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Memory in the cortex of the primate

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Memory is viewed as hierarchical and distributed in primary and association areas of cerebral cortex. Different memory neural networks are interconnected at various levels in this hierarchy, sharing neurons and connections. All memory is essentially associative in its generation, structure and retrieval. External and internal stimuli, to which we attend by virtue of their biological relevance or for other reason, can at any time activate ("turn on") the neuronal network to which they belong by previous association. This is the basis of knowledge and remembering. The reverberation in recurrent circuits may keep the network in an active state, that is, serving behavior, attention and consciousness. Monkey neuropsychological and electrophysiological data, and human tomographic (brain metabolism) evidence are presented supporting these concepts.

Key terms: *association cortex, associative memory, prefrontal cortex.*

INTRODUCTION

In the first place, I will try to present an overall vision of the role of the cerebral cortex in memory, a vision which, although somewhat personal and perhaps too ambitious, harmonizes with the evidence that through many years we have been accumulating in my laboratory. In second place, I will try to suggest a working plan, an agenda for future research, a guide to shed some light on the still obscure but fascinating and complex subject of memory.

More precisely, here it will be discussed (1) how cortical memory is formed; (2) where it is formed; and (3) how it is activated. In relation to the third point, particular attention will be given to one aspect of cortical dynamics about which we have some experience in our laboratory. It concerns the dynamic structure of associative networks and their activation during recognition as well as in the temporal retention of memory.

GENERAL PRINCIPLES

I will start by stating some general principles of memory that derive from neuropsychological and neurophysiological work in the last years. Some of these principles are still in an embryonic stage, reason for which we cannot blindly accept them. However, for the sake of brevity, they can be accepted at least as working hypotheses and as premises for the experiments that I shall try to summarize below:

1. Memory is a widely distributed function. All neural systems have memory. Each component of the central nervous system, each system or subsystem of the brain has its memory, memory whose contents strictly depends on the information processed by it; thus, there is sensory memory in sensory systems, visual memory, auditory memory, haptic memory, *etc*, ... motor memory in motor systems, visceral memory in visceral control systems, *etc*. In each of these systems,

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memory forms an integral part in the processing of the information in which the system specializes; in fact, representation and processing share the same neuronal networks within each system. Therefore, in neurophysiological terms it does not make much sense to speak of systems of memory, but it does make sense to speak of *memory of systems*. This is a Copernican turn that I believe is worth making in our way of thinking if we intend to get to some understanding of the neurobiological basis of memory.

2. Systems that interest us are cortical systems, and therefore we will be speaking of the memory of the cerebral cortex, as *cortical memory*. This fits everything, that is, all classes of memory that are investigated in modern neuropsychology. In the perceptual sectors of associative cortex, at different levels in its hierarchy, we find from down to top unimodal sensory memory, multimodal sensory memory, episodic memory, semantic memory and conceptual memory. Cortical memory is therefore the basis of what we call cognitive memory, the base of knowledge and personal experience. On the other hand, in the associative sectors of the frontal lobe, we find the plans, action schemes and programs in all aspects of motility (skeletal, ocular, phonetic, *etc*), from the more abstract to the more concrete, all plans and programs constituting what we call motor memory. Moreover, there in the frontal lobe, we find the mechanisms of organization of the actions in the temporal domain in order to implement those plans and motor programs.

3. A cortical memory, of any kind, the "engram", so to speak, is a more or less extended *neuronal network* of interconnected neurons. Depending on its complexity and its conceptual or semantic contents, this network may be circumscribed to a specific cortical area or can be extended to different areas with association tentacles of varying length and convolutedness. Some of these association tentacles cross from one hemisphere to the other through the corpus callosum. Thus, in its neurobiological aspect, all memory is a fundamentally associative structure, defined by the neuronal assemblies constituting it and by their connections. Similarly, in its psychological aspect, all memory is an associative phenomenon. It is formed by association, is maintained by association, and is evoked, remembered, by association.

4. The structure and contents of cortical memory are hierarchically organized, as corresponds to the organization of the information processing systems constituting these networks. This hierarchical organization is adjusted, at least in a crude manner, to the phylogenetic and ontogenetic order that, as we know, is a hierarchical development. To understand this better, it is worth observing the ontogenetic map of human cortex.

Figure 1 presents the ontogenetic map according to Flechsig (1901) and Von Bonin (1950). Numbers do not indicate here different architectonic areas, but the order in which the different cortical areas become myelinated, that is, the order in which their extrinsic and intrinsic fibers develop their myelin sheaths. Somehow there is a certain correlation between myelinization and the other indexes of ontogenetic maturation around and after birth, and the map thus approximately reflects the maturation of neocortical systems and the functionally hierarchical development of these systems. This development and its hierarchy themselves result from the -also hierarchical- phylogenetic evolution of the cortex.

Thus, at the lowest level of cortical hierarchy, I find the primary sensory and motor areas, here in black and with the lowest numbers (Fig 1). These are presumably the first ones to develop. Soon after birth, the organization and connectivity of these areas is complete, and their functions are practically identical to those of the adult organism, although it is also true that before they must undergo some critical postnatal periods of functional exercise. These areas could be considered as the anatomical basis of what I call *phyletic memory*, or species memory (Fuster, 1994). This would be a form of elementary memory, common to all the members of a species, that has developed through innumerable generations and by the same mechanisms of temporal coincidence as those involved in the generation of individual memory, of which we will speak below. The term "phyletic memory", although seeming a little esoteric and arbitrary, does not need to alarm anyone, since I use it to characterize

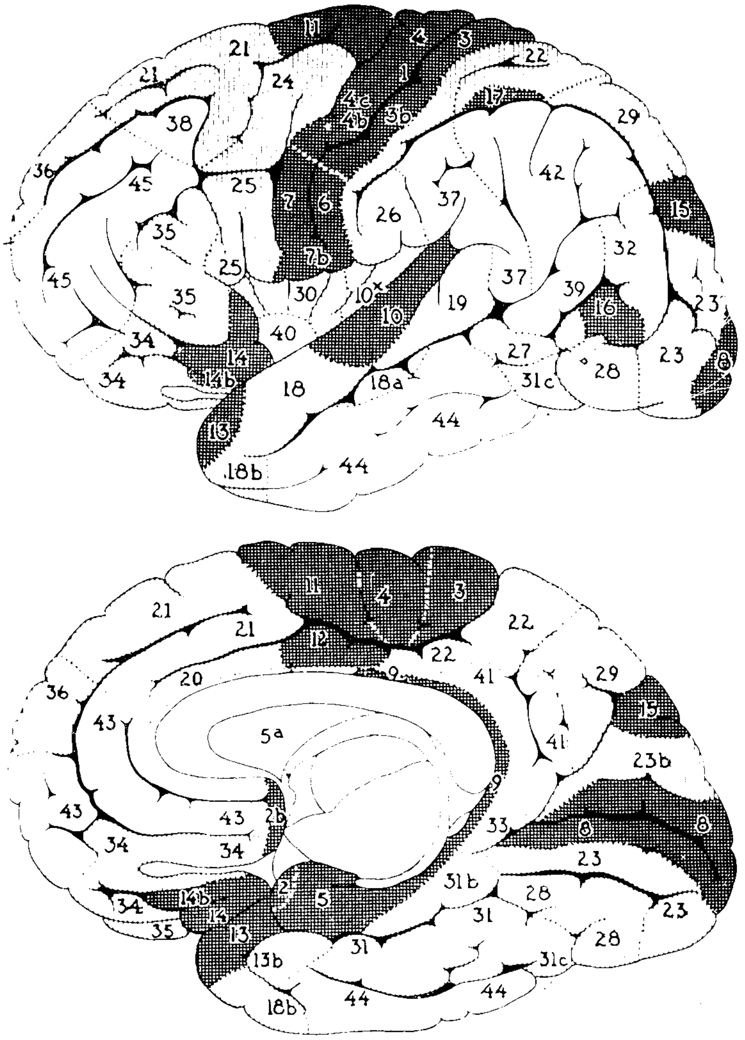

Fig 1. Myelogenetic map of the human cortex.

something that is perfectly well established. It is nothing more than a different term for the sensory and motor devices we are born with.

Thus, the neuronal networks of primary cortex, with their proverbial modules and columns, would constitute the basis of the mnemonic cortical hierarchy, predisposed to "re-cognize" what the species already knows, that is, the most elementary sensory and motor attributes. Beyond and over those primary areas in the connective and developmental trajectory, are the areas labeled in gray (Fig 1), and then in white, constituting the association cortex and conforming the personal memory networks. These networks are formed there to represent and process the naturally idiosyncratic information that the individual accumulates along its life. Some caveats are necessary before going on:

1. What I just said does not imply that the structure of primary areas comes to us already specified and unchangeable at birth. In the first place, there are *critical periods* in their development, to which I have alluded, where use is necessary for the definitive functional maturation of these areas. These would be like training periods of phyletic memory, needed by the organism in order to freely practice it. In second place, it has been well demonstrated that these primary areas retain their plasticity even in the adult, a fact that is apparent in the spontaneous or induced

rehabilitation of their functions after certain lesions (Merzenich and Kaas, 1982).

2. This does not mean either that the substrate of *associative memory* comes to the world to be made. On the contrary, all its cytoarchitectonic and neurochemical structure seems already genetically determined, at least in the monkey. What probably remains to be done is the synaptic infrastructure at the finer levels, that is, the proteic basis determining the variability and facility of transmission of preexisting synapses. It is there where individual memory will take its place.

3. In any case, the transitions between primary and associative cortices, that is, between phyletic and individual memory, are gradual in all their respects. Both of them keep an intimate relationship, with no clear border between them, neither at a physiological nor at a psychological level. In fact, there are no seams between sensation and perception, between sensory and perceptual memory.

The ontogenetic map points to another general division between the two basic memory categories we have been talking about: post-rolandic cortex, with its large associative region, is involved not only in the processing of perception but in perceptual memory, including all those memory forms that are acquired by the senses (declarative, episodic, semantic, *etc*). Pre-rolandic cortex, on the other hand, is mainly involved in the processing and representation of action (including the so-called "procedural memory").

The cytoarchitectonic map of Figure 2 (Brodmann) shows the two components, perceptual and motor, of the anatomical substrate of *language*, with their adjacent areas, housing perceptual and motor memory for the highest and more exclusive cognitive activity of man.

MEMORY FORMATION

The mechanisms of memory formation are not precisely known yet, but we do know some of the general principles of this process, which I will refer to even if in a summarized manner. In the first place, it is known that in order to form new memory the

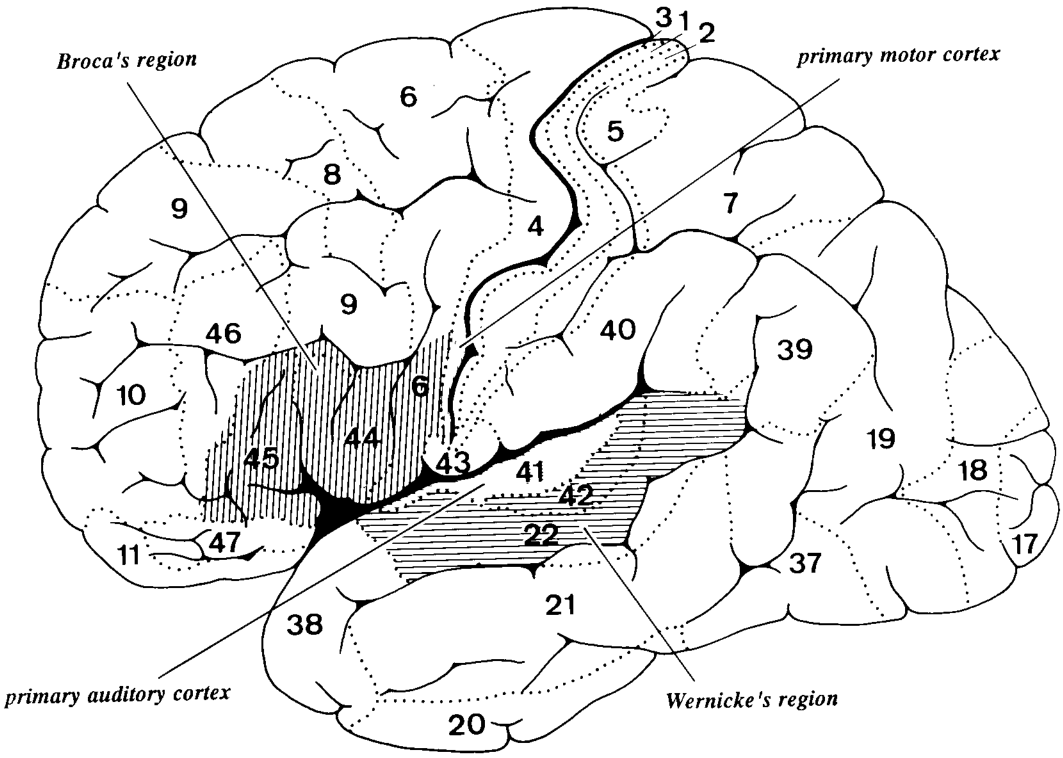

Fig 2. Brodmann's architectonic map. Language areas marked by shading.

functional integrity of the hippocampus is needed, which is a sector of phylogenetically primitive cortex. The hippocampus is reciprocally well connected with all associative cortical regions (Fig 3). It is through these connections, by a mechanism that we do not know well as yet, that the hippocampus determines the formation, or I would better say the expansion of cortical memory networks. What supposedly happens is that through a synaptic facilitation mechanism, like long-term potentiation, and by mediation of certain glutaminergic transmitters and some substances such as nitric oxide, the hippocampus facilitates certain changes in the synaptic structure of neocortical neurons and with that the establishment of cortical neural networks and the memory they sustain. I only need to add that in the process also participates in some way the amygdala, and that both, hippocampus and amygdala, participate not only in the formation but also in the activation, evocation and remembering of cortical memory.

What is it that specifically happens in the cortex, for a new memory to be formed? Here we have to introduce the principles proposed by Hebb more than forty years ago (Hebb, 1949), especially the principle of *synchronous convergence*, or of temporal coincidence, that has been widely demonstrated in primitive organisms (Carew *et al*, 1984), such as the mollusk, by Kandel and colleagues (Fig 4). However, it must be

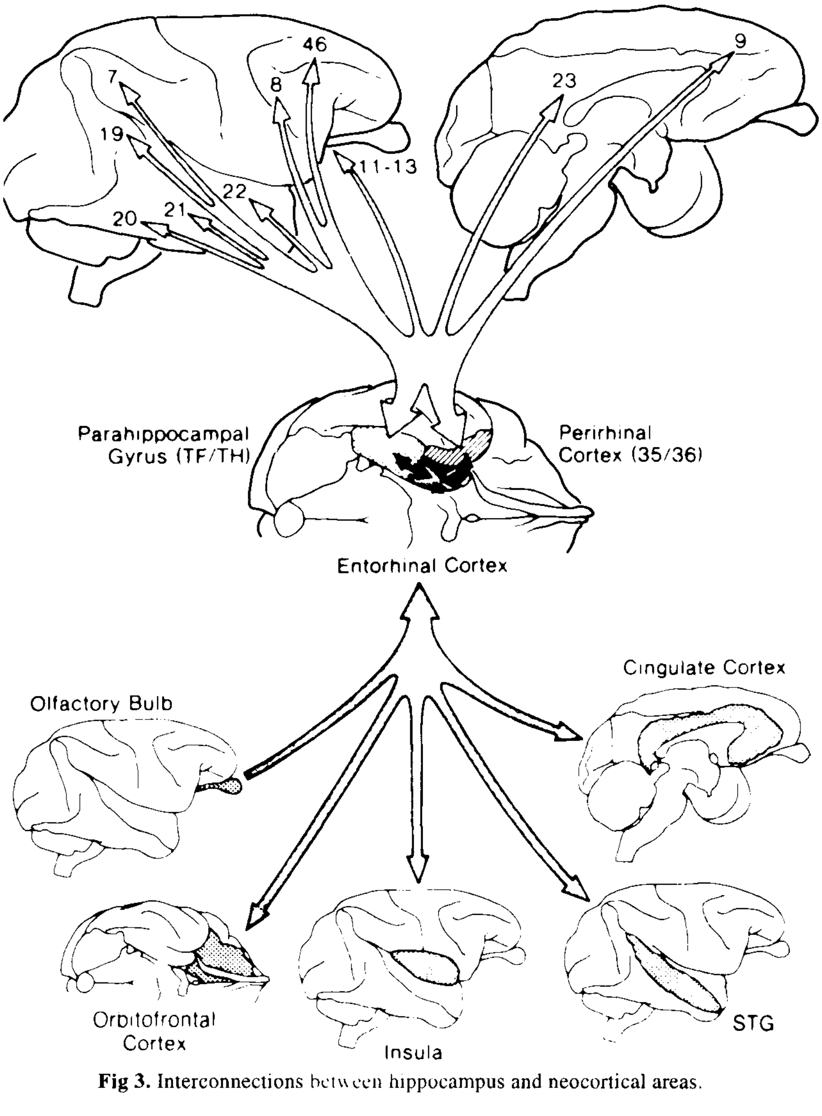

Fig 3. Interconnections between hippocampus and neocortical areas.

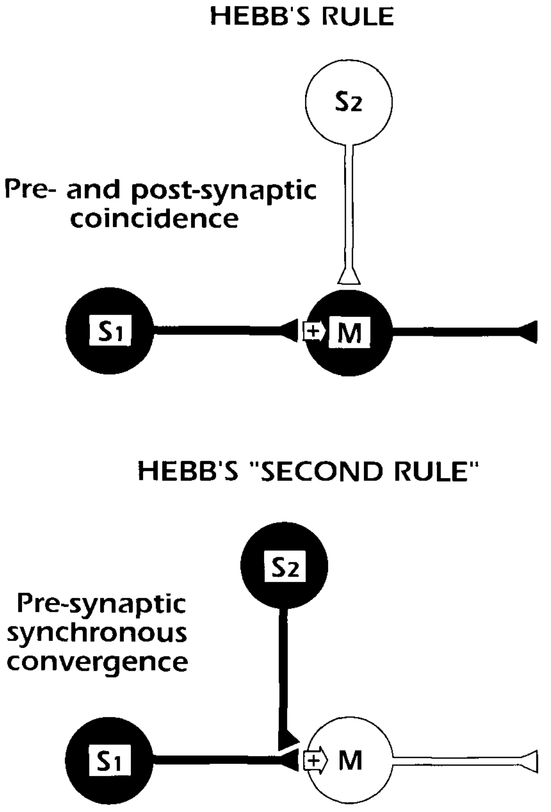

Fig 4. Hebb's principles of synaptic facilitation in memory formation.

mentioned that the principle is much more general than what Hebb supposed. It applies as much to the conditioned reflex as to the highest associative memory, be it either perceptual or motor. It is also worth noting, to understand its universal value, that temporal coincidence does not need to be perfect: that there is a certain range or temporal latitude, some time window within which distinct afferences can enter and become linked. Furthermore, these afferences, which can be of infinite number and variety, do not need to be only external. For example, an external stimulus may coincide with the evocation of an established memory; both work as "coincident stimuli", one external and the other internal, which expands, enriches or refines preexisting memory. Naturally, afferences of visceral origin may also, by the same mechanism, participate in the generation of memory.

In Figure 5, it is shown in a schematic form how do we go from temporal coincidence to the neural network. The scheme illustrates the main elements of neuronal connectivity in associative areas of the cerebral cortex: convergence, divergence and recurrence. Two stimuli coincide in time, facilitating the mutual synaptic contacts between the neuronal assemblies that they represent. When the stimuli disappear, the mnemonic track they leave is precisely in these same assemblies that, together, linked by potentiated synapses (in white) constitute the memory network. This memory is established and defined by its contacts and its new relations. And thus it stays, latent, until any one of the stimuli that formed it arrives and by itself reactivates the whole network, re-evoking the memory.

In this way, by interactions between cortex and limbic system, whose mechanisms we do not yet understand, memory networks can be formed by auto-organization, without other principles than coincidence and use. The paths of memory become established in the association cortex, in an autonomous way and through use.

I will now dedicate the rest of this article to some already established dynamic aspects of memory, with which we have some experience in our laboratory. Specifically, I will discuss the temporal reactivation of memory and the mechanisms of its active retention when the goals of behavior and thought require it. The subject is important because active short-term memory is in a way the basis of consciousness. As Francis Crick is fond of saying, consciousness is inconceivable without a mechanism of short-term retention.

ACTIVE MEMORY

When an animal has to recall a perceptual memory fragment in order to execute a motor act in the near future, a broad network of associative memory becomes and remains active. This network is constituted partly by neurons in the posterior associative region corresponding to the sensory modality of the respective memory and also by neurons in the frontal associative cortex representing the respective motor act. The dimensions and contours of this network, and the importance of its activation for the temporal retention of

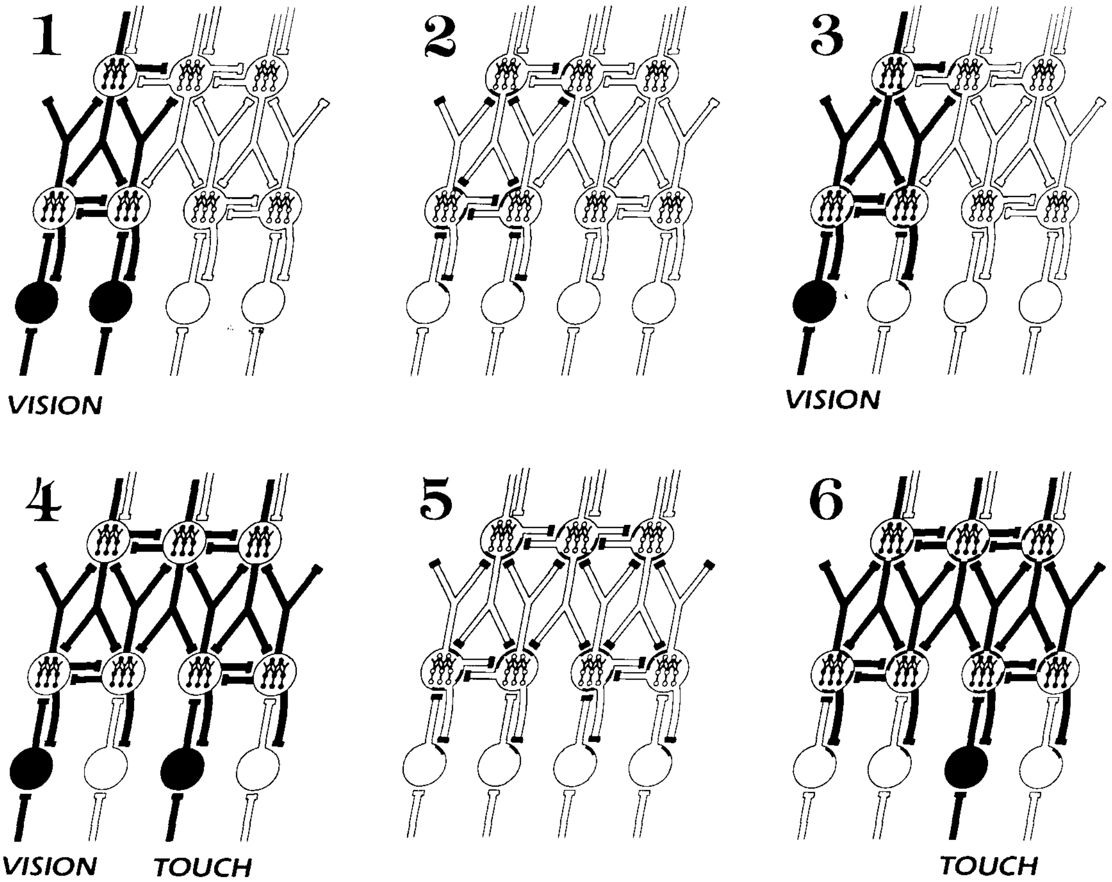

Fig 5. Schematic diagram of memory formation in neural networks. Active neurons in black. On top, temporal coincidence of two visual stimuli (1), remaining facilitated synapses (2), and reactivation of the memory network by only one of the stimuli (3). Below (4, 5 and 6), similar processes for stimuli of two different modalities.

memory, have been subject of many studies in our laboratory by use of the reversible lesion method, by selective cooling of cortical areas. I will not deal with this issue since this is not the place to do it.

What I will discuss, although only briefly, are some functional phenomena of the activation of memory networks at a cellular level in the monkey and at a level of cortical metabolism in man.

It was probably in our laboratory where for the first time the cellular phenomena of active memory in association cortices were observed: first in the frontal (Fuster and Alexander, 1971), then in the inferotemporal (Fuster and Jervey, 1981) and more recently in parietal cortices (Koch and Fuster, 1989). In the first cortices, prefrontal and inferotemporal, the phenomenon has been posteriorly replicated and observed in several other laboratories in USA, France, Japan and Scandinavia.

Below, I will present some examples of the activity of cortical cells during retention of short-term memory. Figure 6 indicates some behavioral paradigms of short-term memory. Each trial consists of: (1) the presentation of a sensory stimulus that the animal must remember; (2) a delay period; and, at the end of it, (3) a motor act according to the nature of the stimulus. It must be kept in mind that in the trained animal all stimuli are known and therefore they are part of long-term memory. The task simply requires the successive activation, in successive trials, of memory of one or another stimulus. Each is a piece of established memory, of long-term memory that at the moment mobilizes the whole memory, activating the whole network, including the associations of the

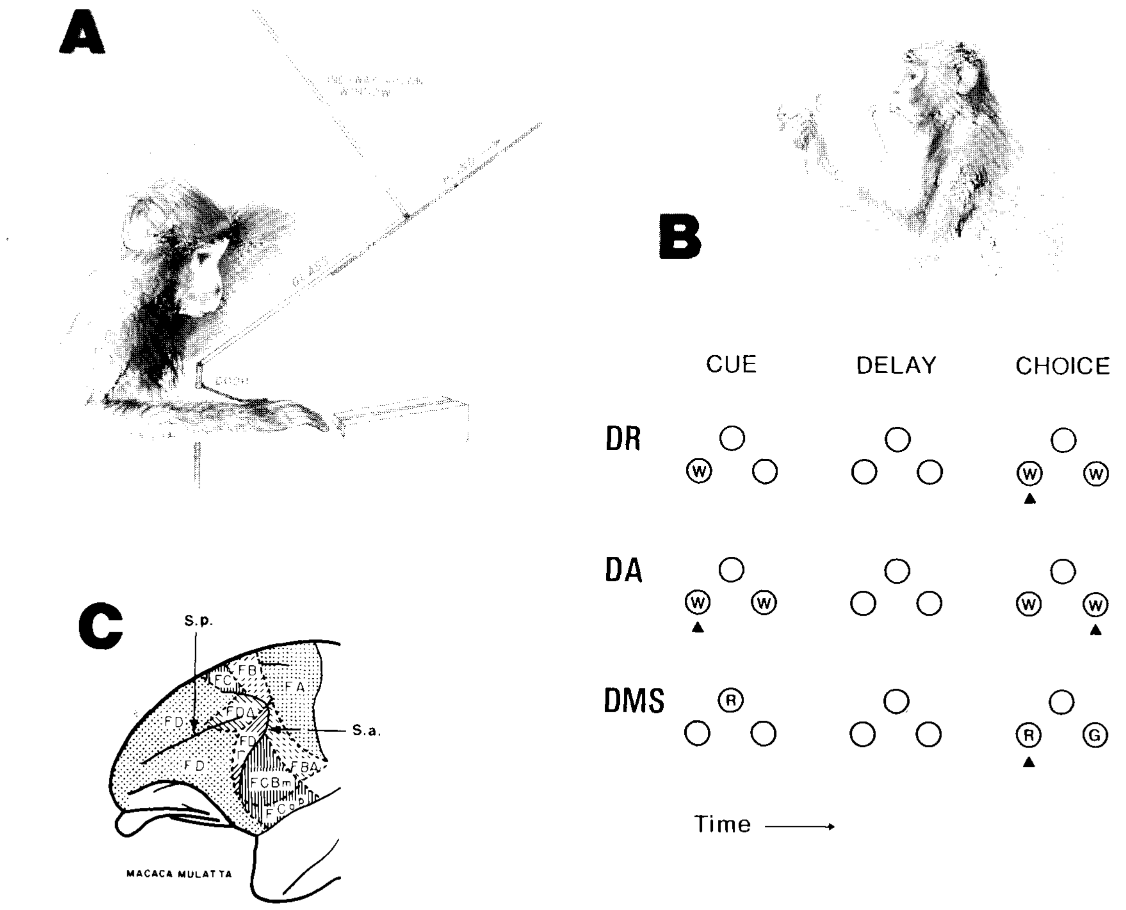

Fig 6. **A**. classical delayed response task. **B**. Indirect-method delay tasks on automated apparatus. **C**. Monkey's cytoarchitectonic map; lesions of area FD impair performance in all delay tasks.

stimulus with the place, with motor memory, with what the monkey has to do, and with the memory of the reward if he does the task right. All this is part of the mnemonic network activated by association when the stimulus appears.

After what I have said about the network's extension, and about the many things that are associated with the stimulus, we should suppose that while the monkey remembers it and prepares for the motor response, widespread neuronal populations are activated in the posterior perceptual cortex, in frontal cortex, and even in the hippocampus, which is also involved in recognition. This is what is observed recording units in short-term memory tasks.

If the stimulus that the monkey must remember is visual, then the most active neurons must naturally be those of the inferotemporal cortex (Fuster and Jervey, 1981), since this cortex is so to speak the center of visual memory (Fig 7). However, not everything is activation. The neuron of Figure 8 is inhibited by the stimulus, be it red or green. If the stimulus, the color that the monkey has to remember, is red, then during the delay period the neuron activates considerably and keeps active during most of the delay period. It is as if, at the stimulus arrival, the neuron was for a moment left in a "tabula rasa" state in order to best receive and retain what it is specific for, which is the color red, doing this of course not by itself but with the help of its companions in the neural network.

With my colleagues of the University of California at San Diego, David Zipser and collaborators (Zipser *et al*, 1993), we are investigating with *empirical models* the mechanisms of short-term active memory.

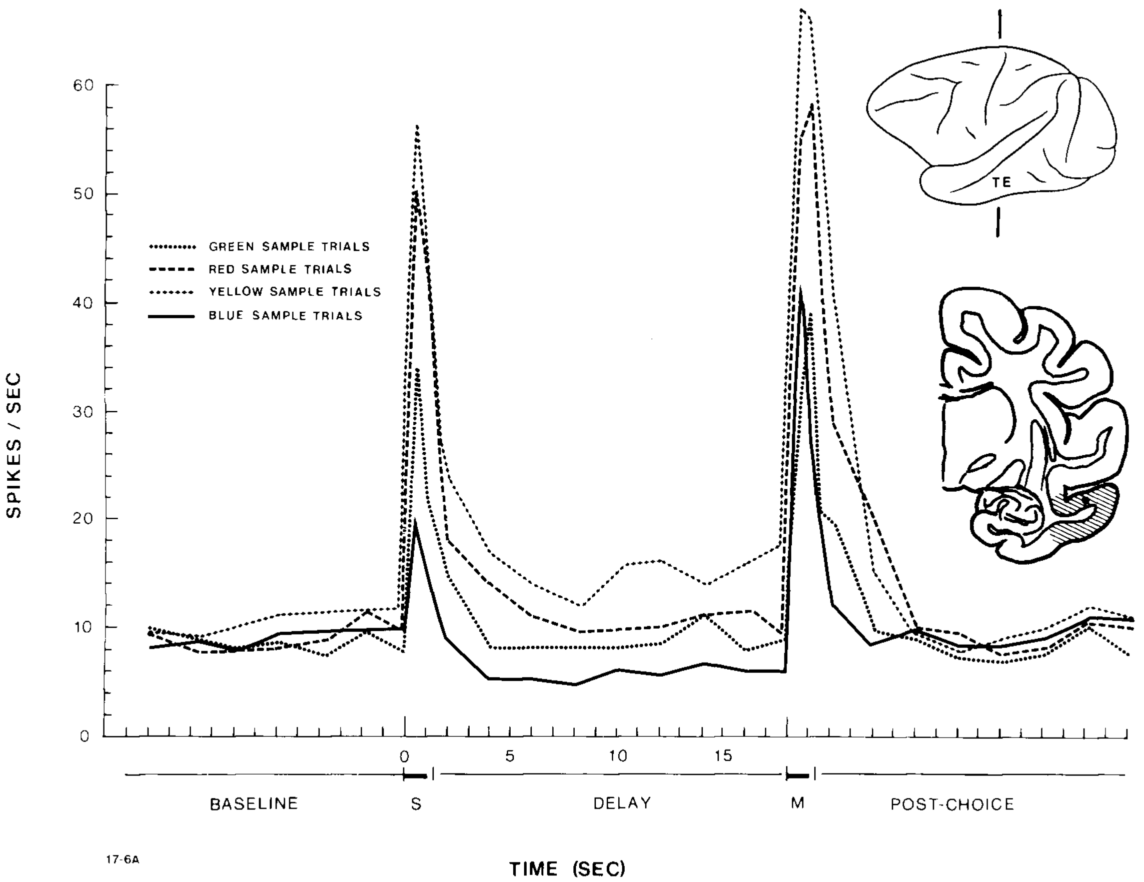

Fig 7. Frequency histograms of the activity of an inferotemporal cell (location marked by dot in brain diagram at right) during delayed matching to sample with four colors. S, sample period; M, match period. Note differences in cell discharge during sample stimulus, during choice (M), and, most important, during memorization of sample color.

Among the several computational models that we have developed, there is one whose "units" simulate with extraordinary similarity the behavior of inferotemporal neurons during short-term memory. The model's architecture is essentially based in recurrent circuits (Fig 9). In the trained model, and using the adequate parameters, one finds units that scarcely differ from the real ones (Fig 10). In any case, it must be kept in mind that the model does not explain how things really happen in the brain. What the model tells us is that short-term active memory is perfectly compatible with the activation of recurrent circuits in a neuronal network with preexisting synaptic weights, which harmonizes with what we have just said about the relation between established and active memory.

In order to determine what happens with memory activation in a different sensory modality, haptic (tactile, from the Greek *haptein*, to touch, palpate), we must observe the activity of neurons in tactile associative memory during retention tasks of objects perceived by manual handling. In fact, we also find memory cells there, that is, neurons that seem to retain tactile information during the delay period in a short-term memory task (Koch and Fuster, 1989; Zhou and Fuster, 1992). What is most surprising is that here we find them not only in association areas such as area 5, but very near the entry of the somatic system, in primary sensory areas (areas 1, 2 and 3). The difference with the visual system is noteworthy, since there we could not find memory cells until well into the associative system, in the inferotemporal areas. The difference may be explained by the fact that the tactile system processes information mainly in series, while the visual system does it in parallel. The haptic system works by temporal integration.

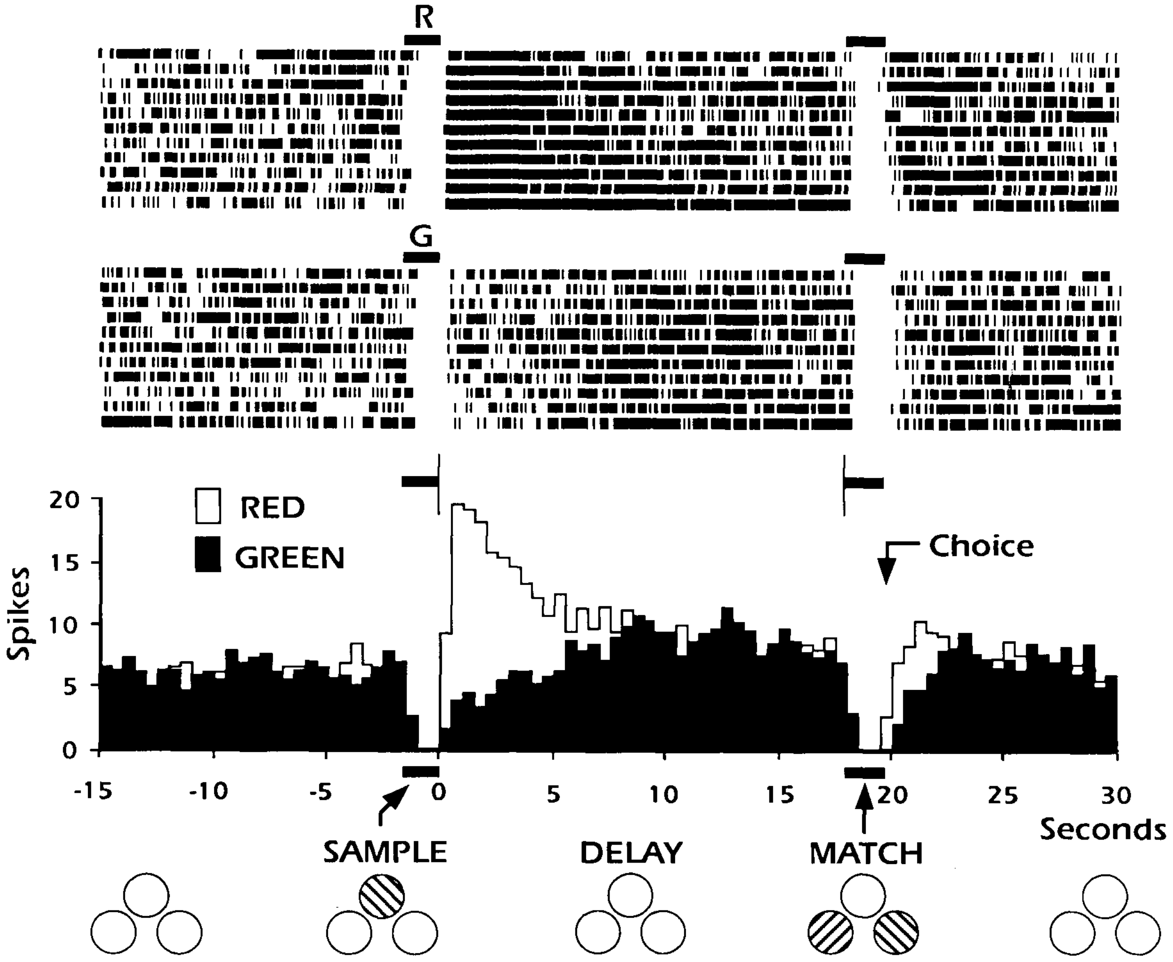

Fig 8. Rasters and frequency histograms of the activity of an inferotemporal cell during delayed matching (paradigm below). Note inhibition at sample and match, and differential activation during memorization of red.

What matters, in last instance, is that tactile perception, more than visual perception, needs a mechanism of short-term memory already in the early processing stages. It is as if phyletic memory had already its own short-term memory in primary areas.

Now we will see some examples of active memory in the sectors of *frontal associative cortex*, where not only motor memory is represented but is also where behavior is organized in the temporal axis (Fuster, 1989). There we find two main types of memory cells: those of the sensory type, that code information of any sensory modality for the motor act that will take place, and those of the motor type, coding this act. During the delay period, the formers decrease their firing, as if looking backwards in time to the sensory information that is waning, while the latter ones accelerate, as if anticipating and predicting movement. Through a visuomotor task using colors, where each color is associated to a certain probability of manual movement, Javier Quintana and I (Quintana and Fuster, 1992) were able to show that the cells that presumably code for the motor memory increase their firing in proportion to the probability with which the monkey can predict the motor act that he will have to perform (Fig 11). These cells seem to participate not only in the network representing the act but in the network that prepares it, which undoubtedly is to some extent the same.

Lastly, I want to show that things are probably not very different in man, at least regarding the role of the *prefrontal cortex*. With my associates in Los Angeles

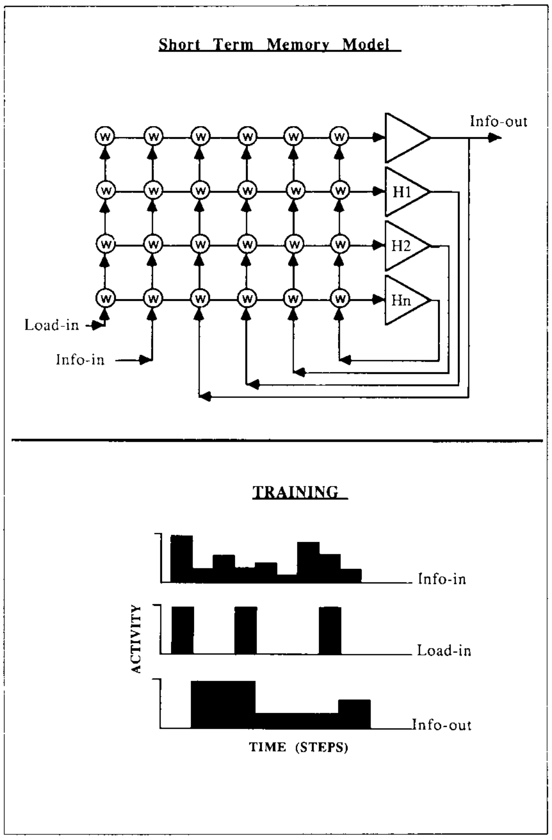

Fig 9. Scheme of the architecture and "training" features of a computer model of active short-term memory.

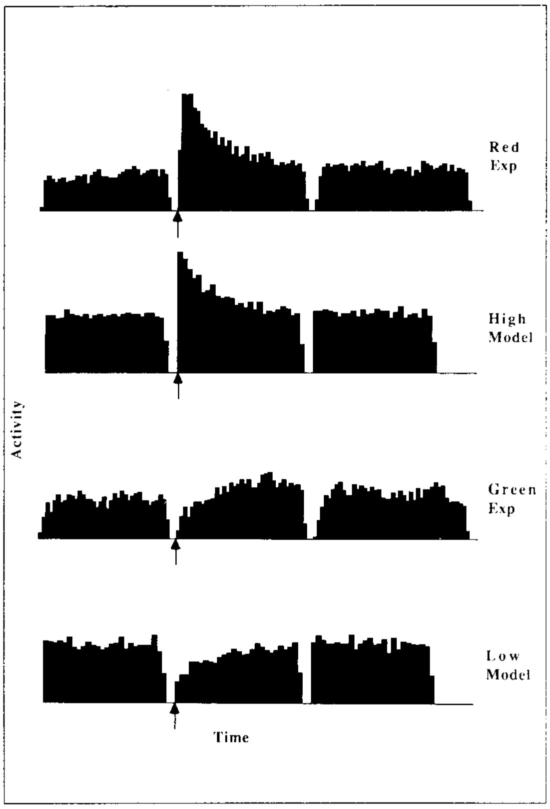

Fig 10. Simulation by model in Figure 9 of neuron in Figure 8.

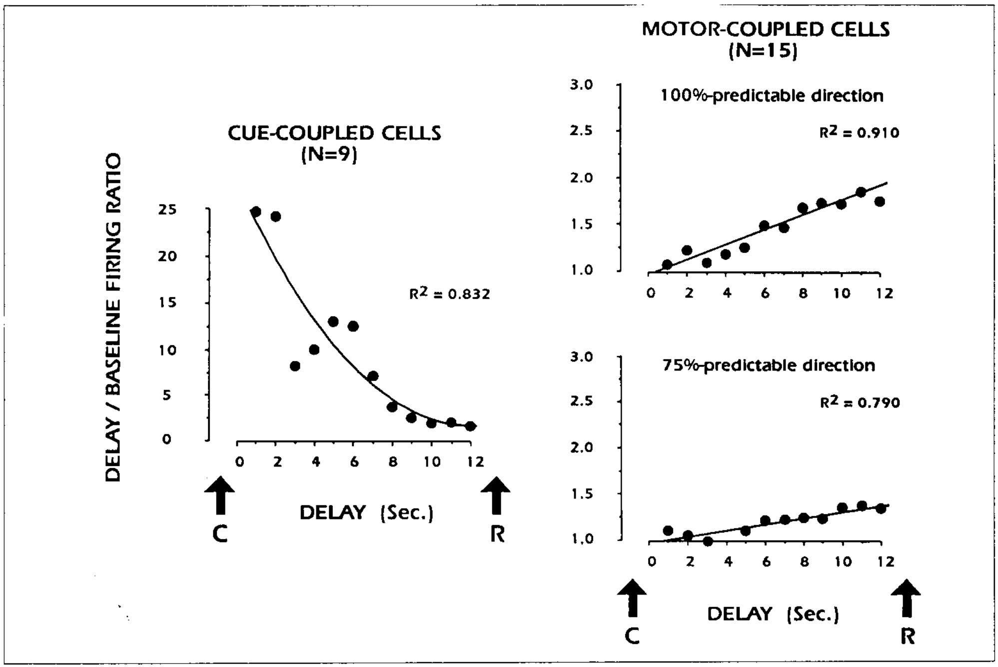

Fig 11. Activity of prefrontal cells during the delay of a delay task with probabilistic relationship between stimulus (color) and motor response (C, cue; R, response). At left, cells related to color; at right, cells related to motor response. Note that motor-coupled cells show gradual increase of firing as the motor response approaches, and that the slope of that increase is related to the probability with which the monkey can predict the direction of response.

(Schwartz *et al*, 1995), we have been investigating metabolic activity of cerebral cortex during visual short-term memory. Here, instead of using colors, as in the monkey, we used more complex stimuli, such as abstract drawings (Fig 12). The task is as follows. A trial begins with an alert signal. Then, an abstract image, the sample, appears. Follows the delay period, the period of active memory, and finally a second image appears. If this second image is identical to the sample, the subject presses a button with one hand; if not, he presses another button with the other hand. There is also a control task, identical to the first (the same stimuli, the same motor responses), with the difference that there memory of the image is not required: both stimuli appear at almost the same time, with minimal delay.

Before executing the two tasks, radioactive glucose was injected to 18 volunteers, and subsequently, during both tasks and during the uptake of the isotope by the central neurons, tomographic (PET) images of the brain were obtained. Many areas were activated by the tasks. What most interests us here is that prefrontal cortex is vividly activated, especially during the memory task. If the metabolic activations produced by the two tasks are subtracted, a map such as that on Figure 13 results, showing that during the memory task there is a higher activation of Brodmann's areas 9, 10 and 46. Motor and premotor areas are also relatively activated. This is probably due to the fact that even if both tasks require the same number of motor responses with the two hands, the subjects spend more time preparing a response in the memory task than in the control.

CONCLUSIONS

Certainly, the data I have presented offer a partial vision of cortical memory. However, at least they give us an idea of the principles

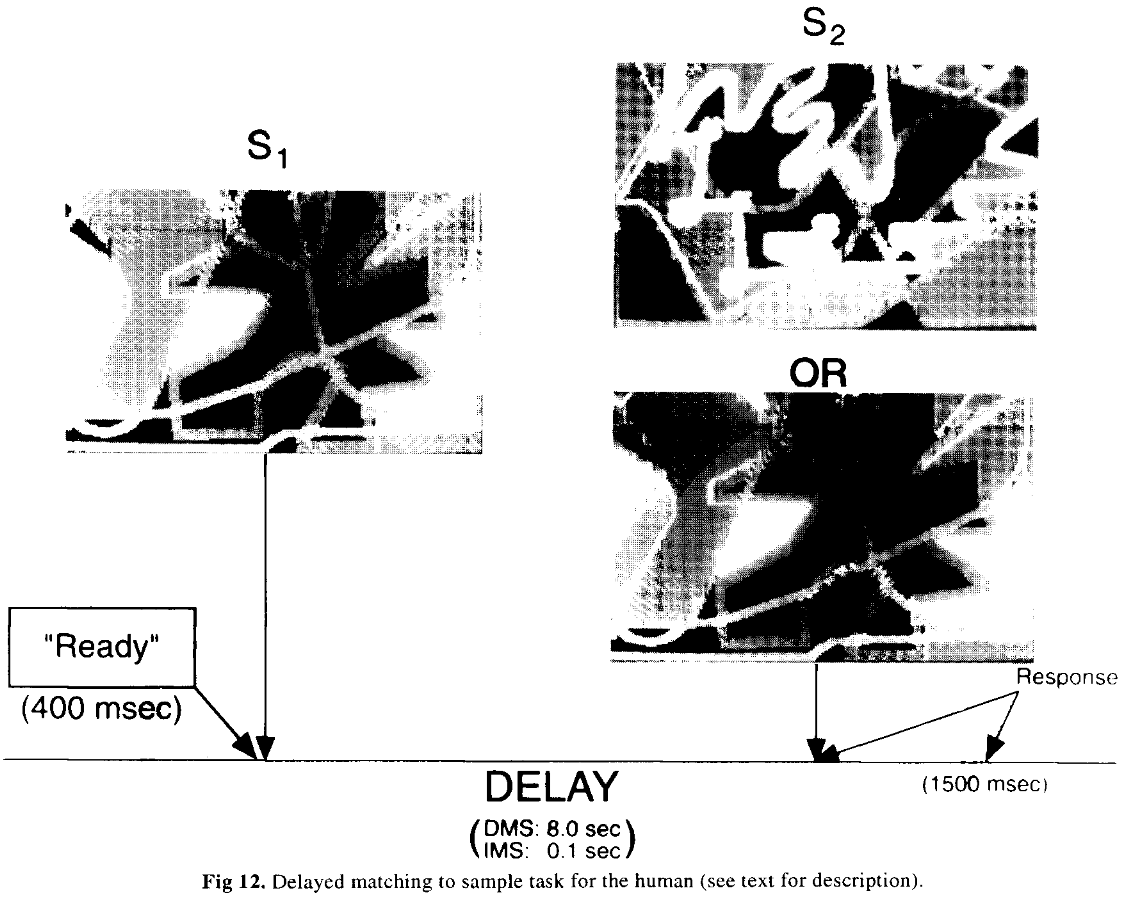

Fig 12. Delayed matching to sample task for the human (see text for description).

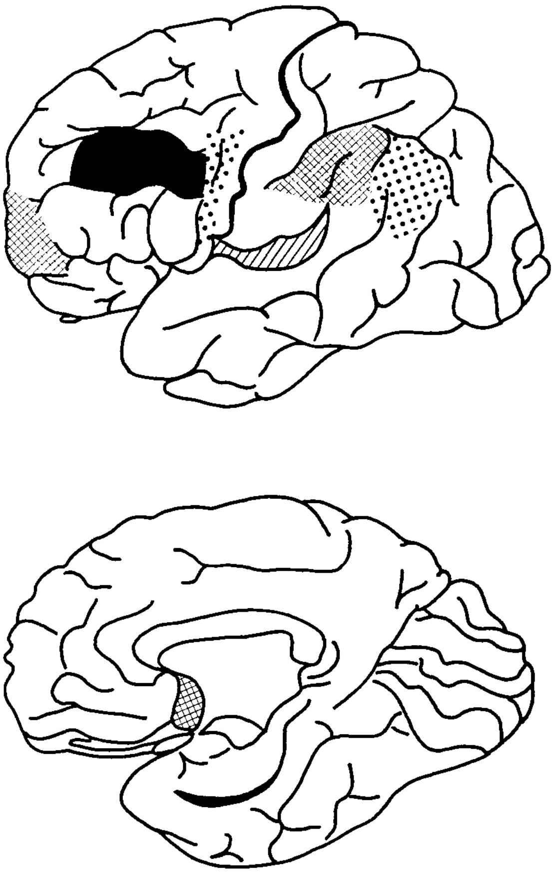

Fig 13. Areas in which activation in memorization (memory task) exceeds activation in control (no-memory task). Black area (dorsolateral prefrontal) is activated the most during visual memorization.

of distribution and operation of cortical memory. We only need to underline these principles in the wider context of human memory.

1. As I mentioned, the vision of individual memory that guides our research is hierarchical. For sure, the data on memory structure and dynamics I have referred to are limited to what happens at relatively low levels in the hierarchy, at the unimodal perceptual memory level and the manual motor memory level. My position here is that what happens at these low levels of memory and associative cortex is paradigmatic, qualitatively similar to what happens at higher levels.

2. As we ascend in the hierarchy of cortical memory, networks gain not only in hierarchical level, that is, complexity, but also in extension, that is, in diffusion in every sense. This means that memories and their networks are not strictly stratified but they overlap among them at several levels. In fact, it cannot be otherwise considering that all memories and their networks share neurons and connections. This concept is fundamental in order to clear the existing confusion in the neuropsychological taxonomy of memory.

3. Above phyletic memory –if we accept the concept– is unimodal memory, and above it multimodal, and then episodic memory, which is a kind of associative memory, as all the others, but with space and time associations; and over them is semantic memory, and above it, conceptual memory. All of them are associative. What happens is that, as we go up, knowledge, memory and the network are all anchored in a larger number of connections, that is, associations. With it, they become more resistant to aging and injury.

4. With aging and cortical injury, the memory of an episode is lost, but not that of the name or of the concept; of the category, but not of the procedure. This is not because semantic, episodic and procedural memories are in different places in the brain. It is simply because some are better anchored by associations than others. There is no reason to suppose that the memory to play chess, for example, occupies a separated and different cortex from the memory of the day and place we learned to play it. But, because of their lability and specificity, place and time associations are more vulnerable and susceptible to be forgotten.

5. Some external or internal stimuli to which we attend by virtue of their biological relevance or for whatever reason, may, at any given moment activate the cortical network, they can so to speak, "turn it on" (to use Braitenberg's [1978] term). This is the essence of recognition or remembering. If the network needs to stay active to dial the telephone number, to complete the arithmetic operation or the discourse, or, as in the case of our monkey, to choose between red and green, there must be a mechanism, probably of reverberation in the network, as our experiments and models indicate, maintaining the excitation of the network over a certain level until the organism achieves its goal.

REFERENCES

BONIN G von (1950) Essay on the Cerebral Cortex. Springfield, Ill: Charles C Thomas

BRAITENBERG V (1978) Cell assemblies in the cerebral cortex. In: HEIM R, PALM G (eds) Theoretical Approaches to Complex Systems. Berlin: Springer-Verlag. pp 171-188

CAREW TJ, HAWKINS RD, ABRAMS TW, KANDEL E (1984) A test of Hebb's postulate at identified synapses which mediate classical conditioning in *Aplysia*. J Neurosci 4: 1217-1224

FLECHSIG P (1901) Developmental (Myelogenetic) localisation of the cerebral cortex in the human subject. Lancet 2: 1027-1029

FUSTER JM (1989) The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe. New York: Raven

FUSTER JM (1994) Memory in the Cerebral Cortex: An Empirical Approach to Neural Networks in the Human and Nonhuman Primate. Cambridge, MA: MIT Press

FUSTER JM, ALEXANDER GE (1971) Neuron activity related to short-term memory. Science 173: 652-654

FUSTER JM, JERVEY J (1981) Inferotemporal neurons distinguish and retain behaviorally relevant features of visual stimuli. Science 212: 952-955

HEBB DO (1949) The Organization of Behavior. New York: John Wiley and Sons

KOCH KW, FUSTER JM (1989) Unit activity in monkey parietal cortex related to haptic perception and temporal memory. Exp Brain Res 76: 292-306

MERZENICH MM, KAAS JH (1982) Reorganization of mammalian somatosensory cortex following peripheral nerve injury. Trends Neurosci 5: 434-436

QUINTANA J, FUSTER JM (1992) Mnemonic and predictive functions of cortical neurons in a memory task. Neuroreport 3: 721-724

SCHWARTZ BE, HALGREN E, FUSTER JM, SIMPKINS F, GEE M, MANDELKERN M (1994) Cortical metabolic activation in humans during a visual memory task. Cereb Cortex (in press)

ZHOU Y, FUSTER JM (1992) Unit discharge in monkey's parietal cortex during perception and mnemonic retention of tactile features. Soc Neurosci Abstr 18: 706 (Abstract)

ZIPSER D, KEHOE B, LITTLEWORT G, FUSTER JM (1993) A spiking model of short-term active memory. J Neurosci 13: 3406-342