REVIEW ARTICLE

From sensation to cognition

M.-Marsel Mesulam

The Cognitive Neurology and Alzheimer's Disease Center, Departments of Neurology and Psychiatry and Behavioral Sciences, Northwestern University Medical School, Chicago, USA

Correspondence to: M. Mesulam, Cognitive Neurology and Alzheimer's Disease Center, Northwestern University Medical School, 320 East Superior Street, 11–450, Chicago, IL 60611, USA. E-mail: mmesulam@nwu.edu

Summary

Sensory information undergoes extensive associative elaboration and attentional modulation as it becomes incorporated into the texture of cognition. This process occurs along a core synaptic hierarchy which includes the primary sensory, upstream unimodal, downstream unimodal, heteromodal, paralimbic and limbic zones of the cerebral cortex. Connections from one zone to another are reciprocal and allow higher synaptic levels to exert a feedback (top-down) influence upon earlier levels of processing. Each cortical area provides a nexus for the convergence of afferents and divergence of efferents. The resultant synaptic organization supports parallel as well as serial processing, and allows each sensory event to initiate multiple cognitive and behavioural outcomes. Upstream sectors of unimodal association areas encode basic features of sensation such as colour, motion, form and pitch. More complex contents of sensory experience such as objects, faces, word-forms, spatial locations and sound sequences become encoded within downstream sectors of unimodal areas by groups of coarsely tuned neurons. The highest synaptic levels of sensory-fugal processing are occupied by heteromodal, paralimbic and limbic cortices, collectively known as transmodal areas. The unique role of these areas is to bind multiple unimodal and other transmodal areas into distributed but integrated multimodal representations. Transmodal areas in the midtemporal cortex, Wernicke's area, the hippocampal–entorhinal complex and the posterior parietal cortex provide critical gateways for transforming perception into recognition, word-forms into meaning, scenes and events into experiences, and spatial locations into targets for exploration. All cognitive processes arise from analogous associative transformations of similar sets of sensory inputs. The differences in the resultant cognitive operation are determined by the anatomical and physiological properties of the transmodal node that acts as the critical gateway for the dominant transformation. Interconnected sets of transmodal nodes provide anatomical and computational epicentres for large-scale neurocognitive networks. In keeping with the principles of selectively distributed processing, each epicentre of a large-scale network displays a relative specialization for a specific behavioural component of its principal neuropsychological domain. The destruction of transmodal epicentres causes global impairments such as multimodal anomia, neglect and amnesia, whereas their selective disconnection from relevant unimodal areas elicits modality-specific impairments such as prosopagnosia, pure word blindness and category-specific anomias. The human brain contains at least five anatomically distinct networks. The network for spatial awareness is based on transmodal epicentres in the posterior parietal cortex and the frontal eye fields; the language network on epicentres in Wernicke's and Broca's areas; the explicit memory/emotion network on epicentres in the hippocampal–entorhinal complex and the amygdala; the face-object recognition network on epicentres in the midtemporal and temporopolar cortices; and the working memory-executive function network on epicentres in the lateral prefrontal cortex and perhaps the posterior parietal cortex. Individual sensory modalities give rise to streams of processing directed to transmodal nodes belonging to each of these networks. The fidelity of sensory channels is actively protected through approximately four synaptic levels of sensory-fugal processing. The modality-specific cortices at these four synaptic levels encode the most veridical representations of experience. Attentional, motivational and emotional modulations, including those related to working memory, novelty-seeking and mental imagery, become increasingly more pronounced within downstream components of unimodal areas, where they help to create a highly edited subjective version of the world. The prefrontal cortex plays a critical role in these attentional and emotional modulations and allows neural responses to reflect the significance rather than the surface properties of sensory events. Additional modulatory

influences are exerted by the cholinergic and mono-aminergic pathways of the ascending reticular activating system. Working memory, one of the most prominent manifestations of prefrontal cortex activity, prolongs the neural impact of environmental and mental events in a way that enriches the texture of consciousness. The synaptic architecture of large-scale networks and the manifestations of working memory, novelty-seeking behaviours and mental imagery collectively help to loosen the rigid stimulus–response bonds that dominate the behaviour of lower animal species. This phylogenetic trend has helped to shape the unique properties of human consciousness and to induce the emergence of second-order (symbolic) representations related to language. Through the advent of language and the resultant ability to communicate abstract concepts, the critical pacemaker for human cognitive development has shifted from the extremely slow process of structural brain evolution to the much more rapid one of distributed computations where each individual intelligence can become incorporated into an interactive lattice that promotes the transgenerational transfer and accumulation of knowledge.

Introduction

A major task of the CNS is to configure the way in which sensory information becomes linked to adaptive responses and meaningful experiences. Small brains cope with this challenge by shifting the detection of significant events to peripheral organs. In the frog, for example, the inner ear is selectively tuned to spectral and temporal properties of species-specific mating calls (Capranica, 1978) and the retinotectal projection contains 'bug perceiver' fibres that respond best when a dark object, smaller than a receptive field, enters that field, stops, and moves about intermittently (Lettvin *et al.*, 1959). Although this type of automatic pattern detection maximizes the limited processing capacity of the CNS, it also restricts the range of events that can be identified and the flexibility with which they become interpreted.

Inflexible bonds between sensation and action lead to instinctual and automatic behaviours that are resistant to change, even when faced by negative consequences. For example, frogs whose optic nerve has been cut and allowed to fully regenerate after a 180° rotation of the eye will repeatedly snap at mud and moss on the ground when presented with a fly above the head (Sperry, 1965); a turkey hen, whose protective maternal instincts dictate an attack on any moving object that fails to utter the characteristic peep of her chicks, will peck her own newly hatched progeny to death if she is made deaf (Schleidt and Schleidt, 1960); a herring gull whose eggs have been displaced to an adjacent and clearly visible site will proceed to incubate the emptied original nest and ignore the clutch of eggs lying right next to her (Tinbergen, 1951); and rats with crossed sensory nerves in the hind limbs, one of which is inflamed, will hop on three legs to protect the healthy rather than the sore foot (Sperry, 1965).

Advanced mammals with an intact CNS are less vulnerable to the emergence of such inflexible patterns. With the exception of some autonomic, brainstem and spinal reflexes, the behaviour of primates displays a much greater latitude in translating sensation into action, so that identical sensory events can potentially trigger one of many different reactions, depending on the peculiarities of the prevailing context. A stimulus that deserves to be approached in one setting may need to be avoided in another; highly desirable consummatory acts may need to be postponed in the presence of danger; the same glass may appear half-full or half-empty depending on mood; and a *petite madeleine* can trigger a spectrum of reactions ranging from brief salivation to a torrent of words that can hardly be contained by seven volumes of compact prose. This loosening of stereotyped stimulus–response linkages endows the organism with the biological freedom to choose one of many potentially available responses. The resultant coarse mapping of responses onto circumstances creates a setting where the rules of competitive selection can operate to promote rapid change and adaptation.

Streams of sensory processing in amphibians, reptiles and birds are kept on a short leash: the synaptic interval between the onset of a sensory event and its closure in the form of multimodal convergence, perceptual recognition, motivational valuation and action is brief, usually of the order of one or two synapses (Ingle, 1975; Northcutt, 1978; Gorlick *et al.*, 1984; Gaillard, 1990). The CNS of advanced mammals displays major modifications in this plan of organization. The fidelity of sensory encoding is enhanced by reserving vast areas of the cerebral neocortex for modality-specific processing. The opportunities for subsequent integration are enhanced by the development of extensive multimodal association areas. And an intrinsic bias emerges to pursue novelty and flexibility rather than sameness and stereotypy. The emergence of behavioural flexibility in mammals can be attributed to an expansion of the synaptic bridge that links sensation to action and recognition. An excessive length in such a synaptic bridge could have led to unacceptable delays in reacting to the environment, whereas too many lanes could have undermined the capacity for

integration. As will be shown below, primate evolution reflects a compromise between such extremes: the synaptic chain that links sensation to action has been lengthened, but not by too many synapses; and the bridge between the two has been broadened by the introduction of numerous parallel lines of communication, but with ample opportunities for integrative interaction among individual channels.

The neural systems that bridge the gap between sensation and action provide the substrates for 'intermediary' or 'integrative' processing. The behavioural outcome of intermediary processing is known as 'cognition', and includes the diverse manifestations of memory, emotion, attention, language, thought and consciousness. The synaptic volume dedicated to intermediary processing shows a marked increase in phylogeny and occupies the great majority of the cerebral cortex in advanced primates and cetaceans. These intermediary areas of the brain enable identical stimuli to trigger different responses depending on the situational context, past experience, present needs and contemplated consequences.

The neurons that support intermediary processing are located predominantly within the 'association' and 'limbic' areas of the cerebral cortex. The importance of the cerebral cortex to behaviour varies from species to species. In the fish, frog and pigeon, decortication produces little change in sensation or locomotion (Ferrier, 1876; Northcutt, 1978). Extensive neocortical lesions in hamsters, cats and monkeys cause considerably lesser and more reversible functional deficits than analogous lesions in humans (Lashley, 1952; MacLean, 1982). Furthermore, cortical lesions may be far more effective than tectal lesions in causing deficits such as hemispatial neglect in monkeys, whereas the converse relationship is seen in cats (Mesulam *et al.*, 1977). These observations point to the existence of a trend towards a progressive corticalization of function, and suggest that cognition, defined as the behavioural outcome of intermediary processing in the cerebral cortex, becomes established as an obligatory rather than a facultative correlate of information processing in the course of evolution.

The synaptic arrangement of neural pathways involved in intermediary processing provides biological constraints that shape the nature of cognition and comportment. The goal of this review is to sketch some of the principles that guide the organization of these pathways. Several limitations will become apparent in the course of the following account. First, much of the discussion will be limited to the cerebral cortex and will omit the very important contributions of subcortical structures such as the thalamus, striatum, claustrum and brainstem. Second, only visual and auditory streams of processing will be discussed in any detail. Third, although domains such as perception, language, memory, attention and emotion will be addressed, this will be done in a very limited fashion, to provide highly selective examples of common principles that link sensation to cognition. Fourth, although several phylogenetic trends will be mentioned, including numerous references to the CNS in the frog, only

the monkey and human brains will be discussed in any serious detail. Fifth, the subject matter will lead to a discussion of consciousness, but only in the form of a brief incursion into realms of immense philosophical complexity.

Behavioural neuroanatomy of the cerebral cortex
Functional zones

The human cerebral cortex contains ~20 billion neurons (Pakkenberg and Gundersen, 1997). The absence of clear anatomical demarcations has encouraged the development of numerous independent approaches to the subdivision of the cerebral cortex. The resultant maps can be divided into two groups: those based primarily on structural (architectonic) features, and those based primarily on functional affiliations. Proponents of one school have constructed a wide variety of cortical maps, ranging in complexity from the map of Exner (1881), which boasted hundreds of sharply delineated subdivisions, to the more modest and also more widely accepted ones of Brodmann (1909), the Vogts (Vogt and Vogt, 1919), von Economo (Economo and Koskinas, 1925) and Flechsig (1920). The second school is more difficult to identify since few of its proponents have produced systematic surveys of the entire brain. Members of this second school include theoreticians of brain function such as Campbell (1905), Broca (1878), Abbie (1942), Filimonoff (1947), Yakovlev (1959) and Sanides (1970). The thinking of this school has led to the subdivision of the cerebral cortex into the five major functional subtypes that will be described below: primary sensory–motor, unimodal association, heteromodal association, paralimbic and limbic (Mesulam, 1985*b*). The principal factual base for this parcellation is derived from anatomical, physiological and behavioural experiments in macaque monkeys. The homologies to the human brain have been inferred from comparative cyto-architectonics, electrophysiological recordings, functional imaging, and the behavioural effects of focal lesions. Unless stated otherwise, the descriptions in this section can be assumed to apply to the brains of both species.

The primary sensory and motor cortices are easily delineated on cytoarchitectonic and functional grounds. The primary visual cortex [also known as V1, striate cortex, calcarine cortex or Brodmann area (BA) 17] covers the banks of the calcarine fissure; the primary auditory cortex (also known as A1, or BA 41–42) covers Heschl's gyrus on the floor of the Sylvian cistern; the primary somatosensory cortex (also known as S1 or BA 3b) covers the anterior flank of the postcentral gyrus; the primary gustatory cortex is probably located in the fronto-insular junction in BA 43; and the primary motor cortex (also known as M1) includes BA 4 and probably also a posterior rim of BA 6 in the precentral gyrus. The primary sensory areas provide an obligatory portal for the entry of sensory information into the cortical circuitry, whereas the primary motor cortex provides a major gateway

for relaying complex motor programmes into bulbar and spinal motoneurons. The primary sensory areas (where densely packed small neurons give rise to a distinctive koniocortical architecture) and the primary motor cortex (where large pyramidal neurons give rise to a distinctive macropyramidal architecture) represent the most highly differentiated and specialized subdivisions of the cerebral cortex (Mesulam, 1985b).

Sensory-fugal processing starts with the transfer of information from primary sensory areas to unimodal association areas. These areas fulfil three criteria: (i) their major source of sensory-fugal projections is located in primary sensory areas and other unimodal association areas in that modality; (ii) the constituent neurons respond to stimulation predominantly, if not exclusively, in that particular sensory modality; and (iii) lesions lead to behavioural deficits confined to tasks under the control of that particular sensory modality. Unimodal areas can be divided into upstream and downstream components: upstream areas are only one synapse away from the relevant primary sensory area whereas downstream areas are at a distance of two or more synaptic units from the corresponding primary area.

The unimodal visual association cortex can be divided into an upstream peri-striate component which includes areas BA 18–19, and a downstream temporal component which includes the inferotemporal regions (BA 21–20) in the monkey, and the fusiform, inferior temporal and perhaps parts of the middle temporal gyri in humans.[1] The unimodal auditory association cortex covers the superior temporal gyrus (BA 22) and perhaps also parts of the middle temporal gyrus (BA 21) in the human (Creutzfeldt *et al.*, 1989). The connectivity of the monkey brain would suggest that the posterior parts of the superior temporal cortex (BA 22) display the properties of upstream auditory association cortex whereas the more anterior parts of this gyrus and the dorsal banks of the superior temporal sulcus may fit the designation of downstream auditory association cortex (Pandya and Yeterian, 1985). In the monkey brain, rostral BA 5 represents the upstream component of somatosensory unimodal association cortex, whereas caudal BA 5 and BA 7b may represent its downstream components (Pandya and Yeterian, 1985). In the human, unimodal somatosensory association cortex may include BA 5, parts of BA 7 and perhaps BA 2. The subdivision of unimodal auditory and somatosensory association cortices into upstream and downstream areas remains to be elucidated in the human brain. Premotor regions (anterior BA 6 and caudal BA 8) fulfil the role of motor association areas because they provide the principal cortical input into the primary motor cortex.

The next stage of sensory-fugal processing occurs in

heteromodal association areas, which are characterized by three criteria: (i) they receive convergent inputs from unimodal areas in more than one modality; (ii) unit recordings show that constituent neurons respond to stimulation in more than one sensory modality or that neurons responding to one modality are interspersed with those that respond to another; (iii) lesions always yield multimodal behavioural deficits. The monkey brain has heteromodal areas in the prefrontal cortex (BA 9, 10, 45, 46, anterior BA 8, anterior BA 11–12), in the inferior parietal lobule (parts of BA 7), in the banks of the superior temporal sulcus (junction of BA 22 with BA 21), and in the parahippocampal region (Pandya and Yeterian, 1985). In the human brain the analogous realms of the heteromodal cortex are located in the prefrontal cortex, the posterior parietal cortex (posterior BA 7, BA 39–40), parts of the lateral temporal cortex (probably corresponding to parts of BA 37 and BA 21) and portions of the parahippocampal gyrus (parts of BA 35–36). The unimodal and heteromodal areas are characterized by a six-layered homotypical architecture. The columnarization and laminar differentiation of neurons is more conspicuous in unimodal than heteromodal areas. If primary sensory and motor areas constitute the most highly specialized and differentiated parts of the cortex, unimodal and heteromodal areas occupy the two subsequent levels of differentiation.

A further stage of sensory-fugal processing occurs in a group of areas designated paralimbic. These areas provide a zone of gradual cytoarchitectonic transition between the homotypical isocortex and the more primitive allocortex of core limbic structures. The primate brain contains five paralimbic regions: the caudal orbitofrontal cortex (caudal BA 11–12, BA 13), the insula (BA 14–16), the temporal pole (BA 38), the parahippocampal gyrus (BA 27, 28 and parts of BA 35), and the retrosplenial-cingulate-parolfactory complex (BA 23–26 and BA 29–33). These paralimbic formations can be divided into two groups. The temporopolar-insular-orbitofrontal regions merge into each other and constitute the olfactocentric subdivision of the paralimbic belt because they provide a transition between the olfactory allocortex and the homotypical cortex. The amygdala is the major core limbic structure associated with this set of paralimbic regions. The parahippocampal and posterior cingulate regions constitute the hippocampocentric subdivision of the paralimbic zone because they provide a transition between the hippocampal formation (including its induseal rudiment) and the homotypical cortex. These two subdivisions collectively form a gapless paralimbic ring which encircles the medial and basal components of the cerebral hemispheres (Mesulam and Mufson, 1985).

The last cortical stage in the sensory-fugal stream of information processing occurs within five core limbic formations: the hippocampal complex, the amygdaloid complex, the prepiriform olfactory cortex, the septal area and the substantia innominata. These regions are characterized by two properties: they display a primitive allocortical architecture (palaeocortical in the case of olfactory areas,

---

[1] Approximately half of middle temporal gyrus (MTG) neurons respond to speech (Creutzfeldt *et al.*, 1989; Vincent *et al.*, 1997). However, some tasks based on visually presented faces, words and objects can also activate the MTG (Vandenberghe *et al.*, 1996; Gorno Tempini *et al.*, 1997; Schultz *et al.*, 1997). At this time it is not clear whether all of the MTG should be classified as heteromodal cortex or whether it should be divided into sections of unimodal auditory, heteromodal, and unimodal visual cortex.
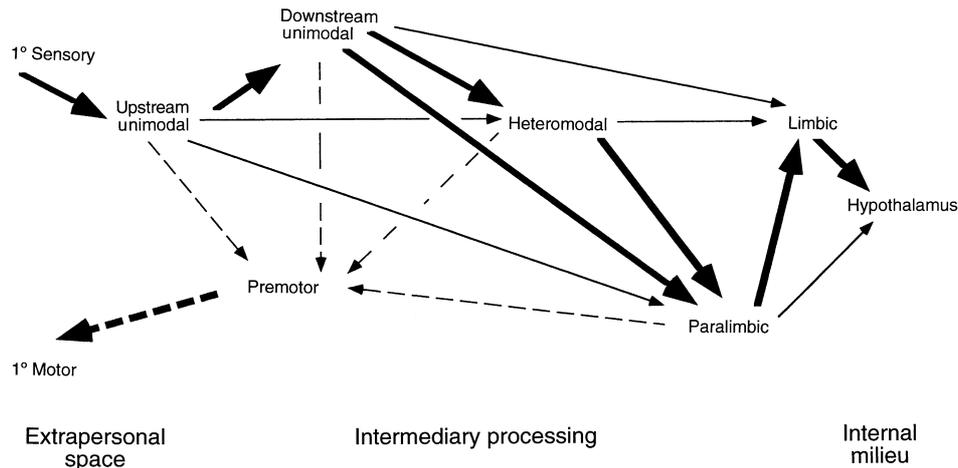
Fig. 1 The straight arrows illustrate monosynaptic sensory-fugal neural connections in the visual and auditory modalities. The thick arrows represent more massive connections than the thin arrows. The broken arrows illustrate motor output pathways. The latter are not discussed in this review.

archicortical in the case of the hippocampus, and corticoid in the case of the amygdala, septum and substantia innominata), and they have massive reciprocal connections with the hypothalamus.

The entire cortical surface can thus be divided into five functional zones which collectively display a continuous spectrum of cytoarchitectonic differentiation from the most highly differentiated primary sensory–motor areas to the least differentiated limbic structures. This architectonic hierarchy is paralleled by a relative hierarchy (or polarization) of connectivity. Figure 1 illustrates the sensory-fugal gradient of connectivity which sequentially conveys sensory information about the extrapersonal environment from the primary sensory to the upstream unimodal, downstream unimodal, heteromodal, paralimbic and limbic areas of the monkey brain (Pandya *et al.*, 1981; Mesulam and Mufson, 1985; Pandya and Yeterian, 1985; Van Essen, 1985; Morán *et al.*, 1987; Morecraft *et al.*, 1992; Aggleton, 1993). Some connections, as in the case of the projection from the posterior superior temporal gyrus to the entorhinal cortex (Amaral *et al.*, 1983), cross levels. However, such connections are not as prominent as those that extend between two adjacent levels. Figure 1 is based on the organization of visual and auditory pathways. Although somatosensory pathways follow many of the same principles of organization, they also display unique properties such as the existence of monosynaptic connections between primary sensory and primary motor areas. Olfactory and gustatory pathways have been excluded from this analysis because they represent chemical senses and follow a different plan of organization, reflecting a closer relationship to the internal than to the external milieu.

As noted above, only the constituents of the limbic zone have massive reciprocal monosynaptic connections with the hypothalamus, a nuclear complex that functions as the principal coordinator of the homeostatic, autonomic and hormonal aspects of the internal milieu. In keeping with this connectivity, the behavioural affiliations of the limbic zone are polarized towards the internal milieu and deal with the regulation of emotion, motivation, memory and autonomic–endocrine function. The opposite pole of this spectrum is occupied by the primary sensory–motor areas, which display the most highly differentiated cytoarchitecture and which are polarized towards the extrapersonal world rather than the internal milieu. The zones of unimodal, heteromodal and paralimbic areas are inserted between these two extremes and act as neural bridges that link the inside to the outside world so that the needs of the internal milieu can be discharged according to the opportunities and restrictions presented by the extrapersonal environment. Within the context of these behavioural affiliations, the unimodal and heteromodal areas are most closely involved in perceptual elaboration and motor planning, whereas the paralimbic areas play a more critical role in channelling emotion and motivation to behaviourally relevant intrapsychic and extrapersonal targets. This functional landscape of the cerebral cortex provides the basic template for linking sensation to cognition in the primate brain.

Connections and multimodal convergence

The literature of the 1940s and 1950s expressed considerable ambivalence about the status of the cerebral cortex in mental functioning and tended to ignore the seminal contributions of Hughlings Jackson, Ferrier, Charcot, Dejerine, Wernicke and Liepmann. Wilder Penfield (1938), for example, had attributed the highest levels of integration to thalamic activity and Karl Lashley (1952) had raised serious doubts about the existence of functional specializations in the association cortex, even in the monkey. The modern resurgence of interest in the cerebral cortex can be traced to the publication of the 'disconnexion syndromes' papers by Norman Geschwind (1965). Based on a comprehensive review of the literature, Geschwind suggested that the critical neural substrate of mental function revolved around precisely

organized cortico-cortical pathways that interconnect behaviourally specialized regions of the cerebral cortex. This inference was particularly interesting, since very little was known then about the details of cortical connectivity. At about the same time, new methods based on the selective silver impregnation of degenerated axons were becoming available and enabled a detailed investigation of cortico-cortical connectivity in monkeys. The basic organization of these connections was described in two classic papers, one by Pandya and Kuypers (1969) and the other by Jones and Powell (1970). These papers outlined an orderly and hierarchical connectivity, mostly consistent with Geschwind's account, for linking sensory cortices to primary, secondary and sometimes even tertiary modality-specific association areas, which in turn sent convergent projections to multimodal sensory association zones. Such multimodal sensory convergence areas were identified in the posterior parietal, lateral prefrontal and temporal cortices of the rhesus monkey.

The field of neuroscience had been primed to anticipate such a sequential organization through the work of Hubel and Wiesel (1965), who had demonstrated a hierarchy of simple, complex and hypercomplex neurons in the primary visual cortex, each successive level encoding a more composite aspect of visual information. The discoveries of Pandya and Kuypers and of Jones and Powell seemed to be extending this serial and convergent organization from the realms of the primary sensory cortex and sensation to those of the association cortex and cognition. A great deal of emphasis was placed on the pivotal role of multimodal convergence as the final and supreme site of integration for all aspects of mental function, including the storage of memories, the formation of concepts and the acquisition of language (Geschwind, 1965; Pandya and Kuypers, 1969; Jones and Powell, 1970; Van Hoesen et al., 1972; Pandya and Seltzer, 1982; Mesulam, 1985b).

While the importance of serial processing and multimodal convergence to cognitive function was widely accepted, some potentially serious computational limitations of such an arrangement were also acknowledged (Rumelhart and McClelland, 1986; Goldman-Rakic, 1988; Mesulam, 1990). The surfacing of these concerns coincided with the development of far more powerful neuroanatomical methods, based on the intra-axonal transport of horseradish peroxidase and tritiated amino acids, which started to show that the sensory-fugal flow of information was more complicated than previously surmised. The classic description of visuo-fugal pathways, for example, had assumed that information from V1 (BA 17) is transferred successively and serially to a first-order visual association area, V2 (BA 18), then to a second-order visual association area corresponding to BA 19, and finally to a third-order association area in the inferotemporal cortex. The newer methods revealed a somewhat different picture. The entire extent of V1 did indeed project to V2 (BA 18) in a topographically well-ordered fashion. However, V1 and V2 then gave rise to multiple parallel pathways that projected to numerous discrete

peristriate visual association areas, located mostly within BA 19 and designated V3, V4, V5 (MT), VP, V6 (PO) and so on (Felleman and Van Essen, 1991). The further occipito-fugal flow of visual information took the form of two divergent multisynaptic pathways. One was directed dorsally towards the parietal cortex and was specialized for encoding the spatial attributes of visual information, and the second was directed ventrally towards downstream visual association areas of the temporal lobe and was specialized in the identification of faces and objects (Ungerleider and Mishkin, 1982; Mesulam, 1994a). This expanded view of visuo-fugal pathways will provide a starting point for exploring a new form of connectivity that links sensation to cognition.

From sensation to perception
The representation of visual experience

Figure 2a contains a schematized summary of cortical connectivity in the visual system of the monkey brain and is based on the review by Felleman and Van Essen (1991). Virtually all of these connections are reciprocal. They are represented on a template of concentric circles where each circle is separated from the next by at least one unit of synaptic distance. V1 occupies the first synaptic level. The ascending synaptic levels in Fig. 1 follow a 'downstream,' 'feed-forward,' 'sensory-fugal' or 'bottom-up' direction with respect to the visual modality, whereas descending levels can be described as following an 'upstream,' 'feed-back,' 'sensory-petal' or 'top-down' direction.

Primary visual cortex (V1) is the exclusive cortical recipient of projections from the magnocellular and parvocellular layers of the lateral geniculate nucleus and provides a precise retinotopic mapping of the visual fields. In addition to retinotopic location, its neurons are sensitive to orientation, movement, binocular disparity, length, spatial frequency, wavelength and luminance. Aggregations of neurons that are preferentially sensitive to colour, stereopsis, orientation and movement form a multidimensional mosaic of columns, layers and cytochrome oxidase-reactive (or -negative) modules (Van Essen, 1985). Areas V2, V3, V4 and V5 (MT) are monosynaptically connected with V1 and therefore constitute 'upstream' visual association areas at the second synaptic level, whereas MST (medial superior temporal area), LIP (lateral intraparietal sulcus), the posterior and anterior inferotemporal cortex (PIT and AIT), temporal area TF (BA 20) and the caudal inferior parietal lobule (BA 7a) constitute some of the 'downstream' visual association areas at the third and fourth synaptic levels.[2] The cortical nodes at the second and perhaps also third synaptic levels fulfil the criteria for unimodal visual association areas as described above. When taken as a whole, area TF and area 7a display features of heteromodal cortex but appear to

---

[2] Parts of V4 receive monosynaptic input from V1, but this may not be seen in every case (Felleman and Van Essen, 1991). Area V4 may therefore have parts that should be designated upstream visual association cortex and parts that more closely fit the definition of a downstream visual association cortex.
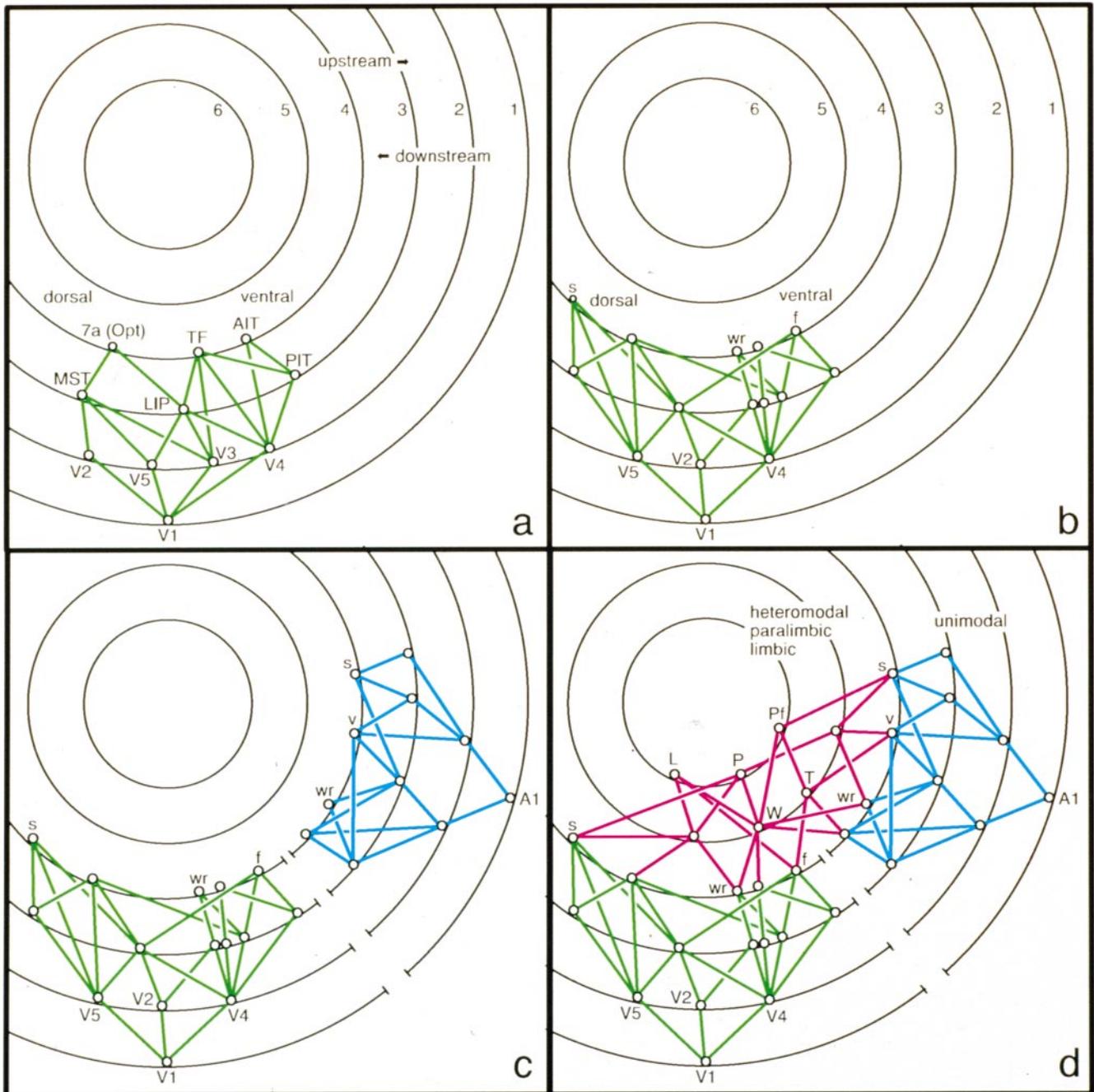
Fig. 2 Each concentric ring represents a different synaptic level. Any two consecutive levels are separated by at least one unit of synaptic distance. Level 1 is occupied by the primary sensory cortex. Small empty circles represent macroscopic cortical areas or 'nodes', one to several centimetres in diameter. Nodes at the same synaptic level are reciprocally interconnected by the black arcs of the concentric rings. Coloured lines represent reciprocal monosynaptic connections from one synaptic level to another. (**a**) Visual pathways as demonstrated by experimental neuroanatomical methods in the macaque brain. (**b**) The inferred organization of the homologous visual pathways in the human brain. (**c**) Visual (green) and auditory (blue) pathways in the human brain. (**d**) Visual (green), auditory (blue) and transmodal (red) pathways in the human brain. In **b**, **c** and **d**, the anatomical details of individual pathways are inferred from experimental work in the monkey. The anatomical identity of many of the nodes is not specified because their exact anatomical location is not critical. This review is guided by the hypothesis that these types of anatomical interconnections and functionally specialized nodes exist in the human brain even though their exact location has not yet been determined. The terms 'dorsal' and 'ventral' in **a** and **b** refer to the separation of visuo-fugal pathways, especially at the fourth synaptic level, into dorsal and ventral streams of processing. The gaps in the circles at the first four levels indicate the absence of monosynaptic connections between modality-specific components of auditory and visual pathways. Abbreviations: A1 = primary auditory cortex; AIT = anterior inferotemporal cortex; f = area specialized for face encoding; L = hippocampal–entorhinal or amygdaloid components of the limbic system; LIP = lateral intraparietal cortex; MST = medial superior temporal cortex; P = heteromodal posterior parietal cortex; Pf = lateral prefrontal cortex; s = area specialized for encoding spatial location; PIT = posterior inferotemporal cortex; T = heteromodal lateral temporal cortex; TF = part of medial inferotemporal cortex; v = area specialized for identifying individual voice patterns; V1 = primary visual cortex; V2, V3, V4, V5 = additional visual areas; W = Wernicke's area; wr = area specialized for encoding word-forms; 7a(Opt) = part of dorsal parieto-occipital cortex.

have subregions (such as Opt in the inferior parietal lobule and the caudal part of area TF) that may be engaged predominantly in the processing of visual information (Mesulam *et al.*, 1977; Pandya and Yeterian, 1985; Andersen *et al.*, 1990). The nodes at the fourth synaptic level in Fig. 2a represent these relatively modality-specific subregions of areas 7a and TF.

The primary dimension of visual mapping is retinotopic and is achieved by finely tuned neurons which provide an exquisitely ordered spatial representation of the visual fields in V1. Other dimensions of visual experience, such as colour and motion, are mapped in V1 and V2 by coarsely tuned neurons, and become more fully encoded at further synaptic stages such as V4 and V5. Nodes at upstream synaptic levels tend to contain neuronal groups specialized for encoding relatively elementary attributes of visual experience, whereas nodes at more downstream levels are organized into neuronal groups specialized for encoding more composite features. The gradual increase of response latency, visual field size and response complexity in the progression from V1 to V2, V4, PIT and AIT confirms the existence of a synaptic hierarchy in the organization of visuo-fugal pathways. Although a visual event activates nodes at higher levels of this hierarchy with increasing latencies (11 ms between V1 and V2 and 9 ms between V1 and V5, but 40 ms from V1 to PIT–AIT), all areas eventually become concurrently active in the course of visual processing (Raiguel *et al.*, 1989; Dinse and Kruger, 1994). It seems as if each node is continually passing on information to the others rather than fulfilling its part of the processing and then transmitting a completed product to the next station (Tovèe, 1994).

The specialization of V4 for colour perception and of V5 for movement perception have been documented extensively in the monkey (Van Essen, 1985). In humans, studies based on functional imaging have shown that the posterior parts of the lingual and, to a lesser extent, fusiform gyri (ventral BA 19) display selective activation in response to colour stimulation (Lueck *et al.*, 1989; Chao *et al.*, 1997). This area constitutes a human homologue of the colour-sensitive V4 region of the monkey since its unilateral destruction leads to a contralateral loss of colour perception (hemi-achromatopsia) without equivalent impairments of acuity, movement perception or object identification (Damasio, 1985; Mesulam, 1994*a*). Other functional activation studies have shown that a lateral occipitotemporal area at the confluence of BA 19 and 37 shows selective activation in response to visual motion (Watson *et al.*, 1993). This region appears to represent the human homologue of area V5 in the monkey. Its destruction causes a state known as akinetopsia where the patient cannot perceive visual motion, although acuity and colour perception may be relatively preserved (Zeki, 1991; Zihl *et al.*, 1991; Mesulam, 1994*a*). The clinical dissociation of achromatopsia from akinetopsia proves that the V1 projections to V4 and V5 are organized largely in parallel rather than in series. The presence of such parallel pathways would be expected to increase processing efficiency by allowing the simultaneous analysis of individual attributes associated with a visual event.

The elementary sensory features encoded at the first two synaptic levels are used by more downstream areas along the ventral visuofugal pathway for the discrimination of form and complex patterns. In the monkey, for example, a posterolateral inferotemporal region (area TEO or PIT at the junction of lateral BA 19 with BA 20–21) plays a critical role in form and pattern discrimination (Yaginuma *et al.*, 1982). A homologous area in the human brain includes parts of the fusiform gyrus (BA 19 and 37), just anterior to V4, and probably extends into the adjacent lingual and inferior occipital gyri (Halgren *et al.*, 1997; Kanwisher *et al.*, 1997*b*). This area appears to be involved in the construction of shape from simpler visual features since it becomes activated by tasks that require attention to both simple and complex shapes and does not give differential responses to upright versus inverted faces, real versus nonsense objects, or novel versus familiar stimuli (Corbetta *et al.*, 1991; Haxby *et al.*, 1994, 1997*b*; Martin *et al.*, 1996; Clark *et al.*, 1997; Kanwisher *et al.*, 1997*b*). In comparison with the brain of the macaque, the downstream components of the ventral visuo-fugal pathway in the human appear to have been transposed ventromedially, probably in response to the expansion of the lateral temporal and posterior parietal cortices.

If the identification of visual events and objects had to be based on a sequential compilation of the colour, form and motion data encoded at the first three synaptic levels, perception would probably take an inordinately long time and might not allow the rapid recognition of frequently encountered and behaviourally significant patterns. This potential limitation is overcome at the fourth synaptic level, where neuronal groups selectively tuned to specific visual categories promote the rapid identification of entities such as faces, objects and words. In the monkey, the anterior inferotemporal area (AIT or anterior BA 20–21) contains neuronal ensembles specialized for face and object identification (Gross *et al.*, 1972; Desimone, 1991). In the human brain, functional imaging studies, electrophysiological evoked responses and the location of lesions in patients with the syndrome of prosopagnosia indicate that the homologous areas specialized for face and object identification are located predominantly within the mid-portion of the fusiform gyrus (BA 37 and BA 20) (Damasio, 1985; Sergent *et al.*, 1992; Allison *et al.*, 1994; Puce *et al.*, 1996).

The 'face' area in the human brain ('f' in Fig. 2b) is more strongly activated by faces than by other objects (Kanwisher *et al.*, 1997*a*). It is also more strongly activated by upright and intact faces than by inverted or scrambled ones, but does not show a differential response to familiar versus novel faces (Gorno Tempini *et al.*, 1997; Haxby *et al.*, 1997*b*). This area therefore appears to encode faces at a categorical or generic level, prior to the stage of individual recognition. The fourth synaptic level of the human brain contains additional regions specialized for the identification of other common objects such as chairs and houses (Ishai *et al.*,

1997). An area specialized for the encoding of word-forms and word-like letter-strings ('wr' in Fig. 2b) has also been identified in this region, at a location perhaps slightly more lateral to that of the fusiform face area (Nobre *et al.*, 1994; Puce *et al.*, 1996). A second potential visual word-form identification area may be located in a more lateral occipito-temporal region, at the confluence of BA 19 with BA 37 (Petersen *et al.*, 1988). Considering the extremely recent emergence of written language in human phylogeny and its relatively late acquisition in ontogeny, the organization of the word-form area is almost certainly not genetically or epigenetically programmed. A more likely possibility is that it represents an experiential modification of neuronal subgroups within populations tuned to the encoding of faces and objects. The visual word-form areas could thus mediate a sort of processing where written words are handled as objects rather than as symbols.

The fourth synaptic level also contains components of the dorsal visuofugal pathways ('s' in Fig. 2b), where relatively more elementary retinotopic and visuomotor information leads to the selective identification of extrapersonal targets. Neurons in parts of area 7a of the macaque, for example, can compute the allocentric coordinates of extrapersonal events by combining retinotopic location with information about eye position (Zipser and Andersen, 1988). Some of these neurons display tuning for locations in head-centred coordinate space and show response enhancements to spatial positions containing events that will become targets of visual or manual grasp (Mesulam, 1981; Andersen *et al.*, 1985). Functional imaging experiments based on tasks of spatial localization indicate that the analogous region in the human brain may be located in the dorsal occipito-parietal region, at the junction of BA 19 with BA 7 (Haxby *et al.*, 1994).

Representation of individual faces and objects

Neuronal ensembles within downstream visual association areas provide representations of objects and faces through a process of group encoding. The tuning is broad and coarse: one neuron may be activated by several faces and the same face may excite several neurons (Rolls, 1987). The face neurons in the inferotemporal cortex are selectively tuned to category-specific canonical features such as intereye distance, style of hair, expression, and direction of gaze (Yamane *et al.*, 1988). Neurons tuned to similar object features form vertical columns measuring ~0.4 mm in diameter. Several adjacent columns responsive to similar effective features may be linked to form larger 'patches' or modules measuring several millimetres (Harries and Perrett, 1991; Tanaka, 1996). Groups of such patches may form interconnected but distributed ensembles collectively tuned to the set of canonical features that define an object class. The tangential inter-patch connections that are necessary for establishing such an organization could be stabilized during the period of cortical development and subsequently strengthened by experience

through the mediation of temporally correlated multifocal activity (Löwel and Singer, 1992).

Although neurons in a given column respond preferentially to similar canonical features of an object or face, optimal tuning properties vary among constituent cells so that columnar activation may encode generic properties whereas the activities of individual cells within the column may help to encode distinguishing (subordinate) features of individual exemplars (Fujita *et al.*, 1992). In response to an object, a small subset of neurons in a given column can fire maximally and set constraints to guide and restrict the interpretation of less active neurons within the same ensemble (Geisler and Albrecht, 1995). Identification can thus start by matching the coarse (or generic) features and then focusing on finer (subordinate) detail. A visual entity may be represented by a small number of modules, each broadly selective for some reference object or face, which collectively measure the similarity of the target stimulus to the reference entities (Edelman, 1998). This type of encoding, also known as second-order isomorphism, is thought to be computationally more parsimonious than representations based on a more direct isomorphic matching of the target shape (Edelman, 1998).

The face-responsive ensembles display considerable plasticity so that some neurons alter their firing rate to a given face when it becomes more familiar or when a new one is added to the set (Rolls *et al.*, 1989), suggesting that the identity of an individual face is not encoded by fixed rates of firing but by the relative firing frequencies (and perhaps interneuronal correlation patterns) across the entire ensemble. The processing parsimony offered by this organization is substantial (Erickson, 1982). A very large number of faces can be encoded by a small number of neurons, recognition can be graded (rather than being all-or-none) and based on partial information, the same information can be probed through multiple associations, generalizations based on a few common features (or analysis based on differences) can be achieved rapidly, the progression from categorical to subordinate identification can proceed smoothly, and damage or refractory states in a subset of neurons within the ensemble can lead to a graceful, partial degradation of function. These neurons can achieve the rapid detection of behaviourally relevant, recurrent and composite visual events, obviating the need for a cumbersome compilation of the more elementary sensory features. The general principles that guide the visual identification of faces probably also apply to the encoding of other classes of objects, words and spatial targets.

In the frog's brain, the equivalent process of object identification begins in the retina and is largely completed one synapse later in the tectum. In the primate brain, at least four synaptic levels of cerebral cortex are devoted to identifying a bug and transforming its location into a target for action. The disadvantages of the increased synaptic distance are partially offset by the insertion of parallel pathways (AIT, for example, can receive inputs either through

PIT or directly from V4) and the extensive myelination of the axons. The advantages of this more flexible arrangement are extensive: we can identify the individual species of bug, comment on its function, remember the experience for future reference, let it inspire poetry,[3] and, if necessary, inhibit the tendency for immediate predatory action in order to plan a strategy for approach, avoidance or attack.

The anatomical areas that play crucial roles in the identification of colour, movement, faces, words, objects and spatial targets display relative rather than absolute specializations. For example, V4 is specialized for colour perception but also participates in spatial attention, the identification of salience and the encoding of form (Moran and Desimone, 1985; Schiller, 1995; Connor *et al.*, 1996). In turn, the processing of colour information may involve not only V4 but also a part of the lateral peristriate cortex (Corbetta *et al.*, 1990). Furthermore, neuronal ensembles selectively tuned to canonical features of faces participate, although to a lesser extent, in encoding other visual entities (Rolls, 1987). It is quite likely that several ensembles, each composed of neurons optimally tuned to a different category, form an interdigitating or partially overlapping mosaic and that the predominant type of ensemble varies from one location to another.[4] This organization has been designated 'selectively distributed processing' (Mesulam, 1994*c*; Seeck *et al.*, 1995) to set it apart from other models based on equipotentially distributed processing (Lashley, 1929), parallel distributed processing (Rumelhart and McClelland, 1986) and modular processing (Fodor, 1983).

Although the flow of visual information shown in Fig. 2b obeys a core hierarchy, it also contains many nodes of convergence and divergence embedded within multiple parallel pathways. This arrangement offers the well-known computational advantages of parallel processing. It also helps to sort the undifferentiated visual information that impinges on the eye into attributes that become available for new combinatorial permutations. This process may be likened to the prismatic diffraction of white light into primary colours which, in turn, become available for creating a large number of secondary and tertiary colours not present in the original spectrum.

Auditory experience

The primary dimension of auditory mapping is tonotopic. The superior temporal plane of the monkey contains three tonotopic maps, one each in areas A1, R and CM, raising the possibility that the primate cerebral cortex contains multiple auditory areas just as it contains multiple visual areas (Rauschecker *et al.*, 1997). Two of these areas, A1 and

R, receive the most extensive input from the primary thalamic auditory relay nucleus in the ventral medial geniculate. They can be activated directly by pure-tone responses whereas area CM depends on inputs from A1 and R for its pure-tone responses and is more responsive to complex broad-band stimuli and high-frequency sounds used for sound localization. These three areas may occupy cortical nodes at the first two synaptic levels of auditory pathways.

The complex cytoarchitecture and connectivity of the superior temporal gyrus in the monkey brain suggest that multiple association areas with hierarchies and interconnections analogous to those described in the visual system are also likely to exist in the auditory modality. Pitch and tone discrimination are accomplished at the level of A1 and closely related upstream auditory association areas of the posterior superior temporal gyrus, whereas the identification of more complex auditory sequences, the discrimination of species-specific calls and the detection of sound motion and localization engage downstream auditory association areas in the superior temporal gyrus (Colombo *et al.*, 1996).

As in the case of visual pathways, the auditory pathways of the monkey brain may be divided into dorsal and ventral processing streams. Area Tpt of the posterior superior temporal gyrus, for example, may play a prominent role in the dorsal audio-fugal stream of processing, and may be specialized for detecting the spatial localization of sound sources, whereas the more anterior and ventral parts of the superior temporal gyrus may be specialized for identifying complex auditory sequences and species-specific vocalizations (Leinonen *et al.*, 1980; Heffner and Heffner, 1984; Colombo *et al.*, 1996). The role of the superior temporal gyrus in the auditory identification of species-specific calls appears analogous to the role of inferotemporal cortex in face identification, both processes serving crucial functions in social communication.

A similar organization may exist in the human brain. Neurons in A1 are tuned to pure tones and pitch, whereas those of the mid to anterior parts of the human superior temporal gyrus are relatively unresponsive to pure tones and non-linguistic noises but respond to specific phonetic parameters of spoken language (Petersen *et al.*, 1988; Démonet *et al.*, 1992; Zatorre *et al.*, 1994). The superior temporal gyrus neurons are broadly tuned to the segmentation and sequencing of phonemes as well as to their coherence within polysyllabic and compound words (Creutzfeldt *et al.*, 1989). They encode speech at a presemantic level, since they respond to spoken real words as readily as to distorted backward speech (Creutzfeldt *et al.*, 1989). They may thus be analogous to the visual word-form neurons of the fusiform and occipitotemporal areas where word-forms are processed as perceptual patterns rather than symbols. The middle temporal gyrus in the human brain (BA 21) appears to contain a further downstream auditory association area, since approximately half of its neurons give highly selective responses, mostly in the form of suppression, to

---

[3] *Just so much honour, when thou yield'st to me,/Will waste, as this flea's death took life from thee.* John Donne, *The Flea.*

[4] The 'specialization' of an anatomical region for a certain task can theoretically be assessed by calculating the sum of changes (in metabolism, relative frequency of firing or cross-correlation of activity) across the entire region of interest when responding to one versus another class of stimuli.

understandable speech but not to distorted speech (Creutzfeldt *et al.*, 1989).

These observations suggest that the flow of auditory information in the human brain may follow a template similar to the one in the visual modality (Fig. 2c). Although the evidence is not as easily interpreted as in the case of visual pathways, it appears that upstream auditory areas tend to encode more elementary features such as frequency and pitch, whereas downstream areas may contain neuronal groups that encode more composite features related to the identification of words ('wr' in Fig. 2c), the localization of sound sources ('s' in Fig. 2c), the categorization of object-specific sounds, and perhaps also the characterization of individual voice patterns (area 'v' in Fig. 2c).

Sensory fidelity and memory in unimodal areas

One of the most important principles in the organization of the primate cerebral cortex is the absence of interconnections linking unimodal areas that serve different sensory modalities. In the monkey, for example, the auditory association cortex in BA 22 has no direct connections with the visual association cortex in BA 19, BA 20 or BA 21 (Pandya and Yeterian, 1985). Neurons in visually responsive areas such as BA 19–21 do not respond to auditory stimuli, and neurons in auditory cortices such as BA 22 do not respond to visual stimuli. This is particularly interesting since many of these unimodal association areas receive monosynaptic feedback projections from heteromodal cortices which are responsive to both auditory and visual stimuli. The sensory-petal (or feedback) projections from heteromodal cortices therefore appear to display a highly selective arrangement that actively protects the fidelity of sensory tuning during the first four synaptic levels of sensory-fugal processing.

Virtually every neuron and synapse in the CNS can potentially alter its excitability or efficacy in a manner that allows the storage of information for periods of time ranging from a few milliseconds to a lifetime. The molecular and cellular bases of such learning include a broad spectrum of phenomena such as reversible alterations in the conductance of ionic channels, long-term potentiation (or depression), changes of synaptic efficacy, and the expression of genes which alter the structure and number of synapses (Bailey *et al.*, 1996; Bear, 1996). Durable learning effects, however, would be least desirable among neurons of the first synaptic level, where the accurate registration of new inputs necessitates a rapid return to a narrowly tuned baseline, whereas they would be highly useful at more downstream levels, where synaptic plasticity, induced by life experiences, could play a critical role in the adaptive modification of response patterns.[5]

[5] Breuer expressed this succinctly when he said that the mirror of a telescope cannot at the same time be a photographic plate (Breuer and Freud, 1895). Although experience-induced changes have been reported in primary sensory areas in the adult brain of phylogenetically more advanced species (Creutzfeldt and Heggelund, 1975; Wiesel, 1981; Cruikshank and Weinberger, 1996), they tend to be less common than in association or limbic areas, and require more drastic circumstances such as prolonged exposure to anomalous visual input, nerve section and limb amputation.

In keeping with these expectations, prominent learning effects have been identified in downstream unimodal association areas of the cerebral cortex. In the monkey, for example, when pattern α is paired with pattern β in a paired-associates task acquired prior to the recording period, an AIT neuron responsive to β but not to α will increase its firing in anticipation of β towards the end of the delay period following stimulation by α, showing that it has learned the arbitrary association between the two stimuli (Naya *et al.*, 1996). Neurons in AIT also display a familiarity response to faces encountered as long as 24 h ago, indicating that the initial exposure had been stored in long-term memory (Fahy *et al.*, 1993). These observations have led to the suggestion that the downstream visual association cortices in the temporal lobe act as a 'memory storehouse' for object vision (Mishkin, 1982; Naya *et al.*, 1996). Analogous long-term memory encoding probably exists in the downstream components of unimodal auditory association cortices, although these phenomena have not been investigated as extensively as those in the visual modality. Modifications of synaptic efficacy, such as those necessary for long-term potentiation and depression, have been obtained in the human middle and inferior temporal gyri and could mediate similar long-term encoding (Chen *et al.*, 1996).

The foregoing comments indicate that the neural nodes in Fig. 2c can both identify and record visual and auditory events. Furthermore, evanescent cross-modal coherence of the visual and auditory features encoded by the nodes in Fig. 2c could arise through the temporal synchrony of the two sensory channels during the actual unfolding of an event. Modality-specific cortices may thus initially appear to provide all the necessary ingredients for the stable registration of experience. A brain that contained only those components shown in Fig. 2c, however, would face serious challenges if an associative synthesis or retrospective reconstruction of the relevant experience became necessary. It would be impossible, for example, to encode the relationships between the visual and auditory components of the experience, since the two sets of unimodal cortices have no interconnections. Experience for such a brain would therefore tend to be incoherent across multiple channels of sensory processing. The unimodal association areas in Fig. 2c would be sufficient for deciding if the sensory features of two words or two faces are identical or not, and even for distinguishing one object category from another, but could not lead from word to meaning, from physiognomy to recognition, or from sensory events to coherent experiences. Such transformations of sensation into cognition necessitate the participation of a different class of cortical areas that can be classified as transmodal.

From perception to recognition: transmodal gateways

Transmodal areas and binding

Transmodal areas include all heteromodal, paralimbic and limbic areas and occupy the fifth and sixth synaptic levels

in Fig. 2d. Their only common feature is the absence of specificity for any single modality of sensory input. They receive afferents predominantly from the more downstream parts of unimodal areas and from other transmodal regions (Fig. 1). These connections are reciprocal and enable transmodal areas to provide a site for multimodal convergence and also to exert a 'top-down', 'sensory-petal' or 'feedback' influence upon unimodal areas.

Everyday experiences unfold in multiple modalities. The establishment of a durable record of experience, and its associative incorporation into the existing base of knowledge, necessitate multimodal integration. The desirability of such integration (or binding) had been articulated and its presence postulated on multiple occasions. The most widely acknowledged version was introduced more than three centuries ago by Descartes, who proposed a convergence of sensory information within the pineal gland, where the immaterial mind could observe the representation of experience provided by the material brain. Although Cartesian dualism has attracted severe and often justified criticism (Dennett and Kinsbourne, 1992), the convergence that it postulated continues to be as compelling now as it was then. Its organization, however, appears to entail more than a spatial confluence within a single theatre where, in Dennett and Kinsbourne's words, 'it all comes together' for the benefit of its immaterial spectator. As will be shown in the following discussion, the brain favours a distributed type of Cartesian convergence where there are multiple theatres and where the actor and spectator are one and the same.

The neuroanatomy of the 1960s and 1970s identified several areas for multimodal convergence, raising the possibility that these might be the sites where a multidimensional synthesis of knowledge, memory and experience could be taking place. The logistic and epistemological arguments against such a purely conver-gent organization of knowledge have been enumerated on multiple occasions (Goldman-Rakic, 1988; Mesulam, 1990; McClelland, 1994). Two of these objections are most relevant to this review: (i) if knowledge of α was encoded in convergent form by a small number of neurons within a transmodal area, the brain would have to resolve the cumbersome problem of conveying α-related information in all relevant modalities to the one highly specific address where this convergent synthesis is located; (ii) the modality-specific attributes of α would succumb to cross-modal contamination during the process of convergence and the sensorial fidelity of the experience would be lost. This second circumstance can be likened to the mixing of yellow and blue to obtain green, a process which precludes the subsequent extraction of the original hues from the resultant mixture.

Both objections can be addressed by assuming that the role of transmodal nodes is not only to support convergent multimodal synthesis but also, predominantly, to create directories (or address codes, maps, look-up tables) for binding distributed modality-specific fragments into coherent experiences, memories and thoughts. This alternative process

can be likened to obtaining green by superimposing a blue and a yellow lens, which can then be separated from each other to yield back the original uncontaminated colours. Transmodal areas allow multidimensional integration through two interactive processes: (i) the establishment, by local neuronal groups, of convergent cross-modal associations related to a target event; and (ii) the formation of a directory pointing to the distributed sources of the related information. Transmodal areas can thus enable the binding of modality-specific information into multimodal representations that have distributed as well as convergent components.

Transmodal areas are not necessarily centres where convergent knowledge resides, but critical gateways (or hubs, sluices, nexuses) for accessing the relevant distributed information (Mesulam, 1994*c*). Paradoxically, they also provide 'neural bottlenecks' in the sense that they constitute regions of maximum vulnerability for lesion-induced deficits in the pertinent cognitive domain. Transmodal areas in different parts of the brain share similar principles of organization, each in relation to a specific cognitive domain. Examples that will be examined in this review include the pivotal role of midtemporal and temporopolar cortices in face and object recognition, Wernicke's area in lexical retrieval, the hippocampal–entorhinal cortex in explicit memory, the prefrontal cortex in working memory, the amygdala in emotion, and the dorsal parietal cortex in spatial awareness.

Face recognition and associative agnosias

Downstream visual association cortices are essential for the categorical encoding of faces and objects. By itself, this information would provide an isolated percept devoid of meaning or context. The ability of this modality-specific perceptual information to activate the relevant multimodal associations that lead to recognition requires the mediation of transmodal cortical areas. In the monkey, for example, unimodal AIT neurons are sensitive to the sensory properties of face stimuli whereas more downstream transmodal neurons of the superior temporal sulcus are also tuned to more complex aspects of faces such as their expression and familiarity (Young and Yamane, 1992). In humans, the perceptual identification of unfamiliar faces activates unimodal visual association areas in the fusiform region, whereas the recognition of familiar faces also activates transmodal nodes, including those in the lateral midtemporal cortex (Gorno Tempini *et al.*, 1997). Other transmodal areas, such as those in the temporopolar cortex, also appear to play an important role in face recognition, since their involvement in neurological lesions frequently impairs the ability to recognize famous faces (Tranel *et al.*, 1997). Transmodal areas in the midtemporal and temporopolar cortex (represented by area 'T' in Fig. 2d) may therefore act as gateways for binding the additional associations (such as the name, voice, expression, posture, and private recollections) that collectively lead to the recognition of familiar faces.

Some neurological lesions lead to a specific face

recognition deficit known as associative prosopagnosias.[6] This syndrome is most commonly caused by bilateral lesions in the mid to anterior parts of the lingual and fusiform gyri. Bilateral lesions in this part of the brain are not infrequent since the posterior cerebral arteries which supply the relevant regions arise from a common basilar trunk. In the scheme of Fig. 2d, associative prosopagnosia can potentially arise from one of three different types of interruption in the connections between area 'f' and transmodal node 'T': (i) the visual input into region 'f' of the fusiform face area may be interrupted by a more upstream lesion; (ii) area 'f' may be damaged directly; (iii) the output from area 'f' to the inferotemporal heteromodal cortex ('T' in Fig. 2d) may be interrupted by a more downstream lesion. In all three instances perception (as tested by the ability to tell if two faces have an identical shape) can be relatively intact, presumably because more upstream areas of the occipito-temporal cortex remain intact. Although a prosopagnosic patient cannot recognize familiar faces by visual inspection, recognition becomes possible when information in a non-visual modality, for example the voice pattern characteristic of that person, becomes available. This auditory information can presumably access transmodal area 'T' through area 'v' of the unimodal auditory cortex in Fig. 2d, leading to the activation of the other distributed associations that lead to recognition. Furthermore, a face that is not consciously recognized can occasionally still elicit a physiological emotional response (Bauer, 1984; Tranel and Damasio, 1985), presumably because the damage is located downstream to 'f' and interrupts its connections to area 'T' but not to limbic areas such as those represented by area 'L' in Fig. 2d.

The most conspicuous manifestation of prosopagnosia is the impaired recognition of familiar faces, including the patient's own face. However, patients with prosopagnosia can also display impaired subordinate-level recognition of additional object categories (Damasio, 1985). Such patients may have no difficulty in the generic recognition and naming of object classes (for example, they may recognize and name a car as a car or a face as a face) but may not be able to determine the make of a particular car, recognize a favourite pet, or identify a personal object from among other examples of the same category. This additional feature of prosopagnosia raises the possibility that area 'f' may also participate in the identification of objects other than faces or, alternatively, that most lesion sites may involve immediately adjacent regions that encode additional object categories.

If prosopagnosia represents an impairment of subordinate-level recognition, associative visual object agnosia represents an impairment that extends to the level of categorical recognition. The patient with this syndrome can neither name a familiar object nor describe its nature. While a prosopagnosic patient can tell that a face is a face and a pencil is a pencil, a patient with object agnosia is unable to perform this task but retains the ability to determine if two objects are perceptually identical or not. In analogy to prosopagnosia, object agnosia appears to represent a disconnection between visual association areas involved in the categorical encoding of visual entities and transmodal nodes analogous to 'T' in Fig. 2d.

The question may be asked why all visual agnosias are not of this type. If the fusiform and inferior occipital areas specialized for face and object identification are organized as described above, how can a prosopagnosic patient with damage to these areas continue to name and identify objects and faces at a categorical level? Conceivably, the encoding of proprietary features that lead to subordinate classification may require more information than the encoding of generic features. The identification of unique exemplars would thus necessitate the participation of a larger group of neurons or further downstream processing. Object agnosia may therefore represent the outcome of a more extensive or more upstream lesion than that associated with prosopagnosia. Although clinical reports show that the lesions in object agnosia appear very similar to those in prosopagnosia, minor differences in lesion size or location could easily escape detection in case studies based on cerebrovascular accidents.

A second potential distinction between prosopagnosia and object agnosia may be based on the memory systems that support the recognition of generic versus proprietary information. The generic recognition of familiar objects is part of semantic knowledge, whereas the recognition of familiar faces and objects is more closely related to autobiographical experience. Although prosopagnosia and object agnosia are usually seen after bilateral lesions, these syndromes do occasionally arise after unilateral lesions, in which case prosopagnosia tends to result from lesions in the right hemisphere and object agnosia from lesions in the left (Farah and Feinberg, 1997). This dissociation is interesting since the right hemisphere appears to have a greater role in the activation of autobiographical memories (Fink *et al.*, 1996).

Associative agnosias have also been identified in the auditory modality. Patients with a condition known as auditory object agnosia fail to associate the ringing of a telephone or the siren of an ambulance with the corresponding entity, even though more elementary auditory perceptual abilities remain relatively preserved. This syndrome may reflect a disconnection of unimodal auditory areas specialized for encoding auditory properties of familiar objects from transmodal nodes (such as 'T') that coordinate their multimodal recognition. The lesions that give rise to auditory agnosia typically involve the auditory association cortex, but the more detailed anatomical correlates of this relatively rare syndrome remain to be elucidated (Spreen *et al.*, 1965).

Associative agnosias arise when unimodal areas specialized for categorical perceptual encoding fail to access transmodal gateways that lead to explicit multimodal recognition and conceptual knowledge. The transmodal areas involved in this process are not centres for convergent conceptual knowledge, but optimal conduits for accessing the relevant distributed

---

[6] This syndrome should be differentiated from *apperceptive* prosopagnosia, where the face recognition deficit results from faulty visuospatial perceptual synthesis.

associations. These syndromes highlight the importance of sensory-fugal pathways to the process of recognition and offer a neuroanatomical basis for the distinction between perception and recognition. Other cognitive domains, such as explicit memory, language, spatial awareness and emotion, display analogous principles of organization but revolve around transmodal gateways located in different parts of the brain.

Arbitrary associations of sensory experience: explicit memory and language
Explicit/declarative/episodic memory

The encoding of space, colour, movement and form displays considerable species-specific invariance and is relatively unaffected by peculiarities of individual experience. Much of mental content, however, is based on idiosyncratic associations which endow percepts and events with personal significance. The recording and explicit recall of these arbitrary relationships require the establishment of long-term memories. The long-term storage of individual experience becomes increasingly more important in nervous systems where the linkage of sensation to cognition is complex, and where experience can alter the contingencies signalled by a sensory event. It would seem superfluous to evolve a personal system of explicit memory if future contingencies are identical to those of the past, and if the significance of sensory events does not vary from one time to another, or from one individual to another. In the frog, where a certain retinal pattern invariably signals a bug to be snapped at, regardless of context or experience, the encoding of individual encounters would appear relatively unimportant. In fact, even the most rudimentary form of conditioning has been quite difficult to establish in frogs (Russek, 1969).

The situation is drastically different in the primate brain. Each component of the unimodal and transmodal cortex appears to participate in learning arbitrary associations in its own area of specialization. The inferotemporal cortex encodes new information in memory tasks related to faces and complex visual patterns (Sobotka and Ringo, 1993; Naya *et al.*, 1996; Owen *et al.*, 1996; Squire and Zola, 1996), the midtemporal cortex in memory tasks related to words (Ojemann *et al.*, 1988), the dorsal parietal cortex in memory tasks related to spatial relationships (Roland and Friberg, 1985; Owen *et al.*, 1996), and the posterior parietal and prefrontal cortices in memory tasks involving multimodal associations (Kapur *et al.*, 1996; Haxby *et al.*, 1997a).

In accessing established knowledge, such as the name of a colour, the meaning of a word or the identity of a familiar face, recall is based on rich and stable associations that have been consolidated for many years. In order to encode and access new facts and experiences, however, fragile and initially sparse linkages have to be established, nurtured and inserted into the matrix of existing knowledge. This kind of learning, also known as explicit, declarative or episodic

memory,[7] is critically dependent on a special type of binding subserved by transmodal nodes within the limbic system,[8] especially within its hippocampal and entorhinal components.

The first case report describing the onset of severe amnesia in a patient with bilateral hippocampal damage was published in 1900 by Bechterew. Since then, a very large number of clinical observations have shown that limbic lesions, especially those that involve the hippocampal–entorhinal complex, completely abolish the conscious recall of new and recent events while allowing relatively more effective access to remote memories and semantic knowledge (Scoville and Milner, 1957; Signoret, 1985; Mesulam, 1988; Nadel and Moscovitch, 1997). Lesions outside the limbic system do not lead to similar deficits.

The amnestic state caused by limbic lesions is characterized by dissociation between the explicit/declarative/episodic recording of new experience, which is severely impaired, and the implicit learning of motor tasks and perceptual associations, which is relatively preserved. An amnestic patient, for example, may develop new motor skills, improve performance in priming and stem completion tasks, and learn to avoid situations that have recently been associated with aversive consequences, even when he or she has no conscious memories of the relevant experiences (Claparède, 1911; Milner *et al.*, 1968; Schacter, 1995). In addition to the impairment of new learning (anterograde amnesia), these patients also display a retrograde amnesia for events that occurred before the onset of the limbic lesion, and a gradual shrinkage of the time period encompassed by this retrograde amnesia in the course of recovery (Benson and Geschwind, 1967). The shrinkage of the memory impairment during recovery suggests that some of the memories lost to retrograde amnesia had not been obliterated, but had become impossible to retrieve.

These observations, especially those related to the shrinkage of the retrograde amnesia, suggest that the limbic system is unlikely to be a central storage site for memories. According to a model of explicit memory which is gradually attracting considerable support, facts and events are initially recorded at multiple sites with an anatomical distribution that reflects the modality- and category-specific aspects of the relevant information. This information is relayed, through reciprocal multisynaptic pathways, to transmodal nodes within the limbic system. These transmodal nodes appear to

---

[7] *Explicit memory* refers to voluntary and conscious recall that can be reported overtly; *episodic memory* refers to the explicit recall of personal experiences, including their temporal and spatial contexts and the feeling of having been there; *semantic memory* refers to the explicit recall of general and invariable facts related to the world around us; *declarative memory* is a collective term referring to episodic and semantic memories and is usually used as a synonym for explicit memory; *implicit memory* refers to circumstances where exposure to a task or stimulus influences future performance even when the subject has no conscious awareness of the experience related to the prior exposure.

[8] The interconnected components of the limbic system include the cortical areas in the paralimbic and limbic zones, the limbic nuclei of the thalamus (such as the midline, anterior and magnocellular dorsomedial nuclei), and the hypothalamus (Mesulam, 1985b).

play their critical roles by establishing a directory that guides the binding of the modality- and category-specific fragments of individual events into coherent multimodal experiences (Mishkin, 1982; Damasio, 1989; Mesulam, 1990; McClelland, 1995; Squire and Zola, 1996; Nadel and Moscovitch, 1997). In addition to its binding function, the hippocampal–entorhinal complex also appears to promote the stable encoding of new associations in other parts of the neocortex, including unimodal sensory areas (Halgren *et al.*, 1985; Eichenbaum *et al.*, 1996; Higuchi and Miyashita, 1996).

When a critical volume of the limbic system is destroyed, new associations become more fragile and the process of binding is jeopardized. Consequently, fragments of new and recent events cannot be integrated interactively into the overall fabric of consciousness with the type of coherence that is necessary for declarative recall. However, some of the information related to new events continues to be encoded in the neocortical association cortex in a manner that supports implicit learning. The unbound, fragmentary form of this information helps in understanding why implicit learning tasks such as priming are so sensitive to the surface (rather than associative) properties of the stimuli and why they are resistant to transmodal generalization (Schacter, 1995). There is probably no fundamental difference in the type of encoding that is involved in implicit versus explicit memory. In implicit memory, the information remains in the form of isolated fragments, mostly within unimodal and heteromodal association areas; in explicit memory it becomes incorporated into a coherent context through the binding function of limbic nodes. In keeping with this formulation, tasks of explicit memory lead to the activation of medial temporolimbic as well as neocortical areas, whereas tasks of implicit memory lead to the activation predominantly of neocortical areas (Squire *et al.*, 1992; Haxby *et al.*, 1997*a*; Seeck *et al.*, 1997).

One of the most important components of the amnestic state is retrograde memory loss. Retrograde amnesia is usually much more severe for events that occurred just before the onset of the limbic lesion than for those of the distant past,[9] and more severe for autobiographical-episodic experiences than for semantic knowledge (Nadel and Moscovitch, 1997). In general, the severity of the anterograde amnesia in patients with hippocampal–entorhinal lesions tends to be correlated with the severity of the retrograde component, suggesting that the limbic components are as crucial for encoding as they are for retrieval (Nadel and Moscovitch, 1997). The hippocampal subregions that participate in retrieval may be different from those that participate in encoding (Gabrieli *et al.*, 1997), providing a potential explanation for the emergence of major dissociations between retrograde and anterograde amnesia in some patients (O'Connor *et al.*, 1992).

The emergence of retrograde amnesia and the temporal gradient that it displays in some patients suggest that the hippocampal–entorhinal complex and association neocortex are involved in a continuing process of reconstruction,

[9] This is known as Ribot's gradient.

updating and associative elaboration, which collectively lead to the consolidation of new memories. At the initial stage of encoding, a new fact or event has few associations and depends on the limbic system for maintenance and coherent retrieval. In time, as additional linkages become established through reciprocal connections with other transmodal and unimodal areas, the relevant information can be probed through numerous associative approaches and becomes less dependent on the limbic system. The participation of the hippocampal–entorhinal complex in retrieval is likely to be most critical for the most recently acquired memories, for those that have limited resonance with other mental contents, for those that have been registered casually rather than intentionally, for those with relatively weak emotional valence, for those that require extensive cross-modal integration, for those that have been recalled rarely and have therefore failed to establish associative elaboration, and for those that require the reactivation of idiosyncratic contextual anchors related to temporal and spatial circumstances. The existence of such multiple factors helps to explain why the vulnerability of a memory to retrograde amnesia is not always a simple function of its time of acquisition and why clear temporal gradients are not universally found in amnestic patients.

Memory consolidation appears to involve a gradual increase in the density of the matrix that binds the components of the memory to each other and to other aspects of mental content. The outcome is to increase the number of associative approaches through which the memory can be probed. The hippocampal–entorhinal complex may well participate in the retrieval of all autobiographical and episodic memories, recent and remote, and even in the retrieval of the semantic knowledge related to arbitrary facts about the world, but it may no longer be critical for the recall of facts and events that have established a rich matrix of associations. In keeping with this formulation, functional imaging experiments show that the magnitude of hippocampal–entorhinal activation during memory retrieval is inversely proportional to the strength of encoding (Petersson *et al.*, 1997). The transmodal nodes that play a critical role in the retrieval of consolidated knowledge remain outside the limbic system. Examples include the relationship of transmodal midtemporal and temporopolar cortices to the recognition of familiar faces and, as will be shown below, that of Wernicke's area to the recognition of words. Thus even the most massive hippocampal–entorhinal lesions sustained during adulthood spare areas of consolidated knowledge such as the recognition of familiar faces and lexical retrieval.

Why is new learning dependent on the limbic system? A tentative answer may be based on the constraints that the CNS faces: the number of neurons is fixed with little hope of obtaining new ones, every existing neuron is already occupied by previously stored information, new information needs to be written on top of existing items, and the amount of new information is boundless. The CNS may therefore need to be protected from learning too rapidly and indiscriminately,

since this could jeopardize the stability of existing knowledge (McClelland, 1995). An initial filtering is provided by attentional systems which select subsets of behaviourally relevant events for further consideration. The limbic system appears to erect a second line of defence. It provides a mechanism that allows the rapid learning of behaviourally relevant relationships, but in an initially transient (limbic-dependent) form that may induce a relatively small amount of permanent change in the association cortex. This transitional period may allow new memories to enter associative readjustments before being assimilated in a more permanent form and also to compete with each other, allowing only the fittest to solidify their hold on precious synaptic space. Through these processes, the limbic system simultaneously satisfies the need to limit the indiscriminate influx of new learning and the need to adapt to a rapidly changing environment (McClelland, 1994).

The question may also be asked why a function as vital as explicit memory should display a critical dependency on a phylogenetically primitive part of the brain such as the limbic system. One explanation is that explicit and declarative memory could have developed to recall contingencies associated with food and danger. In the course of phylogenetic development, the scope of explicit memory could have expanded beyond the confines of appetitive and defensive behaviours while maintaining its anatomical dependency on the limbic system. The obligatory involvement of the limbic system in memory and learning also ensures that sensory events with high emotional and motivational valence will enjoy a competitive advantage. Furthermore, the limbic system is particularly prone to long-term potentiation effects, and is also one of the few areas that continue to display axonal sprouting during adulthood (Benowitz *et al.*, 1989; Bliss and Collinridge, 1993). These properties make the limbic system highly suitable for serving a critical role in the organization of new learning.

Unravelling the processes by which directories for multimodal binding are constructed within transmodal areas, including those of the limbic system, continues to pose formidable challenges. The Hebbian rule of covariance (Cruikshank and Weinberger, 1996) and the existence of reciprocal neural interconnections between unimodal and transmodal areas may provide two essential ingredients for this process. Figure 3 attempts to illustrate how synchronous activity in two unconnected unimodal areas can leave a record of this relationship in a transmodal area so that the future activation of one can elicit the reactivation of the other. In this diagram, A and B represent sensory components of the same event. Temporally synchronous activation of A and B will lead to synchronous activation in Ta and Tb within transmodal node Tr. The rule of covariance is expected to elicit a strengthening of the Ta–Tb and Tb–Ta synapses so that the next isolated excitation of either A or B will lead to the preferential conjoint activation of the other member of the pair, rather than area C. The 'memory' in this process is collectively encoded in A, B and Tr. Area Tr participates
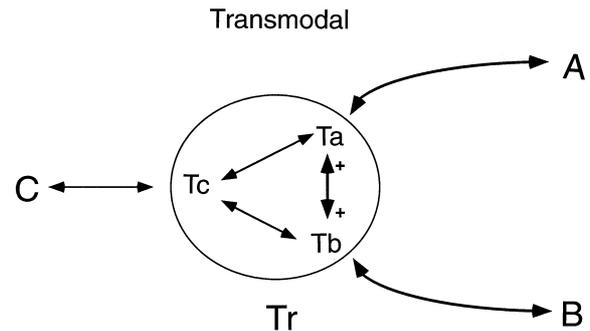
Fig. 3 A, B and C represent unimodal areas of the cerebral cortex. Tr represents a transmodal node of the cerebral cortex. Ta, Tb and Tc represent neuronal groups within T that are preferentially interconnected with A, B and C, respectively. Arrows denote monosynaptic reciprocal connections. The circuit A–Ta–Tb–B is emboldened to show the preferential strengthening (+) of the Ta–Tb and Tb–Ta synapses upon the simultaneous activation of A and B.

in the encoding of the memory both because it contains the directory which points to A and B and also because it contains some convergent synthesis of A and B. There are two kinds of plasticity involved in this process: (i) local changes in A or B—for example, a face that has become familiar may elicit an altered firing pattern in the face-responsive regions of the visual association cortex (Rolls *et al.*, 1989); and (ii) remote changes in the pattern of additional areas that are conjointly accessed by Tr—for example, as a result of increasing familiarity the face may elicit activation in a different set of distant association areas (Gorno Tempini *et al.*, 1997).

Figure 3 also helps to illustrate how such a circuit can support the three major forms of remembering: associative retrieval, voluntary recall and recognition. Associative retrieval occurs when one sensory component, such as A, leads to the activation of the entire template; voluntary recall reflects the access to both A and B through the intrinsic top-down activation of the relevant transmodal area Tr, and recognition occurs when the input matches the existing template. Area Tr in Fig. 3 could represent the hippocampal–entorhinal complex in the process of explicit memory; midtemporal or temporopolar cortices in face and object recognition; and, as will be shown below, Wernicke's area in lexical retrieval, the amygdala in motivation, and the posterior parietal cortex in directed spatial attention. In the case of explicit memory, a lesion in Tr does not obliterate the entire 'memory', but interferes with the coherent binding of its distributed features. The information encoded in A and B remains relatively unchanged in a manner that can sustain processes related to implicit learning.

The registration and recall of recent experience involves a great deal of sorting, associative search, recombination, selection and reintegration. The heteromodal cortices of the frontal and parietal lobes play a critical role in controlling these aspects of memory formation and recall. These transmodal nodes seem to participate in numerous memory-

related functions, including the reconstruction of context and temporal order, the guidance of encoding and retrieval, and the associative search of internal data stores. They also provide contextual constraints to keep the reconstructed memories within the bounds of plausibility. Damage to the prefrontal cortex increases the effort needed for encoding and retrieval, causes an impoverishment of associative linkages that are necessary for reconstructing context and temporal order, decreases the speed with which internal data stores are searched, and also increases the tendency to confabulate (Mesulam, 1995*b*; Moscovitch, 1995; Curran *et al.*, 1997). In keeping with these clinical observations, almost all tasks of explicit memory yield consistent activation in heteromodal association cortices, especially in prefrontal areas (Tulving *et al.*, 1994).

The process of explicit memory represents one of the most fundamental means of incorporating sensory information into cognition. It allows each individual to construct a unique record of experience and knowledge based on events of personal significance. A memory has no anatomical boundaries. Its encoding and retrieval involve almost all parts of the association cortex, but with an orderly anatomical distribution of component processes: relevant unimodal and transmodal areas encode the sensory aspects; the limbic system binds this information into a coherent whole; and prefrontal and other heteromodal areas guide the orderliness of storage and retrieval.

Words and language

Language is based on a special kind of relationship between sensation and cognition. It allows the formulation and communication of experiences, thoughts and memories through the mediation of arbitrary symbols known as words. The arbitrary associations between word and meaning eventually enter the realm of consolidated knowledge and, as in the case of familiar face and object recognition, become coordinated by transmodal nodes outside the limbic system. The encoding and activation of associations related to language follow principles of organization that are quite analogous to those involved in object recognition and explicit memory.

Wernicke's and Broca's areas in the left hemisphere are the two perisylvian transmodal nodes that provide pivotal gateways for linking sensory word-forms to the arbitrary associations that encode their meanings. The critical role of Broca's area (BA 44–45) in articulation, syntax and grammar and in the processing of verbs and function words has been demonstrated by multiple clinical and imaging studies (Benson, 1985; Mesulam, 1990; Daniele *et al.*, 1994; Nobre and Plunkett, 1997). Broca's area is consistently activated by tasks of word generation, and patients with damage to this part of the brain have difficulty in tasks of confrontation naming but not in tasks of word comprehension (Benson, 1985; Petersen *et al.*, 1988; Martin *et al.*, 1996). The participation of Broca's area in naming therefore appears to

be related mostly to the stage of word retrieval. Damage to Wernicke's area (posterior third of BA 22 and immediately adjacent parts of the heteromodal cortex in BA 39–40), on the other hand, causes severe comprehension as well as naming deficits. This is one of the very few lesion sites that gives rise to two-way naming deficits where the patient can neither retrieve the name of an object nor point to the appropriate object when the name is supplied by the examiner.

These observations may initially suggest that Wernicke's area could be the site of a central lexicon where word representations are stored. Three sets of clinical correlations, however, suggest a different interpretation: (i) patients with damage to Wernicke's area pour out an excessive volume of well-articulated words, although the resulting speech conveys little meaning; (ii) lesions that interrupt auditory or visual input to Wernicke's area cause modality-specific comprehension deficits for spoken or written words but leave intact the ability to verbally articulate thoughts and intentions; and (iii) lesions that spare Wernicke's area but interrupt its connections with other parts of the association cortex impair language comprehension and the ability to translate thoughts into words. Such observations have led to the conclusion that Wernicke's area is as unlikely to be a central repository for the mental lexicon as the hippocampal–entorhinal complex is to be a central bank for recent memories. Instead, the role of Wernicke's area might be conceptualized as that of a neural gateway that coordinates reciprocal interactions between the sensory representations of word-forms and the arbitrary (second-order or symbolic) associations that give them meaning. According to this formulation, damage to Wernicke's area does not necessarily obliterate word representations but makes it impossible to understand (decode) words in any modality of input, or to link (encode) percepts and concepts into corresponding word-forms. Thus, the relationship of Wernicke's area to lexical knowledge is analogous to the relationship of transmodal areas in the midtemporal cortex to the recognition of familiar faces, and the relationship of the hippocampal–entorhinal complex to the encoding and retrieval of recent experiences.

Functional imaging experiments have started to provide considerable support for this view and have led to novel and occasionally unexpected insights. Two types of lexical retrieval tasks have been used in these experiments: sensorially evoked and conceptually (or semantically) evoked. Sensorially evoked tasks where the subject is asked to name colours, actions, tools, familiar faces and animals can each lead to the relatively selective activation of separate and discrete regions of the temporal lobe, very few of which appear to overlap with Wernicke's area (Martin *et al.*, 1995; Damasio *et al.*, 1996; Martin *et al.*, 1996; Chao *et al.*, 1997). The naming of animals and tools, for example, activates the visual association cortex in the vicinity of the fusiform object identification areas of the ventral temporal lobe; the naming of colours activates an area near the colour-responsive area V4 in the left hemisphere; and the naming of tools and of the actions related to their use activates an additional posterior

midtemporal area slightly anterior to the movement-responsive area V5 and a premotor area (also activated by imagined hand movements), both in the left hemisphere (Martin *et al.*, 1995, 1996). Conceptually evoked lexical retrieval experiments have led to analogous results. For example, the generation of a colour word, characteristic of an object shown to the subject in the form of a black-and-white drawing, leads to activations near the colour area V4 (Martin *et al.*, 1995). It appears, therefore, that lexical retrieval is a highly distributed function and that the naming of visual entities and features is mediated by areas adjacent to those that support the perceptual encoding of the corresponding entities and features. This relationship holds when the lexical labelling is triggered by a sensory event in the outside world and also when it is directed to the conceptual knowledge of objects as retrieved from semantic memory. Lexical knowledge related to objects is thus anchored to the perceptual mapping of the corresponding experience.

These functional imaging experiments might have led to the conclusion that the naming of visual entities is entirely controlled by a set of category-specific lexical retrieval sites located distinctly outside of Wernicke's area. In fact, lesions and electrical stimulations in these areas are known to yield naming deficits, some of which can be category-specific (Ojemann, 1983; Benson, 1985; Damasio *et al.*, 1996). However, the clinical experience mentioned above also shows that the most severe and generalized naming deficits occur as a consequence of damage to Wernicke's area and adjacent perisylvian regions. The category-specific lexical retrieval areas located outside Wernicke's area therefore appear to be necessary but not sufficient to support naming. These areas could provide category-specific prelexical or implicit representations that need to be transformed into explicit outputs (in the form of spoken, written or signed words) through the intervention of Wernicke's area and other components of the language network.

Figure 4 outlines a neural organization that is consistent with these observations. According to this figure, sensorially evoked verbal naming entails multiple steps: (i) the visual input triggers the processes of sensory and perceptual encoding (in the regions indicated by 'Per' in Fig. 4); (ii) a nearby 'intermediary' lexical labelling area is activated (shown by 'Lex' in Fig. 4); (iii) projections from 'Lex' reach Wernicke's area, which acts as a transmodal gateway for activating a corresponding auditory (phonological) word-form so that the word can be articulated through the mediation of Broca's area and other premotor regions. Conceptually evoked lexical labelling takes a similar course except that area 'Lex' becomes activated by an internally generated representation evoked by semantic knowledge, probably through the intervention of transmodal gateways that mediate object recognition, such as area 'T' in Fig. 2D.[10]

The reverse process of word comprehension related to visual entities and features has not been investigated in as much detail by functional imaging. However, a similar organization may exist such that words are first encoded as perceptual entities in the word-form areas of auditory or visual association cortex; this representation is relayed through Wernicke's area and induces optimal resonance in corresponding intermediary lexical areas ('Lex' in Fig. 4), leading to the activation of the associations that define the meaning of the word. Wernicke's area would thus appear to play a central role in lexical retrieval and comprehension by acting as a transmodal gateway which links the perceptual aspects of a word form to the distributed associations that define its meaning. The organization outlined in Fig. 4 helps to explain why naming deficits arise after lesions in so many different parts of the temporal lobe, why some of these lesions can give rise to category-specific anomias and also why lesions in Wernicke's area give rise to global naming deficits.

The intermediary lexical areas in Fig. 4 ('Lex') contain part of the distributed knowledge pertaining to colours, actions, faces and objects. The location of the regions that provide access to the additional conceptual attributes of these visual features and entities seems to follow a similar organization. Thus, conceptual knowledge related to animals is most likely to become impaired by lesions that involve the fusiform region, whereas conceptual knowledge related to tools is more likely to become impaired by more laterally situated lesions that involve the posterior midtemporal cortex, in the vicinity of V5 (Tranel *et al.*, 1997). Despite this similarity of anatomical organization, the areas that are critical for lexical access are probably not identical to those that are critical for accessing additional aspects of conceptual knowledge. Thus, anomic patients may have no difficulty describing the use and nature of objects they cannot name, probably because access to the transmodal gateways that mediate object recognition remains intact. This dissociation of lexical from conceptual knowledge provides the anatomical basis for the separation of thought from language.

Although its spontaneous development only in humans endows language with a sense of uniqueness, its neurological foundations are quite analogous to those of other cognitive domains (Nobre and Plunkett, 1997). Word-forms (verbal and written), for example, are likely to be encoded within unimodal areas according to the principles that also guide the encoding of faces and objects. Lexical labelling, furthermore, can be conceptualized as a component of object recognition in the sense that a name is as much an attribute of an object as its colour, location or past associations. Word comprehension is also an object recognition task where the perceptual features first lead to the categorical identification of a word as a word, then to a subordinate level identification of the individual word, and finally to the establishment of

---

[10] This organization can also provide a neurological substrate for cognitively-based models of speech production. According to Morton (1969), for example, the mental lexicon is a collection of logogens, each sensitive to its own conceptual or perceptual information. All logogens are simultaneously active but only some reach threshold in response to a given set of inputs and then induce a phonological code which eventually results in word output. The 'intermediary' lexical areas in Fig. 4 could provide potential anatomical substrates for logogens.
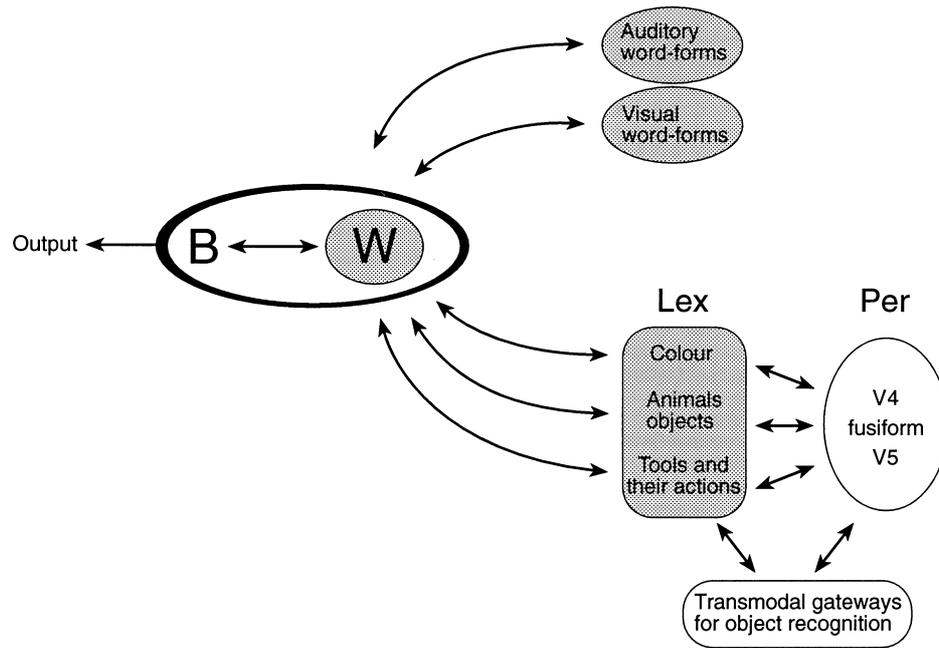
Fig. 4 A highly simplified schematic representation of some aspects of lexical retrieval and word comprehension. Arrows represent reciprocal neural connections. Abbreviations: B = Broca's area; Lex = areas for encoding prelexical representations related to colours, tools and actions; Per = areas for encoding sensory and perceptual features related to colour (V4), faces and objects (midfusiform area), and movement (V5); W = Wernicke's area. Output refers to speech or writing. The transmodal gateways that mediate object recognition include area T in Fig. 2D. Their organization is discussed in the section 'From perception to recognition: transmodal gateways'. The auditory and visual word-forms are encoded in the auditory and visual 'wr' nodes shown in Fig. 2D)

the multiple arbitrary associations that define its meaning through the mediation of transmodal nodes in perisylvian language areas. Word recognition and retrieval thus proceed according to principles that also guide object recognition and associative recall, except that the critical transmodal gateways are located in the perisylvian cortex rather than the midtemporal or temporopolar cortex.

The analogy between the neural organization of language and object recognition is further emphasized by the existence of two types of verbal associative agnosias, known as pure alexia and pure word deafness. In contrast to prosopagnosia and object agnosia, which emerge when visual information cannot access area 'T' in Fig. 2D, pure alexia (word blindness) emerges when areas that encode visual word-forms are disconnected from visual input or when they cannot communicate with Wernicke's area and related components of the language cortex. This usually happens when a lesion of area V1 in the left hemisphere (which by itself yields a right homonymous hemianopia) occurs in conjunction with a lesion of the splenium, a region of the corpus callosum which conveys visual information from one hemisphere to the other. The splenial lesion interferes with the transcallosal transfer of visual information from the intact visual areas of the right hemisphere to the visual word-form areas ('wr' in Fig. 2D) and transmodal language areas (area 'W' in Fig. 2D) of the left hemisphere. These areas thus become completely disconnected from ipsilateral as well as contralateral visual

input. The patient with pure alexia is not blind since objects and faces presented to the left hemifield can be identified with no difficulty. There is also no aphasia since Wernicke's area and other core language areas are intact. However, upon being asked to read, the patient appears illiterate since language-related transmodal nodes such as area 'W' in Figs 2D and 4 can no longer receive word-form information in the visual modality.

A similar analysis applies to pure word deafness, which arises when area 'wr' in unimodal auditory cortex is cut off from auditory input or when it cannot communicate with relevant transmodal nodes in area 'W', usually as a consequence of bilateral lesions in the superior temporal gyrus or a unilateral lesion in the left hemisphere. The patient with pure word deafness is not deaf and can readily interpret environmental sounds since parts of the primary auditory cortex and the auditory association areas are usually intact. Such patients are not aphasic and show no impairment of reading, writing or speaking since their language areas are intact. When exposed to speech, however, the patient reacts to it as an alien tongue that cannot be deciphered since the auditory information cannot reach language-related transmodal nodes such as those of Wernicke's area.

Domains as different as object recognition, explicit memory and lexical knowledge can thus share common principles of organization. In each case, specialized transmodal nodes act as critical gateways for looking up and binding distributed

multimodal information upon being queried by relevant unimodal inputs. Each of these processes entails convergence, but much of the convergence is based on knowing where to look up the information rather than on the presence of a privileged site 'where it all comes together'.

Selective enhancement of sensory experience through attentional modulation
Working memory and other 'top-down' processes

The processing capacity of the CNS is finite and necessitates a predominantly sequential rather than parallel approach to ambient sensory information (Broadbent, 1958; Baddeley, 1996). This situation creates a potentially serious limitation since important events can be brief, occur in clusters, and unfold on a noisy background full of distractors. If the interaction with the environment had to depend on brief neural responses which sequentially focused on only one event at a time, the resultant stream of consciousness might lack the coherence and associative depth necessary for object recognition, explicit memory and lexical retrieval.

If, on the other hand, the neuronal response to a brief sensory event could be prolonged beyond the duration of the actual event, linkages with past memories, lexical labels and other events in the environment would become more likely despite the limitations of real-time processing capacity. Such a prolongation of neural responses is achieved by the intervention of working memory, a special type of attentional process which enables the temporary, on-line holding of information for durations that fall between those of iconic memory and those of long-term 'off-line' storage. Working memory enriches the texture of consciousness by transforming information access from a sequential and disjunctive process, where only one item can be heeded at any given instant, to a conjunctive pattern where multiple items become concurrently available (Fig. 5). Working memory determines the number of parallel channels of information that can be handled on-line in a way that keeps them accessible, interactive and transiently protected from interference. The span of working memory could be likened to the number of balls that a juggler can simultaneously hold in the air. Performance in tasks of digit span and delayed matching-to-sample reflects the integrity of working memory. Daily activities that range from holding a telephone number in mind to considering alternative perspectives and outcomes in solving a problem rely on working memory.

In a typical experiment on working memory, a monkey is first briefly shown a sample cue (a colour, pattern or location), exposed to a variable delay, and rewarded for responding to a subsequent test stimulus only if it matches the sample. The crucial component of working memory is the delay period during which the animal has to maintain a mental representation of a cue which is no longer visible. Neurons in the inferotemporal and posterior parietal cortex have been shown to give differential responses during delay periods of up to 20 s, as if they were prolonging the impact of the cue or anticipating its reappearance. Each part of the unimodal association cortex seems to participate in the maintenance of working memory in its own area of specialization. Neurons with increased activity during delay periods are seen in the inferotemporal cortex in experiments where the stimuli are colours or visual patterns, and in the posterior parietal cortex when the stimuli are spatial locations (Fuster, 1990; Constantinidis and Steinmetz, 1996). Furthermore, working memory performance in visual and auditory tasks is severely impaired after damage to the inferotemporal and superior temporal cortices, respectively (Horel, 1984; Colombo *et al.*, 1996).

In some instances the inferotemporal or posterior parietal neurons that are sensitive to the cue are also the ones that subsequently maintain a higher delay activity when the memory of that same cue must be kept active. In other cases the two types of responses are dissociated from each other so that neurons that respond to the cue are different from the ones that are active during the subsequent delay. Some neurons that are active during the delay show stimulus specificity (will only respond during delays that follow a particular colour), whereas others do not (Fuster, 1990; Desimone, 1996).

Although unimodal association areas can sustain the process of working memory within their own preferred sensory domain, the lateral prefrontal transmodal cortex appears to play a uniquely critical role in orchestrating working memory in all domains of neural processing. Prefrontal neurons display selective delay firing that is maximal for specific faces, objects or spatial locations, in a way that could maintain the internal representation of a cue that is behaviourally relevant but no longer part of ambient reality. The stimulus-specificity of the delay activity is more pronounced and robust in the prefrontal cortex than in the inferotemporal or parieto-occipital cortex (Desimone, 1996). At least in monkeys, some anatomical segregation has also been reported so that the dorsolateral part of the prefrontal cortex (which receives a dense projection from dorsal posterior parietal cortex) is more involved in working memory tasks for spatial locations whereas its ventrolateral part (which receives a dense projection from the inferotemporal cortex) is more involved in working memory tasks for objects (Wilson *et al.*, 1993).

One of the most remarkable properties of these prefrontal neurons is a resistance to interference. For example in an A·B·C·D·A paradigm (where the cue and its match are separated by distractors), a prefrontal neuron which is known to emit a selective delay activity following the presentation of A continues to show high delay activity after B, C and D and maintains it until the reappearance of A (Desimone, 1996). Prefrontal neurons may therefore play a critical role in protecting the contents of working memory from distraction. An equally interesting property of prefrontal neurons is their ability to display delay activity when the
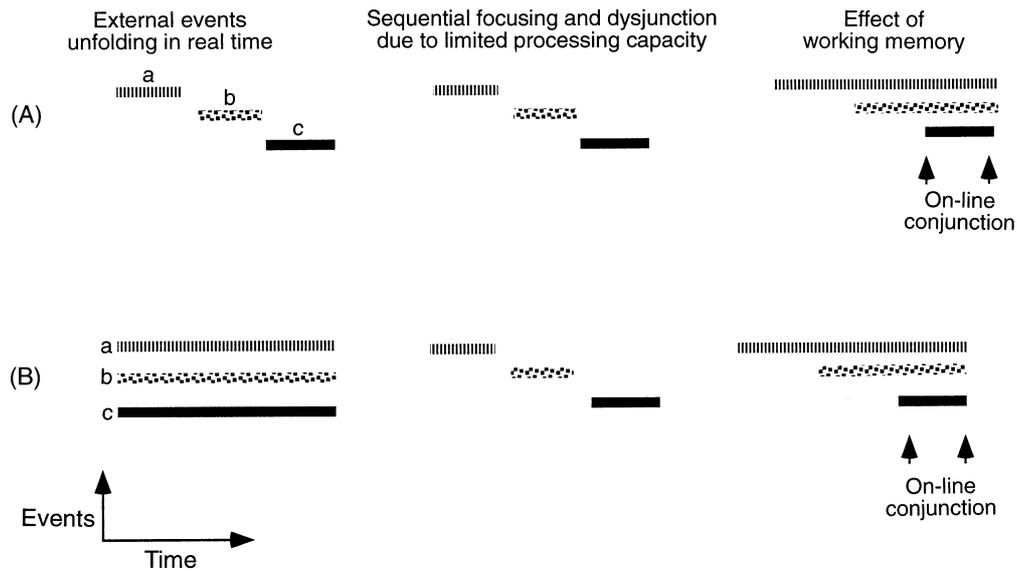
Fig. 5 In both **A** and **B**, a, b, and c represent three discrete events. (**A**) Events a, b and c happen consecutively (left row). The limited-capacity processing system attends to a, b and c sequentially as they unfold (middle row), without overlap. The temporal expansion introduced by working memory creates a mental on-line conjunction of the three events (right row). (**B**) Events a, b and c happen simultaneously (left row). The limited-capacity processing system attends to them one at a time, without overlap (middle row). The temporal expansion introduced by working memory restores on-line conjunction (right row).

task requires the retention of convergent properties such as the spatial location and the form of an object. In one experiment, for example, monkeys were given a task that required them to retain first the identity of an object and then its location. After having retained object information in the initial delay, many prefrontal neurons switched modes and conveyed spatial information in the second delay (Rao *et al.*, 1997). In keeping with these neurophysiological data, lesions of the prefrontal cortex in the monkey impair performance in all types of working memory tasks and also decrease the selectivity of delay activity in inferotemporal neurons (Fuster *et al.*, 1985; Desimone, 1996). As a transmodal zone at the fifth and sixth synaptic levels, the prefrontal cortex (area 'Pf' in Fig. 2D) is interconnected with numerous transmodal and downstream unimodal areas and is therefore in a position to exert a top-down modulation of delay activity in multiple perceptual and cognitive realms. The prefrontal cortex thus plays the role of a critical transmodal gateway which co-ordinates the multimodal aspects of working memory in a manner that may be analogous to the role of other transmodal areas in the co-ordination of object recognition, explicit memory and lexical access.

The importance of the human prefrontal cortex to working memory had been inferred from cases of brain damage (Mesulam, 1986). This relationship was demonstrated with functional imaging as early as 1973 by Risberg and Ingvar, who found that reverse digit span tasks resulted in haemodynamic activations that were maximal over the frontal lobes. Since then, numerous studies have confirmed the presence of frontal lobe activation during working memory tasks based on verbal, perceptual and spatial stimuli (Fiez

et al., 1996; McCarthy *et al.*, 1996). Working memory and related attentional functions can also influence the effectiveness of memory encoding and retrieval. This relationship may help to explain why the prefrontal cortex is so frequently activated by tasks of explicit memory. It is important to emphasize, however, that working memory and explicit memory are behaviourally and neurologically distinct phenomena. Lateral prefrontal cortex lesions that interfere with working memory do occasionally impair the efficiency of encoding and retrieval but almost never give rise to the severe amnesias seen in patients with lesions of the limbic system. Conversely, limbic lesions that devastate explicit learning usually leave working memory abilities quite intact.

The multisynaptic pathways that link sensation to cognition increase the range of neural reverberations that a sensory event can induce. Working memory enhances this effect by promoting an additional temporal dilation of neural activity within each node of Fig. 2D. Working memory prolongs the impact of experience and enables the on-line integration of multiple domains of neural activity without the need to transfer them into and out of long-term storage. Through the mediation of working memory, representations of external events and internal phenomena can unfold concurrently and interactively while they remain transiently protected from distraction so that the focus of attention can move from one to the other, creating new combinatorial assortments which, in turn, join the resultant stream of consciousness. This type of process would seem to be quite critical for integrating scenes, events and internally generated representations into a coherent conscious experience, and for allowing present events to enter into associative interactions with past

memories, the present context and contemplated goals. Despite this potentially crucial role of working memory in modulating the texture of consciousness, patients with severe frontal lobe lesions and severe impairments of working memory appear to maintain all external manifestations of consciousness, although at a possibly reduced level of complexity. There is, therefore, relatively little support for a modern sort of Cartesianism which would substitute the frontal lobe for the pineal gland as the final seat that sensation must reach before it can hope to gain access to consciousness (Crick and Koch, 1995).

The influence of the prefrontal cortex upon the delay activity of unimodal neurons during working memory tasks provides an example of top-down processing. As has been mentioned above, top-down processing is a generic term for all sensory-petal pathways, especially those that emanate from transmodal areas. The top-down processing of the prefrontal cortex in working memory is analogous to the top-down processing of the hippocampal–entorhinal cortex in explicit memory and of Wernicke's area in lexical access. Other top-down processes that contribute to the attentional modulation of sensory experiences include mental imagery, novelty-seeking behaviours and the influence of emotion and motivation upon neural activity. The prefrontal cortex plays an important integrative role in each of these attentional processes.

Mental imagery

Mental imagery refers to the activation of sensory representations that are not part of ambient reality. It could be conceptualized as a special type of attentional process targeted to internal representations. The neural substrates for mental imagery appear to include the same areas that would have supported the corresponding acts of perception if the imagined scene were actually unfolding in the external world. Functional imaging experiments, for example, have shown that the visualization of spatial relationships leads to the activation of the dorsal occipitoparietal cortex, whereas the visualization of objects leads to the activation of ventral occipito-temporal visual areas (Roland and Gulyás, 1994; Sakai and Miyashita, 1994). There may even be some retinotopic organization since visualizing larger objects (which presumably subtend a greater visual angle in the mind's eye) leads to more extensive activation in the part of V1 that maps the more peripheral aspects of the visual fields (Kosslyn *et al.*, 1993).

Activation during mental imagery has been shown in almost all of the primary, upstream and downstream visual areas. Primary and upstream visual areas such as V1–V5 may be activated predominantly by imagery that emphasizes internal sensory detail and mental rotation, whereas inferotemporal visual association areas may be activated predominantly by imagery tasks that reactivate stored memories (Roland and Friberg, 1985; Kosslyn *et al.*, 1994; Sakai and Miyashita, 1994). Even in imagery tasks that are optimally effective, however, the activation of V1 appears to be less robust and less consistent than activation in the other visual cortices (Sakai and Miyashita, 1994).

Virtually any sphere of sensory processing could potentially become the target of mental imagery. Mental rotations and other reconfigurations of visual percepts could subserve non-verbal thinking, whereas the mental activation of auditory word-forms and related associations could support inner speech and verbal thinking. Functional imaging suggests that the lateral prefrontal cortex plays a particularly important role in the top-down processes related to mental imagery (Kosslyn *et al.*, 1994), a role that is consistent with the critical influence of this area upon interrelated attentional processes such as working memory. There is no convincing evidence yet, however, that prefrontal lesions impair mental imagery.

Mental imagery provides one of at least three settings where the activation of sensory areas can transcend the constraints imposed by external reality. The two other examples include working memory, where the representation of a sensory experience is prolonged beyond the duration of the stimulus, and anticipatory paired-associate responses, where sensory representations become activated in expectation of an event which is not yet present in reality.

Novelty-seeking

Some sensory events elicit a greater neural response because of objective properties such as excessive brightness, loudness or noxiousness. Others do so on subjective grounds, because they have become relevant to current needs, because they have acquired special associations in the course of past experience, or because they are novel. The preferential enhancement of responses to novel stimuli is a luxury that only advanced brains can afford. In primitive animals the CNS contains numerous neural circuits, exemplified by the 'bug detectors' in the frog, for identifying familiar patterns on the basis of partial evidence and for linking them to automatic responses. The frog may not be able to distinguish one bug from another or a wind-swept leaf from a bug, but the processing efficiency offered by this arrangement appears to offset the attendant limitation in the resolution of reality.

The bias for perceiving sameness and emitting automatic responses represents a 'default mode' of brain function and leads to behaviours that can also be designated as instinctual, stereotyped or stimulus-bound. One consequence of this organization is to enhance efficiency and reliability, but another is to promote premature closure, perseveration and response rigidity, phenomena frequently encountered in the behaviours of less evolved species, of infants and of brain-injured humans. The CNS of more advanced species has compensated for these limitations by developing specialized neural circuits for the rapid detection of unfamiliar events and for inhibiting automatic response tendencies that have become contextually inappropriate.

Play and novelty-seeking behaviours, for example,

represent an antitheses to the pursuit of sameness. Such behaviours are inconspicuous in amphibians and reptiles, emerge in birds, and reach their most exuberant expression in advanced mammals, especially primates. In humans, sensory deprivation and monotony induce restlessness and even vivid hallucinations (Heron, 1957). Monkeys will work hard in a setting where the only reward is a peek through a window, and human subjects who are given a choice between familiar and simple versus novel and complex patterns, will consistently spend more time viewing the latter (Butler, 1953; Berlyne, 1960). The tendency for seeking novelty may even have survival value: in a prospective study of 2153 community-dwelling elderly subjects, those with a higher baseline level of 'curiosity' had a better chance to be alive and well 5 years later (Swan and Carmelli, 1996).

Nearly all transmodal and downstream unimodal nodes in Fig. 2D respond more actively to novel stimuli in their specific domains of specialization (Brown *et al.*, 1987; Wilson and Rolls, 1993; Berns *et al.*, 1997). However, the frontal lobe plays a particularly critical role in this realm of neural function. The P300 response elicited by novel or deviant stimuli, for example, is critically dependent on the integrity of the prefrontal cortex; an N2–P3 response which is maximal over the prefrontal cortex appears to determine the attentional resources that will be allocated to novel events; and the region of the frontal eye-fields belongs to a distributed network for exploring the extrapersonal space and seeking motivationally relevant targets (Mesulam, 1981; Knight, 1984; Daffner *et al.*, 1998). Patients with damage to various components of the prefrontal cortex display placid disinterest in novel aspects of the environment, inability to inhibit previously rewarded responses when reinforcement contingencies change, and vulnerability to perseveration, impulsivity and stimulus-bound behaviours (Leimkuhler and Mesulam, 1985; Mesulam, 1986). The prefrontal cortex thus seems to play an essential role in enhancing the impact of novelty and inhibiting habitual reactions that have become inappropriate. These multiple attentional functions of the prefrontal cortex and its role in various forms of response selection have led to the suggestion that it fulfils an 'executive' function in the linkage of sensation to cognition and behaviour.

The valuation of sensation

Emotion, mood and motivation modulate the neural impact of sensory events in a manner that reflects the subjective value of these events to the individual. These partially overlapping processes are closely related to the functions of the hypothalamus and other components of the limbic system, especially the amygdala and the paralimbic areas with which it is interconnected. The relationship of the amygdala to emotion was emphasized by Downer (1962), who showed that naturalistic sensory events triggered appropriate emotional responses in the monkey only if the sensory information had access to an intact amygdala. The amygdala also plays an important role in altering the impact of previously neutral stimuli that become linked to emotionally relevant events. For example, initially neutral auditory stimuli start to elicit amygdaloid activation only after they become associated with fear (LeDoux *et al.*, 1983). In humans, amygdaloid stimulations evoke emotionally charged memories whereas amygdaloid lesions cause states of hypoemotionality and interfere with the acquisition of conditioned emotional responses (Gloor *et al.*, 1982; Aggleton, 1993; Bechara *et al.*, 1995). In one patient, neurological damage involving the visuo-amygdaloid pathways led to the cancellation of a subscription to *Playboy*, apparently because the visual evocation of erotic feelings became blunted (Bauer, 1982).

The amygdala is reciprocally interconnected with unimodal sensory association cortices in the superior and inferior temporal gyri (Aggleton, 1993). Through these connections, the amygdala can selectively modulate sensory responses in a manner that reflects their intrinsic or acquired emotional relevance. In analogy to the organization of the other transmodal nodes in the cerebral cortex, the amygdala (represented by node 'L' in Fig. 2D) appears to act as a neural gateway for binding the sensory representations of primary and secondary reinforcers with each other and with the neural correlates of emotional and motivational valence.

The amygdala has a dual role in relation to attention and memory. Its role in attention is to selectively enhance the processing resources allocated to ambient events with high emotional and hedonic valence. Its role in memory is to encode the implicit and explicit emotional correlates of experience. The latter aspect of amygdaloid function can be conceptualized as complementary to that of the hippocampal formation, but with a selective emphasis on the association of sensory experiences to emotional valence (Cahill *et al.*, 1995). The roles of the hippocampus and of the amygdala in memory can be dissociated from each other. Hippocampal lesions interfere with the explicit recall of specific events but not with the autonomic responses they elicit on the basis of their emotional significance, whereas amygdaloid lesions leave explicit recall intact but abolish the associated autonomic responses (Bechara *et al.*, 1995).

The frontal lobe also participates in the modulation of neural responses to events that have become motivationally significant. Identical sensory stimuli, for example, can elicit dramatically different responses from lateral prefrontal neurons when their relationships to reward-producing responses are altered (Sakagami and Niki, 1994). Furthermore, an arbitrary sensory cue elicits greater responses from dorsolateral prefrontal neurons when it signals the impending delivery of a preferred food item, such as a piece of apple or cabbage, than when it signals a less favourite food such as a raisin (Watanabe, 1996). Their pronounced anatomical connectivity with the amygdala suggests that the paralimbic sectors of the orbitofrontal area might play a particularly prominent role in the emotional modulation of experience (Morecraft *et al.*, 1992). In fact, damage to orbitofrontal cortex can cause severe disruptions in the

linkage of experience to the appropriate emotional state and can lead to extensive impairments of judgement, insight and comportment. However, a blunting in the emotional and motivational colouring of sensory experience is also seen in patients with lesions in the more dorsolateral parts of the prefrontal cortex. These observations suggest that the dorsolateral and orbitofrontal components of the prefrontal cortex and the amygdala collectively modulate the neural impact of experience by encoding the acquired significance of sensory events rather than their surface properties.

The modulatory effects of emotion and motivation influence the attentional resources allocated to a sensory stimulus. Attention is difficult to define but easy to detect. It usually refers to an enhancement in the selectivity, intensity and duration of neuronal responses to events that have become emotionally and motivationally relevant. The attentional component of a neural response can be conceptualized as a vector with a magnitude and a direction. The direction of the vector is determined by the specialization of the neurons that express the attentional effect. Thus, inferotemporal neurons show attentional enhancement to behaviourally relevant visual patterns, posterior parietal neurons to spatial targets, pyriform neurons to odorants, and Wernicke's area to words (Bushnell *et al.*, 1981; Nobre and McCarthy, 1994; Desimone, 1996; Eichenbaum *et al.*, 1996). The magnitude of the attentional vector in each of these cortical areas is under two types of influences: bottom-up influences emanating from the ascending reticular activating system (ARAS), and top-down influences emanating from the limbic and prefrontal cortices. The ARAS modulates the intensity of attention according to the general level of arousal and wakefulness, whereas the limbic and frontal cortices provide modulations based on factors such as novelty, emotion, motivation, intention and past experience. One manifestation of the top-down influence of prefrontal cortex upon the attentional vector is known as working memory and has been reviewed above.

Attention, emotion and motivation introduce a value system to sensory processing. These value-based modulations allow the CNS to sculpt sensory experience into a subjective landscape. The effects of attention can be detected at every synaptic level of Fig. 2D. For example, some neurons in the primary auditory cortex respond to a sound only when the animal appears to attend to its source (Hubel *et al.*, 1959). Numerous experiments in primates and humans have also shown, however, that attentional responses are more common and prominent at higher synaptic levels, especially in the heteromodal cortex and downstream components of the unimodal cortices (Mesulam, 1985*a*; Sakai and Miyashita, 1994; Maunsell, 1995). Motivational modulation seems to display a similar pattern. In the monkey, for example, hunger modulates the neuronal response to palatable liquids almost exclusively at the final stage of the multisynaptic taste pathways in the orbitofrontal cortex (Rolls, 1987).

These observations suggest that early sensory processing, especially at the first two synaptic levels of the template in Fig. 2D, is relatively protected from value-based modulations.

This arrangement allows internal states to influence sensory-fugal processing only after the essential features of sensory events have been encoded. In fact, there is little adaptive sense in altering responses to shapes, motion or colour, whereas it makes a lot of sense to modulate responses to specific faces, objects or locations. The organization of sensory-petal (top-down) connections is consistent with this polarization, since transmodal cortices have very few monosynaptic projections to primary sensory areas and send fewer projections to upstream than to downstream components of unimodal areas. In the frog, the situation may be quite different. Attention can dramatically alter the response properties of visually responsive tectal neurons at the first central synapse of visuo-fugal pathways, and can induce an obligatory change in the nature of all the visual input that the brain receives (Lettvin *et al.*, 1961). Significance and appearance are therefore much more tightly yoked to each other in the frog than in the primate.

Modulatory pathways of the reticular activating system

The initial accounts of the ARAS had focused on its thalamo-cortical components. More recent work has shown that the ARAS also contains several sets of projections that arise from relatively small regions of the basal forebrain and brainstem and that reach the cerebral cortex without a synapse in the thalamus. These modulatory pathways mediate the state-dependent regulation of neural responses in accordance with changes of arousal, mood and circadian phase (Mesulam, 1995*a*). The cholinergic pathways that extend from the nucleus basalis of the basal forebrain (the Ch1–Ch4 cell groups) to the cerebral cortex are the most massive of all modulatory pathways. Others include histaminergic projections from the hypothalamus, dopaminergic projections from the substantia nigra–ventral tegmental area, serotonergic projections from the raphe nuclei, and noradrenergic projections from the nucleus locus coeruleus. Each of these pathways has a slightly different pattern of cortical distribution and physiological effect. For example, serotonergic pathways are directed predominantly to cortical interneurons whereas the cholinergic pathways are directed predominantly to projection neurons (Smiley and Goldman-Rakic, 1996; Smiley *et al.*, 1997).

Cortical cholinergic innervation reaches all cortical regions but is most intense within limbic areas (Mesulam, 1996). The major effect of acetylcholine upon neurons of the cerebral cortex is mediated through the m1 subtype of muscarinic receptors and causes a prolonged reduction of potassium conductance so as to make cortical neurons more receptive to sensory stimulation (Sato *et al.*, 1987; McCormick, 1990). Cholinergic neurons of the nucleus basalis are particularly sensitive to novel and motivationally relevant stimuli (Wilson and Rolls, 1990). Furthermore, the novelty-related P300 response in the human cerebral cortex can be abolished by

cholinergic antagonists (Hammond *et al.*, 1987). In addition to playing a role in novelty-seeking behaviours, cholinergic projections may also modulate attentional processes related to working memory. For example, locally infused cholinergic blockers interfere with the accuracy of saccadic eye movements only when they are guided by spatial working memory but not when they are guided by ambient visual targets (Dias *et al.*, 1996).

In addition to these short-term effects, acetylcholine may promote the establishment of long-term plasticity and synaptic efficacy during the acquisition of new associations (Huerta and Lisman, 1993; Cruikshank and Weinberger, 1996; Woolf, 1996; Baskerville *et al.*, 1997). Although the basal forebrain cholinergic nuclei project to all cortical areas, they receive cortical input only from the limbic system. Thus, only behaviourally significant events which activate the limbic system can effectively induce a rapid change of activity in the nucleus basalis (Mesulam, 1996). Such limbic activation of the nucleus basalis and the resultant release of acetylcholine in cortical areas would enhance the response of unimodal and heteromodal areas to the target sensory event, and selectively increase the responsivity of the limbic system to the resultant input. Through these processes, cholinergic activation can influence the preferential registration and binding of significant events within the context of the circuitry shown in Fig. 3. Cortical cholinergic projections can thus selectively enhance the immediate and long-term impact of sensory events that are novel and motivationally relevant.

The dopaminergic cells of the substantia nigra–ventral tegmental area are also selectively sensitive to motivationally relevant stimuli and to cues that signal their existence (Schultz, 1997). These neurons appear to encode deviations between the prediction and occurrence of reward and may therefore convey teaching signals for learning appetitive behaviours (Schultz, 1997). In keeping with these tuning properties, the dopaminergic projections from the ventral tegmental area to the cerebral cortex and nucleus accumbens appear to play an important role in mediating the neural processes related to substance addiction (Pich *et al.*, 1997). As in the case of cholinergic projections, ascending dopaminergic inputs can also enhance the working memory capacity of neurons in the frontal lobe (Goldman-Rakic, 1996). The nucleus locus coeruleus provides another CNS site where neurons can encode the behavioural significance rather than surface appearance of sensory stimuli (Aston-Jones *et al.*, 1997). The noradrenergic projection from the nucleus locus coeruleus to the cerebral cortex increases the signal-to-noise ratio of sensory responses in the cerebral cortex and therefore enhances the sharpness of neural tuning to significant sensory events (Foote *et al.*, 1983; Levin *et al.*, 1988). Through β-adrenergic synapses in the amygdala, ascending noradrenergic pathways are also thought to mediate the preferential storage and retrieval of emotionally relevant memories (McGaugh *et al.*, 1993).

These modulatory projections may also induce pathological biases in the encoding of sensory experience, such as those seen in patients with mania, depression, paranoia and chronic anxiety. Preliminary evidence suggests that the neural response to sensory events may be altered in patients with such conditions. For example, when compared with control subjects, patients with generalized anxiety disorder show greater metabolic activation of the temporal and frontal cortex during the passive viewing of neutral stimuli (Wu *et al.*, 1991). Indirect evidence based on the pharmacological treatment of depression and anxiety with noradrenergic and serotonergic agents and of paranoia with dopamine blockers suggests that the modulatory pathways of the cerebral cortex may play important roles in setting such fixed attitudinal biases in the emotional valuation of sensory experience.

As in the case of cholinergic pathways, the nuclei that give rise to these modulatory projections innervate all parts of the cerebral cortex but receive feedback (top-down) projections from a much more limited set of cortical areas, predominantly from those that belong to the limbic and paralimbic zones of the cerebral cortex (Mesulam, 1987). Additional inputs to these nuclei may also arise in the hypothalamus and other subcortical structures. This asymmetry of cortico-fugal versus cortico-petal connections allows the neurons of the basal forebrain, substantia nigra–ventral tegmental area, brainstem raphe and nucleus locus coeruleus to act as transmitter-specific relays for rapidly modulating the linkage of sensation to cognition throughout the cerebral cortex, and in a manner that is particularly responsive to the activation state of the limbic system. It is unlikely that there will be a one-to-one relationship between any single pathway in the ARAS and individual components of cognition or behaviour. In general, however, the activation of these modulatory pathways provides a mechanism for augmenting the neural responses to novel and motivationally relevant events, facilitating their storage in memory, enhancing their access to on-line processing resources, sharpening the attentional focusing they elicit, and increasing their impact on consciousness.

The organization of neurocognitive networks
Distributed large-scale networks and their cortical epicentres: a model based on the organization of spatial awareness and directed spatial attention

Transmodal nodes in the midtemporal cortex, Wernicke's area and the hippocampal–entorhinal complex transform unimodal sensory input into coherent multimodal assemblies necessary for face and object recognition, naming, and explicit memory. These transmodal areas provide the neural epicentres of large-scale distributed networks (Mesulam, 1990). The organization of such networks has been explored in relation to the process of directed spatial attention.

Observations on patients with focal brain damage, relevant animal experiments and more recent work based on functional imaging show that the distribution of attention within the

extrapersonal space is co-ordinated by a network built around three transmodal areas: one in the region of the frontal eye fields and adjacent parts of the prefrontal cortex, a second in the heteromodal parts of posterior parietal cortex, and a third in the cingulate region (Mesulam, 1981, 1990, 1994*b*; Gitelman *et al.*, 1996; Nobre *et al.*, 1997). The frontal eye field component provides access to a motor map for the distribution of exploratory and orienting acts, the parietal component to a multimodal representation of the extra-personal space, and the cingulate component to a map of expectancy and relevance. Experiments in the rhesus monkey, where an analogous network for spatial attention has been identified, showed that these three cortical epicentres are monosynaptically interconnected with each other and with subcortical structures in the medial pulvinar nucleus and the striatum. Numerous clinical observations have indicated that unilateral damage to any component or connection of this network can lead to contralesional spatial neglect, especially if the lesion is in the right hemisphere (Mesulam, 1981).

Functional imaging experiments show that the part of posterior parietal cortex that is critical for spatial attention (area 'P' in Fig. 2D) is located within the banks of the intraparietal cortex in the human brain (Nobre *et al.*, 1997). Its proposed role in the attentional network is based on its ability to integrate distributed spatial information (originating from 's' in the visual and auditory modalities as shown in Fig. 2D) in all relevant sensory modalities. When this area is damaged, the modality-specific channels of information related to the extrapersonal space may remain intact but cannot be bound into the type of coherent and interactive representation that is necessary for the adaptive deployment of spatial attention. As in the relationship of transmodal nodes to other cognitive domains, posterior parietal cortex is not a dedicated centre for mapping spatial co-ordinates, but a critical gateway for accessing, binding and integrating information related to the conceptual representation and exploration of the extrapersonal space.

The architecture of interconnectivity among the components of the network for spatial awareness was investigated in an experiment where the regions of the frontal eye fields and posterior parietal cortex were each injected with a different retrogradely transported tracer in the same monkey. The pattern of retrograde labelling showed that these two epicentres of the attentional network were interconnected not only with each other and the cingulate gyrus but also with an additional set of 12 identical cortical areas. Furthermore, some thalamic nuclei, including the medial pulvinar, were found to project to both injection sites (Morecraft *et al.*, 1993).

These anatomical details helped to generate the principles of network organization summarized in Fig. 6 (Mesulam, 1990). In this figure, 'A' and 'B' represent two interconnected epicentres of any large-scale neural network. In the attentional network, 'A' and 'B' would stand for the frontal eye fields and posterior parietal cortex; in the face and object recognition

network for midtemporal and temporopolar cortices; in the explicit memory network for the amygdala and the hippocampal–parahippocampal complex; in the language network for Wernicke's area and Broca's area; in the network for working memory and related 'executive' functions for the prefrontal cortex and probably parts of the posterior parietal cortex. The axonal transport experiments in the monkey indicate that if one member of such a pair, say 'A', is interconnected with additional cortical areas such as 1, 2, and 3, then 'B' is also interconnected with the same three cortical areas. Consequently, if 'A' transmits a message, 'B' will receive it directly, but also through the alternative vantage points provided by areas 1, 2 and 3. This arrangement allows parallel processing and introduces multiple neural nodes for seamless transitions between parallel and serial processing. In resolving a complex cognitive problem such as trying to reconstruct a past memory, finding words to express a thought or trying to decide the identity of a face, a set of cortical areas interconnected in this fashion is in a position to execute an extremely rapid survey of a vast informational landscape while considering numerous goals, constraints, scenarios and hypotheses until the entire system settles into a state of best fit (or least conflict) which becomes identified as the solution to the cognitive problem.

A task such as colour naming, for example, would trigger the preferential mobilization of a network such as the one shown in Fig. 6, with Wernicke's and Broca's areas at its epicentres, but with the additional participation of numerous visual, auditory and transmodal areas. Individual neural ensembles at these regions would respond, according to their preferred tuning properties, to the visual, lexical, phonological and articulatory parameters of the task. Some of these relationships are serial. For example, area 'Lex' in Fig. 4 is inserted between area V4 and Wernicke's area. Other interactions occur in parallel. For example, the verbal output may emerge from the simultaneous activation of several ensembles in the superior temporal gyrus, each interconnected with Wernicke's as well as Broca's area, some specialized for encoding the skeleton of the utterance, and others for encoding its internal segments related to initial sound, syllabic structure, and so on (Creutzfeldt *et al.*, 1989; Levelt, 1992). Through a process of iterative and competitive approximation, the pattern that attracts the most neuronal recruitment dominates the network and guides the articulation of the appropriate colour name. Although the primary goal is colour naming, the related neural activity also results in corollary discharges which evoke related semantic associations.

As shown in the anatomical experiments described above, some thalamic subnuclei can project to both epicentres of a large-scale neural network. Because cortical areas tend to have very extensive corticocortical projections, parts of the association cortex are likely to belong to multiple networks intersecting at that point. With rare exceptions, however, thalamic subnuclei have almost no connections among each other (Mesulam, 1985*b*). This arrangement led to the suggestion that thalamic subnuclei could fulfil the very
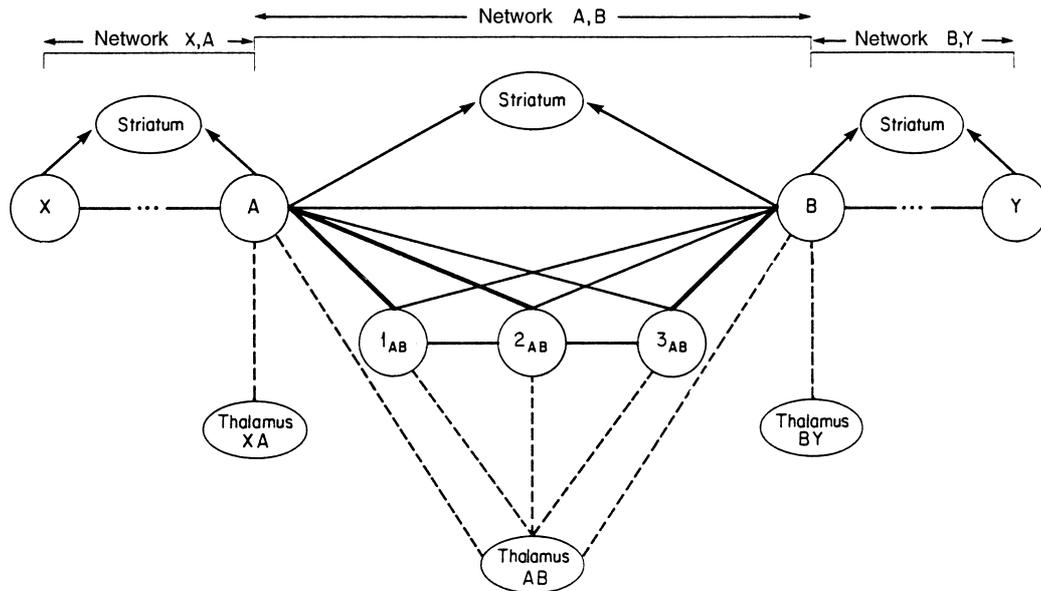
Fig. 6 A general representation of a large-scale neurocognitive network. Lines without arrowheads represent reciprocal connections. The cortical connections to the striatum are not reciprocal. Dashed lines illustrate thalamic projections. Areas A and B represent two epicentres of network A, B. Areas 1AB, 2AB and 3AB represent three additional cortical components of the network. AB, XA and BY represent thalamic subnuclei. Reprinted from *Annals of Neurology* (Mesulam, 1990).

important role of binding components of a given network, or alternatively of setting co-activation boundaries for separating the activity of one network from the activity of others (Mesulam, 1990). A similar view was expressed by Penfield (1975), who suggested that thalamic nuclei could act as integrators of the cortical areas involved in speech and language. Additional anatomical experiments had also shown that interconnected epicentres of large-scale networks are likely to send interdigitating projections to the striatum (Yeterian and Van Hoesen, 1978; Selemon and Goldman-Rakic, 1988). Since the striatum receives cortical inputs but does not project back to the cerebral cortex, the suggestion was made that it could serve the role of an efference synchronizer (or filter) for co-ordinating the outputs of cortical areas in a given network (Mesulam, 1990).

The human brain contains at least five large-scale neurocognitive networks: (i) a right hemisphere-dominant spatial awareness network with epicentres in the dorsal posterior parietal cortex, the frontal eye fields and the cingulate region; (ii) a left hemisphere-dominant language network with epicentres in Wernicke's and Broca's areas; (iii) a memory–emotion network with epicentres in the hippocampal–entorhinal regions and the amygdaloid complex; (iv) a working memory–executive function network with epicentres in the prefrontal cortex and probably the posterior parietal cortex; (v) a face and object identification network with epicentres in the midtemporal and temporopolar cortices. Neuroanatomical experiments in the analogous regions of the monkey brain have shown that the components of these networks are interconnected according to the pattern shown in Fig. 6 (Selemon and Goldman-Rakic, 1988;

Mesulam, 1990). The transmodal components in all of these networks receive their sensory information from the common set of unimodal cortical areas shown in Fig. 2D. The nature of the resultant cognitive transformation is determined by the anatomical location and connectivity of the transmodal epicentres that guide the process.

The large-scale network approach leads to the prediction that several, if not all, network components will be activated concurrently during the performance of a task in the relevant cognitive domain. In keeping with this prediction, tasks related to spatial awareness, language, working memory, explicit memory and object identification have each led to the joint activation of the relevant epicentres noted above (Petrides *et al.*, 1993; McIntosh *et al.*, 1994; Bullmore *et al.*, 1996; Just *et al.*, 1996; Haxby *et al.*, 1997a; Nobre *et al.*, 1997; Rumsey *et al.*, 1997). Figure 2D also shows how each sensory modality could give rise to streams of processing directed to each of the five major neurocognitive networks. The subdivision of sensory-fugal streams of processing into only dorsal and ventral components may therefore represent an oversimplification when applied to the human brain.

A central feature in the organization of the large-scale network outlined in Fig. 6 is the absence of one-to-one correspondences among anatomical sites, neural computations and complex behaviours (Mesulam, 1990). According to this organization, an individual cognitive or behavioural domain is subserved by several interconnected macroscopic sites, each of which subserves multiple computations, leading to a distributed and interactive but also coarse and degenerate (one-to-many and many-to-one) mapping of anatomical substrate onto neural computation and computation onto

behaviour. Since many sites within the association cortex are likely to serve several intersecting networks, an individual lesion, even when confined to a single cytoarchitectonic field, may impair multiple domains of cognitive function. Conversely, some lesions (or electrical stimulations) may remain behaviourally silent under certain conditions because alternative parallel channels may become available. Furthermore, the same cognitive function may be impaired by lesions in many different parts of the brain, as long as these regions remain within the confines of the relevant network. For the more practical purposes of neurobehavioural assessment, this model predicts that no cognitive task can ever provide a specific test for detecting damage within a single region of association cortex, and that the clinician need not look for multiple lesions just because the patient shows more than one cognitive deficit.

Selectively distributed processing and shifts of network affiliations

Although all cortical nodes of a given network (for example A, B, 1_{AB}, 2_{AB} and 3_{AB} in Fig. 6) contribute to the co-ordination of the same cognitive function, they are not interchangeable. Each node displays specialization for a specific behavioural component of the relevant domain. This specialization is relative rather than absolute. For example, Wernicke's area occupies the phonological/lexical/semantic pole of the network but also participates in articulation and syntax, whereas Broca's area occupies the articulatory/syntactic pole of the network but also participates in phonological discrimination and lexical generation (Mesulam, 1990). In the case of spatial localization, the frontal eye fields occupy the motor/exploratory pole of the relevant network but also participate in the compilation of a perceptual representation, whereas the posterior parietal cortex occupies the sensory/representational pole but also participates in the programming of exploratory movements (Mesulam, 1981). In the limbic network, the hippocampal complex is most closely related to explicit memory but also plays a role in emotional modulation whereas the amygdaloid complex is most closely related to emotional modulation but also participates in the encoding of emotionally salient memories (Cahill *et al.*, 1995; Mongeau *et al.*, 1997).

This functional organization fits the designation of selectively distributed processing (Mesulam, 1994*c*; Seeck *et al.*, 1995). The plausibility of selectively distributed processing was probed experimentally in subjects undergoing depth electrode recordings as they were being investigated for the surgical treatment of epilepsy. The subjects were shown a large number of faces and common objects and were asked to engage in one of four tasks: detection of familiarity, perceptual matching, perceptual categorization, and working memory. Recording sites were located in the hippocampus, amygdala, inferotemporal cortex and lateral prefrontal cortex. A recording site was noted to be engaged

by a given task if the averaged evoked potentials to two contrasting stimuli (e.g. familiar vs unfamiliar faces) differed beyond the 1 standard error range for each (Seeck *et al.*, 1995).

The results showed that all four recording sites were engaged by several of these tasks, but each with a distinct profile. The hippocampus was the one area that did not seem to show a definite preference for one task over another, probably because none of the tasks required long-term explicit memory. The probability of activation in the amygdala was highest when the goal of the task was the detection of familiarity; in the inferotemporal cortex, when the goal was perceptual categorization or perceptual matching; and in prefrontal cortex, when the goal was to hold information in working memory. These results are consistent with an organization based on selectively distributed processing. They also support the contention that there are no object or face 'centres' in the brain, and that the anatomical distribution of stimulus-induced activation is a probabilistic function determined by the goal of the task rather than the nature of the stimulus.

According to the principles of selectively distributed processing, many cortical nodes are likely to participate in the function of more than one network. Conceivably, top-down connections from transmodal areas could differentially recruit such a cortical node into the service of one network or another. For example, Friston showed that a region of the inferotemporal cortex was able to yield differential activation to faces versus other objects only when there was a high level of activation in a region of the medial posterior parietal cortex (Friston, 1997). In another experiment, the same set of subjects were given two tasks, one of face identification and the other of spatial attention (McIntosh *et al.*, 1994). A region that corresponds to the parietal component of the attentional network (BA 7), a region of prefrontal cortex (BA 46) related to the frontal component of the same network, and a part of inferotemporal cortex (BA 21) were activated by both tasks. However, the activation of BA 7 in the task of object identification was much more strongly correlated with the activation of BA 21 than with that of BA 46, whereas the reverse relationship was observed during the attentional task, where the activation of BA 7 was more strongly correlated with that of BA 46 than BA 21. These results suggest that individual cortical areas can dynamically shift affiliation from one network to another depending on the overall goal of the task.

The mechanisms underlying these shifts are poorly understood. Changes in behavioural context can alter the way in which the activity of a neuron is temporally correlated with the activity of another in the same area of the cerebral cortex (Vaadia *et al.*, 1995). These effects could allow a rapid association and dissociation of local clusters into distinct functional subgroups, each favouring a different network linkage. Such dynamic network reconfigurations occur in the stomatogastric ganglion of decapod crustaceans, where they appear to be controlled by monoaminergic inputs (Harris-Warrick and Marder, 1991). Furthermore, in the lamprey the

same group of neurons mediates swimming, burrowing and crawling, and can be reoriented from one task-specific network to the other by serotonin through the modulation of a calcium-activated potassium current (Ayers *et al.*, 1983). Conceivably, network realignments in the primate brain could also be influenced by the modulatory monoaminergic and cholinergic pathways of the cerebral cortex.

Overview and speculations on the evolution of human consciousness

In the frog, the distance from sensation to cognition is short. Only a very limited amount of sensory information can enter the CNS, its fidelity is lost within a synapse or two due to attentional modulation and convergence, and there is an almost immediate closure of processing in the form of obligatory skeletal or autonomic responses. The major difference between humans and frogs is not based on brain size, but on the synaptic distance that separates an initial sensory response from recognition, interpretation and action. The organization of the synaptic template shown in Fig. 2D allows each sensory event to trigger an almost boundless variety of cognitive and behavioural outcomes while at the same time maintaining accuracy and reliability. In such a system adaptability is based on diversity, competition and choice rather than on fail-safe, stereotyped mechanisms.

The sensory-fugal streams of processing that transform sensation into cognition start at the first synaptic level where sensation is initially mapped by finely tuned neurons into a primary dimension, retinotopic for vision and tonotopic for audition. The second synaptic level participates in more complex integrations and also in the extraction of attributes such as colour and motion. The third and fourth synaptic levels play critical roles in the perceptual and categorical identification of patterns and entities such as faces, objects, words, and extrapersonal targets by ensembles of coarsely tuned neurons organized according to the principles of selectively distributed processing.

The fidelity of modality-specific encoding is actively protected through the first four synaptic levels. Motivational, emotional, and attentional modulations based on the internal state and experience of the individual are relatively weak at the first two synaptic levels but become increasingly more influential at higher synaptic levels, where they help to create a subjectively sculpted version of the world. There is a hierarchical organization of the synaptic levels in Fig. 2D, but the hierarchy becomes less and less strict at more downstream stages of processing. Individual nodes at each level have parallel connections with nodes at adjacent levels and the vast majority of all connections are reciprocal, creating multiple opportunities for feed-forward and feed-back interactions. Each node in this template acts as a nexus for receiving convergent afferents and sending divergent efferents. This arrangement facilitates rapid feature extraction, differential analysis, integrative synthesis and associative elaboration.

The transfer of information from the first to the fourth synaptic level does not follow the model of an assembly line where each level, having accomplished a finite job, terminates its engagement as it delivers a product to the next higher level for further processing. Instead, several levels remain active as the pertinent information is conveyed from one node to the other, so that the identification of a face or word reflects the combined outcome of concurrent activity at many of the relevant synaptic levels. There is also no initial triage, so that any visual input can potentially activate most nodes in Fig. 2B. However, an input with canonical features that elicit more robust activation in the face area of the temporal lobe has a greater chance of being processed as a face, whereas another, with canonical features that elicit greater activation in the word-form areas, has a greater chance of being processed as a word. The selectively distributed processing model also indicates that faces activate not only the face area but also, although to a lesser extent, other visual association nodes, so that the final modality-specific neural representation of a face can be considered as a plane that has its highest peak over the face area but which also has lesser peaks and valleys over numerous other nodes in Fig. 2B.

The fifth and sixth synaptic levels contain transmodal gateways serving two interactive purposes: (i) they have neurons that provide a site for multimodal convergence at the level of group encoding; and (ii) they bind transmodal and unimodal areas into coherent multimodal groupings. Transmodal nodes are critical for transforming perception into recognition, words into meaning, scenes and events into experiences, and spatial locations into targets for exploration. Each transmodal zone acts as one of several epicentres for a large-scale distributed network, and each epicentre displays a relative specialization for specific behavioural components of the domain subserved by that network. Each transmodal zone can also potentially belong to several intersecting networks and can dynamically shift allegiance from one to the other depending on the goal of the task. Network components are interconnected with an architecture that enables parallel processing and that also allows rapid transitions from parallel to serial processing.

Since the nature, purpose and consequences of environmental events are relatively unpredictable, a new event is likely to activate all networks, at least initially. The steps of perceptual identification, deployment of spatial attention, naming, association with past experiences, assessment of present context, planning of options, inhibition of automatic responses and prediction of consequences proceed simultaneously and interactively. The process can be characterized as a rapid and iterative succession of mental scripts, scenarios and hypotheses that are triggered by interactions between environmental events and internal representations. The most relevant ensembles and networks gradually dominate the landscape of neural activity as they become more and more resonant with the goals and constraints of the prevailing context. The solution to the cognitive problem or task is defined as the settling of the entire system

into a state of best fit. This is not the final product in a hierarchical assembly line, but a complex surface with many peaks and valleys, spread over much of the cerebral cortex.[11] There is, therefore, both localization (phrenology) and equipotentiality, but the localization is distributed and the equipotentiality displays regional selectivity.

Facts and events that need to be encoded in memory are composed of modality-specific sensory components. The initial encoding of these components occurs within unimodal areas and provides the immediate substrates of perceptual information that can be tapped by implicit memory. The construction of a consciously accessible and explicitly identifiable memory necessitates the transformation of these isolated fragments into a coherent multimodal representation. The multimodal binding that subserves this process is co-ordinated by the hippocampal–entorhinal complex and related limbic structures. Since behaviourally relevant events are more likely to elicit limbic activation, this arrangement promotes the preferential learning of behaviourally relevant experiences. An initial entry into explicit memory does not guarantee longevity. Newly encoded memories remain more heavily dependent on the integrity of limbic connections for months to years as they gradually become consolidated through extensive associative linkages. Consolidation is a life-long bidirectional process: it is enhanced by associative linkages and may decrease if the memory remains dormant for a long period of time. During the early period of consolidation, the new associations remain vulnerable as they compete for limited synaptic space. Those that survive become part of the ever-changing matrix of knowledge and start to influence the way in which new learning becomes incorporated. Once memories are consolidated, the binding of their constituents becomes more dependent on transmodal areas outside the limbic system and they become less vulnerable to limbic lesions. The hippocampus and related limbic structures could thus be conceptualized as maintaining a nursery for memories in gestation. One purpose of this prolonged limbic tutelage may be to protect the cerebral cortex from the disruptive influence of too many erratic changes, many of which may later turn out to have been unimportant (McClelland, 1995).

The template in Fig. 2D illustrates the multiple paths that link sensory information to perception, recognition and recollection. Since informational channels are noisy and entropy tends to increase as information is transferred from one node to another, private perceptions and recollections at the higher synaptic levels are unlikely to contain faithful replicas of the real-life events they represent. The influence of emotion, motivation and selective attention introduce additional subjective biases. Each individual consciousness may thus be embedded within the illusory reality of a reconstructed present and the personal mythology of an approximated past. It is important to realize, however, that

the biological purpose of perceptual and mnemonic abilities is not necessarily to enhance representational fidelity but rather to optimize the adaptive value of the behaviours that are guided by the relevant percepts and recollections.

From a strictly behavioural point of view, the existence of consciousness might be inferred when a living organism responds to environmental events in an adaptive way that is not entirely automatic. According to such a definition, consciousness is a property shared by a multitude of species. There are, however, differences of detail. The path from sensation to cognition in the frog is straight and narrow, leading to an equally modest texture of consciousness. In the human brain, the multiple paths inserted between the first and sixth synaptic levels of Fig. 2D and the additional influence of working memory introduce a vast spatial and temporal expansion of the neural landscape that links sensation to cognition. Working memory, in particular, greatly expands the horizon of consciousness by lengthening the temporal influence of internally or externally generated events and by increasing the number of processing channels that can be accommodated simultaneously. The impact of working memory on the quality of consciousness may resemble the impact of resonance, reverberation and dynamic range on the quality of the auditory experience in a concert hall (Beranek, 1996). Human consciousness is not a special faculty occupying a specific site of the brain but an integrative manifestation of many CNS systems, including all cortical networks reviewed above (Delacour, 1997).

Not all sensory events that activate nodes in Fig. 2D are necessarily accessible to consciousness. Some facts and events can be encoded in ways that covertly influence subsequent behaviour even when the subject appears to have no conscious awareness of the relevant information. As already mentioned, such dissociations between the implicit and explicit encoding of information have been demonstrated in amnestic patients. In other settings, patients who appear to be blind by traditional testing may nonetheless reach accurately towards a visual target within their blind field (Weiskrantz *et al.*, 1974); those who cannot consciously identify a familiar face may still emit a galvanic skin response as a covert sign of recognition (Bauer, 1984; Tranel and Damasio, 1985); and others, who cannot recognize words or faces they have been asked to memorize, display priming effects in stem completion and recognition paradigms (Warrington and Weiskrantz, 1974; Moscovitch, 1982; Schacter, 1995; Seeck *et al.*, 1997). The conscious awareness of some sensory experiences may be delayed by up to 500 ms beyond the time of the initial cortical response, during which the incoming impulses appear to acquire 'neuronal adequacy' (Libet, 1966, 1982). It appears, therefore, that the accessibility of an event to explicit consciousness and introspective commentary is the by-product of a special type of cortical activity and not an automatic consequence of sensory input. Access to the level of explicit consciousness would appear to be most likely for components of experience

---

[11] Functional imaging emphasizes the peaks and therefore gives the impression of a sharper localization.

that can elicit coherent binding and multimodal associative elaboration through the intercession of transmodal nodes.

According to the organization of the template in Fig. 2D, the same event can potentially elicit numerous alternative representations and the same goal can be reached through equally numerous means. The consequences of this organization permeate all aspects of behaviour and underlie the uniquely human aptitude for discovering multiple solutions to similar problems. All conspecific frogs tend to fancy the same type of bug and display a similar snapping style. Humans, however, have conjured up an almost infinite number of solutions to satisfy the need for clothing, shelter, food and communication. Although the basic verbal messages transmitted from one individual to another have not varied much from one social group to another or from one epoch to the next, they have nonetheless become expressed in thousands of different languages. If there ever was a pre-Babel epoch, it must have happened before humans emerged as a species or before the template in Fig. 2D assumed its present form.

The template in Fig. 2D allows the emergence of a large number of alternative trajectories as sensation becomes transformed into cognition. In the course of this process, obligatory one-to-one linkages between stimulus and response are transcended, creating a setting that encourages mental relativism. The realization that identity is not violated even as the same object acquires different sensory properties when viewed from different points in space (because of parallax) or time (because of aging), that an act may be condoned in one context but not in another, and that individual variations in perspective may lead to alternative interpretations of the same event are some examples of this mental relativism. An important component of mental relativism is the capacity to assume another person's perspective, an ability which is probably unique to humans,[12] and which emerges relatively late in cognitive development (Selman, 1971).

The neural substrate of mental relativism would appear to be based on the ability to establish multiple representations of the same fact, and to realize that such representations (for example, the reflection of the self in the mirror) constitute alternative manifestations of the same basic phenomenon. This type of neural computation is not automatic. A male turtle, for example, will fight its own reflection in the mirror from dawn to dusk; only specially trained monkeys give any sign of rudimentary self-recognition in front of a mirror; and many demented patients will react to their reflections as if they were intruders (Ajuriaguerra *et al.*, 1963; Harless, 1979; Gallup *et al.*, 1980; Hauser *et al.*, 1995).

A tolerance for multiple alternative representations may provide the critical ingredient that sets the special flavour of human consciousness. It is reasonable to assume that animals have a relatively simple sort of consciousness, the content of which is closely determined by the here-and-now of immediate needs and sensations. A more complex form of consciousness would be expected to emerge if some critical mass of neurons, freed from the household chores of sensation and action, could afford to form alternative and annotated representations of ambient events.[13] One consequence of this process could be the emergence of an observing self who becomes differentiated from the sensory flux and who can therefore intentionally comment (introspect) on experience.[14] Such a capacity for introspection and intentionality may have generated first the sense of a 'commenting self' separate from the experiencing body, then the belief that others also have commenting selves, and, ultimately, that these other commenting selves believe that others also have commenting selves.

These additional dimensions of human consciousness are likely to have created the driving force for the development of symbolic communications, including language. Thought, defined as the cerebral activity that intervenes between sensation and action, is likely to arise in all experiencing organisms of sufficient CNS complexity, and may therefore be said to exist in many animal species. Animals can also communicate, but in a concrete and reflexive fashion where a specific set of emotive states or external events triggers a specific call or gesture. The development of a communication system based on consensually sanctioned arbitrary labels such as words, however, would appear to require not only the ability to transcend concrete stimulus–response linkages, but also the presence of an intentional, observing self and the belief in the existence of other self-conscious individuals who will be able to decipher the message. Language, in this sequence of events, becomes a consequence of thought, not its cause. As Vygotsky (1962) has said, a thought may be compared to a cloud shedding a shower of words.

The development of language is likely to have shaped the course of cognitive evolution by enabling the emergence of a uniquely human phenomenon known as civilization. Frogs may have consciousness, brilliant apes may display occasional bursts of symbolic communication, but only humans build civilizations. The impact of this distinction becomes particularly significant within an evolutionary context. Humans and their closest cousins, apes, parted ways ~5 million years ago. During the subsequent 4 million years evolutionary pressures led to expansion of cranial volume, the assumption of an erect posture, and the descent of the larynx into a position that enabled a richer vocal output (Donald, 1991). In contrast to this relatively brisk pace of

---

[12] Preprogrammed behaviours such as the broken wing display of a plover trying to lure predators away from her offspring do not fit the description of voluntary shifts of perspective, although they do depend, in an automatic sort of way, on assumptions concerning the point of view of the predator.

[13] The role of prefrontal cortex in this development needs to be given considerable prominence. It is probably the only part of the brain that makes no essential contribution to routine sensory, skeletomotor or autonomic function. It is also the part of the brain that shows the greatest expansion in the primate line of evolution. The prefrontal cortex could be conceptualized as a luxury dividend that phylogeny offered primates and that catalysed the ability to transcend a stimulus-bound existence.

[14] A most poignant example is in Genesis. 'Then God said "Let there be light"; and there was light. *And God saw that the light was good...*'

biological evolution, the pace of cognitive change during these 4 million years was painfully slow and seems to have been confined predominantly to the transition from the use of accidentally sharpened stones by *Australopithecus* to the use of deliberately sharpened ones by *Homo erectus*. Modern humans entered the scene only 50 000 to 100 000 years ago. During the short interval since then, our species has leaped from caves to skyscrapers, from the drawings of Lascaux to the mosaics of Pompei, and from cannibalism to nouvelle cuisine.[15] Brain structure, however, has probably shown no substantial change during this interval. How can brain function change so radically when brain structure has remained relatively stable?

At least part of the answer lies in the transition of the bottleneck from individual to group cognition through the mediation of language and civilization. Civilization depends on two major ingredients: adaptability to rapid change, and the ability to transfer knowledge of procedures and relationships from one individual to another and from one generation to the next.[16] The former ingredient, the ability to tolerate change, is a luxury that only the most advanced brains can afford. It might take a very long time, for example, to convince a frog to change its eating habits. In contrast, adaptability to change, in fact an overwhelming urge to seek novelty and alternative vantage points, is a major characteristic of the human CNS and the principal determinant of the cognitive relativism described above. The second ingredient of civilization, the inter-individual transfer of knowledge, is a by-product of the capacity to communicate complex and abstract relationships through the mediation of language. Such a transfer of knowledge would have fostered the development of civilization by liberating each individual member of a social group from the need to re-invent the wheel and by promoting a gradual transgenerational accumulation of knowledge. A pivotal outcome of this process would have been to shift the pacemaker for cognitive advance from the painfully slow process of physical brain evolution to the far more rapid and dynamic pace of computational evolution where each individual intelligence could potentially become a constituent link in a massively parallel network.

In preliterate societies, the contribution of each link to this process was undoubtedly limited by the synaptic capacity and lifespan of individual biological memories. The invention of writing is likely to have overcome this limitation by introducing a new and infinitely expandable, extracorporeal memory.[17] Through the advent of writing, progress would no longer be contingent on a few wise men with phenomenal memories and communicative skills. Even those of modest talent could have access to vast libraries containing the distilled wisdom of all humanity. The development of writing would thus have triggered the second and even steeper acceleration of cognitive evolution.

The hypothetical sequence of events outlined above is based on the following milestones: the horizon and complexity of consciousness became augmented by the spatio-temporal dilation of the pathways that lead from sensation to cognition; the enrichment of consciousness and the resultant ability to step back from real-time events enabled the emergence of intentionality and introspective commentary; the realization that other members of the species were similarly disposed encouraged symbolic communication; the resultant transgenerational accumulation of knowledge led to the establishment of culture and civilization; civilizations then became the vehicle for further accelerations in the pace of change through additional inventions such as writing. Through these steps, *Homo sapiens* has been able to make giant cognitive leaps without the need for parallel changes in the biological hardware of the brain. Clearly, this sequence of events represents a great oversimplification. Many of these developments could have proceeded simultaneously and numerous intermediate steps could have existed. The purpose in this account, however, has been to show that neurological scenarios based on the template in Fig. 2D could become relevant to the exploration of even the most complex achievements of the human mind, in principle if not in detail.

In the frog, sensation becomes cognition at the first synaptic level. The horizons of consciousness are defined by a rigidly filtered sensory reflection of the immediate present. In the human, sensation merely begins to kindle the creative processes of the mind, and the present is only one point along a continuum of consciousness that extends from the dim past to the distant future. In the eyes of evolution, the frog has a much more extensive record of credibility. However, its future is completely constrained by its past. The human brain has followed a different kind of adaptation based on a continuous pressure to seek and create novelty and change. The resultant texture of human existence, based on the flexibility afforded by the neural pathways that link sensation to cognition, is immensely rich but also potentially quite fragile since not all that is novel is necessarily good. The future of the human race, while almost unlimited in its potential, is therefore also more uncertain than that of the frog.

Acknowledgements

---

[15] Cultural evolution has obviously not been uniformly positive. The same neural template that enabled the serenity of Ryoanji has also enabled Auschwitz. It goes without saying that purpose in biology is constrained by survival, not by value. The neural connections in Fig. 2D enable the human mind to transcend stimulus–response bonds but do not specify the contents or consequences of the resultant activities.

[16] A rudimentary and stimulus-bound form of inter-individual transfer of information can be discerned in other species in the form of 'observational learning' but its scope is very limited, usually confined to consummatory behaviours.

[17] Writing was apparently invented by a Sumerian king, some 5000 years ago, who was loath to fire his loyal but forgetful messenger.

References

Abbie AA. Cortical lamination in a polyprotodont marsupial, Perameles nasuta. J Comp Neurol 1942; 76: 509–36.

Aggleton JP. The contribution of the amygdala to normal and abnormal emotional states. [Review]. Trends Neurosci 1993; 16: 328–33.

Ajuriaguerra J, Strejilevitch M, Tissot R. A propos de quelques conduites devant le miroir de sujets atteints de syndromes démentiels du grand âge. Neuropsychologia 1963; 1: 59–73.

Allison T, McCarthy G, Nobre A, Puce A, Belger A. Human extrastriate visual cortex and the perception of faces, words, numbers, and colors. [Review]. Cereb Cortex 1994; 5: 544–54.

Amaral DG, Insausti R, Cowan WM. Evidence for a direct projection from the superior temporal gyrus to the entorhinal cortex in the monkey. Brain Res 1983; 275: 263–77.

Andersen RA, Essick GK, Siegel RM. Encoding of spatial location by posterior parietal neurons. Science 1985; 230: 456–8.

Andersen RA, Asanuma C, Essick C, Siegel RM. Corticocortical connections of anatomically and physiologically defined subdivisions within the inferior parietal lobule. J Comp Neurol 1990; 296: 65–113.

Aston-Jones G, Rajkowski J, Kubiak P. Conditioned responses of monkey locus coeruleus neurons anticipate acquisition of discriminative behavior in a vigilance task. Neuroscience 1997; 80: 697–715.

Ayers JA, Carpenter GA, Currie S, Kinch J. Which behavior does the lamprey central motor program mediate? Science 1983; 221: 1312–4.

Baddeley A. The fractionation of working memory. [Review]. Proc Natl Acad Sci USA 1996; 93: 13468–72.

Bailey CH, Bartsch D, Kandel ER. Toward a molecular definition of long-term memory storage. [Review]. Proc Natl Acad Sci USA 1996; 93: 13445–52.

Baskerville KA, Schweitzer JB, Herron P. Effects of cholinergic depletion on experience-dependent plasticity in the cortex of the rat. Neuroscience 1997; 80: 1159–69.

Bauer RM. Visual hypoemotionality as a symptom of visual–limbic disconnection in man. Arch Neurol 1982; 39: 702–8.

Bauer RM. Autonomic recognition of names and faces in prosopagnosia; a neuropsychological application of the Guilty Knowledge Test. Neuropsychologia 1984; 22: 457–69.

Bear MF. A synaptic basis for memory storage in the cerebral cortex. [Review]. Proc Natl Acad Sci USA 1996; 93: 13453–9.

Bechara A, Tranel D, Damasio H, Adolphs R, Rockland C, Damasio AR. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. Science 1995; 269: 1115–8.

Bechterew W von. Demonstration eines Gehirns mit Zerstörung der vorderen und inneren Theile der Hirnrinde beider Schläfenlappen. Neurol Zentbl 1900; 19: 990–1.

Benowitz LI, Perrone-Bizzozero NI, Finklestein SP, Bird ED. Localization of the growth-associated phosphoprotein GAP-43 (B-50, F1) in the human cerebral cortex. J Neurosci 1989; 9: 990–5.

Benson DF, Geschwind N. Shrinking retrograde amnesia. J Neurol Neurosurg Psychiatry 1967; 30: 539–44.

Benson F. Aphasia and related disorders: a clinical approach. In: Mesulam M-M, editor. Principles of behavioral neurology. Philadelphia: F. A. Davis, 1985. p. 193–238.

Beranek L. Concert and opera halls: how they sound. New York: American Institute of Physics, 1996.

Berlyne D. Conflict, arousal and curiosity. New York: McGraw-Hill; 1960.

Berns GS, Cohen JD, Mintun MA. Brain regions responsive to novelty in the absence of awareness. Science 1997; 276: 1272–5.

Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. [Review]. Nature 1993; 361: 31–9.

Breuer J, Freud S. Studien über Hysterie. Leipzig: Deuticke; 1895.

Broadbent DE. Perception and Communication. Oxford: Pergamon Press; 1958.

Broca P. Anatomie comparée des circonvolutions cérébrales. Le grand lobe limbique et la scissure limbique dans la série des mammifères. Rev Anthropol 1878; 1: 385–498.

Brodmann K. Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Leipzig: J. A. Barth, 1909.

Brown MW, Wilson FA, Riches IP. Neuronal evidence that inferomedial temporal cortex is more important than hippocampus in certain processes underlying recognition memory. Brain Res 1987; 409: 158–62.

Bullmore ET, Rabe-Hesketh S, Morris RG, Williams SCR, Gregory L, Gray JA, et al. Functional magnetic resonance image analysis of a large-scale neurocognitive network. Neuroimage 1996; 4: 16–33.

Bushnell MC, Goldberg ME, Robinson DL. Behavioral enhancement of visual responses in monkey cerebral cortex: 1. Modulation in posterior parietal cortex related to selective visual attention. J Neurophysiol 1981; 46: 755–72.

Butler RA. Discrimination learning by rhesus monkeys to visual-exploration motivation. J Comp Physiol Psychol 1953; 46: 95–8.

Cahill L, Babinsky R, Markowitsch H, McGaugh JL. The amygdala and emotional memory [letter]. Nature 1995; 377: 295–6.

Campbell AW. Histological studies on the localization of cerebral function. Cambridge: University Press; 1905.

Capranica RR. Auditory processing in anurans. [Review]. Fed Proc 1978; 37: 2324–8.

Chao LL, Weisberg JA, Wiggs CL, Haxby JV, Ungerleider LG, Martin A. Cortical regions associated with perception, naming and knowledge of color. Neuroimage 1997; 5 (4 Pt 2): S54.

Chen WR, Lee S, Kato K, Spencer DD, Shepherd GM, Williamson A. Long-term modifications of synaptic efficacy in the human inferior and middle temporal cortex. Proc Natl Acad Sci USA 1996; 93: 8011–5.

Claparède M. Récognition et moiité. Archs Psychol (Genève) 1911; 11: 79–90.

Clark VP, Maisog JM, Haxby JV. FMRI studies of face memory using random stimulus sequences. Neuroimage (4 Pt 2) 1997; 5: S50.

Colombo M, Rodman HR, Gross CG. The effects of superior temporal cortex lesions on the processing and retention of auditory information in monkeys (Cebus apella). J Neurosci 1996; 16: 4501–17.

Connor CE, Gallant JL, Preddie DC, Van Essen DC. Responses in area V4 depend on the spatial relationship between stimulus and attention. J Neurophysiol 1996; 75: 1306–8.

Constantinidis C, Steinmetz MA. Neuronal activity in posterior parietal area 7a during the delay periods of a spatial memory task. J Neurophysiol 1996; 76: 1352–5.

Corbetta M, Miezin FM, Dobmeyer S, Shulman GL, Petersen SE. Attentional modulation of neural processing of shape, color and velocity in humans. Science 1990; 248: 1556–9.

Corbetta M, Miezin FM, Dobmeyer S, Shulman GL, Petersen SE. Selective and divided attention during visual discriminations of shape, color, and speed: functional anatomy by positron emission tomography. J Neurosci 1991; 11: 2383–402.

Creutzfeldt O, Ojemann G, Lettich E. Neuronal activity in the human lateral temporal lobe. I. Responses to speech. Exp Brain Res 1989; 77: 451–75.

Creutzfeldt OD, Heggelund P. Neural plasticity in visual cortex of adult cats after exposure to visual patterns. Science 1975; 188: 1025–7.

Crick F, Koch C. Are we aware of neural activity in primary visual cortex? Nature 1995; 375: 121–3.

Cruikshank SJ, Weinberger NM. Evidence for the Hebbian hypothesis in experience-dependent physiological plasticity of neocortex: a critical review. [Review]. Brain Res Rev 1996; 22: 191–228.

Curran T, Schacter DL, Norman KA, Galluccio L. False recognition after a right frontal lobe infarction: memory for general and specific information. Neuropsychologia 1997; 35: 1035–49.

Daffner KR, Mesulam M-M, Scinto LFM, Cohen LG, Kennedy BF, West WC, et al. Control of novelty-seeking behavior by the frontal lobes: an event-related potential study. Neuroreport 1998; 9: 787–91.

Damasio AR. Disorders of complex visual processing: agnosias, achromatopsia, Balint's syndrome, and related difficulties of orientation and construction. In: Mesulam M-M, editor. Principles of behavioral neurology. Philadelphia: F. A. Davis; 1985: 259–88.

Damasio AR. The brain binds entities and events by multiregional activation from convergence zones. Neurol Comp 1989; 1: 123–32.

Damasio H, Grabowski TJ, Tranel D, Hichwa RD, Damasio AR. A neural basis for lexical retrieval. Nature 1996; 380: 499–505.

Daniele A, Giustolisi L, Silveri MC, Colosimo C, Gainotti G. Evidence for a possible neuroanatomical basis for lexical processing of nouns and verbs. Neuropsychologia 1994; 32: 1325–41.

Delacour J. Neurobiology of consciousness: an overview. [Review]. Behav Brain Res 1997; 85: 127–41.

Démonet J-F, Chollet F, Ramsay S, Cardebat D, Nespoulous J-L, Wise R, et al. The anatomy of phonological and semantic processing in normal subjects. Brain 1992; 115: 1753–68.

Dennett DC, Kinsbourne M. Time and the observer: the where and when of consciousness in the brain. Behav Brain Sci 1992; 15: 183–247.

Desimone R. Face-selective cells in the temporal cortex of monkeys. J Cog Neurosci 1991; 3: 1–8.

Desimone R. Neural mechanisms for visual memory and their role in attention. [Review]. Proc Natl Acad Sci USA 1996; 93: 13494–9.

Dias EC, Compaan DM, Mesulam M-M, Segraves MA. Selective disruption of memory-guided saccades with injection of a cholinergic antagonist in the frontal eye field of monkey [abstract]. Soc Neurosci Abstr 1996; 22: 418.

Dinse HR, Kruger K. The timing of processing along the visual pathway in the cat. Neuroreport 1994; 5: 893–7.

Donald M. Origins of the modern mind. Three stages in the evolution of culture and cognition. Cambridge (MA): Harvard University Press; 1991.

Downer CL de C. Interhemispheric integration in the visual system. In: Mountcastle VB, editor. Interhemispheric relations and cerebral dominance. Baltimore: Johns Hopkins University Press; 1962. p. 87–100.

Economo C von, Koskinas GN. Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen. Wien: Springer; 1925.

Edelman S. Representation is representation of similarities. Behav Brain Sci. In press 1998.

Eichenbaum H, Schoenbaum G, Young B, Bunsey M. Functional organization of the hippocampal memory system. [Review]. Proc Natl Acad Sci USA 1996; 93: 13500–7.

Erickson RP. The across-fiber pattern theory: an organizing principle for molar neural function. Contrib Sens Physiol 1982; 6: 79–110.

Exner S. Untersuchungen über die Localisation der Funktionen in der Grosshirnrinde des Menschen. Wien: W. Braumuller; 1881.

Fahy FL, Riches IP, Brown MW. Neuronal activity related to visual recognition memory: long-term memory and the encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex. Exp Brain Res 1993; 96: 457–72.

Farah MJ, Feinberg TE. Visual object agnosia. In: Feinberg TE, Farah MJ, editor. Behavioral neurology and neuropsychology. New York: McGraw-Hill; 1997. p. 239–44.

Felleman DJ, Van Essen DC. Distributed hierarchical processing in the primate cerebral cortex. [Review]. Cereb Cortex 1991; 1: 1–47.

Ferrier D. The functions of the brain. London: Smith, Elder; 1876.

Fiez JA, Raife EA, Balota DA, Schwarz JP, Raichle ME, Petersen SE. A positron emission tomography study of the short-term maintenance of verbal information. J Neurosci 1996; 16: 808–22.

Filimonoff IN. A rational subdivision of the cerebral cortex. Arch Neurol Psychiatry 1947; 58: 296–311.

Fink GR, Markowitsch HJ, Reinkemeier M, Bruckbauer T, Kessler J, Heiss W-D. Cerebral representation of one's own past: neural

networks involved in autobiographical memory. J Neurosci 1996; 16: 4275–82.

Flechsig PE. Anatomie des menschlichen Gehirns und Rückenmarks. Leipzig: Verlag von Georg Thieme; 1920.

Fodor JA. The modularity of mind: an essay on faculty psychology. Cambridge (MA): MIT Press; 1983.

Foote SL, Bloom FE, Aston-Jones G. Nucleus locus coeruleus: new evidence of anatomical and physiological specificity. [Review]. Physiol Rev 1983; 63: 844–914.

Friston KJ. Imaging cognitive anatomy. Trends Cogn Sci 1997; 1: 21–7.

Fujita I, Tanaka K, Ito M, Cheng K. Columns for visual features of objects in monkey inferotemporal cortex. Nature 1992; 360: 343–6.

Fuster JM. Inferotemporal units in selective visual attention and short-term memory. J Neurophysiol 1990; 64: 681–97.

Fuster JM, Bauer RH, Jervey JP. Functional interactions between inferotemporal and prefrontal cortex in a cognitive task. Brain Res 1985; 330: 299–307.

Gabrieli JDE, Brewer JB, Desmond JE, Glover GH. Separate neural bases of two fundamental memory processes in the human medial temporal lobe. Science 1997; 276: 264–5.

Gaillard F. Visual units in the central nervous system of the frog. [Review]. Comp Biochem Physiol A 1990; 96: 357–71.

Gallup GG Jr, Wallnau LB, Suarez SD. Failure to find self-recognition in mother-infant and infant-infant rhesus monkey pairs. Folia Primatol (Basel) 1980; 33: 210–9.

Geisler WS, Albrecht DG. Bayesian analysis of identification performance in monkey visual cortex: nonlinear mechanisms and stimulus certainty. Vision Res 1995; 35: 2723–30.

Geschwind N. Disconnexion syndromes in animals and man. I. [Review]. Brain 1965; 88: 237–94.

Gitelman DR, Alpent NM, Kosslyn SM, Daffner K, Scinto L, Thompson W, et al. Functional imaging of human right hemispheric activation for exploratory movements. Ann Neurol 1996; 39: 174–9.

Gloor P, Olivier A, Quesney LF, Andermann F, Horowitz S. The role of the limbic system in experiential phenomena of temporal lobe epilepsy. Ann Neurol 1982; 12: 129–44.

Goldman-Rakic PS. Topography of cognition: parallel distributed networks in primate association cortex. [Review]. Annu Rev Neurosci 1988; 11: 137–56.

Goldman-Rakic PS. Regional and cellular fractionation of working memory. [Review]. Proc Natl Acad Sci USA 1996; 93: 13473–80.

Gorlick DL, Constantine-Paton M, Kelley DB. A ^{14}C-2-deoxyglucose autoradiographic investigation of sensory inputs to the optic tectum of Rana pipiens. J Comp Physiol A 1984; 154: 617–24.

Gorno Tempini ML, Price C, Vandenberghe R, Josephs O, Kapur N, Cappa SF, et al. Functional anatomy of a common semantic system for names and faces. Neuroimage 1997; 5 (4 Pt 2): S560.

Gross CG, Rocha-Miranda CE, Bender DB. Visual properties of neurons in inferotemporal cortex of the macaque. J Neurophysiol 1972; 35: 96–111.

Halgren E, Dale AM, Sereno MI, Tootell RBH, Marinkovic K, Rosen BR. Location of fMRI responses to faces anterior to retinotopic cortex. Neuroimage 1997; 5 (4 Pt 2): S150.

Halgren E, Wilson CL, Stapleton JM. Human medial temporal-lobe stimulation disrupts both formation and retrieval of recent memories. Brain Cogn 1985; 4: 287–95.

Hammond EJ, Meador KJ, Aung-Din R, Wilder BJ. Cholinergic modulation of human P3 event-related potentials. Neurology 1987; 37: 346–50.

Harless M. Social behavior. In: Harless M, Morlock H, editors. Turtles. Perspective and research. New York: John Wiley; 1979: 475–92.

Harries MH, Perrett DI. Visual processing of faces in temporal cortex: physiological evidence for a modular organization and possible anatomical correlates. J Cogn Neurosci 1991; 3: 9–24.

Harris-Warrick RM, Marder E. Modulation of neural networks for behavior. [Review]. Annu Rev Neurosci 1991; 14: 39–57.

Hauser MD, Kralik J, Botto-Mahan C, Garrett M, Oser J. Self-recognition in primates: phylogeny and the salience of species-typical features. Proc Natl Acad Sci USA 1995; 92: 10811–4.

Haxby JV, Clark VP, Courtney M. Distributed hierarchical neural systems for visual memory in human cortex. In: Hyman BT, Duyckaerts C, Christen Y, editors. Connections, cognition and Alzheimer's disease. Berlin: Springer Verlag; 1997a. p. 167–80.

Haxby JV, Martin A, Clark VP, Hoffman EA, Schouten JL, Ungerleider LG. The processing of faces, inverted faces and other objects in the ventral object vision pathway. Neuroimage 1997b; 5 (4 Pt 2): S4.

Haxby JV, Horwitz B, Ungerleider LG, Maisong JM, Pietrini P, Grady CL. The functional organization of human extrastriate cortex: a PET–rCBF study of selective attention to faces and locations. J Neurosci 1994; 14: 6336–53.

Heffner HE, Heffner RS. Temporal lobe lesions and perception of species-specific vocalizations by macaques. Science 1984; 226: 75–6.

Heron W. The pathology of boredom. Scient Am 1957; 196: 52–6.

Higuchi S-I, Miyashita Y. Formation of mnemonic neuronal responses to visual paired associates in inferotemporal cortex is impaired by perirhinal and entorhinal lesions. Proc Natl Acad Sci USA 1996; 93: 739–43.

Horel JA. Cold lesions in inferotemporal cortex produce reversible deficits in learning and retention of visual discriminations. Physiol Psychol 1984; 12: 259–70.

Hubel DH, Henson CO, Rupert A, Galambos R. 'Attention' units in the auditory cortex. Science 1959; 129: 1279–80.

Hubel DH, Wiesel TN. Receptive fields and functional architecture in two non-striate visual areas (18 and 19) of the cat. J Neurophysiol 1965; 28: 229–89.

Huerta PT, Lisman JE. Heightened synaptic plasticity of

hippocampal CA1 neurons during a cholinergically induced rhythmic state. Nature 1993; 364: 723–5.

Ingle D. Sensorimotor function of the midbrain tectum. II. Classes of visually guided behavior. Neurosci Res Program Bull 1975; 13: 180–5.

Ishai A, Ungerleider LG, Martin A, Maisog JM, Haxby JV. fMRI reveals differential activation in the ventral object vision pathway during the perception of faces, houses, and chairs. Neuroimage 1997; 5 (4 Pt 2): S149.

Jones EG, Powell TP. An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. Brain 1970; 93: 793–820.

Just MA, Carpenter PA, Keller TA, Eddy WF, Thulborn KR. Brain activation modulated by sentence comprehension. Science 1996; 274: 114–6.

Kanwisher N, McDermott J, Chun MM. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci 1997a; 17: 4302–11.

Kanwisher N, Woods RP, Iacobini M, Mazziotta JC. A locus in human extrastriate cortex for visual shape analysis. J Cogn Neurosci 1997b; 9: 133–42.

Kapur S, Tulving E, Cabeza R, McIntosh AR, Houle S, Craik FI. The neural correlates of intentional learning of verbal materials: a PET study in humans. Brain Res Cogn Brain Res 1996; 4: 243–9.

Knight RT. Decreased response to novel stimuli after prefrontal lesions in man. Electroencephalogr Clin Neurophysiol 1984; 59: 9–20.

Kosslyn SM, Alpert NM, Thompson WL, Maljkovic V, Weise SB, Chabris CF, et al. Visual mental imagery activates topographically organized visual cortex: PET investigations. J Cogn Neurosci 1993; 5: 263–87.

Kosslyn SM, Alpert NM, Thompson WM, Chabris CF, Rauch SL, Anderson AK. Identifying objects seen from different viewpoints. A PET investigation. Brain 1994; 117: 1055–71.

Lashley KS. Brain mechanisms and intelligence: a quantitative study of injuries to the brain. Chicago: University of Chicago Press; 1929.

Lashley KS. Functional interpretation of anatomic patterns. Res Pub Assoc Res Nerv Ment Dis 1952; 30: 529–47.

LeDoux JE, Thompson ME, Iadecola C, Tucker LW, Reis DJ. Local cerebral blood flow increases during auditory and emotional processing in the conscious rat. Science 1983; 221: 576–8.

Leimkuhler ME, Mesulam MM. Reversible go-no go deficits in a case of frontal lobe tumor. Ann Neurol 1985; 18: 617–9.

Leinonen L, Hyvarinen J, Sovijarvi AR. Functional properties of neurons in the temporo-parietal association cortex of awake monkey. Exp Brain Res 1980; 39: 203–15.

Lettvin JY, Maturana HR, McCulloch WS, Pitts WH. What the frog's eye tells the frog's brain. Proc Inst Radio Engin 1959; 47: 1940–51.

Lettvin JY, Maturana HR, Pitts WH, McCulloch WS. Two remarks on the visual system of the frog. In: Rosenblith WV, editor. Sensory communication. Cambridge (MA): MIT Press; 1961. p. 757–76.

Levelt WJ. Accessing words in speech production: stages, process and representations. [Review]. Cognition 1992; 42: 1–22.

Levin BE, Craik RL, Hand PJ. The role of norepinephrine in adult rat somatosensory (SmI) cortical metabolism and plasticity. Brain Res 1988; 443: 261–71.

Libet B. Brain stimulation and the threshold of conscious experience. In: Eccles JC, editor. Brain and conscious experience. New York: Springer Verlag; 1966. p. 165–81.

Libet B. Brain stimulation in the study of neuronal functions for conscious sensory experiences. Hum Neurobiol 1982; 1: 235–42.

Löwel S, Singer W. Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. Science 1992; 255: 209–12.

Lueck CJ, Zeki S, Friston KJ, Deiber M-P, Cope P, Cunningham VJ, et al. The colour centre in the cerebral cortex of man. Nature 1989; 340: 386–9.

MacLean PD. The co-evolution of the brain and the family. Anthroquest 1982; 24: 1, 14–5.

Martin A, Haxby JV, Lalonde FM, Wiggs CL, Ungerleider LG. Discrete cortical regions associated with knowledge of color and knowledge of action. Science 1995; 270: 102–5.

Martin A, Wiggs CL, Ungerleider LG, Haxby JV. Neural correlates of category-specific knowledge. Nature 1996; 379: 649–52.

Maunsell JH. The brain's visual world: representation of visual targets in cerebral cortex. [Review]. Science 1995; 270: 764–9.

McCarthy G, Puce A, Constable RT, Krystal JH, Gore JC, Goldman-Rakic P. Activation of human prefrontal cortex during spatial and nonspatial working memory tasks measured by functional MRI. Cereb Cortex 1996; 6: 600–11.

McClelland JL. The organization of memory. A parallel distributed processing perspective. Rev Neurol (Paris) 1994; 150: 570–9.

McClelland JL. Constructive memory and memory distortions: a parallel-distributed processing approach. In: Schacter DL, Coyle JT, Fischbach GD, Mesulam M-M, Sullivan LE, editors. Memory distortion. Cambridge (MA): Harvard University Press; 1995. p. 69–90.

McCormick DA. Cellular mechanisms of cholinergic control of neocortical and thalamic neuronal excitability. In: Steriade M, Biesold D, editors. Brain cholinergic systems. Oxford: Oxford University Press; 1990: 236–64.

McGaugh JL, Introini-Collison IB, Cahill LF, Castellano C, Dalmaz C, Parent MB, et al. Neuromodulatory systems and memory storage: role of the amygdala. [Review]. Behav Brain Res 1993; 58: 81–90.

McIntosh AR, Grady CL, Ungerleider LG, Haxby JV, Rapoport SI, Horwitz B. Network analysis of cortical visual pathways mapped with PET. J Neurosci 1994; 14: 655–66.

Mesulam M-M. A cortical network for directed attention and unilateral neglect. [Review]. Ann Neurol 1981; 10: 309–25.

Mesulam M-M. Attention, confusional states and neglect. In:

Mesulam M-M, editor. Principles of behavioral neurology. Philadelphia: F. A. Davis; 1985a. p. 125–68.

Mesulam M-M. Patterns in behavioral neuroanatomy. Association areas, the limbic system, and hemispheric specialization. In: Mesulam M-M, editor. Principles of behavioral neurology. Philadelphia: F. A. Davis; 1985b. p. 1–70.

Mesulam M-M. Frontal cortex and behavior. Ann Neurol 1986; 19: 320–5.

Mesulam M-M. Asymmetry of neural feedback in the organization of behavioral states. Science 1987; 237: 537–8.

Mesulam M-M. Neural substrates of behavior: the effects of brain lesions upon mental state. In: Nicholi AM Jr, editor. The new Harvard guide to psychiatry. Cambridge (MA): Harvard University Press; 1988. p. 91–128.

Mesulam M-M. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. [Review]. Ann Neurol 1990; 28: 597–613.

Mesulam M-M. Higher visual functions of the cerebral cortex and their disruption in clinical practice. In: Albert DM, Jakobiec FA, editors. Principles and practice of ophthalmology. Philadelphia: Saunders; 1994a. p. 2640–2653.

Mesulam M-M. The multiplicity of neglect phenomena. Neuropsychol Rehabil 1994b; 4: 173–6.

Mesulam M-M. Neurocognitive networks and selectively distributed processing. Rev Neurol (Paris) 1994c; 150: 564–9.

Mesulam M-M. Cholinergic pathways and the ascending reticular activating system of the human brain. Ann N Y Acad Sci 1995a; 757: 169–79.

Mesulam M-M. Notes on the cerebral topography of memory and memory distortion: a neurologist's perspective. In: Schacter DL, Coyle JT, Fischbach GD, Mesulam M-M, Sullivan LE, editors. Memory distortion. Cambridge (MA): Harvard University Press; 1995b: 379–85.

Mesulam M-M. The systems-level organization of cholinergic innervation in the human cerebral cortex and its alterations in Alzheimer's disease. [Review]. Prog Brain Res 1996; 109: 285–98.

Mesulam M-M, Mufson EJ. The insula of Reil in man and monkey. In: Peters A, Jones EG, editors. Cerebral cortex, Vol. 4. New York: Plenum Press; 1985. p. 179–226.

Mesulam MM, Van Hoesen GW, Pandya DN, Geschwind N. Limbic and sensory connections of the inferior parietal lobule (area PG) in the rhesus monkey: a study with a new method for horseradish peroxidase histochemistry. Brain Res 1977; 136: 393–414.

Milner B, Corkin S, Teuber HL. Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of H.M. Neuropsychologia 1968; 6: 215–34.

Mishkin M. A memory system in the monkey. Phil Trans R Soc Lond B 1982; 298: 85–95.

Mongeau R, Blier P, de Montigny C. The serotonergic and noradrenergic systems of the hippocampus: their interactions and the effects of antidepressant treatments. [Review]. Brain Res Brain Res Rev 1997; 23: 145–95.

Moran J, Desimone R. Selective attention gates visual processing in the extrastriate cortex. Science 1985; 229: 782–4.

Morán MA, Mufson EJ, Mesulam MM. Neural inputs into the temporopolar cortex of the rhesus monkey. J Comp Neurol 1987; 256: 88–103.

Morecraft RJ, Geula C, Mesulam MM. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. J Comp Neurol 1992; 323: 341–58.

Morecraft RJ, Geula C, Mesulam M-M. Architecture of connectivity within a cingulo-fronto-parietal neurocognitive network for directed attention. Arch Neurol 1993; 50: 279–84.

Morton J. Interaction of information in word recognition. Psychol Rev 1969; 76: 165–78.

Moscovitch M. Multiple dissociations of function in amnesia. In: Cermak LS, editor. Human memory and amnesia. Hillsdale (NJ): Lawrence Erlbaum; 1982. p. 337–70.

Moscovitch M. Confabulation. In: Schacter DL, Coyle JT, Fischbach GD, Mesulam M-M, Sullivan LE, editors. Memory distortion. Cambridge (MA): Harvard University Press; 1995. p. 226–51.

Nadel L, Moscovitch M. Memory consolidation, retrograde amnesia and the hippocampal complex. [Review]. Curr Opin Neurobiol 1997; 7: 217–27.

Naya Y, Sakai K, Miyashita Y. Activity of primate inferotemporal neurons related to sought target in pair-association task. Proc Natl Acad Sci USA 1996; 93: 2664–9.

Nobre AC, McCarthy G. Language-related ERPs: scalp distributions and modulation by word type and semantic priming. J Cogn Neurosci 1994; 6: 233–55.

Nobre AC, Plunkett K. The neural system of language: structure and development. [Review]. Curr Opin Neurobiol 1997; 7: 262–8.

Nobre AC, Allison T, McCarthy G. Word recognition in the human inferior temporal lobe. Nature 1994; 372: 260–3.

Nobre AC, Sebestyen GN, Gitelman DR, Mesulam M-M, Frackowiak RS, Frith CD. Functional localization of the system for visuospatial attention using positron emission tomography. Brain 1997; 120: 515–33.

Northcutt RG. Forebrain and midbrain organization in lizards and its phylogenetic significance. In: Greenberg N, MacLean PD, editors. Behavior and neurology of lizards. Rockville (MD): National Institute of Mental Health; 1978. p. 11–64.

O'Connor M, Butters N, Miliotis P, Eslinger P, Cermak LS. The dissociation of anterograde and retrograde amnesia in a patient with herpes encephalitis. J Clin Exp Neuropsychol 1992; 14: 159–78.

Ojemann GA. Brain organization for language from the perspective of electrical stimulation mapping. Behav Brain Sci 1983; 6: 189–230.

Ojemann GA, Creutzfeldt O, Lettich E, Haglund MM. Neuronal activity in human lateral temporal cortex related to short-term verbal memory, naming and reading. Brain 1988; 111: 1383–403.

Owen AM, Milner B, Petrides M, Evans AC. Memory for object features versus memory for object location: a positron-emission tomography study of encoding and retrieval processes. Proc Natl Acad Sci USA 1996; 93: 9212–7.

Pakkenberg B, Gundersen HJG. Neocortical neuron number in humans: effect of sex and age. J Comp Neurol 1997; 384: 312–20.

Pandya DN, Kuypers HG. Cortico-cortical connections in the rhesus monkey. Brain Res 1969; 13: 13–36.

Pandya DN, Seltzer B. Association areas of the cerebral cortex. Trends Neurosci 1982; 5: 386–90.

Pandya DN, Yeterian EH. Architecture and connections of cortical association areas. In: Peters A, Jones EG, editors. Cerebral cortex. New York: Plenum Press; 1985. p. 3–61.

Pandya DN, Van Hoesen GW, Mesulam MM. Efferent connections of the cingulate gyrus in the rhesus monkey. Exp Brain Res 1981; 42: 319–30.

Penfield W. The cerebral cortex in man. Arch Neurol Psychiatry 1938; 40: 417–42.

Penfield W. The mystery of the mind. Princeton, New Jersey: Princeton University Press; 1975.

Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME. Positron emission tomographic studies of the cortical anatomy of single-word processing. Nature 1988; 331: 585–9.

Petersson KM, Elfgren C, Ingvar M. A dynamic role of the medial temporal lobe during retrieval of declarative memory in man. Neuroimage 1997; 6: 1–11.

Petrides M, Alivisatos B, Meyer E, Evans AC. Functional activation of the human frontal cortex during the performance of verbal working memory tasks. Proc Natl Acad Sci USA 1993; 90: 878–82.

Pich EM, Pagliusi SR, Tessari M, Talabot-Ayer D, Hooft van Huijsduijnen R, Chiamulera C. Common neural substrates for the addictive properties of nicotine and cocaine. Science 1997; 275: 83–6.

Puce A, Allison T, Asgari M, Gore JC, McCarthy G. Differential sensitivity of human visual cortex to faces, letterstrings, and textures: a functional magnetic resonance imaging study. J Neurosci 1996; 16: 5205–15.

Raiguel SE, Lagae L, Gulyas B, Orban GA. Response latencies of visual cells in macaque areas V1, V2 and V5. Brain Res 1989; 493: 155–9.

Rao SC, Rainer G, Miller EK. Integration of what and where in the primate prefrontal cortex. Science 1997; 276: 821–4.

Rauschecker JP, Tian B, Pons T, Mishkin M. Serial and parallel processing in rhesus monkey auditory cortex. J Comp Neurol 1997; 382: 89–103.

Risberg J, Ingvar DH. Patterns of activation in the grey matter of the dominant hemisphere during memorizing and reasoning. A study of regional cerebral blood flow changes during psychological testing in a group of neurologically normal patients. Brain 1973; 96: 737–56.

Roland PE, Friberg L. Localization of cortical areas activated by thinking. J Neurophysiol 1985; 53: 1219–43.

Roland PE, Gulyás B. Visual imagery and visual representation [see comments]. Trends Neurosci 1994; 17: 281–7. Comment in: Trends Neurosci 1994; 17: 287–94, Comment in: Trends Neurosci 1994; 17: 514–6.

Rolls ET. Information representation, processing, and storage in the brain: analysis at the single neuron level. In: Changeux J-P, Konishi M, editors. The neural and molecular bases of learning. Chichester: John Wiley; 1987. p. 503–39.

Rolls ET, Baylis CG, Hasselmo ME, Nalwa V. The effect of learning on the face selective responses of neurons in the cortex in the superior temporal sulcus of the monkey. Exp Brain Res 1989; 76: 153–64.

Rumelhart DE, McClelland JL. Parallel distributed processing. Cambridge (MA): MIT Press; 1986.

Rumsey JM, Horwitz B, Donohue BC, Nace K, Maisog JM, Andreason P. Phonological and orthographic components of word recognition A PET–rCBF study. Brain 1997; 120: 739–59.

Russek M. Conditional avoidance in frogs and salamanders. Bol Estud Med Biol 1969; 26: 121–8.

Sakagami M, Niki H. Encoding of behavioral significance of visual stimuli by primate prefrontal neurons: relation to relevant task conditions. Exp Brain Res 1994; 97: 423–36.

Sakai K, Miyashita Y. Visual imagery: an interaction between memory retrieval and focal attention [Review]. Trends Neurosci 1994; 17: 287–9.

Sanides F. Functional architecture of motor and sensory cortices in primates in the light of a new concept of neocortex evolution. In: Noback CR, Montagna W, editors. The primate brain. New York: Appleton-Century-Crofts; 1970. p. 137–208.

Sato H, Hata Y, Hagihara K, Tsumoto T. Effects of cholinergic depletion on neuron activities in the cat visual cortex. J Neurophysiol 1987; 58: 781–94.

Schacter DL. Implicit memory: a new frontier for cognitive neuroscience. In: Gazzaniga MS, editor. The cognitive neurosciences. Cambridge (MA): MIT Press; 1995. p. 815–24.

Schiller P. Effect of lesions in visual cortical area V4 on the recognition of transformed objects. Nature 1995; 376: 342–4.

Schleidt WM, Schleidt M, Magg M. Störung der Mutter-Kind-Beziehung bei Truthühnern durch Gehörverlust. Behaviour 1960; 16: 254–60.

Schultz RT, Gauthier I, Fulbright R, Anderson AW, Lacadie C, Skudlarski P, et al. Are face identity and emotion processed automatically? Neuroimage 1997; 5 (4 Pt 2): S148.

Schultz W. Dopamine neurons and their role in reward mechanisms. [Review]. Curr Opin Neurobiol 1997; 7: 191–7.

Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 1957; 20: 11–21.

Seeck M, Schomer D, Mainwaring N, Ives J, Dubuissson D, Blume H, et al. Selectively distributed processing of visual object recognition in the temporal and frontal lobes of the human brain. Ann Neurol 1995; 37: 538–45.

Seeck M, Mainwaring N, Cosgrove R, Blume H, Dubuisson D, Mesulam M-M, Schomer DL. Neurophysiologic correlates of implicit face memory in intracranial visual evoked potentials. Neurology 1997; 49: 1312–16.

Selemon LD, Goldman-Rakic PS. Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behavior. J Neurosci 1988; 8: 4049–68.

Selman RL. The relation of role taking to the development of moral judgment in children. Child Dev 1971; 42: 79–91.

Sergent J, Ohta S, MacDonald B. Functional neuroanatomy of face and object processing: a positron emission tomography study. Brain 1992; 115: 15–36.

Signoret J-L. Memory and amnesias. In: Mesulam M-M, editor. Principles of behavioral neurology. Philadelphia: F. A. Davis; 1985. p. 169–92.

Smiley JF, Goldman-Rakic PS. Serotonergic axons in monkey prefrontal cerebral cortex synapse predominantly on interneurons as demonstrated by serial section electron microscopy. J Comp Neurol 1996; 367: 431–43.

Smiley JF, Morrell F, Mesulam M-M. Cholinergic synapses in human cerebral cortex: an ultrastructural study in serial sections. Exp Neurol 1997; 144: 361–8.

Sobotka S, Ringo JL. Investigation of long term recognition and association memory in unit responses from inferotemporal cortex. Exp Brain Res 1993; 96: 28–38.

Sperry RW. Physiological plasticity and brain circuit theory. In: Harlow HF, Woolsey CN, editor. Biological and biochemical bases of behavior. Madison: University of Wisconsin Press; 1965. p. 401–24.

Spreen O, Benton AL, Fincham RW. Auditory agnosia without aphasia. Arch Neurol 1965; 13: 84–92.

Squire LR, Zola SM. Structure and function of declarative and nondeclarative memory systems. [Review]. Proc Natl Acad Sci USA 1996; 93: 13515–22.

Squire LR, Ojemann JG, Miezin FM, Petersen SE, Videen TO, Raichle ME. Activation of the hippocampus in normal humans: a functional anatomical study of memory. Proc Natl Acad Sci USA 1992; 89: 1837–41.

Swan GE, Carmelli D. Curiosity and mortality in aging adults: a 5-year follow-up of the Western Collaborative Group Study. Psychol Aging 1996; 11: 449–53.

Tanaka K. Inferotemporal cortex and object vision. [Review]. Annu Rev Neurosci 1996; 19: 109–39.

Tinbergen N. The Study of Instinct. Oxford: Clarendon Press; 1951.

Tovèe MJ. Neuronal processing. How fast is the speed of thought? Curr Biol 1994; 4: 1125–7.

Tranel D, Damasio AR. Autonomic recognition of familiar faces by prosopagnosics: evidence for knowledge without awareness [abstract]. Neurology 1985; 35 Suppl 1: 119–20.

Tranel D, Damasio H, Damasio AP. A neural basis for the retrieval of conceptual knowledge. Neuropsychologia 1997; 35: 1319–27.

Tulving E, Kapur S, Craik FI, Moskovitch M, Houle S. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. [Review]. Proc Natl Acad Sci USA 1994; 91: 2016–20.

Ungerleider LG, Mishkin M. Two cortical visual systems. In: Ingle DJ, Mansfield RJW, Goodale MD, editors. The analysis of visual behavior. Cambridge (MA): MIT Press; 1982. p. 549–86.

Vaadia E, Haalman I, Abeles M, Bergman H, Prut Y, Slovin H, et al. Dynamics of neuronal interactions in monkey cortex in relation to behavioural events. Nature 1995; 373: 515–8.

Van Essen DC. Functional organization of primate visual cortex. In: Peters A, Jones EG, editors. Cerebral cortex, Vol. 3. New York: Plenum Press; 1985. p. 259–329.

Van Hoesen GW, Pandya DN, Butters N. Cortical afferents to the entorhinal cortex of the rhesus monkey. Science 1972; 175: 1471–3.

Vandenberghe R, Price C, Wise R, Josephs O, Frackowiak RS. Functional anatomy of a common semantic system for words and pictures. Nature 1996; 383: 254–6.

Vincent DJ, Dubno JR, Horwitz AR, George MS. An auditory fMRI study comparing passive and active listening to speech. Neuroimage 1997; 5 (4 Pt 2): S189.

Vogt C, Vogt O. Allgemeinere Ergebnisse unserer Hirnforschung. J Psychol Neurol 1919; 25: 279–461.

Vygotsky LS. Thought and language. Cambridge (MA): MIT Press; 1962.

Warrington EK, Weiskrantz L. The effect of prior learning on subsequent retention in amnesic patients. Neuropsychologia 1974; 12: 419–28.

Watanabe M. Reward expectancy in primate prefrontal neurons. Nature 1996; 382: 629–32.

Watson JD, Myers R, Frackowiak RS, Hajnal JV, Woods RP, Mazziotta JC, et al. Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. Cereb Cortex 1993; 3: 79–94.

Weiskrantz L, Warrington EK, Sanders MD, Marshall J. Visual capacity in the hemianopic field following a restricted occipital ablation. Brain 1974; 97: 709–28.

Wiesel TN. The postnatal development of the visual cortex and the influence of the environment. Stockholm: Nobel Foundation; 1981.

Wilson FA, Rolls ET. Neuronal responses related to novelty and familiarity of visual stimuli in the substantia innominata, diagonal band of Broca and periventricular region of the primate basal forebrain. Exp Brain Res 1990; 80: 104–20.

Wilson FA, Rolls ET. The effects of stimulus novelty and familiarity on neuronal activity in the amygdala of monkeys performing recognition memory tasks. Exp Brain Res 1993; 93: 367–82.

Wilson FA, Scalaidhe SP, Goldman-Rakic PS. Dissociation of object and spatial processing domains in primate prefrontal cortex. Science 1993; 260: 1955–8.

Woolf NJ. Global and serial neurons form a hierarchically arranged interface proposed to underlie memory and cognition. [Review]. Neuroscience 1996; 74: 625–51.

Wu JC, Buchsbaum MS, Hershey TG, Hazlett E, Sicotte N, Johnson JC. PET in generalized anxiety disorder. Biol Psychiatry 1991; 29: 1181–99.

Yaginuma S, Niihara T, Iwai E. Further evidence on elevated

discrimination limens for reduced patterns in monkeys with inferotemporal lesions. Neuropsychologia 1982; 20: 21–32.

Yakovlev PI. Pathoarchitectonic studies of cerebral malformations. III. Arrhinencephalies (Holotelencephalies). J Neuropathol Exp Neurol 1959; 18: 22–55.

Yamane S, Kaji S, Kawano K. What facial features activate face neurons in the inferotemporal cortex of the monkey? Exp Brain Res 1988; 73: 209–14.

Yeterian EH, Van Hoesen GW. Cortico-striate projections in the rhesus monkey: the organization of certain cortico-caudate connections. Brain Res 1978; 139: 43–63.

Young MP, Yamane S. Sparse population coding of faces in the inferotemporal cortex. Science 1992; 256: 1327–31.

Zatorre RJ, Evans AC, Meyer E. Neural mechanisms underlying melodic perception and memory for pitch. J Neurosci 1994; 14: 1908–19.

Zeki S. Cerebral akinetopsia (visual motion blindness). A review. [Review]. Brain 1991; 114: 811–24.

Zihl J, von Cramon D, Mai N, Schmid C. Disturbance of movement vision after bilateral posterior brain damage. Further evidence and follow up observations. Brain 1991; 114: 2235–52.

Zipser D, Andersen RA. A back-propagation programmed network that simulates response properties of a subset of posterior parietal neurons. Nature 1988; 331: 679–84.