Defining Neurocognitive Networks in the BOLD New World of Computed Connectivity

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Cognitive functions require the concerted activity of interconnected neuronal clusters that collectively form large-scale networks. In this issue, Seeley and colleagues use resting-state fluctuations of the BOLD signal to highlight the relevance of networks to human brain function and dysfunction.

Neurocognitive networks are defined by their connectivity patterns, but connectivity is notoriously difficult to study in the human brain. In this issue of *Neuron*, Seeley and colleagues use fluctuations in blood-oxygen-level-dependent (BOLD) signals to show that intrinsic connectivity networks, identified by the interareal correlation of spontaneous activity, become the selective targets of specific neurodegenerative diseases (Seeley et al., 2009). The findings have implications for understanding the organization of networks in the healthy brain and their selective vulnerability to neurodegeneration. In order to appreciate the challenges facing the exploration of such large-scale neurocognitive networks in the human brain, it is useful to review some of their properties, as we understand them from the perspectives of behavioral neurology and the experimental primate laboratory.

Neurocognitive networks contain monosynaptically interconnected clusters of cortical and subcortical neurons that become coactivated for the purpose of mediating a definable class of cognitive outputs. Some of the clusters are critical for the relevant outcome, and others are ancillary. The clusters function collaboratively but are not interchangeable, each displaying relative specializations for separate behavioral components of the relevant domain.

One of the most extensively investigated large-scale networks of this type is the frontoparietal spatial attention network (Mesulam, 1999b). In monkeys and humans, damage to this network hinders the attentional capture of events in the contralesional extrapersonal space. The two tightly and reciprocally interconnected hubs of this network are located in the inferior parietal lobule-intraparietal sulcus region (IPL/IPS) and the frontal eye fields (FEF). The IPL/IPS displays a relative specialization for mapping the spatial coordinates of salience, whereas the FEF is more closely involved in the sensory-motor programming needed to navigate the resultant landscape. Each of these two areas is interconnected with sectors of the cingulate gyrus, a network component that mediates the preferential attentional capture of motivationally relevant events. The FEF and IPL/IPS are also interconnected with numerous additional cortical regions (Morecraft et al., 1993). The resultant connectional architecture displays a fascinating feature: any cortical area connected with one of the two epicenters is also connected with the other (Figure 1). Consequently, a message emanating from FEF reaches 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 survey a vast informational landscape related to motivational topography and orienting behaviors so that the focus of spatial attention can be deployed adaptively and flexibly. The FEF-IPL/IPS network is so robust that its principal axis can be identified through coherent fluctuations of the BOLD signal even in anesthetized monkeys (Vincent et al., 2007). However, the additional set of connections shown in Figure 1 does not yet seem resolvable by this approach.

At least five major networks can be identified in the human: the frontoparietal spatial network described above, the left hemisphere perisylvian language network, the limbic network for explicit memory and motivation, the inferotemporal face and object recognition network, and the prefrontal executive function network (Mesulam, 2008). Components of these networks tend to fulfill the features of selectively distributed representation of a cognitive domain, collaborative coactivation, and reciprocal monosynaptic interconnectivity as established by neuroanatomical experiments on homologous areas on the monkey brain. These networks also fulfill the criterion of "double dissociation" in the sense that focal lesions can selectively disrupt one while leaving the others intact. There are undoubtedly additional identifiable networks, but they will need to be validated by fulfilling at least some of the criteria listed above. Resting state fluctuations or their disease-induced perturbations cannot, by themselves, characterize a network, since some diseases can also spread by contiguity and since BOLD fluctuations could, on occasion, reflect hemodynamic rather than functional relationships.

The functions of a network are completely determined by the sensory information it receives and the motor pathways it can access. Most connections of a neuron remain within local clusters, but some reach distant targets. These distant projections play a critical role in defining the functional specializations of neuronal clusters. They also constitute the highways of the brain for transporting not only action potentials but also trophic factors (nerve growth factor), viruses (poliomyelitis), toxins (tetanus), and a "sustaining" influence that has not yet been fully characterized. As a reflection of this sustaining influence, neurons that are cut off from essential projection sites stop functioning properly and may die, even when they remain untouched by the initiating injury,

as shown by the phenomenon of crossed cerebellar diaschisis. Neurons react negatively not only to the loss of their inputs but also to the loss of projection targets, and this effect may propagate itself across synapses, as demonstrated by the phenomena of retrograde and anterograde transsynaptic degeneration (Kovac et al., 2006). Since the most prominent neuronal pathways are those that interconnect network components, these considerations add validity to the point made by Seeley et al. that atrophy caused by neurodegeneration can preferentially propagate within networks.

But how does a disease choose a network as its initial target? One syndrome that has allowed an exploration of this question is primary progressive aphasia (PPA). All three variants of PPA, the *agrammatic*, *semantic*, and *logopenic*, share the common feature of an initially asymmetric degeneration that is more extensive in the language-dominant (usually left) hemisphere. In rare instances PPA is caused by point mutations of the progranulin gene (*PGRN*). However, nearly identical *PGRN* mutations can also cause an entirely different syndrome, based on a different anatomical distribution of degeneration, known as the behavioral variant of frontotemporal degeneration (bvFTD). If identical genetic abnormalities can cause two different phenotypes, what sort of mechanism might be invoked to explain selective vulnerability patterns? One possible resolution to this puzzle emerged from the finding that PPA patients and their first-degree relatives had a much higher incidence of learning disabilities, including dyslexia, when compared to neurological controls and patients with bvFTD (Rogalski et al., 2008). This finding raises the possibility that in some patients PPA arises as a tardive manifestation of a developmental vulnerability of the language network that remains compensated during most of adulthood but that becomes a "locus of least resistance" for a degenerative disease that, in other individuals with other vulnerabilities, would display a different anatomical distribution.

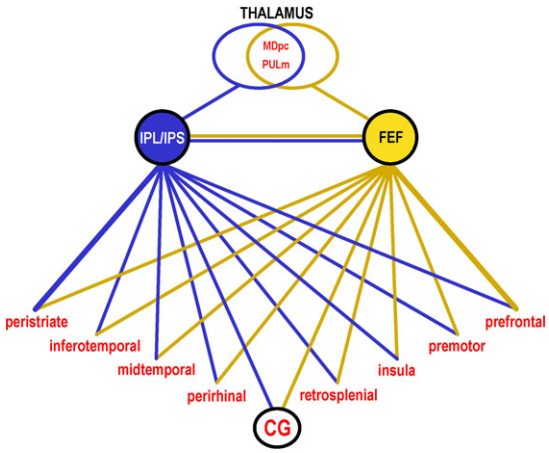

Figure 1. An Example of the Complex Anatomical Architecture of Large-Scale Networks

Retrogradely transported tracers were injected in both cortical hubs of the spatial attention network in the same animal, blue in the IPL/IPS and yellow in the FEF. Areas containing retrogradely labeled neurons (i.e., neurons that project to the injection sites) are listed in red. Retrograde transport was seen in only delimited neuronal clusters within these anatomical regions. The blue lines show projections to the IPL/IPS, and the yellow lines show projections to the FEF. There were no cortical areas that projected to only one of the injection sites. There were thalamic nuclei that projected exclusively to one of the two injection sites, but only thalamic nuclei that projected to both injection sites are shown. CG, cingulate cortex; MDpc, parvocellular part of the mediodorsal nucleus; PULm, medial pulvinar nucleus. Data from Morecraft et al. (1993).

In other neurodegenerative states, the determinants of selective vulnerability are likely to be different. One hypothesis suggests that the neurodegeneration in bvFTD selectively targets a special group of neurons that may be unique to apes and humans (Seeley et al., 2006). In Alzheimer's disease (AD), on the other hand, credible hypotheses related to selective vulnerability need to explain why age is the major risk factor and why the entorhino-hippocampal complex is the initial target of destruction. I outlined a speculative model according to which risk factors of AD, including aging, share the feature of hindering structural neuroplasticity (Mesulam, 1999a). Consequently, parts of the brain that need to sustain the highest level of neuroplasticity through the life span, such as components of limbic cortex, are the most vulnerable. One outcome of the unsustainable neuroplasticity stress in these neurons is neurofibrillary degeneration, and another is the deposition of β-amyloid at sites where their axons terminate. According to this scenario, the neurofibrillary destruction of projections emanating from limbic areas would trigger the well-known spread of neurodegeneration first into paralimbic and then into association areas, closely mirroring the clinical progression of the deficits from an isolated amnesia to dementia. Circumstantial support for this pathogenetic sequence came from a study showing that transmodal areas with the relatively higher densities of connectivity, and presumably with higher neuroplasticity demands, were also more vulnerable to amyloid deposition and dysfunction in AD (Buckner et al., 2009).

Networks provide the scaffolding for the computational architectures that mediate cognitive functions. It is therefore reasonable to assume that the behavioral consequences of damaging a network will reflect the disruption of the computational architecture it supports. One of the first demonstrations of network dysfunctional as an outcome of neurodegeneration was established in AD (Horwitz et al., 1995). Similar evidence was also obtained in patients at the early stages of PPA. In this group of patients, fMRI showed that the relevant hubs of the language network, such as Broca's and Wernicke's areas, were normally activated but that they failed to modulate their effective connectivity during lexical processing tasks, suggesting that the aphasia reflected a disruption of network coherence rather than a failure of the component areas to become activated (Sonty et al., 2007).

A concern that clouds current prospects for exploring neurocognitive networks in the human brain is the lack of information on anatomical connectivity. To be sure, imaging approaches based on diffusion tensor imaging, resting state coherence, and computed effective connectivity will help. But there are gaps, not the least of which is the inability of existing methods to differentiate mono- from multisynaptic connections. The current imaging approaches cannot yet resolve the synaptic details of connectivity revealed by experimental neuroanatomy, details that are likely to be uniquely complex in the human brain, perhaps in

ways that we cannot yet imagine. The article by Seeley et al. highlights the critical importance of neural connectivity for any principled investigation of brain function and dysfunction. It would be a great service to this field if funding were specifically targeted for an international collaboration of cognitive neuroscientists, neuroimagers, and neuroanatomists so that the real connectivity of the human brain could be explored effectively.

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A p75^{NTR} Pivoting Paradigm Propels Perspicacity

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The p75 neurotrophin receptor (p75^{NTR}) is involved in numerous neuronal signaling paths but its fundamental signaling mechanisms are unknown. In this issue of *Neuron*, Vilar et al. show that p75NTR functions as a covalently crosslinked dimer to transduce NGF-induced signaling events.

The 75 kDa neurotrophin receptor (p75^{NTR}) is an important neuronal signaling protein that interacts with numerous ligands and coreceptors to regulate cellular survival and apoptosis, neurite outgrowth and repulsion, myelin formation and long-term depression. The long list of functions ascribed to this one receptor would be hard to believe were it not for the compelling in vivo data that demonstrates its participation in these activities. In the face of this biological reality, at some point or another, almost all cellular neurobiologists will eventually find themselves working a problem involving p75^{NTR}. So in this sense, we all have a stake in deciphering its mechanism of action.

p75^{NTR} was the founding member of the tumor necrosis family receptor superfamily, a group that is characterized by the presence of tandem arrays of cysteine-rich domains (CRDs) in their extracellular regions, which function as ligand binding domains. TNFRS members typically bind trimeric ligands of the TNF family, whereas p75^{NTR} binds dimeric ligands of the neurotrophin family. The molecular details of how neurotrophins transduce signals via p75^{NTR} have been uncertain, but in this issue of *Neuron*, Ibanez and colleagues provide new insights into the mechanisms of p75^{NTR} signal transduction (Vilar et al., 2009).

The authors show that p75^{NTR} exists as a covalently associated dimer in sympathetic neurons and PC12 cells, in cortex, hippocampus, and cerebellum, and when overexpressed in heterologous cells. The oligomer is lost in the presence of reducing agents, indicating that a disulfide linkage mediates this bimolecular association. Each of the cysteines in the p75^{NTR} extracellular domain exist as intramolecular pairs that maintain the receptors' extended structure and its intracellular cysteines exist in a reducing environment unable to support disulfides. So where in p75^{NTR} is the relevant cysteine?

Vilar et al. (2009) identify a cysteine residue within the p75^{NTR} transmembrane domain as the locus for disulfide formation between the p75^{NTR} chains. Introduction of a C257A mutation into the otherwise intact receptor blocks the formation of the covalently linked dimer. However, wild-type p75^{NTR} and p75^{NTRC257A} form cell-surface dimers with equal frequency, indicating that other mechanisms drive p75^{NTR} oligomerization. The p75^{NTR} transmembrane domain also contains an AxxxG motif at position 262–266. This motif is present in self-associating transmembrane domains within integrins and glycophorin A (Kubatzky et al., 2001) and by using the bacterial ToxCAT system and mammalian cell overexpression, Ibanez and colleagues show that the p75^{NTR} transmembrane domain is similarly self-associating. Comparison of the mammalian and reptilian receptor with p75^{NTR} orthologs identified in primitive deuterostomes such as sea urchin and acorn