tips of the hair cells are connected by tiny, but microscopically visible, protein chains. The shear stretches the protein chains. The chains are anchored to an ion channel cover. If the force is sufficiently strong, the cover is lifted and ions can flow into the hair cell, thereby depolarising the cell (see fig. 6). The depolarisation then causes a transmitter release at the bottom of the hair cell, which informs neurons in the inner ear that some sound was detected.

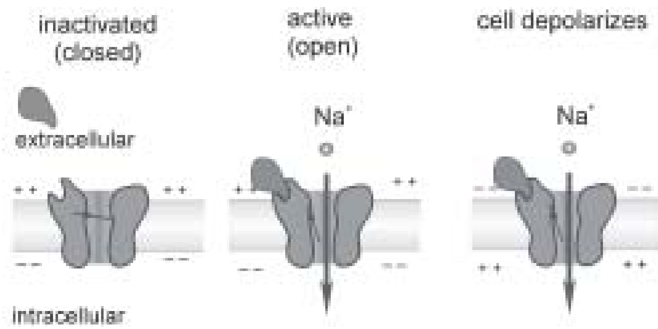

Fig. 7

Receptor/ligand activated channels: A variety of channels are activated when a particular substance ‘binds’ to a receptor. This binding can be viewed as a *key/lock principle*. Activation only occurs when the proper key is inserted into the lock. This insertion causes the receptor protein to change its shape (its ***conformation***). When the receptor is part of the channel protein this conformation change opens the central pore, thereby allowing ions to flow across the membrane (*ionotropic receptor*, see fig. 7).

Sometimes the receptor and the channel protein are separate structures. Ligand binding at the receptor site then triggers a biochemical cascade inside the cell, which eventually will cause the conformation change of the channel protein (*metabotropic receptors*). One important principle is worth mentioning: It is not the key that determines the effect at the cell. A certain key (a protein, a peptide, or even a gas [e.g. Nitrous oxide]) can have different effects at different receptors. Thus, it is the receptor/channel specificity that determines the effect on the cell, not the signalling substance. Signalling substances are called ***transmitter***.

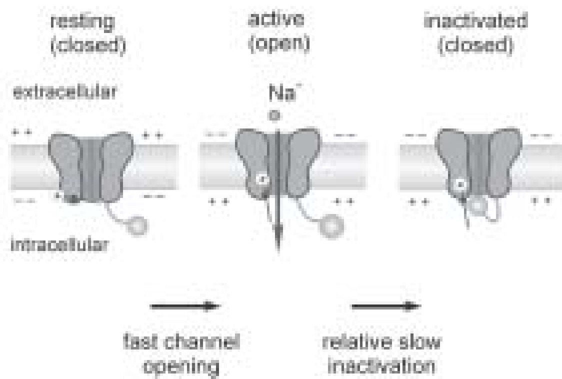

Fig. 8

Voltage gated channel change their conformation when the cell depolarises (see fig. 8). Consider the following scenario: a ligand (the key) binds to a receptor-activated channel and Na^+ ions flow into the cells. This causes the cell to depolarise. Provided the depolarisation is sufficiently strong voltage gated channel will change their conformation, allowing even more Na^+ to flow into the cell, which causes further depolarisation. Thus a chain reaction is triggered, and the electrical charge across the membrane will quickly reverse (within 1 ms). Usually voltage gated channel selective for Na^+ quickly inactivate -- the sudden strong depolarisation causes yet another very quick conformation change (protein balls get sucked up into the pore) and Na^+ ions can no more traverse it. Moreover, quick depolarisation causes K^+ channels to open their gates, however, with a little delay compared to the Na^+ channel. Thus, K^+ channel open shortly after Na^+ channel, and K^+ flows out of the cell (along its electro-chemical gradient). Due to this outflow the neuron quickly re-polarizes -- the cell again becomes negatively charged (positive ions have now flown out!). Thus, within 1 or 2 ms, the initial membrane potential is re-established. This chain of events is triggered when an initial depolarisation is reached (~ –40 mV), and once initiated it cannot be stopped. The whole chain of

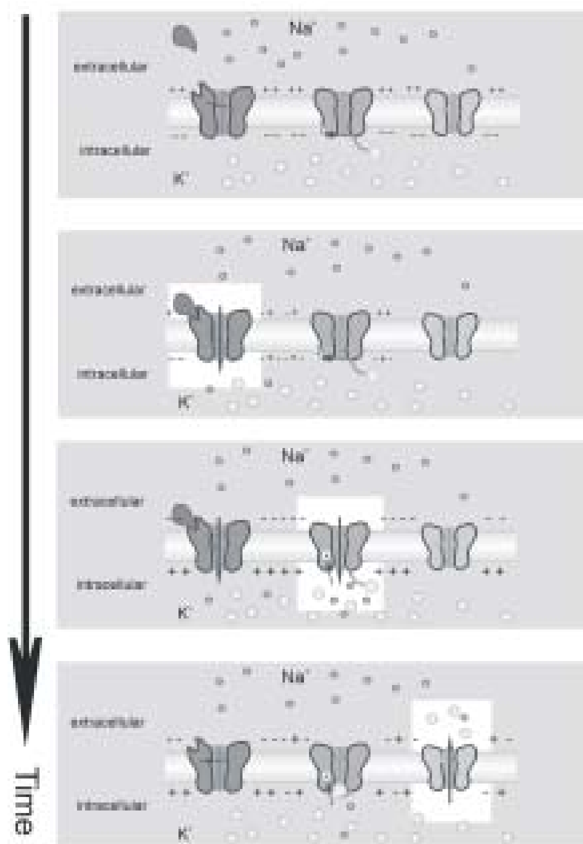

Fig. 9

events (from the moment voltage gated Na^+ channels open) is called the ***action potential***. The sequence of events is illustrated in figure 9. Figure 10 shows the associated change of the membrane potential over time. The fast inactivation of the Na^+ channel has two important consequences: (1) a fast re-polarisation of the cell is possible, and (2) the action potential spreads over the membrane along just one direction. Otherwise the cell's membrane potential would quickly start to oscillate at high frequency. Thus, this mechanism ensures that the flow of information is from the 'input' structures, through the 'integration' structures, and then along the 'output' structures to the next cells.

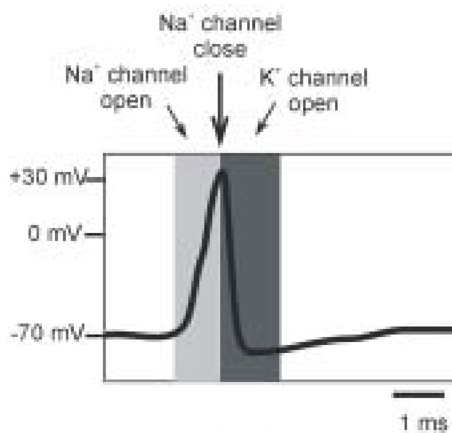

Fig 10

The neuron's visible anatomy: neurons receive most information along their ***dendrites*** (however substantial input can occur at other locations). This information then flows (mostly passively, i.e. usually not by means of an action potential) to the ***soma*** where it is 'integrated' at the ***axon hillock.*** It is here that the depolarisation has to reach ~ -40 mV for an action potential to be elicited. Once elicited, the action potential travels down the ***axon.*** The different anatomical components of a neuron are shown in figure 11.

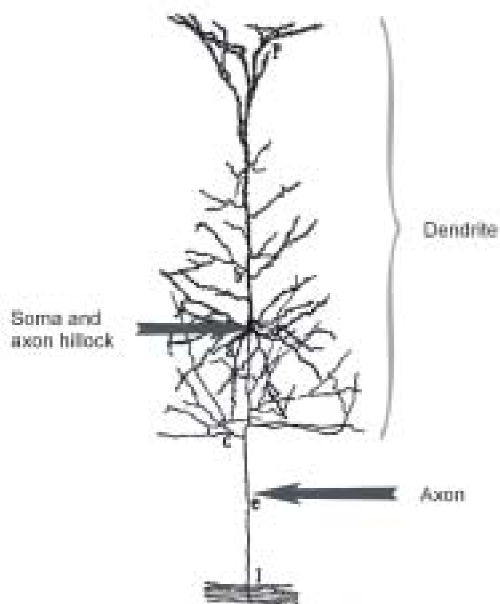

Fig. 11 (after Cajal)

How is this information passed on to the next cell? When the action potential reaches the axon endings, *the electrical signal is transformed into a chemical signal* at special axon sites -- the ***presynaptic terminals.*** The presynaptic terminals contain transmitter filled vesicles. The transmitter from these vesicles is released into the ***synaptic cleft*** when the action potential arrives at the presynaptic terminal. The action potential at the nerve terminal (the presynaptic site) causes Ca^{++} channel to open, whereupon Ca^{++} enters the presynaptic terminal. This entry causes

vesicle fusion with the membrane, thereby releasing the transmitter into the synaptic cleft. The transmitter then diffuses across the cleft and binds to receptors at the ***postsynaptic site*** (usually located on the dendrite of another neuron). The presynaptic terminals, the synaptic cleft and the postsynaptic site together form the ***synapse.*** When the transmitter binds to the receptor the next cycle starts as illustrated in fig 9 (but note that the cycle now happens in another cell). The various steps of synaptic transmission are illustrated in figure 12.

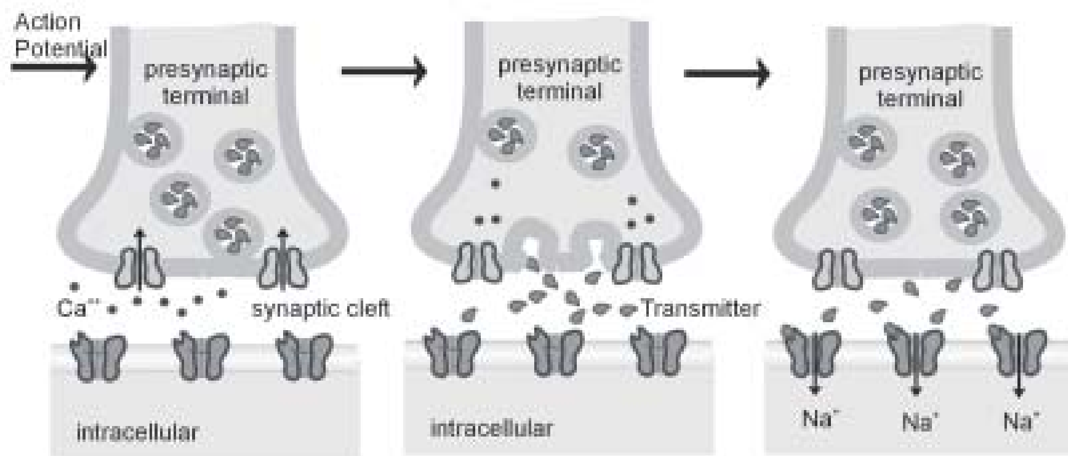

Fig. 12

Measuring, displaying, and quantifying neuronal activity: neuronal activity can be measured by means of microelectrodes either intracellularly or extracellularly. The rapid changes of the membrane potential can be displayed on an oscilloscope or a computer monitor screen. The display will look like the black trace in fig. 10 (see also fig 13.). If a lot of transmitter is released repeatedly onto the presynaptic terminals the postsynaptic neurons will modulate the number of action potentials (they modulate their 'firing rate'). When an appropriate stimulus is applied the neuron usually increases its firing rate. This is demonstrated in figure 13 (see label 'spike train'). To quantify a neurons response a particular stimulus is repeated many times. This will yield a slightly different spike train each time (noisy response!). The individual spike trains can then be plotted above another (fig. 13, raster plot). A method to quantify the firing rate as a function of time and stimulus is to calculate the Peri-Stimulus-Time-Histogram (PSTH). In a PSTH the response period is subdivided into various time bins

(e.g. each 50 ms long) and then the average number of spikes per trial is calculated for each bin (see figure 13, PSTH). It shows the average firing rate per time unit for this cell and a particular stimulation condition.

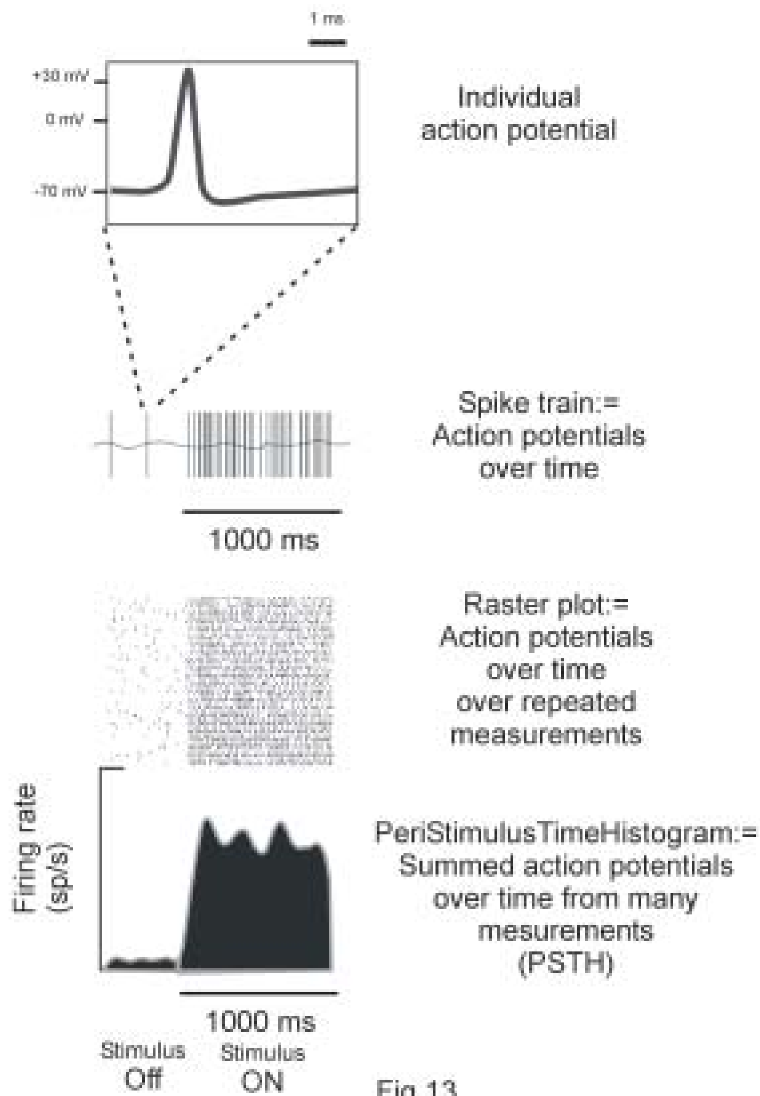

Fig 13

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3 multiple choice question can be found at:

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Session name: Psy 205: Cognition and Emotion Lecture 2

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