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Review

The evolving landscape of human cortical connectivity: Facts and inferences ☆

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ABSTRACT

Human cognitive brain mapping is at a crossroads. On the one hand, it can access a rich data set of synaptic connectivity in the cerebral cortex of the monkey, an animal that lacks many of the complicated behaviors of interest. On the other hand, it is rapidly amassing an even richer data set on the functional map of the human cerebral cortex, but with relatively little hard data on underlying structural connectivity. This second point tends to be blurred in the current literature because of the multiple ways in which the term 'connection' is used in the context of the human brain. In some instances the term is used at a *conceptual* level, to designate a pathway that should be there if the behavior is to be performed. In other instances, it refers to the *computational* demonstration of a functional relationship, the structural basis of which is not necessarily known. A third usage is based on connections that are known to exist in the monkey and that are *inferred* to also exist in the human. The fourth and most direct usage involves connections *structurally proven* to exist in the human. These four usages have been invoked interchangeably to propose connectivistic mechanisms of human cognitive function. To enlarge the currently limited data set on structural connectivity is of considerable importance for conducting biologically more valid explorations of large-scale neurocognitive networks. This challenging goal will require histological laboratory investigations of the human brain to resume their former prominence and to play an increasingly more substantial role in brain mapping research.

Contents

Introduction

Current concepts of brain function rest on the empirically derived principles that each part of the brain has a different set of specializations and that the specializations of a brain region depend on its connections. The first of these principles, the rule of functional localization, was established during the classic era of clinical neurology through the delineation of lesion sites that caused specific behavioral and cognitive impairments. The second principle, the connectivistic basis of local functionality, has a more complex history with roots in antiquity and a modern history heavily weighed toward experimental research in animals. This review will focus first on the pivotal role of connectivity for generating theories of cortical function, and secondly, on the frequently overlooked fact that much of what we think we know about human cortical connections is based on inference rather than hard data. The purpose is not to diminish the value of what we have learned, especially the exciting new results of diffusion imaging, functional connectivity, and resting-state fMRI, but to encourage more laboratory work on the synaptic connectivity of the human cerebral cortex.

Golgi and Cajal, joint recipients of the 1906 Nobel Prize, can be said to have set the stage for modern research on cortical connectivity. Despite its many virtues, however, the Golgi method, upon which Cajal based his monumental work, had a major shortcoming, namely the inability to trace long axonal connections. Although Cajal, and

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then Lorente de Nó, provided exquisite accounts of intra-hippocampal circuitry, their work with the Golgi method yielded virtually no information on pathways through which the hippocampus communicates with cortical areas beyond the entorhinal region. Today's neuroscientist may find it difficult to believe that the Scoville and Milner paper on H. M. (Scoville and Milner, 1957) was published at a time when there was literally no structural evidence of how (or whether) the hippocampus received the sort of neural input from association cortex that would have allowed it to encode multimodal episodic memories.

The limitations of the Golgi method were overcome through the introduction of new methods based on Wallerian degeneration and axonal transport. These developments enabled the detailed delineation of the trajectories, cells of origin, and termination fields of cortico–cortical pathways. The integration of this information with focal ablation and single unit recording experiments in monkeys generated unprecedented insights into the behavioral neuroanatomy of the primate brain. This exciting period of brain research reached its apex in the 1980s and 1990s and is now a distant memory, principally because experimental work in primates became increasingly more burdensome at the same time that it gradually lost its priority for funding.

We are now in the midst of yet another revolution, a revolution powered by spectacularly successful methods for the non-invasive functional and structural imaging of the human brain. Impressive advances in signal acquisition, data analysis, and task design have collectively empowered a multidisciplinary army of investigators to map the cerebral cartography of vision, language, love, lust, greed, altruism, empathy, conflict, and virtually any other mental faculty that can be delineated. The integration of this new information with the classic literature on focal brain damage offers unique opportunities for revising and polishing established concepts of human cognitive function. One missing ingredient is the detail of synaptic connectivity in the human cerebral cortex so that the new insights on localization can be linked to more fundamental biological and computational mechanisms.

There have been numerous attempts at unraveling cortical connectivity in autopsied human brain specimens with methods that have ranged from hand dissection to the tracing of degeneration caused by focal brain damage and the local diffusion of dyes (Mesulam, 2005). The inability to control variables such as post-lesion survival, agonal state, and fixation parameters, and the obvious inability to use axonally transported tracers, have severely limited the quality of the information generated by these approaches. The advent of diffusion tensor imaging (DTI) and diffusion spectrum imaging (DSI) has introduced new possibilities for charting cortico–cortical connectivity in the living human brain through probabilistic tractography. Some of the tractography studies have led to potentially new insights on special features of human brain connectivity (Catani et al., 2005), while others have offered a framework for systematic comparisons of connection patterns in humans and monkeys (Cerliani et al., 2011). Exciting and plausible as some of the results have been, however, it is necessary to keep in mind that DTI and DSI face considerable challenges. Since these methods image the movement of water molecules, the translation of the information into anatomical connectivity remains somewhat conjectural despite the impressive correspondence that has been shown in the monkey brain (Schmahmann et al., 2007). Diffusion imaging and tractography may show that there are white matter bundles headed in the appropriate direction but cannot yet fully specify the cells of origin or synaptic termination fields, two items of information that are necessary to confirm the presence of a neural "connection." Perhaps of even greater concern is whether these methods will be able to trace cortico–cortical projections that are usually quite sparse, that arise from a small proportion of neurons in a given area, and that become intermingled with axons destined for numerous other targets as they travel in the white matter of the cerebrum.

One potential factor that may lead to an overestimation of the information that currently exists on human cortical circuitry is the blurred distinction between computational and actual connectivity. When an investigator injects a fraction of a microliter of a tritiated leucine solution into area A and shows that radioactivity has moved to area B, a monosynaptic connection from A to B becomes established irrevocably and can be generalized to every member of that species. The demonstration of functional or effective connectivity between two areas is a different matter. Such an outcome shows that areas A and B display electrical or hemodynamic responses that are temporally coherent or directionally modulated during the recording session. These phenomena, expressed in terms of complex statistical probabilities, may or may not be mediated through real connectivity. If structural connectivity is the mediator, moreover, this could be through a mono- or multisynaptic pathway, a distinction of momentous neurophysiological consequence for neuronal communications.

In contrast to the situation in the human brain, a great deal of hard data has been gathered on cortical synaptic circuitry in the monkey brain. But, although monkeys have complex brains and behaviors, they do not speak, build tools, or develop civilizations. These differences cannot be blamed solely on the smaller size of their brains. Whales and elephants have larger brains than humans but are also disinclined to display "higher cortical functions" associated with the use of symbols and tools. There must therefore be unique aspects of circuitry, qualitative or quantitative, that underlie what appears to be a gigantic phylogenetic gap of integrative capacity separating the human from the monkey. A venerable and increasingly more sophisticated literature, too extensive to review here, has addressed this question from numerous perspectives (Broca, 1878; Brodmann, 1909; Kaas and Preuss, 2007; Passingham, 2008; Preuss, 2011; Semendeferi et al., 2011). Despite the identification of notable *cellular and morphometric features* that may be more prominent in the human (e.g., dendritic branching of prefrontal pyramidal neurons (Elston et al., 2001), increased glial to neuron ratios (Sherwood et al., 2006), acetylcholinesterase-rich pyramidal neurons (Mesulam and Geula, 1991), von Economo neurons (Nimchinsky et al., 1999; Seeley et al., 2006), planum temporale asymmetry (Gannon et al., 2008), arcuate fasciculus trajectory (Rilling et al., 2008), columnar spacing in frontal cortex (Semendeferi et al., 2011)), relatively little systematic information has emerged on aspects of *cortico–cortical connectivity* that are characteristically human. Perhaps because of this lack of relevant information on definite differences, the convenient assumption has been made that the known connectivity in the monkey can be used to infer the connectivity of the human cerebral cortex. Although many of these inferences may well turn out to be entirely justified, verification is scant.

Brief synopsis of selected behaviorally relevant and empirically verified structural connections in the monkey cerebral cortex

Experimental neuroanatomy has shown that the cerebral cortex of the macaque monkey can be divided into 5 principal zones: *primary sensory-motor*, *modality-selective* (also known as unimodal), *heteromodal*, *paralimbic*, and *limbic*, each characterized by a distinctive cytoarchitecture and connectivity (Felleman and Van Essen, 1991; Mesulam, 2000; Pandya and Yeterian, 1985). Heteromodal, paralimbic and limbic areas are also collectively known as *transmodal cortices* because their neuronal responses are not segregated according to the modality of sensory input.

Information processing streams originating in primary sensory areas reveal a hierarchical organization (Fig. 1). Each primary sensory area projects to numerous modality-selective association cortices. These can be divided into *upstream* components (levels 2 and 3 in Fig. 1), which receive their major inputs from the corresponding primary area, and *downstream* components (level 4 in Fig. 1), which receive their major inputs from upstream modality-selective areas. At the next synaptic stage, heteromodal areas (e.g., cortex of the prefrontal area, inferior parietal lobule, and superior temporal sulcus) receive convergent projections from multiple modality-selective areas and provide prominent sources of cortical projections to paralimbic areas. In turn, paralimbic areas (insula, orbitofrontal, cingulate, parahippocampal,

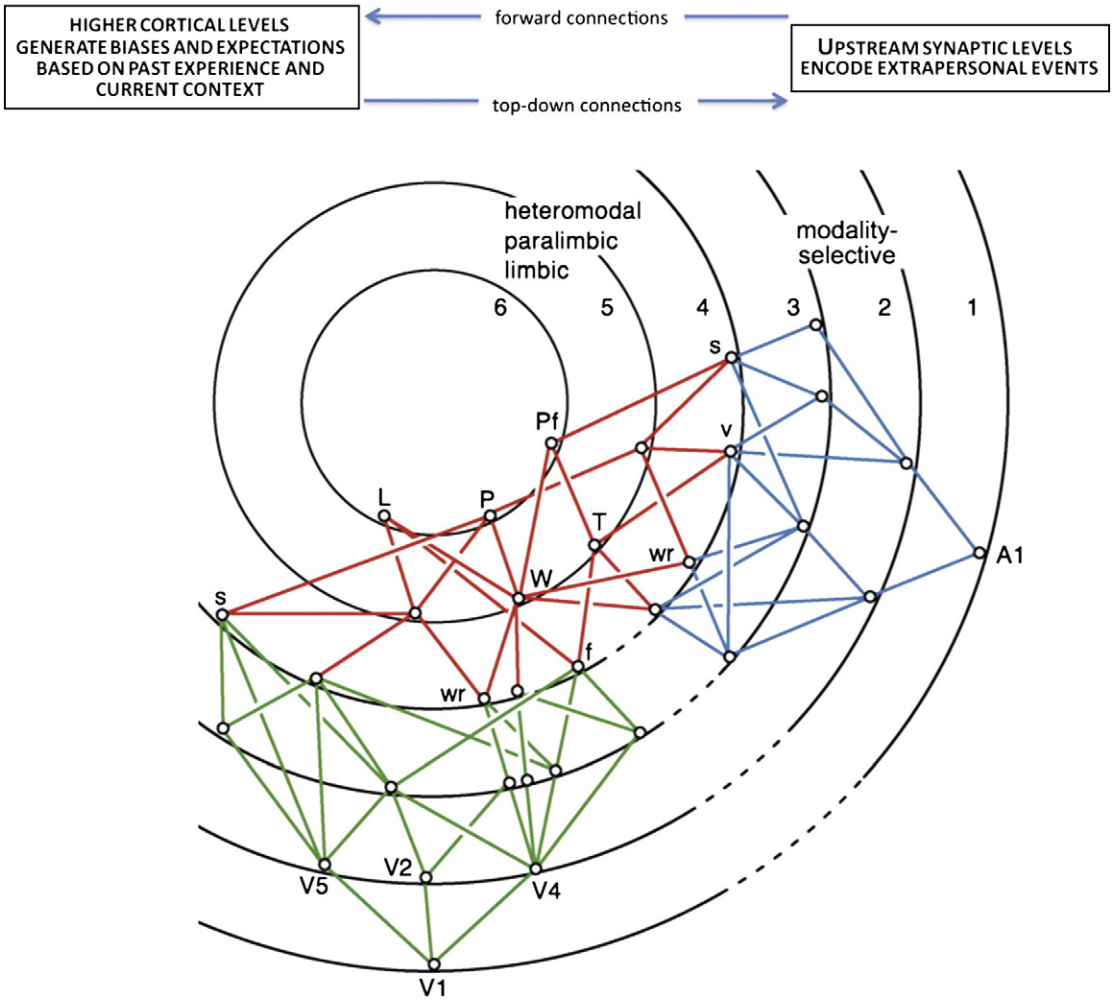

Fig. 1. A synaptic template of visual and auditory processing streams, as established in the monkey and transposed to the human cerebral cortex.Each concentric ring represents a different synaptic "level." Any two consecutive levels are separated by at least one unit of synaptic distance. Level 1 is occupied by the primary sensory cortex, levels 2–4 by modality-selective cortices, and levels 5–6 by transmodal cortex. Colored lines represent monosynaptic connections from one synaptic level to another. Visual pathways are shown in green, auditory pathways in blue and transmodal pathways in red. The dashed lines interconnecting visual and auditory pathways in the first four synaptic levels indicate the scarcity of monosynaptic connections between sensory hierarchies belonging to different modalities. Abbreviations: A1—primary auditory cortex, f—area specialized for face encoding, L—the hippocampal–entorhinal or amygdaloid components of the limbic system, P—heteromodal posterior parietal cortex, Pf—lateral prefrontal cortex, s—area specialized for encoding spatial location in the auditory (blue) and visual (green) modalities, T—heteromodal lateral temporal 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 in the auditory (blue) and visual (green) modalities (Mesulam, 2008).

temporopolar regions) are the principal sources of cortical projections to limbic areas. Limbic areas (e.g., amygdala, hippocampus) and paralimbic cortices are the only parts of the cortex that have substantial connections with the hypothalamus, a region of the brain that functions as a pivotal ganglion for the homeostatic, autonomic, and endocrine aspects of the internal milieu. Projections interconnecting primary, and unimodal components of one modality with those of another are either absent or sparse compared to extensive projections among transmodal areas (Mesulam, 1998). Through this arrangement, primary and modality-selective areas at synaptic levels 1–4 of Fig. 1 maintain the fidelity of sensory representations related to external events while transmodal areas at synaptic levels 5–6 enable the multimodal integration of this information.

In addition to these 'forward' connections that originate in primary sensory areas and run in the sensory-fugal direction, from level 1 to level 6, there are 'backward' (top-down) axonal projections that run in the opposite (sensory-petal, or top-down) direction, from transmodal to multiple modality-selective areas, to serve the purpose of binding distributed information and modulating the information carried by the forward connections according to context and experience (Fig. 1). As summarized in a pivotal review by Friston (2005), forward connections have sparse axonal bifurcations that originate in supragranular layers and terminate largely in the inner granular layer (layer IV), the same layer that receives inputs from modality-specific thalamic nuclei (Friston, 2005; Pandya and Yeterian, 1985). Top-down connections, on the other hand, have abundant axonal bifurcations, a more sprawling territory of distribution, prominent infragranular origins, and terminations that favor agranular layers. Top-down connections are also less hierarchical and tend to jump synaptic levels. In the sensory-fugal (i.e., forward) direction, for example, primary visual cortex (V1), at synaptic level 1 of Fig. 1, obeys the synaptic hierarchy by sending most of its monosynaptic output to peristriate areas at synaptic level 2 of Fig. 1. Very little of V1 output is monosynaptically directed to downstream visual association cortex (e.g., areas TEO and TE) at synaptic level 4, or to limbic/paralimbic areas such as the amygdala at levels 5 and 6. In the top-down direction, however, the amygdala and downstream visual association areas sidestep the hierarchy by sending substantial monosynaptic projections directly to V1 (Aggleton, 1993; Salin and Bullier, 1995). Forward connections elicit obligatory output responses in their downstream targets. As messengers of extrapersonal reality, they are presumably not to be ignored. Top-down (backward) connections, on the other hand, tend to be modulatory. They influence the responses elicited by forward projections according to biases established by past experience and expectations based on current context (Friston, 2005).

Transmodal areas provide pivotal hubs (or epicenters) for neural networks. According to the hub-and-spoke model of large-scale neurocognitive networks (Mesulam, 1990), hubs provide nodal points for receiving and distributing information that is critical for the functionality of the relevant domain. For example, the hippocampo–entorhinal complex of the monkey can be conceptualized as a transmodal hub of an explicit memory network (Mishkin, 1982), a major function of which is to bind distributed information belonging to recent events so that the information can be reactivated coherently in the act of recall. Transmodal network hubs are interconnected in a very special pattern. This has been investigated experimentally in the spatial attention network of the monkey, where the frontal eye fields (FEF) and the inferior parietal lobule/intraparietal sulcus (IPL/IPS) can be considered as two of the pivotal hubs (Mesulam, 1981). In each animal the FEF was injected with diamidino yellow and the IPL/IPS with fast blue. After a suitable survival time, the brain was examined for retrograde transport patterns. The FEF and IPL/IPS were found to be interconnected not only with each other but also with 13 other cortical areas including the cingulate cortex (Morecraft et al., 1993). The resultant connectional architecture displayed a remarkable feature: any cortical area connected with one of the two hubs was also connected with the other. Consequently, a message emanating from FEF can reach the IPL/IPS directly as well as through multiple vantage points relayed by the ancillary nodes of the network. Through this architecture, the network can rapidly bind multiple sets of information related to spatial position, search strategies, and motivational valence so that the focus of spatial attention can be deployed adaptively and flexibly. Another unexpected outcome was the absence of neurons labeled with both dyes in these 13 additional areas, showing that the connectivity architecture of the network does not rely on axonal collaterals. In other words, a network node such as the cingulate cortex projects to FEF and IPL/IPS through independent sets of neurons, not through collaterals of the same set. The integration of the messages sent to the two areas is thus mediated to a large extent through interneurons.

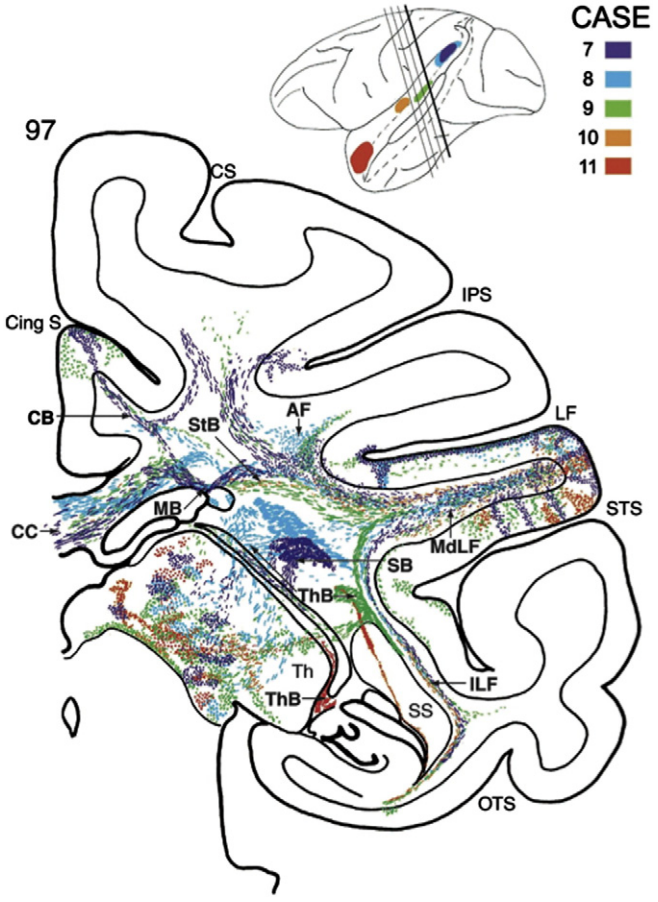

Fig. 2. Intermingling of trajectories and terminal fields in cortical projections of the monkey.This composite diagram of a coronal brain section in the monkey summarizes the fiber trajectories and terminations of projections in five different cases, each with the injection of an anterograde transported tracer as shown in the upper right. The color of fibers and terminals matches the color of the injection site.
From Schmahmann and Pandya (2006).

Neurocognitive formulations based on inferred connectivity

Nothing resembling this rich data set on the connectivity of the monkey brain exists for the human. This has not deterred attempts to link brain function to connection pathways. Four hundred years ago Descartes described a pathway from the retina to the arm muscles (via the pineal) that enabled reaching toward a visual object. The connections he depicted were *conceptual*, connections that *ought to have been present* to enable the observed phenomenon. More elaborate examples of such conceptual associative connectivity appeared in the 19th century in the works of Wernicke, Lichtheim and Charcot, to name a few (Catani and Mesulam, 2008a). Many of these pioneers, especially Dejerine, buttressed their formulations with additional information on actual pathways observed through dissections of white matter in autopsied human brain specimens and the tracing of axonal degeneration following brain damage (Dejerine and Dejerine-Klumpke, 1895). However, the information was meager and could not provide the level of detail that the increasingly more sophisticated behavioral models appeared to need. The obvious solution was to borrow from the experimental neuroanatomy literature and to infer connections in the human based on the information that was emerging in animals. This approach of *inferred structural connectivity*, introduced to modern neuroscience most effectively by Geschwind (1965), continues to influence thinking in this field.

Inferred connectivity provided the basis for proposing a "large-scale distributed network" architecture for the organization of spatial attention, memory, and language in the human brain (Mesulam, 1990). This approach revolved around four interactive steps: 1) delineate the anatomical substrates of a given domain through lesion mapping in patients, functional imaging, event related potentials, and additional informative approaches; 2) identify plausible experimental animal models of the relevant domain; 3) assume that the synaptic connectivity of the plausible animal model also exists in the human brain; 4) use this inferred connectivity to constrain the proposed architecture of large-scale networks underlying the target domain in the human brain.

Fig. 1 depicts synaptically explicit pathways, established in the monkey as described in the preceding section, and transposed to the human brain to provide a connection architecture for large-scale distributed networks. Based on what is known in the monkey, Fig. 1 makes the plausible assumption that sensory information in the human brain is also subject to extensive associative elaboration as it flows along the core synaptic hierarchy of primary sensory (level 1), upstream modality-selective (levels 2 and 3), downstream modality-selective (level 4) and transmodal areas (levels 5 and 6) depicted in Fig. 1. As shown by lesion mapping and by functional imaging, upstream sectors of modality-selective areas encode basic features of sensation such as color, 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 by groups of coarsely tuned neurons. As in the monkey, the role of heteromodal, paralimbic and limbic areas (i.e., transmodal cortices) is not only to promote convergent multimodal synthesis through forward connections but also to bind distributed modality-specific fragments into coherent experiences, memories, and thoughts through top-down connections (Damasio, 1989; Mesulam, 1990, 1998, 2008). Transmodal areas can thus enable the binding of modality-specific information, as initially

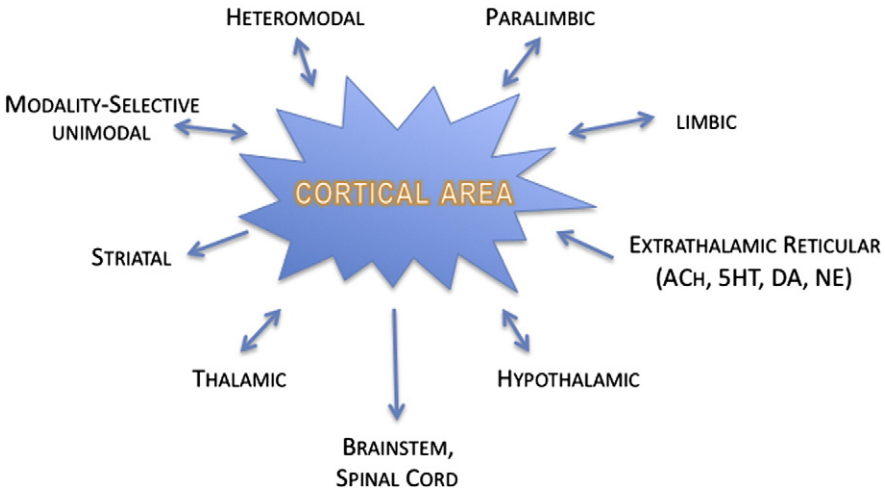

Fig. 3. Classes of connections.Classes of cortical and subcortical connections for each cortical area, as determined in the monkey. The "Extrathalamic Reticular" connections refer to cholinergic inputs from the basal forebrain, dopaminergic inputs from the substantia nigra, noradrenergic inputs from the nucleus locus coeruleus and serotonergic inputs from the midbrain raphe. Abbreviations: Ach—Acetylcholine, DA—Dopamine, NE—Norepinephrine, 5HT—5 Hydroxytryptophan (serotonin).

encoded at levels 1–4 of Fig. 1, into multimodal representations that have distributed as well as convergent components.

The nodes of Fig. 1 provide synaptic sites where sensory-fugal forward pathways, conveying extrapersonal sensory information, can interact with top-down sensory-petal projections that promote the inferential interpretation of incoming information according to context and expectation (Friston, 2005; Mesulam, 2008). Accordingly, many aspects of cognition represent a reciprocal neural dialog between *sensory-fugal* (inward or forward) connections, which reflect the physical nature of external events, and *sensory-petal* (backward or top-down) connections, which insert individual biases and expectations into the interpretation of these events. This arrangement promotes predictive encoding and enables complex brains with sufficient synaptic space to become active seekers of experience rather than stimulus-bound responders to extrapersonal events.

Transmodal nodes at levels 5 and 6 of Fig. 1 provide multimodal integration sites, and therefore hubs or epicenters, for multimodal domains such as spatial attention, episodic memory, executive function, and language. Examples of transmodal hubs include the pivotal role of midtemporal and temporopolar cortices for face and object recognition ("T" in Fig. 1), Wernicke's area in the left temporoparietal junction for lexical associations ("W" in Fig. 1), the hippocampal–entorhinal components of the limbic system for episodic memory ("L" in Fig. 1), and posterior parietal cortex for spatial orientation ("P" in Fig. 1) (Mesulam, 1998). Transmodal areas provide critical gateways for accessing the relevant distributed information but also become "neural bottlenecks" in the sense that they constitute regions of maximum vulnerability for lesion-induced deficits in the pertinent cognitive domain, giving rise to syndromes such as object agnosia, aphasia, amnesia, hypoemotionality, and hemispatial neglect. Damage to the transmodal hub leads to multimodal deficits in that domain whereas damage to more upstream nodes that feed into the hub gives rise to modality-specific impairments of that domain such as pure word deafness or prosopagnosia. Fig. 1, shows that the overall organization is likely to display small-world topology, highly connected hubs, and distributed modularity. In the terminology of graph theory (Bullmore and Sporns, 2009), nodes at levels 1–4 function as "provincial hubs" whereas those at levels 5 and 6 function as "connector hubs."

Characteristics of large-scale neurocognitive networks

The term 'network' is being used more and more frequently in cognitive neuroscience, especially in the field of functional imaging. In some contexts, the term might exclusively designate groups of areas that are interrelated according to a specific computational architecture, such as small world topology or parallel distributed processing. In others, it could be used more loosely to denote areas that happen to be coactivated during an fMRI task. In still other contexts, the usage of the term could be limited to areas that are interrelated according to some specified pattern of structural connectivity (Bressler and Menon, 2010). I use the term 'neurocognitive network' to designate a set of anatomically distinct areas that contribute to the integrity of a given behavioral domain and that display the following 5 cardinal properties (Mesulam, 1990, 1998): 1) Network components can be cortical or subcortical in location and can function as *critical* hubs or *ancillary* nodes. Both types are activated during functional imaging of the relevant domain but only damage to the former causes sustained impairment of the relevant behavior. 2) Critical nodes of a network are *monosynaptically interconnected* and become *coactivated* for the purpose of mediating the relevant domain. 3) The nodes function collaboratively but are not interchangeable, each displaying relative specializations for separate behavioral components of the relevant domain. 4) The behavioral output represents an emergent property of the network, not just the additive product of its components. 5) Nodes do not remain dedicated to a single network and can assemble or disassemble from one network into another.

As described above in the case of the monkey, one of the most extensively investigated networks of this type is the spatial attention network, where the inferior parietal lobule–intraparietal sulcus region (IPL/IPS), the frontal eye fields (FEF), and the cingulate gyrus (CG) constitute three critical hubs that become coactivated during tasks of spatial attention. Each hub provides a critical nexus for the integration of relevant information and also a site where lesions have the greatest probability of disrupting spatial attention (Gitelman et al., 1999; Kim et al., 1999; Mesulam, 1981, 1999; Mohanty et al., 2008; Nobre et al., 1997; Small et al., 2005). The hubs function collaboratively but also have unique specializations. In a figurative sense, the IPL/IPS can be said to encode a perceptual representation of the ambient landscape, the CG to map the distribution of motivational salience within this landscape, and the FEF to compile a strategy for navigating it (Mesulam, 1990, 1999; Mohanty et al., 2008; Small et al., 2005). Based on the close functional parallels to the analogous network in the monkey, the assumption has been made that the architecture of connectivity in this fronto-parieto-cingulate spatial attention network of the human is at least as complex as the pattern described above in the double labeling experiment of the monkey's spatial attention network. These inferred connections have been used to propose a connectivistic neural model that accounts for the integration of spatial and motivational

information and their transformation into strategies for searching behaviorally relevant extrapersonal targets (Mesulam, 1981, 1990, 1999). Diffusion imaging and fMRI have offered substantial support for this model although a rigorous verification of assumptions about the architecture of the underlying synaptic connectivity, inferred from the monkey brain, is not yet available (Corbetta et al., 1993; Egner et al., 2008; Mesulam, 1999; Mohanty et al., 2008; Schotten et al., 2005).

Five major systems in the human brain are likely to fulfill the connectivistic criteria of large-scale distributed networks: the fronto-parietal spatial network described above, the left hemisphere temporoperisylvian language network, the limbic/paralimbic network for explicit memory and motivational salience, the inferotemporal face and object recognition network, and the prefrontal executive function (or transcendent encoding) network (Mesulam, 2008). The default network may well be added as a sixth member of this set (Greicius et al., 2003; Raichle et al., 2001), assuming that it fulfills similar criteria of monosynaptic connectivity (at least in a homologous system of the monkey), distributed functionality, and an identifiable clinical syndrome that can be attributed to its impairment. Additional validation of networks, as integrated biological entities, comes from observations on neurodegenerative diseases where neuronal loss seems to spread preferentially from one network component to another (Mesulam, 2009; Seeley et al., 2009).

Much of the classic literature on brain–behavior relations has focused on impairments caused by the destruction of specific brain areas by stroke or traumatic injury. However, it is also possible to conceptualize impairments that reflect a loss of network connectivity even when the constituent nodes are not necessarily destroyed. The best-known examples are the 'disconnection syndromes' (Catani and ffytche, 2005; Catani and Mesulam, 2008b; Geschwind, 1965). In a disconnection syndrome such as *pure word blindness*, visual and language areas may be functional but reading may be impossible because damage to white matter pathways prevents visual word-form information from reaching critical nodes of the language network. Such network-level impairments can also occur on a physiological basis without structural damage to the axonal pathways. For example, in the neurodegenerative syndrome of primary progressive aphasia, fMRI showed that the two hubs of the language network, Broca's and Wernicke's areas, were normally activated by lexical processing tasks but failed to show task-dependent modulations of effective connectivity, suggesting that the language impairment may reflect, at least in part, a disruption of network coherence rather than a failure of the component areas to become activated (Sonty et al., 2007). A fuller understanding of disconnection syndromes and other network diseases will require a better understanding of structural connectivity of the human cerebral cortex.

Conclusions: challenges and prospects in the pursuit of human cortical connectivity

As the foregoing comments indicate, connectivity in the human brain has been approached at four different levels of evidence: conceptual, inferred, computational and structural. The fourth level is currently populated by the classic 19th century work on dissection and Wallerian degeneration, the few pathways that have been traced with modern histological methodology (e.g., Mesulam, 1979; Raghanti et al., 2008; Selden et al., 1998; Tardif and Clarke, 2001), and the increasingly more sophisticated but relatively indirect approach of diffusion tractography. Its importance notwithstanding, however, little of this existing data on structural connectivity in the human brain can be invoked to provide direct confirmation (or negation) of detailed synaptic organizations such as the one shown in Fig. 1.

One could invoke Plato's Parable of the Cave to emphasize how little we know about real human cortical connectivity. Indeed, some of the missing detail may turn out to be uniquely complex, perhaps in ways

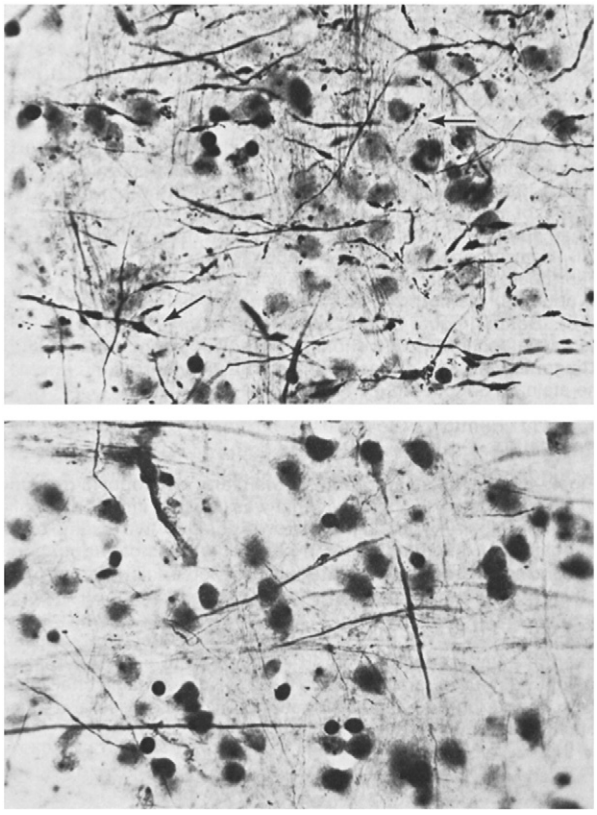

Fig. 4. Termination of visual radiations in layer IVc of the human striate cortex.From an autopsy specimen of a patient who sustained an infarction of visual radiations 22 days before death. The tissue was processed with a modification of the Nauta method. The arrows in the top figure show axonal profiles indicative of preterminal degeneration concentrated in layer IVc. These are not present in the same layer of the contralateral hemisphere (bottom). Magnification was 728× (Mesulam, 1979).

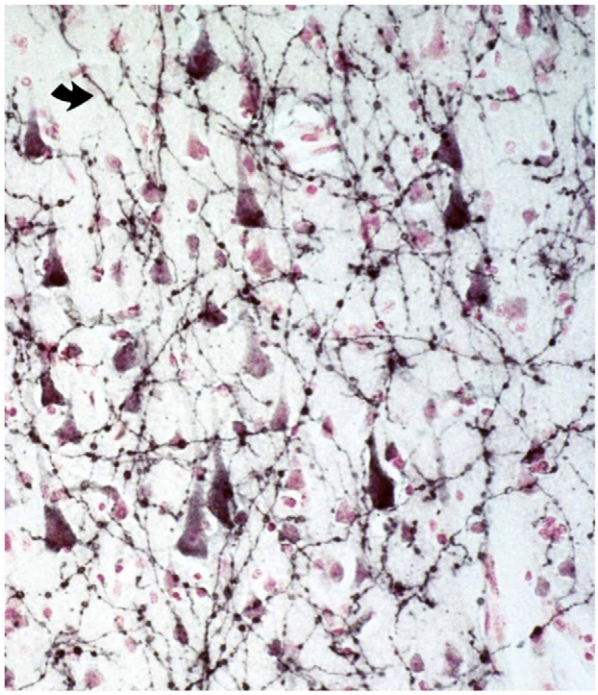

Fig. 5. Cholinergic projections from the basal forebrain to the pyramidal neurons of the human cerebral cortex.The arrow points to an example of an acetylcholinesterase-rich (cholinergic) axon coming from the basal forebrain of the human brain. Many such axons containing presynaptic varicosities are seen innervating cholinoceptive neurons. Magnification 233× (Mesulam and Geula, 1991).

that we cannot yet imagine. Others could argue that the judicious integration of the existing conceptual, functional, inferred and structural information offers as much knowledge as is currently needed and that there is no urgency to ask for more. However, as in all areas of science, it is unlikely that the absence of empirically derived data on the structural connectivity of the human brain will be tolerated for long.

The challenges that face future explorations of human cortical connectivity arise from the immense complexity of the primate brain. Since it is axiomatic that the human brain is at least as complex as the brain of the monkey, a brief glance at details of cortical connectivity in the monkey provides a sobering view of what lies ahead. Fig. 2, based on axonally transported tracer experiments in the monkey by Schmahmann and Pandya (2006), shows that fibers from different origins are intermingled in white matter, that their terminal fields form an intricate mosaic within thalamic nuclei and also interleaved columns in the cerebral cortex. What will it take for diffusion imaging to reveal this level of detail in analogous pathways of the human brain? Fig. 3 lists the classes of connections that each cortical area in the monkey has been shown to have. The "connectome" of an area, in the monkey as well as the human, would need to specify the relative magnitude of each class, including its source and target.

While there is little doubt that fruitful explorations of human cortical connectivity will continue to proceed with DTI, DSI, fMRI and perhaps TMS, the foregoing comments suggest that there is also a need to shift emphasis from the computer to the microscope. A principled investigation of neural connectivity is unlikely to succeed without wet brain research on autopsied or surgically removed human brain specimens. There are isolated examples where such approaches have revealed cortical circuitry with a level of detail that approaches what can be achieved in the monkey (Figs. 4 and 5). Further meaningful progress along these lines will require similar attempts to be pursued and multiplied in laboratories around the world. As part of such a program, new neuroanatomical methods will need to be devised, investigators with new talents will need to be trained, and the human neuroanatomy laboratory will need to receive a high priority in resource allocations. Although progress is likely to be slow, it will fill a major gap of knowledge and also establish a more solid foundation for designing and interpreting functional and diffusion imaging experiments of the future.

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