Network memory

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Our thinking on the cortical organization of primate memory is undergoing a copernican change, from a neuropsychology that localizes different memories in different areas to one that views memory as a distributed property of cortical systems. We are shifting our focus from 'systems of memory' to the memory of systems. The same cortical systems that serve us to perceive and move in the world serve us to remember it. Our memories are networks of interconnected cortical neurons, formed by association, that contain our experiences in their connectional structure. Perceptual and motor memory networks are hierarchically organized in post-rolandic and pre-rolandic neocortex, respectively. Recall, recognition and working memory consist largely in their reactivation, also by association.

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THE CAPACITY TO STORE INFORMATION about oneself and one's environment is present throughout the nervous system. Thus, almost all regions of the brain store memory of one kind or another. In primates, the memory of past experience is stored largely in the neocortex – the phylogenetically newest part of the cerebral cortex. The available evidence indicates that memories subsist in networks of interconnected and distributed neocortical neurons. The cortical substrate of memory, and of knowledge in general, can be viewed as the upward expansion of a hierarchy of neural structures with its base in the spinal cord. Every stage of that hierarchy has two major components, each devoted primarily, if not exclusively, to one of the two basic organismic functions, sensing and acting. The same is true for the cortex, which has a posterior sensory region and a frontal motor one. These store memory in both the short and the long term. The conceptual and empirical background for these tenets is reviewed in this article.

First a little history. The discovery of the motor cortex by Fritsch and Hitzig[1] initiated a long tradition of studies intended to map the physiological functions of the cerebral cortex. The use of electrical stimulation and recording methods led to ever increasing knowledge on the location of sensory and motor areas. Towards the end of the nineteenth century, another methodology began to develop in parallel with the physiological one: the lesion methodology. Subtly taking a theoretical position akin to phrenology, though legitimized by the scientific method, the investigators of the effects of cortical lesions in humans and animals have since then persistently attempted to localize cognitive functions, such as memory, in discrete cortical regions. The effort continues to this day. In the past 50 years, the two currents have tended to converge. Neuropsychologists have refined their methods to match the localizationist precision of physiologists, while the latter have ventured into the cortex of association in the expectation of localizing memories, perceptions and attention there using the same procedures with which they had successfully identified feature detectors or minicolumns.

The neuropsychologist Karl Lashley[2] was the first in modern times to recognize the futility of trying to localize memories. With his failure to locate the site of learned discriminations by selective ablations of the cortex, and with his judicious reflections thereafter, he unwittingly laid the groundwork for a distributed substrate of memory. Almost at the same time, Hebb[3] developed his famous theoretical principles of memory formation at the cellular level.

Friedrich Hayek[4], an Austrian economist (Nobel Prize, 1976) with a profound interest in psychology and the brain, seems to have been the first to postulate what is the core of this paper, namely, the idea of memory and perception represented in widely distributed networks of interconnected cortical cells. Subsequently this idea has received theoretical support, however tangential, from the fields of cognitive psychology, connectionism and artificial intelligence. Empirically, it is well supported by the physiological study and neuroimaging of working memory.

Memory formation: from synapse to network

The acquisition of memory basically consists in the modulation of synaptic contacts between nerve cells[5], a notion first advanced by Ramón y Cajal in 1894 referring to motor memory. Memories are formed by facilitation – and selective elimination – of synaptic links between neuronal aggregates that represent discrete aspects of the environment or the inside of the body. Thus, memories are essentially associative; the information they contain is defined by neural relationships.

Hebb[3] proposed that 'two cells or systems that are repeatedly active at the same time will tend to become associated, so that activity in one facilitates activity in the other.' This may be called the principle of synchronous convergence. By summation of temporally coincident inputs, neurons would become associated with one another, such that they can substitute for one another in making other cells fire. Further, connections between input and output neurons would be strengthened by recurrent fibers and feedback. By these associative processes cells would become interconnected into functional units of memory, or hebbian 'cell assemblies'. The functional importance of synchronous convergence in the mammalian cortex is well documented[6,7].

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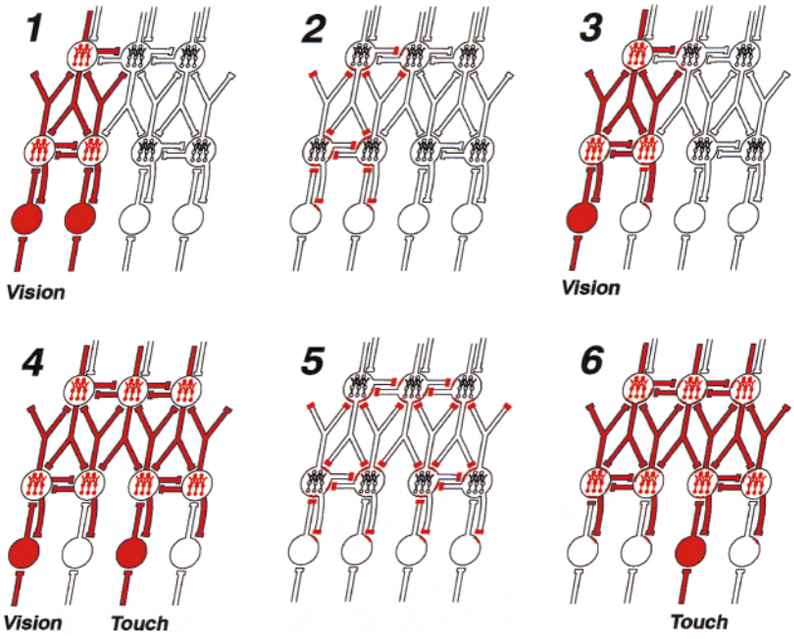

Fig. 1. ***Diagram of memory formation and activation by sensory association.*** *The basic network consists, hypothetically, of 11 groups of neurons (netlets). All known patterns of cortical connectivity are represented: feedforward, feedback, lateral, parallel, convergent and divergent. Active neurons are in red.* **(1)** *Two visual inputs coincide in time; this enhances synaptic efficiency at points of convergence and feedback or re-entry.* **(2)** *Passive long-term memory; marked in red are the facilitated synapses excitable by either input.* **(3)** *One of the inputs activates the new network, which now has some neurons previously activated only by the other input.* **(4)** *A visual and a tactile input coincide.* **(5)** *Facilitated synapses (in red) which are now part of the new bimodal network of long-term memory.* **(6)** *The tactile stimulus activates the network, which now also represents the associated visual input (the palpation of the object conjures its visual image in addition to the tactile one).* Modified from Ref. 9.

Simple sensory memories, or images, are probably formed in cell assemblies or modules of the sensory or parasensory areas of the cortex. The neural representation of our personal memories, however, can only be formed in wide expanses of the cortex of association, a neural substrate with a vast combinatorial power of connections across both modules and areas. For Hayek[4], that wide substrate was a net or 'map' of cortical neurons representing in its connectional structure the associations that make up the essence of any perception and memory. Remarkably, he intuited this concept before anyone knew, as we now do, of the breadth and wealth of corticocortical connectivity in the primate. Furthermore, according to Hayek, that system of connections somehow recorded (by synaptic weights?) 'the relative frequency with which in the history of the organism the different groups of internal and external stimuli have acted together'. To a similar distributed construct, Edelman and Mountcastle[8] later added the architecture of its associated nodes – neuronal groups or modules – and the role of re-entry (feedback) in the association of stimuli not exactly coinciding in time.

It is reasonable to assume, as Hayek did, that memory and perception share, to a large extent, the same cortical networks, neurons and connections. All memory is categorical, as is all perception. Perceiving is the classifying of objects by activation of the associative nets that represent them in memory. Each new perception, or memory, is the expansion of old ones; it simply adds associations to pre-existing nets. The relevant connectivity extends across cortical areas. That connectivity sustains the system of diffuse, overlapping and practically infinite networks that holds personal knowledge and experience[9]. In this scheme, any cell or group of cells can be part of many networks and thus many memories.

Memory networks are most likely to develop, at least partly, by self-organization[10,11] from the bottom up, that is, from sensory or motor cortical areas towards areas of association. They also probably develop in part from the top down, guided by attention and prior memory stored in the association cortex; here the synchronous convergence would be between new inputs and inputs from old reactivated networks. In any case, networks grow on a substrate made of lateral as well as feedforward and feedback connections (Fig. 1).

The result is a hierarchical order of memories and knowledge. Even within a network there would be a hierarchy of nets and neurons and of nets within nets down to the neuronal group, the elementary unit of memory that we might call a netlet. This nesting of nets of unlimited variety adds degrees of freedom and complexity to memory. At the base of the postulated hierarchies are the neuronal assemblies that form the simple sensory and motor memory networks. These are the building blocks for multisensory and complex motor networks, which in turn give rise to the more elaborate and idiosyncratic networks of association cortex supporting the various categories of so-called declarative (explicit), nondeclarative (implicit) and procedural memory[12,13].

The hippocampus seems to play a critical role in the formation of memory networks in association cortex. Patients with hippocampal lesions suffer from anterograde amnesia. They have severe difficulties acquiring and consolidating new memories. Reciprocal connections between the hippocampus and neocortical areas of association are essential for these processes[14,15]. Although the underlying cellular mechanisms are not yet clear, long-term potentiation (LTP) might be amongst them. These mechanisms may involve cortical glutaminergic terminals and certain types of receptors, for example, NMDA. The result of these might be to induce protein molecule changes in the membrane of cortical cells so as to modify their contacts and thus shape their networks. The amygdala, another temporal-lobe structure that appears essential for the evaluation of the affective and emotional significance of perceptions, also plays a putative role in the formation and consolidation of memories. Thus, memory networks appear to be formed in the cortex by such processes as synchronous convergence and self-organization, and under the agency of limbic structures.

Phyletic memory

To understand the formation and topography of memory better, it is useful to think of the primary sensory and motor areas of the cortex as the repositories of a form of largely inborn memory that we may call phyletic memory or 'memory of the species'. At birth, those areas already contain the essential 'experience' of evolution in their synaptic structure, acquired through interacting with the world – that is, the neural representation of the essential features of sensation and movement. Thus, the structure of primary sensory and motor cortices may be considered a fund of memory that the species has acquired in evolution. We can call it memory because, like personal memory, it is information that has been acquired and stored, and can be retrieved ('recalled') by sensory stimuli or

the need to act. It is eminently adaptive, for it contains the long adaptive experience of the species.

Phyletic memory requires 'rehearsal' at the beginning of life, that is, the critical postnatal periods during which primary sensory and motor areas have to be active for early development of their function. Further, there is evidence that primary sensory and motor structures retain their plasticity into adulthood[16,17]. The plasticity of primary cortices after birth (as yet not fully known) and their uniform functional architecture across adult individuals, indicate that, in ways we do not understand, stereotyped function and relative 'hard-wiring' can ultimately emerge from a connective system that is, to a degree, inherently 'soft-wired'.

Phyletic memory is the foundation on which individual memory grows. The latter can be considered the expansion of phyletic memory into the cortex of association. The primary cortices provide this cortex with the elements of experience that, by synchronous association, make or facilitate synapses in the networks of individual memory. However, there is no sharp demarcation between phyletic and individual memory, as the two blend into each other. Any clear-cut dichotomy between them is artificial. So is the dichotomy between primary and association cortex on evolutionary, ontogenetic, hodological and functional grounds. The smooth gradients between the two cortices strengthen our rationale for considering them together as a source and substrate of memory.

As in evolution[18], the neocortex of association seems to undergo greater morphological development later in life than do the primary sensory and motor cortices[19,20]. The neocortex of association, the presumed substrate of most personal memory, does not reach full maturation until young adulthood and probably retains synaptic plasticity throughout life. In the human cortex (Fig. 2), two developmental gradients can be recognized on myelogenetic grounds, one in the posterior cortex (temporal, parietal and occipital), and the other in the cortex of the frontal lobe. The former marks the development of areas mainly involved in perception, the latter that of areas mainly involved in movement and action. Last to develop, by myelogenetic criteria, are the areas of association in temporal and parietal regions, and the prefrontal cortex in the frontal lobe[21]. Myelin formation is but one index of structural maturation, however well it correlates with others. Furthermore, there is further evidence that synaptogenesis takes place at the same ontogenetic time throughout the cortex; the same is true for neurotransmitter receptors. In any case, neither myelin sheaths nor synapses are proof of function. Axons may function without myelin sheaths and synapses may be present but not electrochemically active.

Those two developmental gradients correspond approximately to gradients of connection between areas[22,23]. In the posterior cortex, fibers flow mainly from primary sensory areas into and through areas of association cortex, though feedback connections are present practically every step of the way (reviewed in Ref. 9). In the frontal cortex, the flow is mainly in a reverse direction, that is, from associative (prefrontal) towards primary (motor) cortex, though again with feedback, some of it through basal ganglia and thalamus (reviewed in Ref. 21). It should be emphasized that in both anterior and posterior cortices feedback accompanies feedforward.

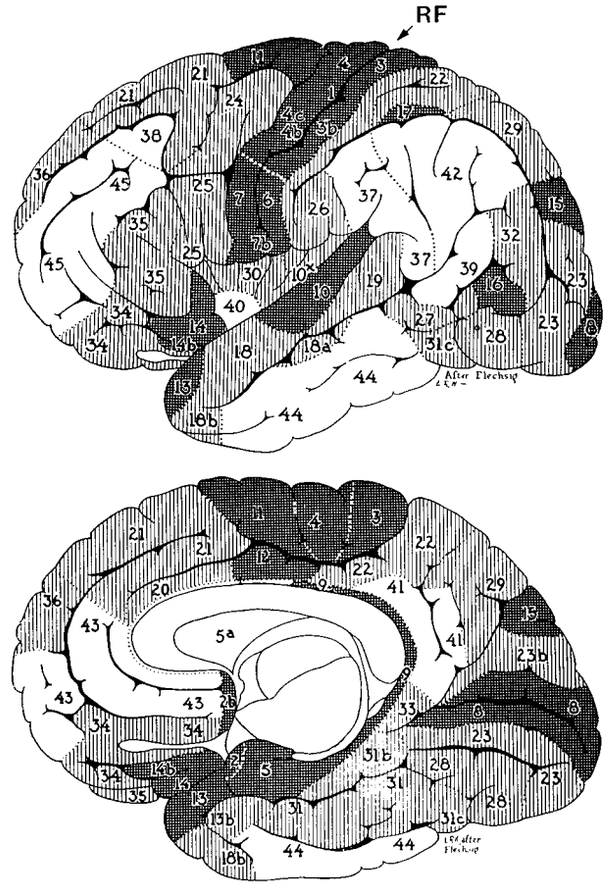

Fig. 2. ***Ontogenetic map of cerebral cortex in the human.*** *Schematic according to Flechsig[19] and modified by Von Bonin. Numbers indicate the order of myelination of the various areas. The rolandic fissure* (RF) *separates the posterior (perceptual) cortex from the frontal (motor) cortex. Primary sensory and motor areas are marked by dark shading; association areas in white or light shading.*

Following ontogenetic gradients, therefore, a system of connections is present in anterior and posterior cortex to mediate the functional transactions between phyletic and individual memory, although the precise mechanisms of those transactions are yet unknown. Primary sensory areas of phyletic memory, representing elementary sensory features, can thus feed information into posterior associative areas, where associations form networks of perceptual memory by temporal coincidence. Feedback would allow the supervised and attention-driven acquisition of new memory. Conversely, motor feedback and so-called efference copy of action[24] would form the motor memory networks of frontal cortex. In the re-enactment of the motor schemes that they represent, these networks guide the elementary innate acts (motor primitives) represented in primary motor cortex and in subcortical motor structures. Viewed in this manner, both perceptual and motor memories derive from phyletic memory. Both are associative, distributed and hierarchically organized.

Perceptual memory

Perceptual memory is memory acquired through the senses. It comprises all that is commonly understood as personal memory and knowledge – that is, the representation of events, objects, persons, animals, facts, names and concepts. There is a hierarchy of perceptual memories that ranges from the sensorially

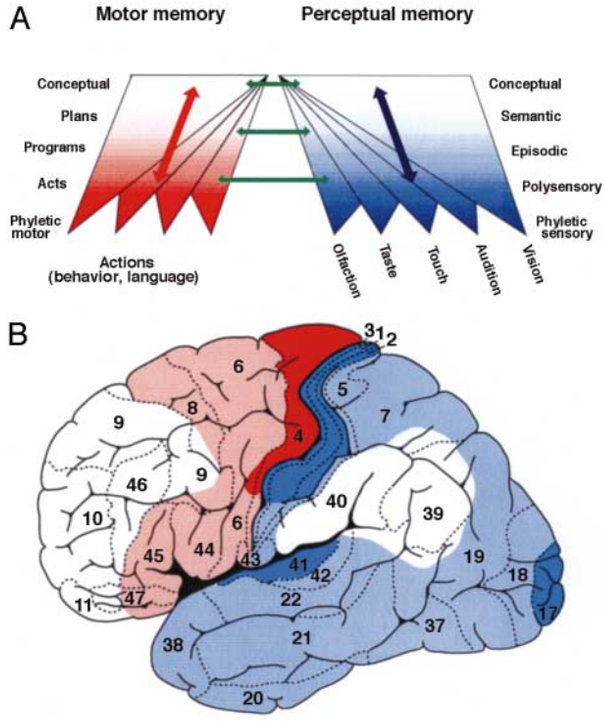

Fig. 3. ***The hierarchies of memory.*** **(A)** *Schematic diagram of the perceptual and motor hierarchies of memory. Overlapping triangles with vertex down (in phyletic memory) symbolize the neural substrate for upward expanding and interconnected networks. Representation of connectivity between different hierarchical levels of memory (blue and red arrows) and connectivity between perceptual and motor hierarchies (green arrows).* **(B)** *Brodmann's cytoarchitectonic map of the cortex depicting with the same color code as the scheme above the approximate distribution of memory categories. Because of the associations between hierarchical levels and the blending between memories of different category (see text), the color demarcations in the map may be useful heuristically but are unrealistically sharp. For example, whereas conceptual and semantic knowledge is solidly anchored by associations to the posterior region marked in white, it probably extends profusely into light-blue areas.*

concrete to the conceptually general. At the bottom are memories of elementary sensations; at the top, the abstract concepts that, although originally acquired by sensory experience, have become independent from it in cognitive operations.

The hierarchy of perceptual memories is matched and supported by a hierarchy of areas in the posterior cortex arranged in developmental and connectional order (Fig. 3). In the lower stages, that hierarchy corresponds to the neural hierarchy for processing and analysis of sensory information. A separate hierarchy of areas has been identified for each of three major sensory modalities – vision, touch, and audition[22,23]. All three converge into the polysensory association cortex and, in addition, into limbic structures of the temporal lobe, the hippocampus in particular. The processing of gustatory and olfactory information takes place mainly in paralimbic cortical areas of the temporal and frontal lobes, and their access to neocortical polymodal areas is still unclear.

The parasensory association areas, that is, those that lie nearest to the sensory cortex, store sensory memory in their networks. Lesion of these leads to agnosias or recognition deficits of the corresponding sensory modality. Microelectrode studies in the monkey show that, during the active (working) memory of sensory stimuli, cells in those areas are persistently activated[9]. Recent studies in monkeys and humans indicate that active perceptual memory may also involve the activation of cells in primary sensory areas, perhaps by backward projection from the association cortex[25,26]. That the same cortical areas serve both for storing perceptual memory and processing sensory information provides neural foundation to the intimate relation between perception and memory. Neural transactions within a common substrate help explain why memory shapes perception, one of the fundamental principles of psychophysics[27].

Ascending the cortical hierarchy of memory (and perception), as we enter the later developing areas (lighter blue areas in the cortical map of Fig. 3), we enter the substrate for more complex and extensive networks of polysensory and declarative (episodic and semantic) memory. Accordingly, as memories develop from their sensory base, they fan upwards; they become broader and more diffuse, encroaching into progressively more widely dispersed cortical domains. At any level, different memories share component nets and cells.

In the higher levels, the topography of memories becomes obscure because of the wider distribution of their networks, which link scattered domains of the association cortex representing separate qualities, however disparate, that have been associated by experience. Because these higher memories are more diffuse than simple sensory memories, they are in some respects more robust. After discrete cortical lesioning, only some of their associated attributes may become resistant to recognition or recall (for example, the name, date, face and place).

There is evidence that declarative memories, both episodic and semantic, are distributed principally in the posterior association cortex. Electrical stimulation of the surface of the posterior cortex induces a variety of sensory and mnemonic experiences, some of which have the characteristics of episodic memory[28,29]. Furthermore, retrograde amnesia can result from lesions of the posterior association cortex[30–32]. However, the idiosyncratic nature and wide distribution of episodic memory networks make it difficult to define their precise cortical topography by current conventional means.

Individuality and wide distribution also make it difficult to localize the subsequent form of declarative memory, that is, semantic memory, or the memory for words, facts and categories. Human neuropsychology, however, provides ample evidence of anomias, semantic aphasias and categorical amnesias from lesions of the posterior association cortex, including Wernicke's area, in the posterior third of the superior temporal gyrus[32–35]. Thus, it is reasonable to conclude, at least tentatively, that semantic memory is held by broad networks within that cortex.

There is no empirical evidence to suggest the topography of conceptual knowledge, the highest level of the perceptual memory hierarchy. This is understandable, as that kind of memory probably has the most widespread cortical distribution, based on multiple particular experiences and profuse cross-modal associations. This widespread distribution of its networks gives it an exceptional robustness. Only massive cortical damage leads to the inability to retrieve and use conceptual knowledge – the 'loss of abstract attitude' described by Kurt Goldstein[36].

So far I have emphasized the hierarchical stacking of perceptual memory categories in progressively higher and more widely distributed networks of the posterior cortex. Networks and memories of different rank are most likely heavily interconnected with one another, explaining the rarity of pure amnesias of any given memory category. Indeed memory categories are intermixed. A simple example will make the point: my memory of the sight and sounds of San Francisco's cable car (sensory memory) is associated with the memory of my last visit to that city (episodic memory), with the meaning of the term 'cable car' (semantic memory) and with the concept of public transportation (conceptual memory).

Thus, perceptual memories and their networks are most likely nested in each other, from the lowest to the highest, and interconnected vertically in the hierarchy (blue two-directional arrow in Fig. 3). Therein lies another reason why memories extend in the hierarchy not only horizontally but vertically, and why a given cell or cell group can be part of many networks or memories.

Some perceptual memory networks have motor associations and extend into the frontal lobe, where they link with motor memory networks. The converse, of course, is also true: motor networks extend into the posterior cortex. The reciprocal associations between sensory and motor cortex are most likely mediated by the long corticocortical fibres that undercross the rolandic (central) sulcus[23]. This reciprocal connectivity between sensory and motor memory (green arrows in Fig. 3) has obvious dynamic implications for sensory–motor integration and working memory.

Motor memory

Motor memory is the representation of motor acts and behaviors. It includes much, if not all, of what has been termed procedural memory. In mammals, the lowest levels of the motor hierarchy are in the spinal cord, brain stem and cerebellum. These structures store the relatively simple forms of motor memory, for example, the repertoire of reflex acts that mediate many of the innate defensive reactions. Much of the motor memory in lower structures qualifies as phyletic, in that it is largely innate, stereotypical and directed to the fulfilment of basic drives. It is also conditionable, subject to neocortical control and modulation. As a consequence, some of those structures, such as the cerebellum, are implicated in cognitive functions.

As first suggested by J. Hughlings Jackson, the cortex of the frontal lobe supports the highest levels of the hierarchy of motor memories (Fig. 3). At the lowest cortical level is the primary motor cortex, the postulated seat of phyletic motor memory, representing and mediating elementary motor acts. These acts are defined and determined by the contraction of specific muscles and muscle groups. Above the primary motor cortex, following the developmental and connective gradients of the motor hierarchy, lies the premotor cortex. In spatial and temporal coordinates, the representation and processing of movement in this cortex are more complex than in the motor cortex. Lesion[37,38] and cell-recording[39,40] studies indicate that premotor networks encode motor acts and programs defined by goal, sequence or trajectory, rather than by specific movement or muscle group. This agrees with the well documented participation of the premotor cortex in the formation of at least the most elementary structures of speech. The more complex and novel programs of behavior and speech appear represented in the next higher level, the prefrontal cortex.

The prefrontal cortex, conventionally considered the association cortex of the frontal lobe, is the highest level of the motor hierarchy[21]. This position connotes a role not only in the representation of complex actions (concepts of action, plans and programs) but in the operations for their enactment, including working memory. The prefrontal cortex develops late, both phylogenetically and ontogenetically, and receives fiber connections from numerous subcortical and limbic structures, as well as from other areas of the neocortex. They convey to it information about internal states and the external environment. Long fiber connections link reciprocally the perceptual memory networks of the posterior cortex with the prefrontal motor networks, thus forming perceptual–motor associations at the highest level.

Neuropsychology indicates that the networks of the prefrontal cortical areas represent the schemas of goal-directed action, commonly referred to as plans. Humans with prefrontal lesions have difficulty remembering, formulating and executing plans of behavior. Monkeys with similar lesions have difficulty learning tasks that require the sequencing of behavioral acts, especially if the acts are separated by temporal gaps. They are exceedingly slow in learning delay tasks (for example, delayed response and delayed alternation). Lesions in both monkeys and humans point to a degree of specificity in the kind of action schemas that different prefrontal regions support. However, regional specificity is overshadowed by the uniformity with which all prefrontal lesions induce a deficit in the formation of internal representations of sequential or temporally extended action ('temporal gestalts'), and in its execution. This deficit extends also to the elaborate spoken language (reviewed in Ref. 21).

After practice, frontal representations of action may become relocated in lower motor structures, notably the basal ganglia. Humans with frontal lesions cannot voluntarily perform complex movement sequences but retain their ability to perform automatic ones, even though these are just as complex and their learning originally required just as much wilful effort. In the monkey, cortical lesions may disrupt the learning of new skills but not the performance of old ones. Neuroimaging confirms the relocation evidence. The prefrontal cortex is only activated at first in the learning of certain complex sequences[41]. As the subject becomes proficient, cerebellar and striatal regions become progressively more active and cortical regions less so[42].

Memory dynamics

At any time in our daily life, the bulk of our long-term memory is dormant and out of consciousness. Presumably, the neuronal aggregates of its networks are relatively inactive (Fig. 1B,E). A network is reactivated when the memory it represents is retrieved by the associative processes of recall or recognition. An internal or external stimulus, whose cortical representation is part of the network by prior association, will reactivate that representation and, again by association, the rest of the network. Neither the stimuli nor

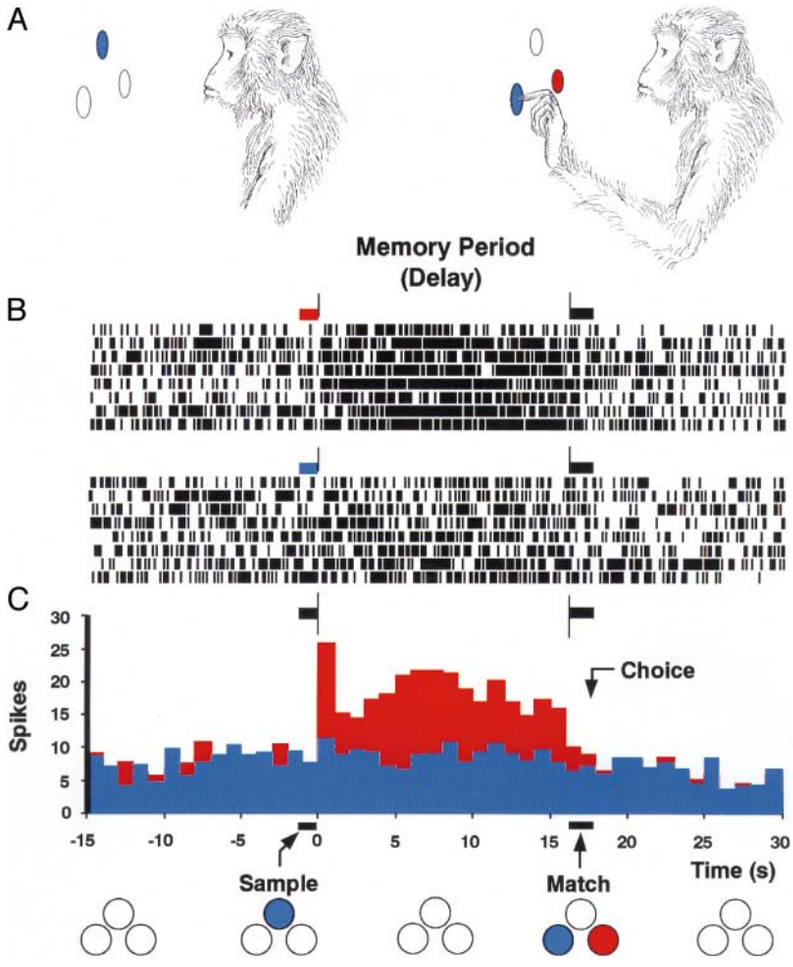

Fig. 4. ***Activity of a cell in the inferotemporal cortex of a monkey in a visual memory task.*** **(A)** *Trial begins with presentation of a sample color, which the animal must retain through the subsequent delay (memory period) for proper match and choice of color at the end of the trial (sample color and its position at the time of match are changed at random).* **(B)** *Cell-firing records from red- and green-sample trials are separated by color in the middle third of the figure (in this figure,* blue *substitutes for* green *for the benefit of deuteranopes).* **(C)** *Average frequency histograms. Note the elevated discharge of the cell during the memory period (16 s between sample and match) in red-sample trials; note also that, after the second appearance of red (for match), and in the absence of need to memorize the color, the activity of the cell drops to pre-trial baseline level.* Modified from Ref. 46.

the activated memory need be conscious. Fragments of a network may be subconsciously activated and still lead to the associative activation of other network components (priming).

In the reactivation of a cortical network, as in its generation, the hippocampus appears to play a crucial role. Patients with hippocampal lesions have trouble not only forming new memories but retrieving old ones. Hence they exhibit retrograde as well as anterograde amnesia[43,44]. Well-learned habits, however, remain retrievable. In any event, since new memory networks are the expansion of old ones, and the latter are reactivated as new memory is formed, the neural processes of memory formation and retrieval, and the roles of the hippocampus in them, are closely related if not identical.

Activated cortical networks can be studied best by electrical methods and neuroimaging. Field-potential research reveals their widespread dimensions and the role of electrical coherence in their activation[45]. Internal network dynamics can be studied by recording the discharge of cortical cells in behaving monkeys. By this means the cells of a network can be seen activated in the recognition and temporary retention of the memory that the network represents. Such is the case in performance of delay tasks, where memories must be retained for the bridging of time gaps in behavior. A delay task is composed of consecutive trials, each essentially consisting of: (1) a sensory cue; (2) a delay during which the subject must retain that cue; and (3) a motor response that is appropriate to the cue and provides evidence of its successful mnemonic retention.

In the trained animal, the cue (memorandum) at the beginning of each trial activates an extensive network comprising all the neuronal representations of perception and action associated with that cue. Both perceptual and motor (procedural) memory are activated. Thus, predictably, the cue excites cells in the posterior cortex involved in the processing of the cue and, in addition, frontal areas involved in the processing of the motor response associated with it. For example, if the cue is visual, cells will be activated in the inferotemporal cortex and also in certain areas of the prefrontal cortex. Because the monkey has to retain the cue through a period of delay for subsequent correct response, the network representing the cue has to stay activated during that period. Thus, inferotemporal memory cells (Fig. 4) will show activation throughout that period[46,47].

In addition, because the cue is a signal for prospective action, it activates a prefrontal network representing that action and preparing the motor apparatus for it[21]. Hence the sustained activation of prefrontal cells during the delay of all memory tasks, regardless of the sensory modality of the cue, though with some areal specificity depending on that modality and on the nature of the motor response. In humans, prefrontal areas are activated while the memorandum is being retained for prospective action[48,49]. Many neuropsychological studies emphasize the spatial aspects of prefrontal working memory. In our experience with neuroimaging[50], prefrontal activation occurs in the human even if the sensory information retained in short-term memory is nonspatially defined (Fig. 5). Prefrontal activation reflects the activation of motor memory and, by functional linkage with the posterior cortex, the persistent activation of perceptual memory as needed for prospective action.

Thus, working memory is the temporary, *ad hoc,* activation of an extensive network of short- or long-term perceptual and motor memory. The perceptual component of that network would be, as any other perceptual memory, retrievable and expandable by a new stimulus or experience. Working memory presumably has the same cortical substrate as the kind of short-term memory traditionally considered the gateway to long-term memory. Both fall under the category of active memory, which differs from passive long-term memory in the state of the network, not in its cortical distribution. A corollary idea is that the cortical dynamics of evoking episodic memory is identical to that of evoking a familiar stimulus, such as the cue in a delay task. Although that cue is represented in the posterior cortex, the prefrontal cortex is essential for its retention towards prospective action. That is the reason why this cortex is so important for the sequencing of behavior, thinking and speech. All three require working memory.

Before considering briefly the mechanisms of working memory, we must re-emphasize its link to long-term

memory. Indeed, the red or green cue (see Fig. 4), for example, is an old memory reactivated. It may not evoke the episodes that led to the acquisition of its meaning, but it certainly evokes that meaning as well as the procedural memory of the task. It is because the monkey has been there before that he can perform the task.

When, as in a delay task, temporal integration demands the retention of old, reactivated perceptual memory across a time gap, that retention is a joint function of the posterior and prefrontal cortex. The likely underlying mechanism is the reverberation of activity through recurrent circuits. Impulse re-entry explains the sustained neuronal discharge that can be observed in both cortices during delay periods. It has been successfully modeled in artificial recurrent networks[11,51]. However, recurrent activation has not yet been empirically identified as the local mechanism of active short-term memory. Other mechanisms are possible, for example, short-term potentiation or transient phosphorylation of neuroreceptors.

In the monkey performing a visual memory task, the impulse re-entry can take place through long reciprocal connections between the inferotemporal and prefrontal cortex. Thus the retention of the cue depends on the functional integrity of both the inferotemporal and the prefrontal components of the network. Consequently, correct performance of the task (see Fig. 4) can be reversibly impaired by temporarily cooling either the prefrontal[52] or inferotemporal[53] cortex. Further, by cooling one of those two cortices, prefrontal or inferotemporal, and by cell recording from the other, more direct evidence of re-entrant activity between them in visual working memory can be obtained[54]. Tonic influences from the prefrontal cortex play a role in the sustained activation of visual memory in the inferotemporal cortex (Fig. 6).

In summary, both the evocation of old perceptual memories and the formation of new ones seem to entail the associative activation of the vast neuronal networks of the posterior cortex that represent them in their connective structure. If an evoked memory is associated with an action (for example, a manual response, a verbal response or a mental operation), then the activated network extends to the frontal lobe. The need to hold memory for prospective action leads to the recruitment of prefrontal networks. These send tonic influences to the posterior cortex and keep the perceptual network active until completion of the action.

Concluding comments

In conclusion, the empirical evidence thus far indicates that, in humans and nonhuman primates, memory is stored in overlapping and widely distributed networks of interconnected cortical neurons. Because cortical connectivity can serve practically infinite potential associations, potential networks are practically infinite, and this fact confers uniqueness to the cognitive memory of a given individual.

According to the views expressed in this article, memory networks are made by simultaneous activation of neuronal assemblies representing external and internal events and inputs, including inputs from reactivated networks of long-term memory. Networks remain open-ended throughout life, subject to expansion and recombination by new experience.

The networks of perceptual and motor memory appear hierarchically organized on a foundation of phyletic memory – that is, primary sensory and motor cortex. Hierarchical organization, however, does not imply that the various individual memories are rigidly stacked and stored in separate cortical domains. Rather, different types of memory – for example, episodic, semantic or procedural – are probably interlinked in mixed networks that span different levels of perceptual and motor hierarchies.

It follows from the present discussion that any attempt to localize different memories or types of memory beyond our general outline might be fruitless.

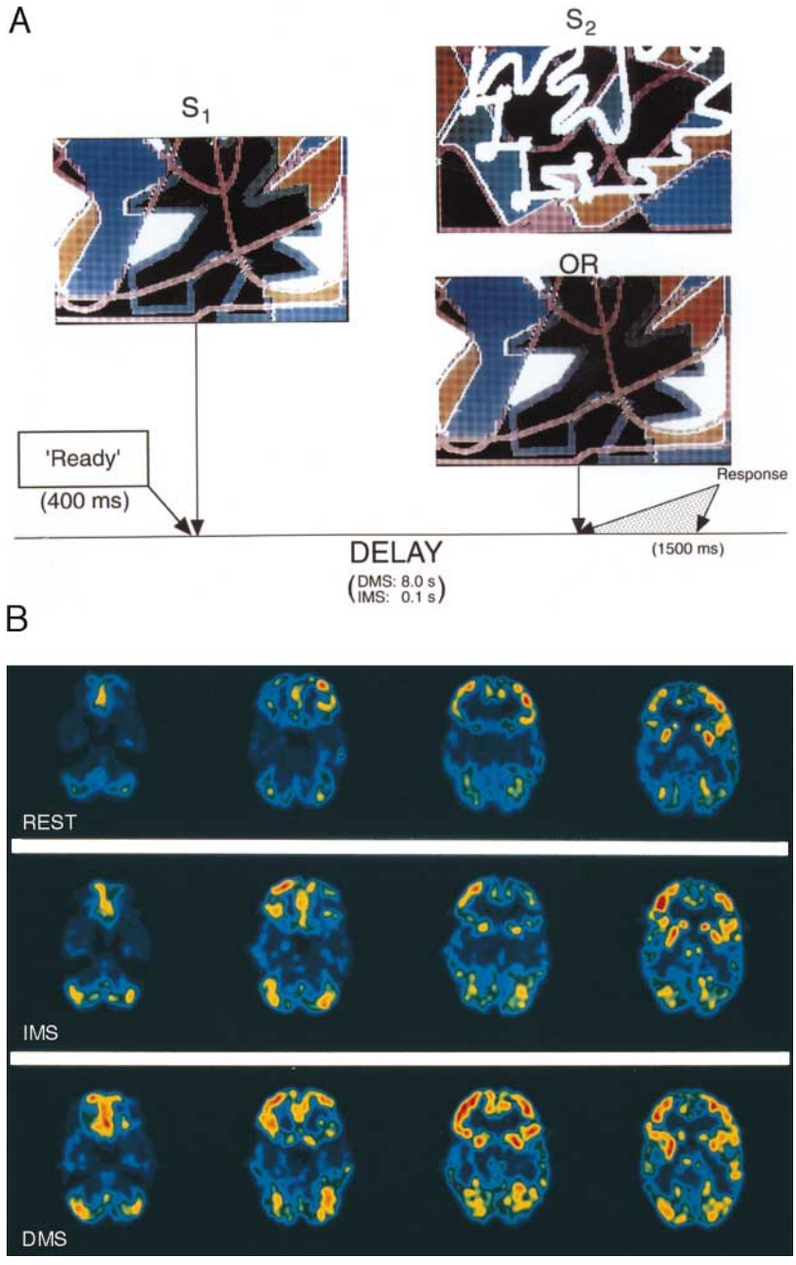

Fig. 5. ***Results from a FDG-PET study of nonspatial working memory in humans.*** **(A)** *Diagram of delayed match-to-sample (DMS) task. Each trial begins with an acoustic signal (ready), immediately succeeded by an abstract picture on a screen. After 8 s delay (memory period), another picture appears, which may or may not be identical to the first. If it is, the subject presses one button, if not, another. Pictures change at random from one trial to the next. A control (no memory) task, immediate match-to-sample (IMS), is identical in every respect to the DMS task but without delay.* **(B)** *Four slices from the scan of one subject after fluoro-deoxyglucose (FDG) uptake at rest and during performance on equal blocks of trials of the two tasks (IMS and DMS). Activation scale ranges from 30 (black) to 256 (red) intensity. Note intense activation of prefrontal cortex and visual areas (upper and lower portions of slices, respectively) during the DMS memory task.*

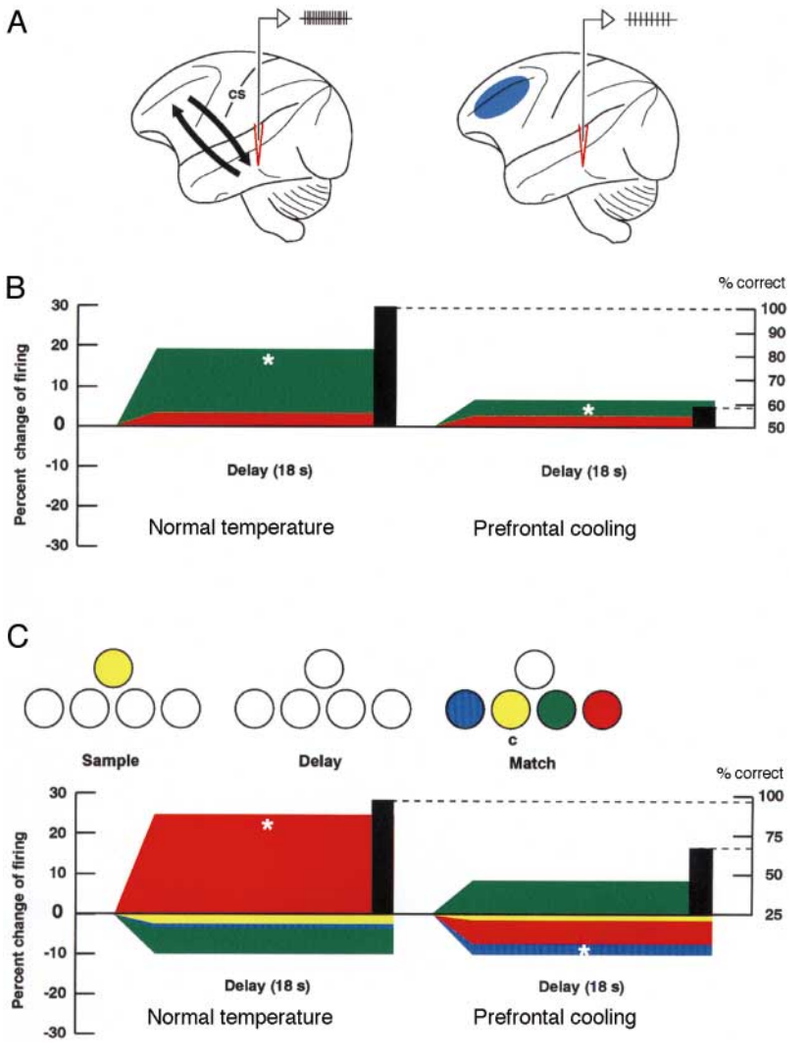

Fig. 6. ***Effects of cooling the dorsolateral prefrontal cortex on memory cells in the inferotemporal cortex during performance of memory tasks.*** *The prefrontal area cooled includes cortex of the inferior dorsolateral convexity, reciprocally connected with inferotemporal cortex.* **(A)** *Diagrams of the monkey's brain schematically indicating inferotemporal–prefrontal connections (arrows), inferotemporal recording microelectrode (red) and the prefrontal area reversibly depressed by cooling bilaterally to 20°C (blue). Abbreviation: CS, central sulcus.* **(B)** *Average activity of an inferotemporal cell in the memory period (delay) of the two-color task in Fig. 3. Colors in the graph match colors of the stimuli-memoranda. The cell is persistently and preferentially activated during retention of green (* denotes statistically significant deviations from pre-trial baseline). Prefrontal cooling attenuates the color differentiation during the delay and causes behavioral performance to drop from 100% to 59% correctness (black bars).* **(C)** *Delayed matching with four colors and delay activity of a cell in this four-color task. Colors in the graph match memoranda. The cell is especially activated during retention of red. Prefrontal cooling abolishes that activation while the animal's performance drops. * denotes statistically significant deviations from pre-trial baseline. Abbreviation: c, correct choice.* Modified from Ref. 54.

Memory is a property of the neurobiological systems it serves and inseparable from their other functions. In the cortex, memory can be allocated to different areas in so far as those functions can. Thus, the perceptual–motor dichotomy of memory distribution has validity inasmuch as perceptual and motor systems can be separated. So does the parceling into sensory and motor memories immediately above their phyletic base. Beyond that, however, the admixture, interconnection and overlap of cortical networks supporting higher memories makes the cortical topography of those memories only plausible within the bounds proposed here. This degree of localization, however, is fully compatible with the appearance, after discrete cortical injury, of selective amnesias for certain forms of semantic memory or for certain attributes of episodic memory. Within the present framework, these amnesias are explainable as the result of injury to certain network nodes of heavy semantic association or to those representing critical fragments of an episodic memory.

These considerations can be extended to deal with more conventional concepts of memory structure and dynamics. Clearly the classic terms representation, retrieval, recall, recognition, short-term memory and long-term memory are still valid for current discourse, but need to be neurobiologically redefined. Representation, in my view, is synonymous with network. Arguably, the smallest memory network (netlet) is the cortical cell group or module representing a simple sensory or motor feature in the interface between the organism and its environment. From there on up, networks (representations) become larger, made of associations between progressively larger numbers of nets, these becoming nets within nets.

All aspects of memory retrieval, including recall and recognition, can be viewed as the activation of network memory, that is, the increased firing of the cortical neurons making up a memory network. To use Braitenberg's term[55], the network would be 'ignited'. It is an intriguing possibility, however, that under certain circumstances (for example, recognition), the activation of a network (that is, the activation of the relational code that a network contains) takes place by rapid correlation of electrical activity (dendritic or action potentials) in all of its components[56]. All elements of the network would thus be activated *d'emblée*, in parallel. Such a mechanism can explain both perceptual binding and memory binding as the associative and correlated activation of the very same network that perception and memory share. This proposition would not only agree with psychophysics but would explain the rapid, context-dependent retrieval of rare and highly specific memories.

At any one time, however, not all elements of an active network need be activated to the same level. In the course of behavior, as argued elsewhere[9], much memory processing can take place in parallel and out of consciousness. Only a limited part of a network may reach, at any given time, a level of activation consistent with consciousness and serial processing. Obviously that would be the case for network components in working memory or under the focus of attention.

Finally, the evidence from microelectrode and imaging studies is forcing us to re-evaluate the neural basis of short- and long-term memory, and to seriously question their structural separateness. As noted above, working memory activates extensive cortical regions. These regions include areas identified as the substrate for the long-term storage of what the working-memory test requires the subject to retain. Thus it appears that both kinds of memory share the same substrate. The evidence we have obtained of functional interactions, in working memory, between neurons in separate cortical areas further argues for a common and widely distributed substrate. Indeed, whatever its cortical distribution, one and the same network probably serves to store a long-term memory, and to retain actively that memory for the short term.

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Central clocking

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The main questions in circadian neurobiology are: how many oscillators are involved; how are their daily oscillations generated and synchronized to the external world; and how do they signal time of day to the organism. The suprachiasmatic nuclei of the hypothalamus (SCN) are well established as the principal circadian oscillator of mammals. Their 10 000 or so 'clock' neurones drive our overt rhythms – the daily patterning we observe in our physiology and behaviour being mirrored perfectly by their spontaneous cycle of neuronal activity. However, they are not our only circadian oscillator, their molecular timekeeping is not understood and the ways in which they communicate with other parts of the brain are more unusual than was previously assumed.

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CIRCADIAN CLOCKS have a powerful influence on when we enter and leave this world, and what we do for most of the intervening period. Spontaneous births are most prevalent at night[1], myocardial infarcts and strokes occur most often in the morning[2], and in between these life events our behavioural and metabolic functions change progressively and predictably over the 24 h cycle. This internal temporal programme matches us to our world and disruption of the programme, as seen for example in shift workers, can carry a severe penalty with poor mental and physical performance, and diminished sense of well-being[3]. Equally, the ageing clock shows a progressive loss of precision and sensitivity to light[4] which might underlie the poor quality of sleep that is such a chronic and characteristic problem for the growing

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