MEMORY
Part 1: Neurochemistry and Spatial Organisation

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Substantial research has been done and is still being done on the biochemical aspects of memory (microphysiology). Furthermore many experiments on sub-human mammals have localized centres in the brain responsible for specific aspects of memory (macro-physiology). Research into computational networks provides models on how neurons associate together to produce the advanced functions of thinking and memory. The aim of this paper is to put together the material relevant to the field of memory gathered from physiology and biochemistry and use computational networks as a model to propose a hypothesis on the functioning of memory.

Early experiments on rats and assessment of lesions in the human brain showed that memory can be divided into short term memory (STM) and long term memory (LTM). It has been shown that structures relating to the limbic system (hippocampus, amygdala etc) are all important but there is no organ which can be classified as the organ of memory. It is generally agreed that memory functionally involves the cooperation of many structures together. This is brought about by plasticity at the level of synapses which permits the establishment of circuits between relevant areas, to memorise percepts.

The hippocampus is necessary to transfer STM to LTM, but both types of memory can still exist without this part of the brain. The amygdala are important in emotional experiences. Thus a monkey whose amygdala have been excised no longer fears human beings. Moreover it is also involved in the establishment of memory. Due to their connections with the hypothalamus, they are probably the organs which permit the establishment of individual experiences in the course of one's life.

Neurochemistry

Early experiments showed that memory can be resolved to a molecular level and that it involves protein. Such proteins have been 'transplanted' and the experience carried from one animal to other. Drugs too can have an effect on memory. These show a state-dependency, in that, if a memory is learnt under the action of a drug, it will only be recalled optimally under the influence of the same drug. The early belief that the 'memory molecule' is Ribonucleic acid is now, not in vogue, its only role being relegated to protein synthesis. Blocking RNA will block protein synthesis, and hence the establishment of memory.

Long term potentiation (LTP), is a long lasting increase in the effectiveness of synaptic transmission. This is triggered by high frequency stimulation of certain presynaptic axons. LTP is produced by a few brief, high frequency bursts of presynaptic action potentials. Larger excitatory postsynaptic potentials (EPSP), enhance the ability of the synapse to trigger action potentials in the postsynaptic neuron; this could be a memory forming mechanism. Note that LTP means a long lasting increase in the EPSP. This has been shown to occur in the hippocampus.

Kauer et al have shown LTP to be divided into two processes: slowly decaying potentiation (SDP) which is short term, and disappears after thirty seconds, and a true LTP which lasts for hours or days. They induced slowly decaying potentiation by applying glutamate, an excitatory neurotransmitter, over the surface of the snyapse. However, the establishment of a true LTP also required electrical excitation of the presynaptic terminals. This demonstrated the need for a second unknown neurotransmitter. Malinow et al have shown that one or more protein kinases are involved in maintaining a true LTP, but these seem not to be involved in the less persistent SDP.

LTP has traditionally been divided into a phase of induction, that includes several seconds during and after tetanic stimulation when the event is initialised and a second phase, maintenance, in which the presynaptic terminal achieves plasticity: (i.e. release of more neurotransmitter during excitation). Induction involves an interplay between pre- and postsynaptic membranes. Hyperpolarization of the postsynaptic membrane during tetanic stimulation of a presynaptic membrane blocks induction of LTP. Thus even though maintenance depends on the presynaptic membrane, induction also occurs postsynaptically.

Induction requires glutamate receptor activation; two types of these are found in the brain: quisqualate/kainate (Q/K) and N-methyl D-

aspartate (NMDA). Blockade of Q/K eliminates the postsynaptic potential normally produced by a single stimulation.

Blockade of NMDA does not affect the postsynaptic potential but blocks induction of LTP during tetanic stimulation.

Strong membranes depolarization and the presence of glutamate are both required to activate NMDA receptors, hence tetanic stimulation is necessary for induction of LTP in a pathway. This could provide a mechanism for associative learning.

The ion channel linked to Q/K is highly selective for Na^+ and Ka^+ ions, while that linked to NMDA also admits Ca^{++}. Activation of NMDA can thus produce a rise of intraneuronal Ca^{++} which is known to be a second messenger that can activate different effector molecules. Three mechanisms of LTP provoking Calcium-activated enzymes have been proposed, all having their limitations.

1. C-kinase hypothesis.

Ca^{++} ions and/or diaclyglycerol activate a C-kinase. C-kinase can also be activated by phorbol esters which act as diacylglycerol analogues. The application of phorbol ester to a slice of hippocampus produces an increased potentiation of synaptic transmission, with many LTP characteristics. This was the first indicator that C-kinase is involved. Membranes of neurones prepared an hour after induction contained twice as much C-kinase as the unpotentiated tissue. C-kinase binds to membranes on activation. The hypothesis is that tetanic stimulation activates C-kinase which phosphorylates proteins, producing LTP (e.g. GAP-43, a protein which is a prominent substrate to C-kinase). However how such a substrate brings about LTP is missing from the hypothesis.

2. CaM kinase hypothesis:

Activation of type II Ca^{++}/calmodulin-dependent protein kinase (CaM kinase), occurs when an increase in calcium, concentration causes the calmodulin Ca^{++} complex to bind to a regulatory domain within the kinase. In the forebrain and hippocampus CaM kinase seems to be a major postsynaptic component (and is found in high concentrations in tissue sections). It is presumably exposed to NMDA receptor-mediated calcium flux. On in vitro activation the kinase phosphorylates appropriate substrate proteins. It also autophosphorylates a threonine residue, this inhibits refolding and allows CaM kinase to remain activated long after the calcium concentration has fallen. This hypothesis has the same weaknesses as above.

3. Calpain hypothesis

Calpain is a calcium activated protease in synaptic membranes. It cleaves cytoskeletal proteins fodrin and MAP2. In vitro it proteolyses several protein kinases, including C-kinase and CaM-kinase, freeing the catalytic domains and producing active kinase molecules that could persist in vivo until destroyed by other proteases. Greenberg et al suggest that enhanced gene expressions for the calpains could increase the level of constitutive kinases in neurons, producing long lasting changes. Malinow et al show that increased concentrations of protein kinases are needed for LTP. When the regulatory domains of the C-kinase and CaM-kinase are blocked by Sphingosine and H7 (a synthetic organic inhibitor) induction of LTP is blocked. (Except in hippocampal synapses).

No one of these hypotheses explains the feedback mentioned above from postsynaptic to presynaptic terminals. Dumuis et al demonstrated that binding of NMDA to its receptors releases arachidonate into the extracellular space. This could be the transynaptic messenger, this is able to travel back.

Dumuis et al experimented on the striatum of 14 to 15 day old mouse embryos. They proposed that glutamate and NMDA, acting at typical NMDA receptors, stimulate the release of arachidonic acid probably by stimulation of a Ca^{++}- dependent phospholipase A2. The results show that glutamate and NMDA responses are mediated by NMDA receptors. It is likely that influx of Ca^{++} through the NMDA receptors triggers the arachidonic acid cascade system. This is also dependent on the activation of a phospholipase A2 (PLA2) on the post-synaptic membrane. When this was blocked by a potent inhibitor (mepacrine) the effects of glutamate were completely abolished. The involvement of a G protein in the coupling between NMDA receptors and PLA2, similar to that described in thyroid cells between alpha-adrenergic receptors and PLA2 is unlikely but cannot be totally excluded, because in the latter system the coupling is also dependent on external Ca^{++}.

It is postulated that arachidonic acid and/or its metabolites (AAM) are released from the postsynaptic cell and act on the presynaptic terminal to trigger an increase in glutamate release or inhibition of glutamate re-uptake.

Combinatorial Systems

There are two known patterns of neuronal communication. These are the topographical and the combinatorial modes of connection. In the topographical arrangement, an input into one neuron makes contact with a second neuron in another region via limited contacts, in approximately a one to one arrangement. This is shown in A in figure 1. Additional input to this arrangement needs only the insertion of a new target neuron without affecting the previous neurons, as shown in B. In a combinatorial arrangement, the neurons are interconnected such that, the input of one neuron affects all the neurons at the target end. A new input to this network will disrupt the combinatorial character of the previous arrangement (D). Thus expansion of topographical networks, only requires addition of neurons whilst that of combinatorial networks also requires the expansion of axons and dendrons.

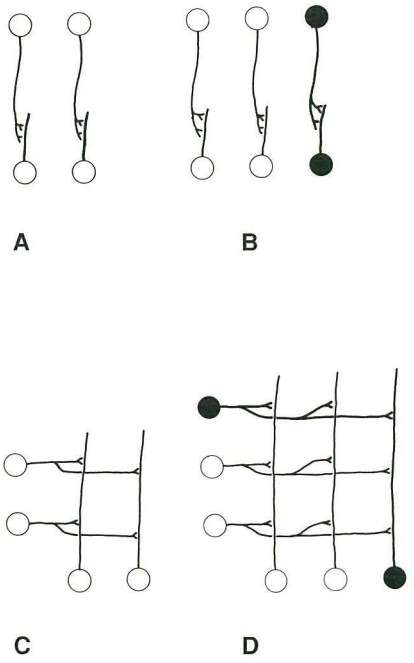

Figure 1. Diagramatic representation of expansion of topographical A → B and combinatorial C → D modes of connection.
(Additional neurones in black)

Evolutionary evidence indicates that most of the organisation of the mammalian cortex is of the combinatorial type (Lynch). Retrograde transport of labels and neuroanatomical studies show that the pyriform cortex is an excellent example of a combinatorial organisation.

The deep layer of the pyriform cortex has connections with the dorsomedial nucleus of the thalamus, which communicates with the frontal cortex. Layer 2 of the pyriform cortex (which communicates with the deep layer) also has projections of its own to the frontal cortex. The deep layer of the entorhinal cortex projects to the neocortex. Its layer 2 however sends fibres to the hippocampus. The dentate gyrus, the primary target of the lateral perforant path communicates profusely with thousands of granule cells – again a combinatorial system. The output of the dentate gyrus is restricted to the regio inferior (CA3) of the hippocampus proper, which itself communicates with a massive commissural association network with itself and the regio superior (CA1). The output of the hippocampus is the deep layer of the entorhinal cortex and the subiculum. The latter sends fibres back to the regio superior and also, to the entorhinal cortex, the ventral forebrain, the anterior thalamus, and the mammillary bodies; whilst the entorhinal cortex sends axons to the temporal neocortex.

Also, the fibres that the DMN sends to the cortex terminate in layers I and III of the cortex in a combinatorial manner as that found in the pallium of the lizard. It seem likely that both vertical and horizontal interactions occur. From comparative studies it can be expected that combinatorial systems are found throughout the cortex and possibly other regions of the forebrain.

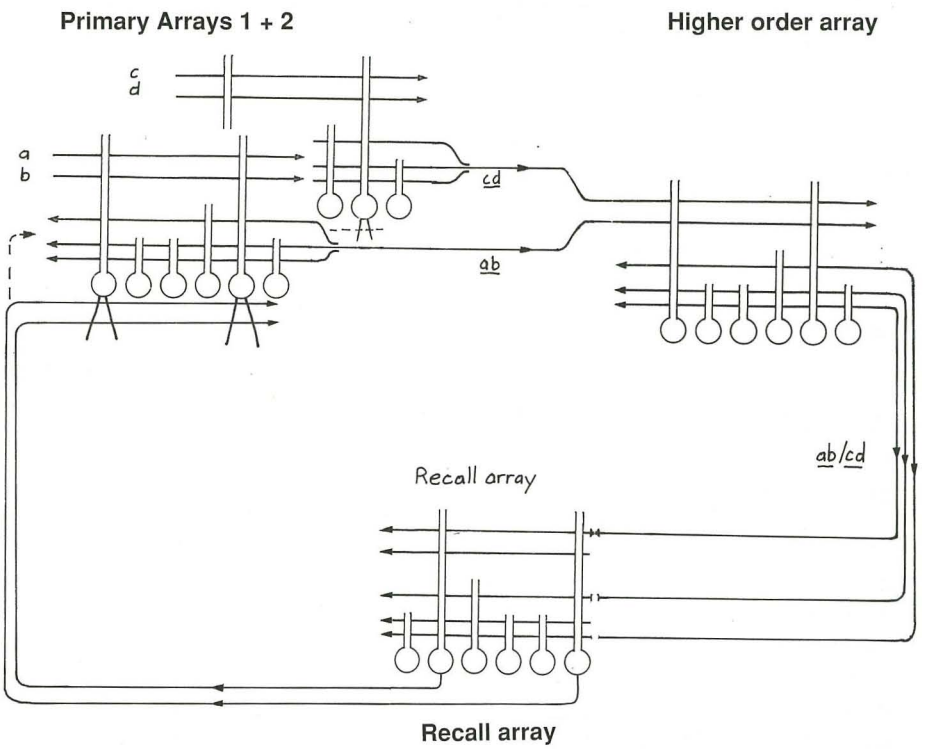

Figure 2: In this circuit (Fig. 2), we have two primary arrays: one where the signals for a and b are generated and another where the signals for c and d are generated. These are associated in a higher order array which produces the signal ab/cd and this then projects feedback fibres on a separate 'recall array'. This recall array projects fibres onto the primary arrays. These produce a discharge at a frequency which is not enough to generate LTP on their own. Potentiation occurs on the primary arrays and does so on those cells which are activated when the recall signal arrives. On subsequent occasions, projections from the second array (that which produces the ab/cd signal) would trigger only those cells in the primary array which had been temporarily associated with the recall fibres the first time the association of ab had occurred with cd. Lynch has also proposed experiments to test the hypothesis, which although still posing problems is a step to understanding how the high frequency required for LTP may be brought about.

Recall

From a physiological point of view the crossing of two chains in combinatorial systems solves many problems. But to be more exact the model must solve psychological problems. Thus the input of B will recall a previous event, A. For example, the smell of cheese will recall from memory the shape, colour and other perceptory identifications of cheese. Lynch has forwarded models of arrays of neurons, one of which is summarized below. These provide suggestions how potentiation can occur in the hippocampus.

Lesions to the hippocampus would not impede short term memory and not even already established long term memories. However the function of forming new long term memories, that is, the capability of transferring STM to LTM is disrupted. The combinatorial hypothesis provides a good explanation for this. Since the hippocampus is the site where connections between various parts of the brain occur, its importance in combinatorial connections with the various regions is established. Thus it is important in establishing long term potentiation of the concerned synapses in the memory circuits. However, damage of the hippocampus will not alter the already established potentiated synapses and thus established LTM will not be disrupted. Short term memory need only involve certain centers which will not include hippocampus directly. There is still the memory of words etc. This shows that the hippocampus is not needed for certain long term memories and it is only the combinatorial network which is disrupted, that is the ability to recall one event from the imposition of another.

In fact, psychologists have concluded that humans use two memory systems, one that stores information or data and a second that processes this according to a new set of "rules" or "procedures". The combinatorial arrays running through the hippocampus provide the second system, while neurons connected through the dorso-medial nucleus of the thalamus (e.g. olfactory-DMN) provide the first.

The hypothesis of combinatorial networks is "firmly grounded" in the field of neuroanatomy but it is still short on data.

The Amygdaloid Complex in Relation to Memory

Experiments by Mishkin and Appenzeller showed that the amygdala are as important, in memory, as the hippocampus. Bilateral removal of the hippocampus and amygdala produced a complete amnesic animal. The animal was completely impaired in experiments regarding association of objects with reward The visual pathways were not affected, as structures with connections to these paths were tested. The amygdala and hippocampus have extensive connections, with the visual pathways, (the latter indirectly). In fact it is the capability of positively associating the reward with the visual system which was impaired. Removal of the hippocampus alone had no effect on this ability. Bilateral removal of the amygdala produced an animal with poor ability to associate, but although slow to learn, was still able to do so. It is removal of both structures, which produces the lack of ability to associate. The following experiment demonstrated this and that the visual path was not damaged:

The animal was presented with an object under which was a reward (food). In a second trial the previous object and another one were presented and the food was put under the new object. The animal thus should learn to associate the food with the novel object. To do this it must remember the previous object. Whenever the trials were performed the two objects were always changed so that the monkey only learned to associate reward with the second object, irrespective of what is was. Animals with bilateral removal of hippocampus and amygdala performed well when the delay between the first and second trial was short, showing that the visual path was not affected. If the interval between the two trials was lengthened however the scores fell to the level of chance.

Moreover the amnesia was global. If the experiment was performed using the ability of touch to recognize instead of sight, the results were the same. Thus the hippocampus and amygdala have the same importance, removing either alone has little or no effect.

Higher Stations

Damage to hypothalamus and thalamus alone impair memory as much as damage to the limbic structures. In fact the limbic system and the diencephalon participate in a circuit rather than independently. This can be shown by damaging the pathways connecting the two areas, producing the same amnesic results.

Tracing the circuit to its possible end, Bachevalier found that surgical lesions to the ventromedial prefrontal cortex also produced this loss of recognition memory. At minimum we have thus these three sites as stations for memory.

Puzzle solved?

We have seen the importance of the limbic system in converting short term memory into long term memory. Here we find its importance in forming associations. A model of how long term potentiation by feedback circuits occurs, has been discussed. Memory occurs in combinatorial circuits which are established by LTP, that causes the plasticity in synapses to "fix" circuits. Damage to any of the above centres thus impedes impulses passing through these combinatorial circuits, preventing long term potentiation. This also explains why previous long term memory is preserved. Long term potentiation has already occurred before damaged to any station is done. When the damage is done the circuits are already "fixed" (synapses have been potentiated) and are thus established. Short term memory will remain intact as this requires paths other than the limbic or diencephalic regions. Damage to these stations however impedes communication with higher combinatorial arrays and hence LTP.

Types of memory

There are other functions of memory, further to simple recognition, for instance spatial relations, e.g. if one visits the Academy of Arts museum in Florence and recognises the statue of David, besides the shape of the statue, one will also remember its relation to the museum. He will remember, or have an idea even where the statue lies even if the museum was visited only once. This "spatial memory" was found to be located in the parietal cortex. Recognition memory, however, is not impaired, if this is damaged. In an experiment performed by Pohl, monkeys were presented with two wells, one of which contained food. The one containing the food was put near a cylinder. Thus the monkeys would learn to associate food, as being in the well, near the cylinder. This was relatively simple for monkeys with infero-temporal lesions, but those with damage to the parietal cortex had impaired spatial memory.

Although the hippocampus and the amygdala can substitute each other in association experiments, the hippocampus is also important in spatial memory, whilst the amygdala are not. Parkinson found this in similar experiments to Pohl performed on these regions.

Amygdala and previous memories

The amygdala, which are really a collection of nuclei have connections with all the sensory systems in the cortex. They are a sort of crossroads in the brain. The same parts of the amygdala which have sensory inputs also send fibres deeper into the brain into the hypothalamus, which is thought to be the source of emotional responses.

Mishkin and Appenzeller give results of experiments which suggest the amygdala as being the site where memory recalls other memories, hence a second candidate, probably more plausible, for combinatorial arrays of recall which may fall into Lynch's model discussed earlier.

In the experiment, monkeys with bilateral removal of the amygdala were allowed to examine objects both in the light (using sight and touch) and in the dark (using touch only). They then had to recognise the object from a pool of forty. The animals performed well. Their visual and tactile memories had remained intact, in keeping with the earlier finding that the hippocampus and amygdala can substitute for each other.

In a second experiment however, the monkeys were allowed to examine the object in the dark and then made to recognise it in the light using their visual system. The group with damage to the amygdala were unable to correlate tactile with visual memory. A control group with damage to the hippocampus were able however to perform the distinction quite well (ninety percent of the time).

Memory and emotion

Kluver and Bucy noticed that monkeys with damage to temporal lobe also lost their fear of humans. This was traced down to the amygdala. The link with familiar objects and their emotional associations had been severed. This observation goes hand in hand with the fact that monkeys without amygdala are slow in learning to associate an object with reward, as pointed out before in this section. In fact Mishkin and Appenzeller found that the amygdala not only receive fibres from all the sensory systems but also in turn send fibres to them. the amygdala are rich in neurons synthesising opium like neurotransmitters known as endorphins. Evidence shows that there are endorphin containing fibres from the amygdala to the sensory systems where they may serve "gatekeeping functions" influencing what is perceived and learned. In this way it is not foul to classify the amygdala as the motivation centre, especially when we know that without motivation, our chances of memorising are much reduced.

Speculation

It was noted initially that current thought of memory formation is the building of input onto previous memories or experiences. The analogy of streams being formed by water rolling down a hill has often been used. The passage of further water will follow the path created by the previous stream but will add onto it, creating new pathways. This is done by the force of gravity acting on the water. The water tries to occupy ever lower energy states (in this case potential energy) and in so doing it seeks new paths which are made possible by the property of the soil in allowing new paths to be formed by the currents.

Something on similar lines is thought to occur in the brain. Considering the combinatorial circuit model suggested before: if for simplicity we take a brain with no information in it, incoming information creates paths, that is synapses are potentiated to create circuits to a great extent at random, within the anatomical pathways described. We have already seen how two separate inputs can affect each other by feedback neurons. Thus new information will follow the same paths but will create more circuits. This is how ideas build on one another and hence learning. The part of understanding is thus nothing but the evaluation of previous knowledge in order to incorporate into this knowledge, the new knowledge that is being perceived. This new knowledge can thus be viewed as following through the paths already there. Correlating previous information is in fact creating combinations between circuits by means of long term potentiation. Naturally, this process can lead to what we define as 'misunderstanding', if either the previous or incoming knowledge was not organised well into the brain network. This can also be due to a state of fatigue of the person, which may implicate that incoming information is led voluntarily by the person along certain paths. An analogy would be respiration which is normally effortless but at any point the person can control the rate of respiration and thus the volume of air entering the body. Similarly in the brain, perceptions are continuously being introduced but unless some effort is made or unless under some emotional state, whatever enters is usually forgotten. An effort to understand will however bring the circuitry into action and incoming information is correlated to what was previously learnt (is led along correct circuital paths).

All this speculation is possible for the combinatorial circuitry model described. Thus as water fell along lines led by potential energy, perceptions enter the brain along potentiated circuitry led by energy states of the neurons. The thoughts fall along 'hills' of energy states and in the process new paths are created.

This is a good way however of demonstrating how to visualise that not all we know is continuously in our presence of mind. Hence the distinction between what is conscious and what is subconscious. Waves of hills are continuously being created and one leads to the others - just as a train of thoughts occurs when one is sitting in a state of 'daydreaming'. Information from the environment can stimulate the formation of energy hills. These can be pursued and thus lead to the activation of other hills (memory) and in some instances potentiate if there is enough evaluation of the perception. This is brought about by the recall mechanisms mentioned earlier. In other instances they are simply omitted; a previous memory may be aroused (an energy hill), that is a previously potentiated circuit, but the perception is not voluntarily evaluated enough to arouse previous experience or curiosity and thus enhance LTP. Let us take the example of memorising the path of the radial nerve in the arm, assuming that the previous knowledge is a memory of the anatomy and relations of the bones and muscles in the region. At the start of the procedure, assuming that the student is active and not simply performing passive reading, what was previously known is remembered. That is, action potentials have passed through the potentiated circuits and various energy hills have been

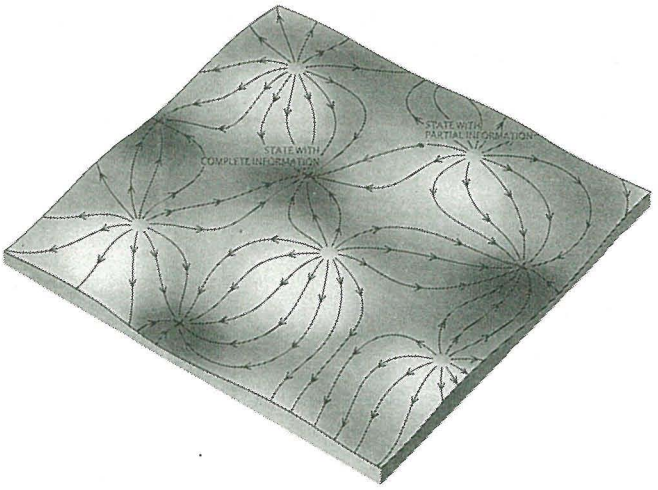

Figure 3: For a clearer understanding of why some thoughts remain and others do not, one can imagine that these energy levels are all in a resting state; 'flat' (as a carpet). *The passage of action potentials through a circuit arouses the energy state of that circuit and an energy 'hill' is created on this imaginary 'carpet'. When one is interested in what is happening around him, he thus activates previous knowledge (fig 3).* The carpet can be viewed as being lifted (forming a hill). That is, the energy levels are created and the incoming information will flow 'downhill'. Thus a medical student on a bus may be hearing conversation but will remember nothing. However if he overhears something relevant to his studies his curiosity is aroused (an energy hill is created) and the information is understood. There is more chance of his remembering the information now. Whether he remembers it weeks after depends on how much he allowed that information to affect his energy states, e.g. he might have been prompted to go and study more about what he had heard. Thus whenever he remembers this topic he will recall the experience on the bus. This experience has been potentiated into his memory store.

'aroused' (again remember that one hill may produce another by the feedback model) producing what one may call a landscape of energy hills. The incoming information relating to the course of the nerve must be understood in relation to what was previously learnt. That is, the information is flowing along the hills, creating new networks in the meantime. These new networks are the basis for the memory of "the course of the radial nerve", and its future recall depends on the potentiation this circuit gets in the presence. Some people potentiate by repetition (but note that this does not mean that a previous effort of understanding was not necessary); others by as much understanding as possible, that is relating what is being learnt to as much previous knowledge as possible (thus the student might compare the upper limb with the lower limb).

It is also known that long term potentiation can decay in certain synapses which shows why the longer time passes, the less detail one tends to remember. However most of the circuit is still intact (not all synapses of the circuit need decay at once because indeed some may be being used in other circuits) and therefore a revision of something will enhance memory. Thus people having seen a film a few years back may still have a 'vague idea' of the film but if on reviewing it they 'will start' remembering and indeed there will be parts which they have completely forgotten. During the film other intact memories will be aroused (a creation of energy hills). One will anticipate what is going to happen next because the action potential flow is led into going down these energy hills. An analogy to computational networks shows this is feasible.

The second part of this article will be published in the following issue.

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