Large-Scale Neurocognitive Networks and Distributed Processing for Attention, Language, and Memory[1]

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Cognition and comportment are subserved by interconnected neural networks that allow high-level computational architectures including parallel distributed processing. Cognitive problems are not resolved by a sequential and hierarchical progression toward predetermined goals but instead by a simultaneous and interactive consideration of multiple possibilities and constraints until a satisfactory fit is achieved. The resultant texture of mental activity is characterized by almost infinite richness and flexibility. According to this model, complex behavior is mapped at the level of multifocal neural systems rather than specific anatomical sites, giving rise to brain-behavior relationships that are both localized and distributed. Each network contains anatomically addressed channels for transferring information content and chemically addressed pathways for modulating behavioral tone. This approach provides a blueprint for reexploring the neurological foundations of attention, language, memory, and frontal lobe function.

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The relationship between brain structure and complex behavior is a central concern of neurology, psychiatry, and cognitive neuroscience. Most contemporary investigators would agree that the serial processing of information along a hierarchy of dedicated centers (the assembly line model of Descartes) could not sustain the rapid computations required for mental activity. According to current concepts, complex behavior is likely to be subserved by neural networks that enable more versatile computational architectures [1–8]. The notion of networks was present in the writings of Hughlings Jackson, Bastian, Hebb, Luria, Lashley, McCulloch, Pitts, and Geschwind, to name a few of the more prominent figures in this field. Recent advances in basic and cognitive neurosciences now allow a more detailed analysis of this subject.

In their trend-setting volumes on parallel distributed processing, McClelland and colleagues [2] explain that people are smarter than existing digital computers because the brain is likely to use a parallel distributed computational strategy particularly well suited to natural tasks. Such tasks usually require the simultaneous consideration of many items of information and constraints. Each constraint may be ambiguous but can play a decisive role in determining outcome. Problems are solved by iteratively seeking to satisfy a large number of weak constraints so that the system can relax into a state of least conflict. In such models, learning could even occur spontaneously, as a by-product of processing activity. In contrast to serial processing models where the process slows down as the number of constraints increases, parallel distributed processing allows an acceleration of the process as additional constraints become exploited [2]. The specific neural computations that underlie individual cognitive functions remain elusive. There is increasing evidence, however, that complex behavioral domains are mapped at the level of multifocal networks and that these networks contain an internal structure commensurate with complex computational architectures such as parallel distributed processing.[2]

Neural networks vary in magnitude. Local networks are confined to single cytoarchitectonic fields or to immediately contiguous areas. Local networks subserving the analysis of shape, spatial location, and object identification have been described [9–11]. In this review, the focus is not on local networks but on large-scale networks, which are composed of widely separated

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[2]The term "parallel distributed processing" will be used in a descriptive sense to designate processing that is both parallel and distributed. This usage does not necessarily coincide with more specific and technical definitions that have also been offered for this type of computational architecture [2].

and interconnected local networks. It is more difficult to specify the neurobiological features and computational algorithms for large-scale networks; however, they provide the only opportunity for addressing the neurological basis of complex cognitive domains. One of the earliest applications of this approach to complex behavior occurred in the area of directed spatial attention, and this network will be used as a paradigm [1]. One goal is to show that the resultant principles are applicable to other realms of behavior including language, memory, and frontal lobe function.

Network for the Distribution of Directed Attention

The ability to direct attention toward motivationally relevant segments of the extrapersonal space is an important requirement for adaptive behavior. Profound disruptions of this function emerge in the form of unilateral neglect. Patients with this syndrome do not necessarily have muscle weakness or primary sensory loss but fail to attend and respond to sensory events within the neglected part of space. The right side of the human brain is dominant for distributing attention across the extrapersonal world. Consequently, severe leftward neglect after right hemisphere lesions is far more common than severe rightward neglect following left hemisphere lesions [1, 12–13].

Neglect behavior can be dissociated into perceptual, motor, and limbic components. There is a perceptual component in the sense that sensory events occurring within the neglected hemispace have a diminished impact on awareness, especially when competing sensory events occur in the contralateral hemispace. Sensory extinction and deficits in the covert (internal) shift of the attentional focus are major manifestations of this component. A disinclination to direct orienting and exploratory behaviors with the head, eyes, and limbs into the neglected hemispace constitutes the motor component of neglect behavior. There is also a limbic or motivational component reflected by a devaluation of the neglected hemispace so that the patient behaves as if nothing important could be expected to emanate from that side of space. Although unilateral neglect is almost always multimodal, the following discussion will emphasize its visual aspects.

In both humans and monkeys, cortical lesions that consistently yield neglect have been described in one of the following three areas: (1) the dorsolateral posterior parietal cortex, (2) the dorsolateral premotor-prefrontal cortex, and (3) the cingulate gyrus. The core cytoarchitectonic entities of these three regions (area PG, frontal eye fields [FEF], and areas 23–24 of the cingulate gyrus) are linked to each other by extensive and reciprocal monosynaptic connections. The additional subcortical areas where lesions are known to cause neglect (the superior colliculus, striatum, and the thalamic pulvinar nucleus) are connected to at least two of these three cortical foci [1].

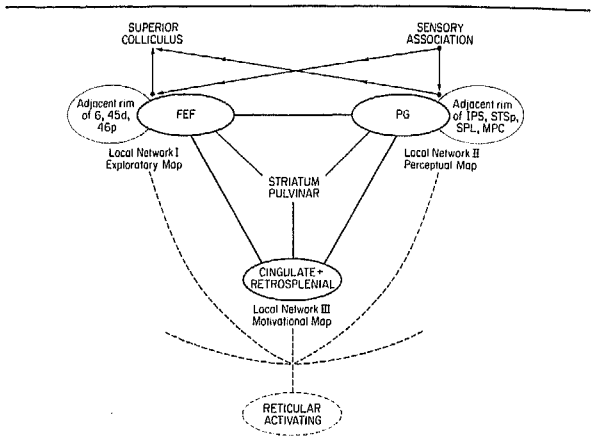


Fig 1. A large-scale network for directed attention. Lesions in any one major site or pathway can cause neglect. For example, frontal lesions can cause neglect just as readily as parietal lobe lesions. FEF = frontal eye fields; IPS = intraparietal sulcus; MPC = medial parietal cortex; SPL = superior parietal lobule; STSp = posterior part of cortex within the superior temporal sulcus; 45d = dorsal part of area 45; 46p = posterior part of area 46; PG, 6 = cytoarchitectonic designations (see Fig 5A).

These considerations led to the suggestion that directed attention is organized at the level of a distributed large-scale network that contains three cortical components (or local networks), each providing a slightly different coordinate system for mapping the environment [1]. The posterior parietal component (centered around area PG) provides a sensory representation of the extrapersonal space, the frontal component (centered around the FEF) provides a map for the distribution of orienting and exploratory movements, and the cingulate component provides a map for assigning value to spatial coordinates. The superior colliculus is more closely affiliated with the motor component, while the pulvinar nucleus and striatum are associated with all three cortical components. An additional contribution is provided by a set of diverse projections to all three cortical components from brainstem and thalamic components of the reticular activating system. This input is probably important for modifying the activation bias (or level of arousal) in each of the major cortical areas. Lesions in any of the components of the resultant large-scale network in Figure 1 or to their interconnections (including the fiber bundles in the hemispheric white matter) can result in neglect. This multiplicity of neglect-causing lesions does not result from a chaotic or diffuse cerebral localization but, instead, reflects the existence of a highly organized and interconnected network subserving directed attention.

Although lesions in any one of several different sites

can cause neglect, the resultant clinical syndromes display distinctive features that reflect the relative specialization of the damaged site. In rhesus monkeys, neglect resulting from unilateral posterior parietal lesions is characterized mostly by contralateral sensory extinction, whereas neglect associated with frontal lesions includes a disruption of exploratory and orienting movements toward the neglected hemispace [14, 15]. Recent observations show that similar distinctions can be made in humans [16, 17].

Anatomical and physiological observations in monkeys have elucidated some of the details associated with the parietal and frontal components of this network. Experiments based on axonally transported markers show that area PG receives extensively preprocessed information from multiple sensory-specific and heteromodal association areas through an orderly downstream cascade of multisynaptic pathways [18]. Reciprocal projections from area PG to the more proximal (upstream) sources of sensory information provide reentrant (feedback) connections. The behaviorally relevant representation of extrapersonal space is likely to arise through reciprocal interactions between an abstract outline in PG and more specific information called up from upstream sensory association areas. According to this view, the perceptual representation (or template) of the extrapersonal world is not contained within area PG in the form of a convergent distillate of sensory information but, instead, in the form of a distributed grid most effectively accessed through area PG. Such a distributed representation would be more flexible and veridical than one encoded exclusively through convergent (and therefore degraded) information in PG.

Some of the neurons in area PG increase firing when the detection of dimming in a contralateral light source is made behaviorally relevant but not when this dimming has no behavioral consequence [19]. Because the physical dimensions of the stimuli remain constant, the differential responses of these neurons appear to reflect the attention-worthiness of the sensory event. Damage to these neurons could promote neglect through the loss of a mechanism that normally enhances the neural impact of attention-worthy stimuli. Ablations that involve area PG also disrupt the animal's ability to determine the relative position of extrapersonal objects in allocentric space and its performance in complex visuomotor mazes [20, 21]. Additional experiments have shown that PG neurons can compute craniotopic spatial position by combining retinotopic visual information with information about eye position [10]. An individual PG neuron, for example, will give variable responses to a stimulus within its retinotopic field depending on eye position, and a stimulus within a given spatial location will elicit maximal firing from a different set of neurons when retinal position changes. Positional information is therefore not hard-wired in the physical arrangement of individual neurons (as in primary visual cortex) but is encoded in the distribution of the two types of inputs (retinotopic location and eye position) over a group of PG neurons. There is also considerable plasticity, since new sets of relationships can be learned as indicated by the rapid adaptation of human subjects to prismatic distortion of visual input [10]. Shifts of neuronal group activation in area PG are the easiest to conceptualize with changes of eye position or stimulus location. Conceivably, such shifts could also occur in the absence of either eye movement or external stimuli, in a way that would enable the covert movement of attention across spatial coordinates under the guidance of internal mental cues. In fact, Posner and colleagues [5] have demonstrated that patients with posterior parietal lesions have difficulty in the covert shifting of attention, specifically because they cannot disengage the focus of attention for contraversive shifts.

The transformation of visual input from retinotopic to craniotopic (and eventually somatotopic) coordinates is important, since motor output for orienting and exploratory movements is organized predominantly in somatotopic space just as the distribution of neglect behavior reflects an interaction between retinotopic and somatotopic coordinates. Area PG is thus in a position to (1) coordinate access to a multidimensional account of external space, (2) specify the spatial location of extrapersonal events, (3) encode (and perhaps modulate) attention-worthiness of sensory events (or locations), presumably by enhancing or quenching the synaptic impact of certain stimuli or spatial coordinates on corresponding groups of PG neurons.

Considerable information has also been gathered on the frontal component of the attentional network. The FEF region contains units that fire just prior to saccades toward behaviorally relevant objects or to their remembered sites [19]. Equivalent spontaneous saccades toward irrelevant targets and saccades in the dark are not associated with similar activity. Recent observations have raised the possibility of supplementary eye fields where eye movements are organized in a more complex and task-related rather than retinotopic space [22]. The superior colliculus, caudate nucleus, and medial pulvinar also contain neurons that fire just before saccades and may also influence the organization of exploratory eye movements [23–25]. The superior colliculus and the FEF have parallel access to eye movements, since damage to one or the other does not impair saccadic eye movements, while damage to both abolishes them [26]. The superior colliculus may be important for foveating the general area of interest, whereas neurons in the FEF may be more important for the finer analysis of that region.

The FEF and the immediately adjacent premotor cortex (area 6) may also coordinate exploratory limb movements. FEF units may subserve orientation to "far space," whereas area 6 units may encode exploration in "near space," defined as the region within an arm's length [27]. In contrast to primary motor cortex where the topographic representation is based on the location of muscle groups in the body, the organization of exploratory limb movements in premotor areas appears to be encoded in more complex coordinates. With arms crossed, reaction time to a light is faster when the responding hand is ipsilateral to the stimulus although the contracting muscles are on the side of the body contralateral to the stimulated hemifield [28]. Patients with unilateral neglect show impaired manual exploration in the neglected hemispace regardless of the limb being used [13]. These examples show that exploratory and orienting behaviors are organized according to the space toward which the movement is directed rather than according to the side of the body that moves [13].

According to these observations, the FEF and area PG have a collective mechanism for specifying whether a location in space (and events within it) will become the target of enhanced neuronal impact, visual grasp, manipulation, or exploration. In the most figurative sense, it could be said that area PG sculpts the subjective attentional landscape, while the FEF and surrounding areas plan the strategy for navigating it. The physiology of the cingulate gyrus is the least well understood aspect of this network. Lesions in the cingulate gyrus do yield a syndrome of contralateral hemispatial neglect in monkeys as well as in humans [29]. Observations with positron emission tomography (PET) have detected cingulate activation during states of increased attentiveness [5]. Conceivably, the cingulate component could introduce a value system into the perceptuomotor mapping of the extrapersonal space. It is reasonable to assume that units in area PG and the FEF receive information about the behavioral (or limbic) relevance of sensory stimuli mostly through their input from the cingulate region and its retrosplenial component [18].

Implicit in the preceding account is a dichotomy between sensory and motor components of directed attention, coordinated respectively by PG and FEF. It is important to emphasize, however, that such dichotomies between action and perception become blurred at this level of the nervous system [1]. Complex perception depends on the ability of sense organs to act as tentacles or feelers for exploring the external world and continuously updating an internal perceptual schema [30]. While the affiliations of area PG are mostly sensory and those of FEF mostly motor, area PG also contains neurons that fire in association with saccades and reaching movements, and the FEF region contains neurons with well-defined receptive fields [19, 31]. Anatomical observations show that the FEF region receives substantial neural input from the same parts of visual and other sensory association areas that also project to the posterior parietal cortex [32, 33]. Furthermore, the intermediate (oculomotor) layer of the superior colliculus receives partially overlapping input from the FEF as well as from area PG [34]. From a behavioral point of view, a sensory representation is necessary for the accurate guidance of exploratory movements just as exploratory movements are necessary for realigning sensory receptors and updating perceptual representations. Although human observations and animal experiments imply that motor and sensory components of unilateral neglect are differentially affected after frontal or parietal lesions, the dichotomy is not absolute [16]. What we see is not the complete absence of one or the other component but the relative salience of one over the other depending on the site of the lesion.

Each of the three cortical components in Figure 1 serves a dual purpose; that is, it provides a local network for regional neural computations and it also provides a nodal point for the convergence and reentrant accessing of distributed information. All three core components are probably engaged simultaneously and interactively by attentional tasks, and it is unlikely that there is a temporal or processing-level hierarchy among them. The resultant phenomenon of directed attention is not the sequential sum of perception plus motivation plus exploration but an emergent (i.e., relational) quality of the network as a whole. It is also important to realize that this large-scale network is implicated primarily in the distribution of spatially addressed attention. The distribution of object-addressed attention requires the additional contribution of visual association areas in the temporal lobe [35].

Areas such as the FEF and PG that are connected to each other by corticocortical pathways are also likely to have interdigitating striatal projections [34, 36]. This arrangement of corticostriatal pathways may enable the striatum to integrate, compare, or synchronize neural computations in the FEF with those in area PG. A similar organization may be discerned in the architecture of corticocortical projections. For example, the FEF as well as area PG each project not only to the cingulate gyrus but also to the banks of the anterior superior temporal sulcus (STSa), prefrontal heteromodal cortex (area 46), medial parietal cortex (MPC), and the inferotemporal TF-TH region [18, 32, 37]. It appears therefore that each member in a pair of corticocortically interconnected regions of association cortex is likely to have additional cortical connections that are shared with the other member of the pair. The connectivity patterns of each member in such a pair need not be identical and can vary either through dif-

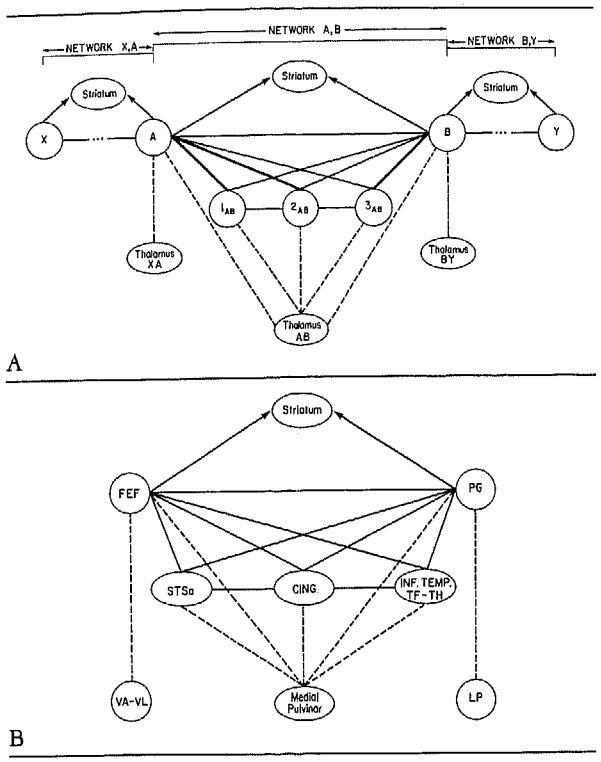


Fig 2. (A) A general representation of a dyadic hub-and-spoke network. The architecture allows parallel processing but also includes points of convergence and sequential routing. Because each cortical area (A, B, 1_{AB}, 2_{AB}, and 3_{AB}) is connected with every other area, there is no hierarchy. Thick lines indicate more intense projections. Dashed lines represent thalamic projections. Only the boundaries are given for networks XA and BY. (B) The attentional network presented in the same format as in (A). Anatomical experiments indicate that the projections from PG and FEF terminate in partially overlapping but mostly adjacent columns and layers in STSa, CING, and TF-TH [34]. This arrangement allows some of the parallelism to be preserved in the connectivity of the network. CING = cingulate gyrus; FEF = frontal eye fields; INF. TEMP. TF-TH = inferotemporal area TF-TH; LP = lateroposterior thalamic nucleus; PG = posterior thalamic area PG; STSa = cortex of the anterior superior temporal sulcus; VA-VL = ventral anterior and ventral lateral thalamic nuclei.

ferences in the relative intensity of an individual connection or by having some unique boundary condition. For example, while the FEF and area PG (and the cortical areas with which they are both interconnected) share medial pulvinar connections, the individual thalamic projection patterns display differences in the sense that area PG (but not the FEF) receives a major input from the lateroposterior thalamus (LP), whereas the FEF receives a major ventral thalamic projection (from VA-VL) that is not shared by area PG [18, 32, 38].

These observations lead to several theoretical considerations. Figure 2A shows the general features of a dyadic hub-and-spoke network formed around two interconnected nodal areas, A and B. A and B share cortical connections with areas 1_{AB}, 2_{AB}, and 3_{AB}, which are in turn reciprocally connected with each other. Information from area A can reach area B both directly and by parallel pathways through areas 1_{AB}, 2_{AB}, and 3_{AB}. In this manner, A can communicate with B both directly and through additional routes that provide alternative vantage points. The resultant network sustains multifocal convergence and some degree of serialization but is especially well suited for the temporally coherent and reentrant sampling of disjunctive [3] informational sets and also for parallel distributed processing. The thalamus (see nucleus AB in Figure 2A) may synchronize all cortical components of this network for common action and could provide network boundaries. The thalamus is well suited to set such boundaries, since there is very little local connectivity between one thalamic relay nucleus and another. The striatum is in a position to receive interdigitating inputs from all cortical components of a neural network and may function as an efference synchronizer. Figure 2B shows an analogous diagram for the attentional network based on neuroanatomical experiments in the monkey [18, 34, 39–41]. The corticocortical connections depicted in this and subsequent diagrams have been shown to be reciprocal, providing the basis for reentrant (feedback) circuitry. All components of the anatomical network in Figure 2B participate in the distribution of spatially directed attention, but they are not equally essential. For example, lesions in area TF-TH or in STSa do not cause neglect behavior. Nodal points that are critical for a given behavior may thus constitute a subset of an anatomical network.

A central feature of networks is the absence of a one-to-one correspondence among anatomical site, neural computation, and complex behavior. This is shown in Figure 3A. Let behavior alpha correspond to directed spatial attention. Its three major neural computations, A1, A2, and A3, are distributed in Sites I, II, and III, which correspond to the FEF, area PG, and the cingulate gyrus. Most but not all of computation A1 is performed in Site I (e.g., the encoding of exploratory movements is done mostly in the FEF but to a lesser extent also in area PG). Each site belongs to several intersecting networks. For example, function C is distributed in an intersecting network that includes Site II. The behavioral components of alpha are designated as alpha 1, alpha 2, and alpha 3 and may correspond to exploratory behavior, perceptual representation, and motivational mapping. The peak of alpha 1 is approximately over Site I, but there is also a tail that extends into the other two sites. The resulting topological plane (with peaks alpha 1, alpha 2, and alpha 3) corresponds to the clinically observed behavior. The vertical organization of the anatomical, computational, and cognitive planes is depicted in Figure 3B. Figure 3

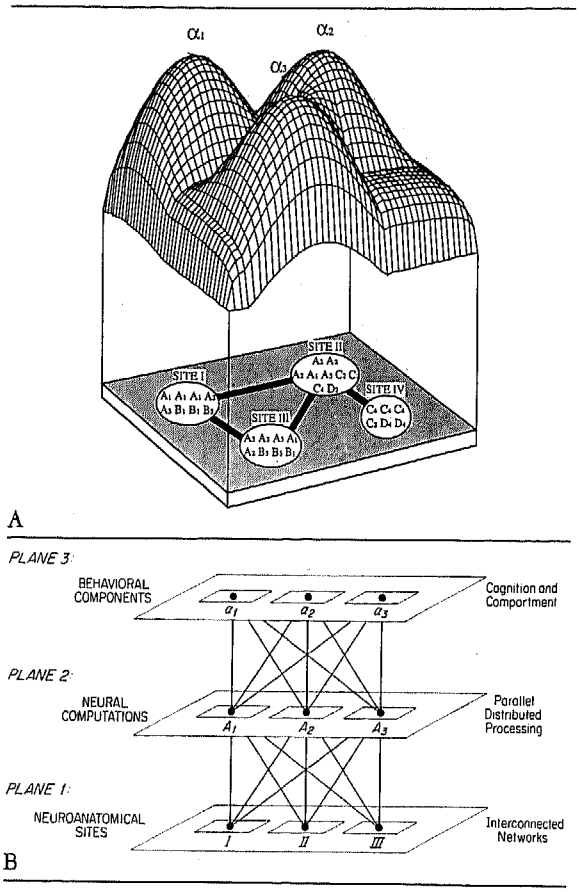


Fig 3. (A) The schematic relationships between anatomical site, neural computation, and behavior. Sites I, II, and III collectively constitute a large-scale network underlying behavior alpha. The alpha 1, alpha 2, and alpha 3 components define the behavioral plane. Site I is most closely associated with alpha 1, Site II with alpha 2, and Site III with alpha 3, but the relationship is not one to one and contains considerable eccentricity. (B) The vertical relationship between the neuroanatomical, computational, and behavioral planes. Thick lines indicate strong interactions, and lighter lines indicate weaker interactions. This configuration reconciles reductionism with emergence; reductionism represents a top-down perspective from behavior to computation and to neural structure, whereas emergence results from looking at the same interactions from a bottom-up perspective. The additional features that emerge during the upward ascent from one level to the next represent the relational architecture among the components and cannot be reduced to a simple list of lower-level constituents.

suggests that the anatomical mapping of behavior is both localized and distributed but neither equipotential (holistic) nor modular (insular or phrenological).

According to Figure 3, each site within association cortex belongs to several intersecting networks so that an individual lesion, even when confined to a single cytoarchitectonic field, is likely to yield multiple deficits. Posterior parietal lesions, for example, cause deficits in complex visuospatial processing in addition to unilateral neglect. Conversely, some lesions (or electrical stimulations) may remain behaviorally silent under certain conditions because alternative parallel channels may become available. The model in Figure 3 helps to explain how anatomical localization is compatible with the fact that lesions in different parts of the brain can yield perturbations of the same overall behavior, why single lesions lead to only partial deficits of a given behavior or to multiple behavioral deficits, and why brain mapping studies (with brain electrical activity mapping [BEAM], single-photon emission computed tomography, or PET) are likely to detect multiple areas of activation in association with individual complex behaviors. For the more practical purposes of neuropsychological assessment, this model predicts that no neuropsychological task can ever be entirely specific for 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.

Figure 3 implies that each behavior is represented in multiple sites and that each site subserves multiple behaviors, 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 behavior. This distributed and degenerate mapping may provide an advantage for computing complex and rapid cognitive operations and sets the network approach sharply apart from theories that postulate a nondegenerate one-to-one relationship between behavior and anatomical site.

Network for Language

The investigation of aphasic patients during the 19th century established the foundations of contemporary behavioral neurology [42, 43]. The dominance of the left hemisphere for language proposed by Broca is now firmly established for the great majority of right handers. The relatively larger size of the posterior language area in the left hemisphere provides one anatomical substrate for this dominance [44]. The irreducible anatomical core of spoken language is commonly traced to the following two areas: Wernicke's area in the temporoparietal junction and Broca's area in the frontal operculum [42]. These two areas and their interconnections appear sufficient for sustaining the basic process of speech repetition. The more complicated aspects of purposeful language also require interactions between these two nodal regions and many other parts of the brain. The cognitive operations that produce language can be divided into components such as phonetics, syntax, and semantics. The mapping of these components onto specific brain regions follows many of the principles outlined for the attention network. The following discussion will focus on spoken language where the input modality is auditory and the output is based on articulatory movements.

There are no strict cytoarchitectonic, topographic, or physiological criteria for delimiting either Wernicke's area or Broca's area. Relatively restrictive definitions would confine Wernicke's area to the posterior one-third of the superior temporal gyrus. A more heuristic approach has been to accept the auditory association cortex of the posterior superior temporal gyrus (TAp) as the core but to include adjacent parts of heteromodal areas 37, 39 (PF), and 40 (PG) within Wernicke's area [45].

Patients with Wernicke's aphasia produce fluent, well-articulated, melodically intact but intensely paraphasic speech. Content words such as nouns are diminished, misused (as in semantic paraphasias), and replaced by ineffective circumlocutions or neologisms. When questioned after recovery, at least some of these patients report having had coherent thought processes that they were not able to express adequately. A profound inability to understand and repeat spoken language is another central feature of the syndrome. Wernicke's aphasia therefore has both receptive and expressive components. A common anatomical correlate of this clinical syndrome is a lesion in Wernicke's area as defined above [46]. PET shows that Wernicke's area displays metabolic activation in subjects who are listening to words, whereas electrical stimulation in this region interferes with language comprehension and naming [47–50]. Consistent with the anatomical properties of Wernicke's area, the resultant aphasia is multimodal and affects spoken as well as written language.

The clinical observations suggest that Wernicke's area lies at the semantic-lexical pole of a language network. At the input stage, it appears to provide an entry point for the chunking of auditory sequences into neural word representations. These representations can then trigger associative permutations that underlie meaning and thought. The lexicon is probably represented by a distributed multidimensional informational matrix rather than a collection of specific word codes. Wernicke's area is thus not a word bank but a nodal bottleneck for accessing a distributed grid of connectivity that contains information about sound-word-meaning relationships. At the output stage, Wernicke's area constitutes a final common pathway for the chunking of thoughts into words that are commensurate with the underlying meaning. The "tip-of-the-tongue" phenomenon shows that the idea-word interface occurs through simultaneous parallel approximations (along dimensions such as word length and initial sound) until a "best fit" is achieved with respect to meaning [51]. When Wernicke's area is destroyed, individual words are not necessarily lost, but their ability to approximate intended thought is diminished leading to circumlocutious and empty speech. Lesions in many other areas also yield word-finding deficits but of lesser severity. The representation of words at the level of single units in Wernicke's area and associated regions is probably both degenerate and coarsely tuned. Individual sound-word-meaning interactions are probably mapped through group encoding in a way that may be analogous to the encoding of perceptual representation and spatial location in area PG of the attentional network.

Broca's area is also without strict architectonic definition. A survey of the literature suggests that Broca's area (i.e., the region associated with Broca's aphasia) includes area 44 at its core but also an adjacent rim of areas 45, 47, 12, and 6. Of these areas, 44 and 6 are premotor (motor association), while areas 45, 47, and 12 are constituents of prefrontal heteromodal cortex [52]. Damage to the motor association component alone seems to elicit a motor deficit confined to language output but not the full clinical syndrome known as Broca's aphasia [53]. Patients with Broca's aphasia have nonfluent (phrase length less than 4–5 words), effortful, dysarthric, and paraphasic speech that is pithy and "telegraphic" in the sense that it heavily favors content words, most of which are appropriate for the intended meaning. Aberrant word order and omissions of articles, prepositions, and morphological features render the speech agrammatical [54]. Some have argued that the agrammatism reflects the dysarthric patient's preference for parsimony; others have argued that agrammatism is a fundamental component of Broca's aphasia, independent of effort or difficulty [54]. Patients with Broca's aphasia have abnormal repetition of speech but preserved comprehension for content words. Among all other perisylvian areas, stimulation in Broca's area causes the most consistent speech arrest and also interferes with oral mimicry [48, 55]. This region of the brain, especially in the left hemisphere, shows metabolic activation in tasks that involve speech production [56].

These observations suggest that Broca's area lies at the syntactic-articulatory pole of the language network. This region could provide a bottleneck for transforming neural word representations (originating from Wernicke's area but also from other parts of the brain) into the corresponding articulatory sequences. The role of Broca's area may not be limited to the sequencing of phonemes, morphemes and inflections into words but may also subserve the sequencing of words into sentences in a way that influences syntax, and therefore, meaning. If Wernicke's area leads to meaning-appropriate content words, Broca's area influences how to order and utter them in the most meaning-appropriate form.

While there is a tendency to think of Wernicke's area as a receptive (or sensory) region and Broca's area as an expressive (or motor) center, recent observations are showing that each area has receptive/sensory as

well as motor/expressive components but with a different flavor and emphasis. For example, patients with Broca's area lesions and nonfluent aphasias experience substantial difficulties not only in producing function words but also in understanding statements the meaning of which are influenced by prepositions and word order [57–59]. Furthermore, auditory stimulation elicits activation of Broca's area and electrical stimulation in this region interferes with phoneme identification, as if this part of the brain were also involved with auditory processing [47, 48]. Some patients have even reported auditory hallucinations on stimulation of this area [55].

Patients with Wernicke's area lesions and fluent aphasias also have "expressive" deficits in the sense that they produce paraphasic and meaning-inappropriate speech. They also display paragrammatisms in the sense that wrong function words are used. The agrammatism in Broca's aphasia may be based on an inability to assign syntactic structure, whereas in Wernicke's aphasia, the patient may display a selection deficit within a correctly assigned category [57]. Furthermore, electrical stimulation in Wernicke's area can interfere with the coordination of oropharyngeal movement and can cause speech arrest but not as frequently or with the same intensity as in Broca's area [48, 55]. In the acute phase, patients with lesions in Wernicke's area are also known to have a transient depression of speech output. The dichotomies of expression/reception, sensory/motor, syntax/semantics are therefore relative rather than absolute at the level of cerebral representation, as would be expected with a network approach to complex behavior.

Physiological recordings during language tasks show that Broca's area and Wernicke's area are activated simultaneously not consecutively [60]. At a neural level, word selection probably occurs simultaneously with the anticipatory programming of syntax and articulation. The articulatory envelope and grammatical structure provide the vehicle in which the words are delivered. There is no hierarchy, since grammatical structure influences word choice just as word choice influences syntax [2]. A similar process probably characterizes speech comprehension. In fact, Broca's area is activated even during silent reading and semantic processing, showing that its role in language is not confined to the articulation of words [48, 50]. The ultimate cognitive product is not the additive effect of sequential operations in Wernicke's area and Broca's area. There are no "centers" dedicated to comprehension, articulation, or grammar but a distributed network in which nodal foci of relative specialization work in concert. The relationship among the anatomical, computational, and psychological planes of the language network follows the pattern shown in Figure 3. As in the attentional network, the two major nodal components, Broca's area and Wernicke's area, are not dedicated to spoken language but also participate in intersecting networks that coordinate praxis, writing, reading, and verbal memory [55].

The classic approach to the neurology of spoken language recognizes the importance of several additional areas and pathways. For example, damage to the supplementary motor area, to the prefrontal heteromodal cortex, or to their connections with Broca's area can produce a nonfluent (Broca-like) aphasia but with preserved repetition [61]. This is known as a transcortical "motor" aphasia. The supplementary motor cortex is thought to play a major role in the initiation and planning of speech output, and the prefrontal heteromodal cortex is thought to play a major role in the retrieval of words from superordinate categories. Some patients with lesions in this area have components of transcortical motor aphasia, while some others show abnormal fluency when asked to retrieve words from specific categories. As previously noted, the heteromodal association areas in the temporoparietal region are likely to play a crucial role in the process that links word to meaning. Damage to this component (or to its connections with the rest of the language network) can yield a transcortical "sensory" aphasia, which is defined as a fluent aphasia with impaired comprehension but preserved repetition. The interconnections between Broca's and Wernicke's areas are crucial for adequate language functions. Lesions that selectively interrupt these connections result in a conduction (or central) aphasia. Patients with this type of aphasia show a severe deficit of speech repetition although comprehension and articulation remain intact. The concordance between words and meaning is also impaired as manifested by frequent paraphasias and circumlocutions. The specialization of the left hemisphere for human language is firmly established. The right hemisphere, however, also contributes to the communicative impact of spoken language through the modulation of emotional-attitudinal prosody and related paralinguistic processes [62, 63].

These considerations lead to the neoclassical language network shown in Figure 4. Damage to the major components or their interconnections will cause aphasia. There will usually be a mixture of receptive and expressive difficulties, with the exception of the following two boundary conditions: (1) damage confined to the auditory input will cause a modality-specific and exclusively receptive difficulty in comprehension of spoken language (i.e., pure word deafness) and (2) damage confined to the motor association core of Broca's area or to its projections to motor areas will cause nonaphasic abnormalities of speech articulation (i.e., aphemia and dysarthria). All other lesions will cause mixed deficits in speech production, grammar, and comprehension but with different combinations

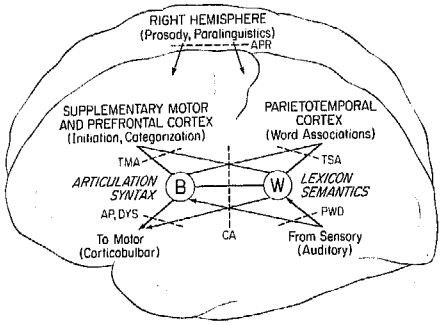
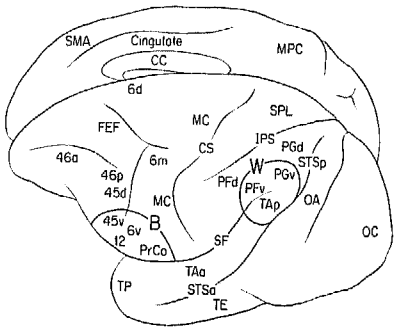
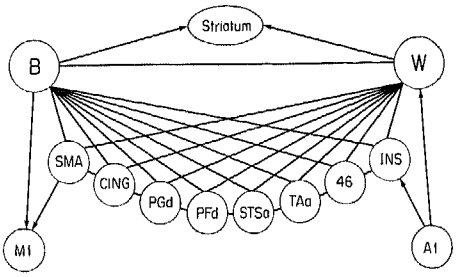


Fig 4. Relationships between brain sites, language function, and aphasia subtypes. Thicker lines indicate more intense connectivity. Broken lines indicate neural lesions that lead to the various language disturbances. AP = aphemia; APR = aprosodia; B = Broca's area and Broca's aphasia; CA = central or conduction aphasia; DYS = dysarthria; PWD = pure word deafness; TMA = transcortical motor aphasia; TSA = transcortical sensory aphasia; W = Wernicke's area and Wernicke's aphasia.



A



B

Fig 5. (A) Lateral and medial surfaces of the cerebral hemispheres in the rhesus monkey. (B) A dyadic hub-and-spoke representation of the language network. All connections are reciprocal and based on anatomical experiments in the monkey. Areas B and W correspond to the composite regions shown in (A). A1 = primary auditory cortex; B = the general area in the monkey that appears homologous to Broca's area in the human brain; CC = corpus callosum; CING = cingulate; CS = central sulcus; FEF = frontal eye fields; INS = insula; IPS = intraparietal sulcus; M1 = primary motor cortex; MC = motor cortex; MPC = medial parietal cortex; OC = primary visual cortex; OA = visual association cortex; PFd and PFv = dorsal and ventral parts of area PF; PGd and PGv = dorsal and ventral parts of area PG; PrCo = precentral opercular cortex; SMA = supplementary motor area; SPL = superior parietal lobule; STSa and STSp = anterior and posterior banks of the superior temporal sulcus; TAa and TAp = anterior and posterior parts of the superior temporal gyrus auditory association area; TE = temporal visual association cortex; TP = temporal pole; 6d, 6m, and 6v = dorsal, middle, and ventral parts of premotor cortex; 12 = area 12; 45d and 45v = dorsal and ventral parts of area 45; 46a and 46p = anterior and posterior parts of area 46; W = the general area in the monkey that appears homologous to Wernicke's area in the human brain.

and emphasis in a manner that is consistent with the anatomical site of the lesion.

There is no good animal model for language. Some assumptions, however, can be made about anatomical homologies. On purely topographical considerations, the region of the rhesus monkey brain corresponding to Broca's area probably includes the ventral parts of areas 45 and 6 (45v and 6v), the dorsal opercular part of area 12, and area PRCO (Fig 5A). Wernicke's area probably corresponds to posterior TA (TAp), the ventral part of areas PF (PFv) and PG (PGv), and perhaps the posterior superior temporal sulcal cortex (STSp) (Fig 5A). Neuroanatomical experiments show that the regions that correspond to Broca's area and Wernicke's area in the monkey brain may each be connected with the same set of at least the following eight interconnected cortical areas: the supplementary motor cortex (SMA), the cingulate gyrus, the dorsal part of area PG (PGd), the dorsal part of area PF (PFd), the cortex of the anterior superior temporal sulcus (STSa), the anterior auditory association cortex (TAa), area 46, and the insula [18, 39, 41, 64–69]. Boundary conditions for the two major components are provided by projections to M1 from Broca's area and projections from A1 to Wernicke's area. It is not clear if there is a shared thalamic nucleus for all the sites in Figure 5B, although the pulvinar oralis and VL would seem likely candidates and these two nuclei are known to participate in language functions [48].

The resultant network shown in Figure 5B fits the model proposed in Figure 2. It can sustain parallel distributed processing in the sense that each of the two major cortical components can communicate not only directly but also through the mediation of several other parallel pathways, allowing for a rapid and multidimensional sampling of a very extensive informational landscape. The network can thus solve a computational problem (such as expressing a thought) by simultaneously (and iteratively) considering many permutations, boundary conditions, and goals. Some components in this network are essential and cause severe aphasia when damaged. Others participate but do not constitute neural bottlenecks so that lesions yield only partial deficits such as naming difficulties.

Patients with damage to language-related areas frequently display dissociations in language tasks. When

asked to repeat speech, some are better at phonologically mediated tasks, some at semantically mediated tasks [70]. These observations have led to the postulation of multiple routes for language processing [70]. Figure 5B provides a neuroanatomical basis for such multiple routes. For example, a phonologically based route for repetition may be mediated through A1-W-B, whereas a more semantically based route may pass through A1-INS-46-B. The addition of the relevant visual pathways into this diagram would provide a basis for the multiple routes that have been postulated for reading and writing [71]. The distributed network approach suggests that all these parallel routes are simultaneously operative in the normal brain. The dissociations seen after brain damage reflect the constraints on the architecture of information flow and not, as the conventional view seems to imply, on the prior existence of fixed routes dedicated to different forms of language processing. Furthermore, the composite nature of Broca's and Wernicke's areas and their multiple connections provide the anatomical basis for the many different subtypes of aphasia that could emerge as a consequence of damage to these two nodal points in the language network [72].

Network for Memory and Learning

Amnestic disorders are common in clinical neurology. The most severe type is designated as the amnestic state or the Korsakoff syndrome. Patients with this condition fulfill the following three criteria: (1) they show a global deficit in new learning, known as an anterograde amnesia, (2) memories acquired within a certain interval before the onset of the amnestic state are not retrievable, and this is known as retrograde amnesia, and (3) there is a relative preservation of attention, visuospatial skills, language, and motivation.

Amnestic states can be caused by lesions in a bewildering array of apparently unrelated sites. This syndrome has been reported with tumors of the third ventricle, corpus callosum, thalamus, and sphenoid wing, with occlusions in the territories of the anterior or posterior cerebral artery, with nutritional diseases affecting the diencephalon (as in the Wernicke-Korsakoff encephalopathy), and also with viral diseases of the temporal lobe [73]. A close analysis of these various conditions shows that they each involve one or more components of a widely distributed but tightly interconnected limbic network (Fig 6A). The correlation between the amnestic state and damage to components of this limbic network has become one of the most reliable principles in behavioral neurology [73–76]. The responsible lesions are usually bilateral but not necessarily in homologous sites. Occasionally, unilateral left-side lesions can result in a global amnestic state, but this is usually less severe and more transient.

As in the other cognitive realms previously discussed, memory and learning can be dissociated into several behavioral components such as registration, storage (encoding), retention, and retrieval (recall). Memory can also be classified according to the modality (e.g., visual and auditory) or material (verbal and nonverbal) that is being processed. Furthermore, recall can be declarative (the verbal report of conscious memories), procedural (the learning of a motor skill),

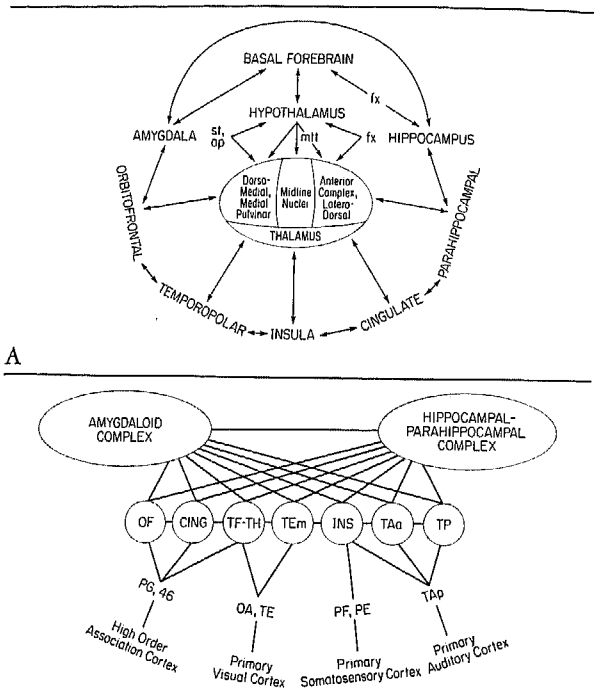


Fig 6. (A) Some components of the limbic network and their interconnectivities. In this diagram, the basal forebrain includes the septal nuclei as well as the nucleus basalis of Meynert. The orbitofrontal, temporopolar, insular, cingulate, and parahippocampal regions are also known as paralimbic areas. The amygdala, basal forebrain, and hippocampus constitute the core limbic areas. ap = ansa peduncularis; fx = fornix; mtt = mamillothalamic tract; st = stria terminalis. (B) The neural connectivity of the memory network expressed in the form of a dyadic hub-and-spoke network, similar to that of the attention and language networks. The specific connections shown in this figure are derived from neuroanatomical experiments in monkeys {66, 125–127}. In this diagram, the hippocampal-parahippocampal complex includes the hippocampus, subiculum, presubiculum, entorhinal cortex, prorhinal, and perirhinal areas. Straight lines indicate reciprocal monosynaptic connections. CING = cingulate gyrus; INS = insula; OA = visual association cortex; OF = orbitofrontal cortex; PE, PF = somatosensory association cortex; PG = heteromodal association cortex of the inferior parietal lobule; TAa and TAp = anterior (downstream) and posterior (upstream) auditory association cortex; TE = upstream visual association cortex of the temporal lobe; TE_m = downstream visual association cortex of the temporal lobe; TF-TH = inferotemporal association cortex; TP = temporal pole; 46 = heteromodal prefrontal association cortex.

or autonomic (the visceral response associated with the experience). Only declarative memory seems to be dependent on the integrity of the neural system depicted in Figure 6A. Patients with the amnestic state can acquire new motor skills although they may have no conscious knowledge of having learned the skills. Prosopagnosic patients who deny recognizing a familiar face may still produce autonomic signs of arousal in response to that face but not to unfamiliar faces [77, 78]. The autonomic and perhaps affective responses to emotionally charged memories may thus be retained even when the verbal content is not available to declarative memory.

Among all the stages of declarative memory, the one designated as registration (short-term or immediate memory) is least dependent on the limbic system and most closely associated with vigilance and concentration. In fact, amnestic patients can have a normal concentration (registration) span. Most patients with the amnestic state have difficulties with both storage and retrieval, and there is generally a positive correlation between the severity of the anterograde and retrograde components of the amnesia [74, 79]. It appears, therefore, that the anatomical sites that mediate storage are also crucial for retrieval. The retention process can be dissociated from retrieval and storage. Amnestic patients with diencephalic lesions, for example, usually show a normal forgetting rate despite abnormal storage and retrieval. In contrast, the amnesia associated with damage to the temporal lobe constituents of the network in Figure 6A (e.g., hippocampus and amygdala) also displays excessive forgetting [80]. Apparently, the temporocortical components of the limbic network are necessary for the maintenance of stored memory traces. After a critical gestation period, routinely used information becomes so massively distributed (i.e., consolidated) that it no longer requires the limbic system for retrieval. Thus, amnestic patients have difficulty storing new memories and also retrieving those that were learned within a certain time period before the ictus but not those that are older [74].

At the most general level of organization, it appears that new memories can be stored only if the pertinent information can access the limbic system [81, 82]. Global amnestic states usually result from damage to the limbic system itself. Modality- or material-specific amnesias, however, can occur with extra-limbic lesions that cause sensory-limbic disconnections. For example, bilateral occipitotemporal lesions interfere with the transfer of visual information into the limbic system and give rise to the dramatic manifestations of prosopagnosia, one of the clearest examples of a modality-specific visual memory impairment [8].

The limbic system receives information about events to be stored through a large number of pathways emanating from unimodal and heteromodal association areas of the cerebral cortex (Fig 6B). It is unlikely that the storage of memory occurs in the form of convergent traces within neurons of the limbic system, since such a process would risk considerable degradation (cross-contamination) of the constituent information. Experience is probably stored in the form of templates distributed across several different cortical regions including upstream sensory association areas where representational fidelity (at least of sensorial experience) is relatively higher [8]. In fact, amnestic states associated with limbic lesions tend to represent primarily a blockage of access into storage and only secondarily an obliteration of existing memory traces. The limbic system is apparently not itself a memory bank but a critical bottleneck for making new experience storable and old experience retrievable. The exact role of the limbic system remains conjectural but probably revolves around the activation of cortico-limbic-cortical circuits that encode the memorability (or hedonic valence) of neural activation patterns resulting from specific experiences. Informational sets endowed with this limbic code seem to acquire a competitive advantage for storage and retrieval.

In addition to assigning hedonic valence, the multiple serial and parallel pathways of Figure 6B could also encode routing maps for the conjoint binding and calling up of distributed information belonging to a single experience. What converges on limbic areas may not be a distilled memory pellet but, instead, a code (or address) indicating where the individual components of a coherent memory are distributed and how they are interrelated. This is particularly important for binding related fragments of information contained within different unimodal association areas, since these areas have very few connections among each other [52]. The limbic system would thus assume a key role during associative recall or perceptual recognition when partial information needs to activate distributed templates related to past knowledge [8]. In such circumstances, partial information (entering through a single unimodal channel) could be activating the relevant distributed template with the help of routing information that is most effectively accessed through the limbic system. According to this model, the process of memory does not reflect serial processing within hierarchically interrelated centers but, rather, distributed processing where the specialization of most components in the network is relative rather than absolute. Individual memories are probably stored throughout the components of Figure 6B but especially within unimodal and heteromodal areas. In turn, retrieval can be initiated from any point in Figure 6B but especially from the paralimbic and limbic components. For example, the evoked recall of experiential memories is much more effective after stimulation of the amygdala than of nonlimbic association cortex [83].

The neural computations performed by the individual constituents of the limbic network remain poorly understood. Depth electrode recordings from patients show that some hippocampal units increase their activity in the recall phase of memory tasks [84]. The hippocampus may also be important for providing a snapshot memory of relative spatial relationships in complex scenes [85, 86]. In the human brain, the right hippocampus appears more closely related to this type of spatial memory deficit, whereas the left hippocampus is more closely associated with memory for verbal material [87]. The amygdala enables the associations between complex (multimodal) sensory information and affective states related to fear or reward [88–90]. Its stimulation in humans frequently elicits the recall of emotionally charged memories [83]. The contributions of the frontal and cingulate components to memory may be important for reconstructing the temporal order of past events [91–93]. The frontal component appears important also for remembering the context in which information was obtained [94].

Hippocampal cells readily demonstrate plastic events associated with learning. For example, pyramidal neurons of the CA1 sector display long-term potentiation, change firing during classic conditioning, and show induction of protein kinase-C synthesis in response to learning [95–97]. Furthermore, the amygdaloid and hippocampal regions are among the few areas that express growth-associated GAP 43 in the adult human brain, indicating that their potential for plasticity may extend into adulthood [98].

Only the handful of areas shown in Figure 6A provide neural bottlenecks that control the process of declarative memory as a whole. The other components shown in Figure 6B participate in the process but are not as critical. Neurons in lateral temporal association cortex of humans and monkeys, for example, have firing patterns linked to memorization [99, 100]. Such association areas are undoubtedly important for conveying sensory-specific information into the limbic system and for containing segments of distributed memory representations. Their involvement by neural injury, however, yields memory deficits that are either partial (e.g., modality-specific) or subtle and transient. As in the case of the attentional and language networks, the individual sites in Figure 6A are not dedicated to memory function but also participate in intersecting networks dealing with other complex behavioral realms including emotional modulation and higher autonomic control [52]. It is not clear if there is a single thalamic nucleus that would perform a role analogous to that of the medial pulvinar in the attention network. Probably the group of midline nuclei comes closest [52, 82]. The primary striatal target of the amygdala and hippocampus is the nucleus accumbens rather than the caudate or putamen.

A Brief Glance at the Riddle of the Frontal Lobes

Prefrontal granular cortex displays a markedly progressive growth in the course of phylogenetic evolution and constitutes one of the most prominent components of the human brain. Despite no obvious role in motor or sensory function, this part of the brain has been implicated in the organization of exceedingly complex mental processes such as judgment, insight, foresight, curiosity, abstraction, and creativity (for review, see [101]).

The vast literature on the behavioral affiliations of prefrontal granular cortex is rich in metaphor and conjecture. The term "executive function" is often mentioned, but its neural mechanism remains enigmatic. Some recent observations appear relevant to this speculative metaphor. In contrast to other parts of the brain where metabolic activation is task-dependent, parts of the frontal lobe show activation without regard to the nature of the task [56]. Prefrontal granular cortex has extremely widespread corticocortical connections with just about every type of sensory and paralimbic association cortex [6, 39, 69]. These connections could enable it to monitor information flow at all levels of complex processing and could account for the task-independent pattern of metabolic activation. Through these widespread connections, the frontal lobes would be in a position to activate a given network, to inhibit another, to influence network combinations, and perhaps even to allow internal readouts in a way that disengages the information processing from the response stage. The frontal lobes would thus allow the highest level of internal representation (of networks rather than of sensory data or motor programs) and would provide an arena for the various networks to play out different scenarios, the most successful of which may then dominate the landscape of neural activity. The computational basis of the executive function would then be twofold, that is, a high density of connections with other networks and a relative isolation from direct participation in elementary perception and movement. Even sizable prefrontal lesions could thus cause little disruption of routine behavior except under circumstances that place a premium on disengaging customary stimulus-response linkages and executing complex internetwork coordinations.

The major neural connections for the head of the caudate and for the dorsomedial nucleus of the thalamus come from prefrontal granular cortex. In accordance with the network theory previously described, the frontal lobe syndrome can be seen in patients with lesions not only in frontal cortex but also in the head of the caudate and probably also in the dorsomedial nucleus [102, 103]. Another circumstance of considerable interest is the emergence of the frontal lobe syndrome as a common manifestation of mul-

tifocal white matter disease or even metabolic encephalopathy [104]. Assuming that the physiological function of the frontal lobe is to integrate networks for combined action, the emergence of the frontal lobe syndrome should come as no surprise in these cases where multifocal partial lesions (none of which are individually severe enough to disrupt specific cognitive domains such as language or memory) collectively undermine internetwork coordination. In fact, clinical experience suggests that subcortical lesions and toxic-metabolic encephalopathies are more frequently encountered causes of the frontal lobe syndrome than lesions which involve prefrontal cortex directly.

State-Setting Projections: the Content Versus the Color of Experience

In the previous discussion, we considered anatomically addressed projection channels for transferring information from one cortical area to another. These projections are reciprocal and respect cytoarchitectonic boundaries. Cortical areas and thalamic nuclei also receive several sets of chemically addressed projections [52, 105, 106]. These arise from relatively small groups of neurons, use a single neurotransmitter, and are very widely distributed, reaching all cortical areas and all thalamic nuclei (Fig 7). The following are the five such projections to the cerebral cortex: (1) cholinergic projections from the nucleus basalis of Meynert [107], (2) histaminergic projections from the hypothalamus [108], (3) dopaminergic projections from the ventral tegmental area [109], (4) serotonergic projections from the brainstem raphe nuclei [110], and (5) noradrenergic projections from the nucleus locus ceruleus [111].

Some of these projections display differential distribution patterns. For example, cholinergic innervation is much more intense in limbic and paralimbic parts of cortex than in primary and association areas [107]. In contrast, cortical norepinephrine projections display a greater density in primary sensory areas [112]. One striking anatomical feature of these transmitter-specific projections is the absence of equally well-developed reciprocal (reentrant) projections from cortex [113]. The nucleus basalis, for example, projects to all parts of cortex but receives cortical projections from only a handful of limbic and paralimbic areas. The other subcortical cell groups shown in Figure 7 also receive sparse cortical projections. These nuclei are particularly well suited for rapidly shifting the activation state of the entire cerebral cortex. Such shifts would be relatively free of cortical feedback and would be controlled primarily by the limbic system, hypothalamus, and brainstem, areas that are intimately linked to basic homeostasis, fundamental drives, and internal pacemakers.

Each of these transmitters may have a different effect on the state of cortical neural processing. Acetylcholine, for example, promotes cortical desynchronization and increases the likelihood of neuronal firing in response to other inputs [114, 115]. Through its pattern of widespread but differential cortical distribution, acetylcholine may act as a gating mechanism for channeling behaviorally relevant sensory information toward components of the limbic system [107], and may also participate in the spatiotemporal binding of hedonically relevant neural patterns into multimodal memory traces. Increased cholinergic tone would therefore promote cortical arousal, motivational valence, and the effectiveness of learning. Norepinephrine increases the signal-to-noise ratio, timing precision, and specificity in the transmission of neural information [110, 116]. The cortical response to the stimulation of a single vibrissa in rats, for example, loses some of its discrete localization when the norepinephrine innervation to cortex is interrupted [117]. At the behavioral level, noradrenergic tone modulates novelty-seeking behavior and also resistance to distraction [118–120], whereas dopaminergic tone influences the encoding of reward and the effort associated with cognitive activity [121–123]. In keeping with these relationships to the more collative aspects of information processing, cholinergic and monoaminergic pathways have been implicated in the modulation of global behavioral states such as vigilance, mood, and motivation.

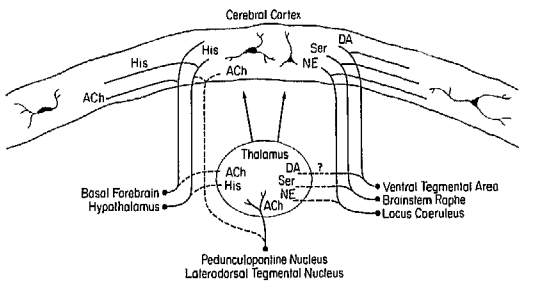


Fig 7. State-setting, chemically addressed connections of thalamus and cortex. Interrupted lines indicate minor connections. A question mark indicates that the existence of the pathway is not yet firmly established. Ach = acetylcholine; DA = dopamine; His = histamine; NE = norepinephrine; Ser = serotonin.

These chemically addressed projections are in a position to alter the tone and coloring of behavior more than its content. Their access to all levels of cortical information processing enables them to influence the emotional-motivational perspective directed toward the environment in a way that could modify the interpretation of experience and its impact on the individual. Many neurons in the cerebral cortex contain receptors for estrogen, testosterone, and other steroids [124]. Alterations in the circulating level of such hormones, as in puberty or menopause, could influence

behavioral states in a manner analogous to the effect of the chemically addressed projection systems.

Anatomically addressed channels provide vectors of information transfer, while chemically addressed systems provide a matrix that influences the state of information processing. The vector and matrix are inextricably intermingled and work in unison within large scale networks. The reticular component of Figure 1, for example, indicates the contribution of chemically addressed projections to the attentional network. All complex behaviors including attention, memory, and language contain components that reflect the contribution of anatomically addressed channels (e.g., the ability to identify a previously rewarded visual stimulus) and also components that reflect the contribution of chemically addressed projections (e.g., the speed of recall).

The pathways shown in Figure 7 provide the neuroanatomical substrate for much of modern psychopharmacology. Their widespread distribution makes it likely that systemically administered agonists could reproduce the effect obtained by the neural activation of the relevant subcortical cell group. In fact, cholinergic, noradrenergic, dopaminergic, and serotonergic agents are frequently used for the therapeutic manipulation of attention, learning, arousal, motivation, and mood. In planning therapeutic strategies for complex behavior, it is useful to keep in mind that the contributions of chemically addressed pathways are much more accessible to pharmacological intervention than the contributions of anatomically addressed pathways.

Summary and Conclusions

Why are there so many connections in the brain? Pathways that carry information from sensory receptors or toward motor effectors have a self-explanatory purpose. But what about the luxuriant web that interlinks limbic, paralimbic, and association areas in almost every possible permutation? Why does area PG project to so many different patches of prefrontal cortex? Why are the various parts of prefrontal cortex interconnected in such intricate patterns? Such complexity, superfluous for a system based on the linear and hierarchical transfer of information, is absolutely essential for networks that sustain distributed and parallel processing.

The neurons of the central nervous system are engaged in the following three operations: (1) reception of sensory signals from outside and from within (input), (2) planning and execution of motor acts (output), and (3) intermediary processing interposed between input and output. Thought, language, selective attention, memory, and almost every aspect of advanced cognition and comportment are the products of intermediary processing networks located primarily in limbic and association areas. These networks contain anatomically addressed channels that convey sensorymotor information from one point to another and chemically addressed pathways that can alter the way in which this information is being processed. Neural pathways arising from sensory receptors and leading toward motor nuclei display hierarchical polarity. In contrast, the flow of information used for intermediary processing displays patterns consistent with parallel and re-entrant processing.

Neurons have a limited number of options for action, that is, they either fire or they do not. And yet, individual neural networks underlie vastly different cognitive operations. Such variations in behavioral affiliation are not based on differences in the nature of the constituent neurons but on differences in the type of input, the access to output, and the architecture of the intermediary processing. Behavior is not contained in the neuron or in the anatomical site but in grids of connectivity that are both localized and distributed. Such networks allow a very large number of computational options to be associated with specific cognitive processes. The flexibility inherent in this system provides the driving force for maximal adaptability to the environment and circumstances. It is adaptability that counts, not whether the sense impression is veridical or the memory precise. As Edelman [3] has pointed out, in such complex nervous systems, every perception is to some extent an act of creation and every memory an act of imagination.

The preceding discussion has emphasized the organizational principles of selected large scale networks. Prospects for further progress in this area are very bright. Novel methods, for example, will undoubtedly enable the exploration of exceedingly challenging issues such as the process of network emergence during neural development, the dynamics of internetwork linkages and boundaries, the nature of interhemispheric and interindividual variations in the fine structure of networks, and the mechanisms that enable them to incorporate change and learning as a byproduct of information processing. The ground that has been covered will hopefully provide directions for future developments along these additional lines of inquiry as well.

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