Neuroimaging insights into network-based neurodegeneration

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Purpose of review
Convergent evidence from a number of neuroscience disciplines supports the hypothesis that Alzheimer's disease and other neurodegenerative disorders progress along brain networks. This review considers the role of neuroimaging in strengthening the case for network-based neurodegeneration and elucidating potential mechanisms.

Recent findings
Advances in functional and structural MRI have recently enabled the delineation of multiple large-scale distributed brain networks. The application of these network-imaging modalities to neurodegenerative disease has shown that specific disorders appear to progress along specific networks. Recent work applying theoretical measures of network efficiency to in-vivo network imaging has allowed for the development and evaluation of models of disease spread along networks. Novel MRI acquisition and analysis methods are paving the way for in-vivo assessment of the layer-specific microcircuits first targeted by neurodegenerative diseases. These methodological advances coupled with large, longitudinal studies of subjects progressing from healthy aging into dementia will enable a detailed understanding of the seeding and spread of these disorders.

Summary
Neuroimaging has provided ample evidence that neurodegenerative disorders progress along brain networks, and is now beginning to elucidate how they do so.

Keywords
connectivity, dementia, diffusion tensor imaging, network, neurodegeneration, resting-state functional MRI

INTRODUCTION

Diseases can move through the brain in various ways and at various speeds. Rasmussen's encephalitis typically begins with a focal abnormality, then appears to spread contiguously over several months, ultimately resulting in diffuse atrophy of the entire ipsilateral hemisphere with no involvement of the contralateral hemisphere [1]. Multiple sclerosis, by contrast, results in patchy, unpredictable focal lesions in the white matter that occur intermittently over years. Neurodegenerative diseases provide a third template of progression, with neuronal dysfunction spreading from a region of focal onset to nonadjacent regions in a predictable pattern that manifests over years. This has been best characterized in Alzheimer's disease, but the same features appear to apply to the spread of other canonical neurodegenerative disorders like Parkinson's disease, progressive supranuclear palsy (PSP), amyotrophic lateral sclerosis, and behavioral variant frontotemporal dementia (bvFTD) [2–5]. This choreographed movement across nonadjacent brain regions suggests that many neurodegenerative diseases progress along discrete brain networks.

The patterned progression across nonadjacent regions does not mandate a network-based mechanism for neurodegenerative diseases. Such a pattern could result from shared susceptibility to neurodegeneration in regions that are not connected. Mitochondrial disorders, for example, tend to involve a predictable set of cell types that are not connected but rather share a prominent dependency on mitochondrial function [6]. So, although there are alternative hypotheses, for most neurodegenerative

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KEY POINTS

- Neuroimaging evidence suggests that neurodegenerative diseases progress along brain networks.
- Advanced network analysis approaches can be used to test models of disease spread.
- Higher resolution functional and structural imaging will allow for increasingly detailed, cortical layer-specific analysis of microcircuits implicated in the earliest stages of disease.

diseases, an abundance of clinical, pathological, cell model, animal model, and neuroimaging evidence has been assembled to support the network-based hypothesis of progression. The unifying theme for this hypothesis is that distinct neurodegenerative diseases progress in distinct patterns that strongly resemble maps of neuronal connectivity [5,7]. The evidence from postmortem human tissue and cellular and animal models is reviewed elsewhere in this issue. Here, we will consider the potential for neuroimaging to support and strengthen this compelling unified theory of neurodegenerative disease. In particular, we will examine neuroimaging evidence that neurodegenerative diseases spread along networks as well as more recent work positing *how* neurodegenerative diseases spread along networks.

Several neuroimaging modalities lend themselves to the characterization of brain networks. Some, like resting-state functional MRI (fMRI) or diffusion tensor imaging (DTI) tractography, provide direct estimates of functional or structural connections within a single subject. Other modalities like structural MRI or fluorodeoxyglucose PET (FDG PET) can be used to infer networks by examining regional covariance of values across a group of subjects. After a brief consideration of the role of voxelwise measures like T1-weighted structural MRI, FDG PET, and amyloid imaging with PET [8], this review will focus mainly on the direct connectivity measures and how they have been used to study networks in neurodegenerative diseases. The bulk of the examples will relate to Alzheimer's disease, in which the vast majority of the work has been done, with occasional poignant examples drawn from other disorders. Multimodal and high-resolution approaches will be considered in the final two sections.

VOXELWISE BRAIN IMAGING

Most imaging techniques divide the brain up into thousands of small cubes known as voxels, warp subjects' brains into a common space, and then compare a variable of interest in the same voxel across two groups of subjects (patients and controls, commonly). This voxelwise comparison is then repeated for each voxel in the standard brain space so that tens of thousands of two-sample *t*-tests are performed, one *t*-test for each voxel. A statistical threshold is determined, (hopefully) incorporating a correction for multiple comparisons, and voxels surviving the threshold are highlighted and typically shown overlaid on a T1-weighted anatomical scan. In addition to comparing a voxelwise measure between two groups, paired sample *t*-tests can be run voxelwise to generate maps of change in glucose metabolism or gray matter density in the same group of subjects at two different points in time. The variable of interest might be gray matter density in voxel-based morphometry (VBM), glucose metabolism in FDG PET, or amyloid tracer uptake in amyloid imaging PET, but the basic methods are similar. In the end, each approach provides a map of brain regions that differ in the variable of interest between patients and controls or within subjects over time. Hundreds of voxelwise imaging studies have been conducted in Alzheimer's disease using a variety of imaging measures, and this literature has been reviewed extensively [9,10]. Although direct inferences about connectivity cannot be made from these voxelwise maps, they can be compared qualitatively with maps of known brain networks. In addition, the voxel-based measures described here can be used in covariance analyses to highlight networks of brain regions whose relative gray matter density, cortical thickness, or glucose metabolism are similar across subjects [11–13]. In contrast to these across-subject covariance maps of network connectivity, the two methods described below provide direct, within-subject maps of network connectivity.

RESTING-STATE FUNCTIONAL MRI

In a subject resting quietly for 8 min during an fMRI scan, the blood oxygen level-dependent (BOLD) signal will fluctuate up and down at a very low frequency (<0.1 Hz). These low-frequency BOLD signal fluctuations are strongly correlated in time across regions that are known to be functionally connected. First demonstrated in a motor network [14], resting-state fMRI has since been used to demonstrate that the brain is segregated into a wide array of 15 or more functional networks mediating a host of sensory, motor, cognitive, and affective functions [15,16]. In Alzheimer's disease, resting-state fMRI has implicated a specific network, known as the default mode network (DMN), that includes

the medial temporal lobes, the posterior cingulate cortex (PCC), inferolateral parietal regions, and the medial prefrontal cortex [17–20] (Fig. 1) [21]. Following the initial description of reduced DMN connectivity in Alzheimer's disease [17], this finding has been replicated several times [22▪,23▪▪] and advanced upstream in the clinical spectrum. Sorg *et al.* [18] reported reduced DMN connectivity in patients with mild cognitive impairment (MCI). Healthy older controls harboring amyloid plaques [as measured by the PET ligand Pittsburgh compound B (PIB)] show reduced DMN connectivity when compared with age-matched and cognition-matched older controls without PIB binding [20,24▪]. Healthy older controls with an apolipoprotein (Apo)E4 allele (an Alzheimer's disease risk factor) tend to show reduced connectivity in the DMN when compared with older controls without the E4 alelle [25,26], although this effect appears to be driven mainly by female E4 carriers [27▪]. DMN connectivity has also been followed downstream in the clinical spectrum of Alzheimer's disease. As the disease progresses, longitudinal studies have shown that DMN connectivity continues to decline, above and beyond what can be accounted for by gray matter loss [28▪]. Cross-sectional studies also demonstrate progressive decline in DMN connectivity across successive disease stages in Alzheimer's disease [29].

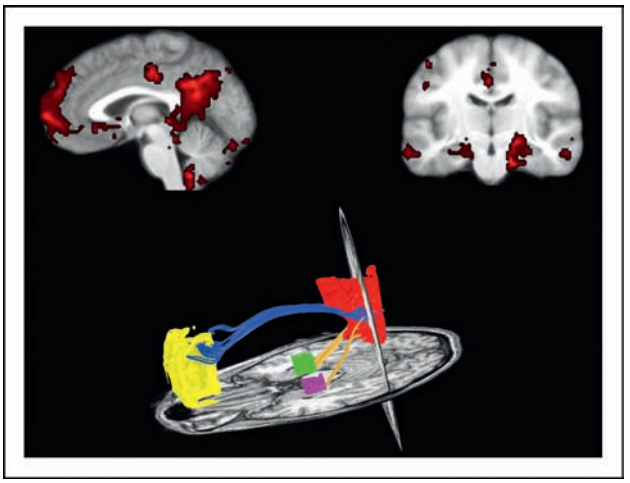

FIGURE 1. Functional and structural connectivity maps of the default mode network. The default mode network has been linked to memory function and is targeted by Alzheimer's disease. Functional connectivity between the posterior cingulate cortex, medial prefrontal cortex, and medial temporal lobes (top) reflects the underlying structural connectivity (bottom). The cingulum bundle in blue connects the posterior cingulate cortex to the medial prefrontal cortex and the descending cingulum bundle in gold connects the posterior cingulate cortex to the medial temporal lobes. Adapted from [21].

This relatively strict mapping of a neurodegenerative disease to a large scale, distributed brain network does not appear to be unique to Alzheimer's disease. Seeley *et al.* [7] demonstrated remarkable overlap between the VBM atrophy maps of five different neurodegenerative diseases and five distinct brain networks revealed by functional connectivity and structural covariance. After Alzheimer's disease, this case has been most compellingly made for bvFTD, in which VBM atrophy maps strongly resemble a resting-state fMRI network linking the dorsal anterior cingulate cortex to the bilateral frontoinsular cortices. This network is important for modulating the autonomic nervous system in response to salient environmental stimuli and so has been called the salience network [30]. Patients with bvFTD have reduced connectivity in the salience network when compared either with controls or with Alzheimer's disease patients [23▪▪,31]. Among bvFTD patients, connectivity in this network declines with declining function [23▪▪]. Although most resting-state fMRI studies focus on positive correlations among regions within a specific network, negative correlations have been demonstrated between DMN regions and salience network regions [32–34]. In the setting of neurodegenerative disease, this relationship appears to result in cross-network disinhibition such that as connectivity in the DMN declines in Alzheimer's disease, connectivity in the salience network increases. Conversely, as salience network connectivity declines in bvFTD, DMN connectivity increases [23▪▪,29,31].

DIFFUSION TENSOR IMAGING TRACTOGRAPHY

While resting-state fMRI provides within-subject maps of functional connectivity, DTI tractography provides within-subject maps of structural connectivity. DTI relies on the sensitivity of MRI to the diffusion of water and the fact that water in fiber tracts does not diffuse symmetrically in all directions, but rather does so preferentially and asymmetrically along the length of the axons [35]. This asymmetry is usually measured as fractional anisotropy, which increases with the greater number of parallel fibers in a given volume. DTI can be used in a voxelwise fashion, and numerous studies have reported that Alzheimer's disease results in reduced fractional anisotropy in white matter tracts linking regions of the DMN such as the descending cingulum bundles (connecting the PCC to the medial temporal lobes) [36–38]. DTI tractography allows for the estimation of the entire fiber tract connecting two regions by

following the diffusion direction of water from one voxel to the next [39]. Tractography can be used in conjunction with voxelwise analyses of fractional anisotropy to reduce the voxel search space from the whole brain down to an a-priori set of tracts, an approach that has similarly revealed reduced fractional anisotropy in the tracts leaving the PCC [40,41].

The tractography approach also provides an additional variable, usually referred to as fiber count or fiber density, which is an estimate of the number of separate fiber paths that can be successfully traced within a given tract. Fiber count is often used as a measure of the strength of structural connectivity between two regions (although there is still some debate in the field about the interpretability of this measure) [42]. Structural connectivity maps have proven useful in distinguishing Alzheimer's disease patients from controls [43▪] and, with higher order network measures described below, in distinguishing healthy older ApoE4 carriers from noncarriers [44▪]. Here again, although many connections have been considered, those tracts connecting regions in the DMN tend to be the most informative in detecting Alzheimer's disease-related changes.

GRAPH THEORY AND NETWORK PROPERTIES

DTI tractography and resting-state fMRI can both be used to generate whole-brain connectivity maps (Fig. 2) [45]. These approaches begin with the definition of a set of structurally or functionally defined brain regions, covering most of the cortical and subcortical gray matter. Then, using either structural or functional connectivity methods, every possible pairwise connection is assessed. Those that pass a predefined threshold are considered valid and a map of all connections between all brain regions is generated [45]. The connections can be binarized (there is or is not a connection between two regions) or weighted (there is a connection and fiber density determines the connection strength). The resulting whole-brain connectivity map can be characterized using measures derived from graph theory, a statistical approach to

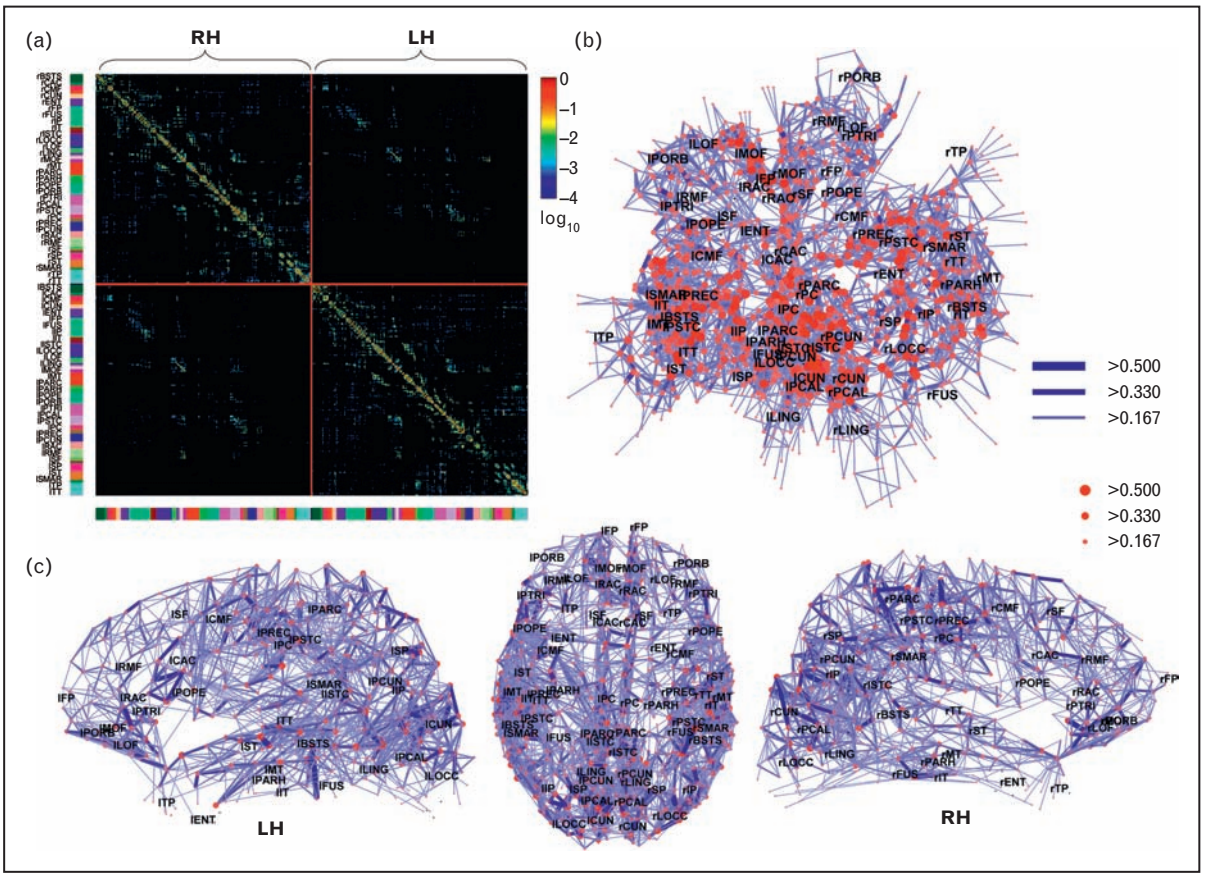

FIGURE 2. A whole-brain connectivity map derived from diffusion tensor imaging tractography. The matrix in (a) shows the strength of pairwise structural connections between 998 structural regions of interest. These regions and their connections can then be displayed topologically as a large network composed of several smaller subnetworks (b) or anatomically for the left and right hemispheres (LH and RH, respectively) (c). Adapted from [45].

the study of networks [46]. Graph theory is applied to networks of all kinds in the biological and social sciences and comes with its own vocabulary: applied to brain imaging, the whole-brain network is a graph, brain regions in the graph are called nodes, and connections between nodes are called edges. Graph theory allows for several summary measures that can be useful in characterizing the efficiency of a network, such as the characteristic path length (number of edges) between any two nodes, the clustering coefficient (how often two nodes connected to a third node are connected to each other), and small-worldness (a combination of path length and clustering coefficient such that a small-world network has a high average clustering coefficient and low characteristic path length). Small-worldness is thought to optimize efficiency of information transfer in a network.

Graph theoretical approaches to understanding Alzheimer's disease and other neurodegenerative diseases have become increasingly popular. Numerous studies – using functional connectivity, structural connectivity, and structural covariance – have reported a variety of deficits in whole-brain connectivity. The general theme is that small-worldness is disrupted in Alzheimer's disease [47] due to a variety of specific (and minimally replicated) deficits including lower clustering coefficient [48], reduced long-range connectivity [49,50], and increased path length [51]. One recent study has extended this approach upstream in the clinical spectrum, demonstrating that the brain network of healthy older ApoE4 carriers has reduced small-worldness [44▪]. The application of graph theory to brain imaging networks is still in its early days. The lack of replicability in the specific Alzheimer's disease deficits reported is likely due to the plethora of distinct preprocessing and analysis techniques applied by different laboratories. As this subfield matures, consensus on optimal analysis techniques should lead to better replicability. One finding that has been replicated relates to the fact that the PCC, a key node in the DMN, is a major hub in whole-brain connectivity maps [45,52]. This means that, like an airport hub, the PCC tends to be connected to many other nodes and can serve as a way station between two nodes that are not directly connected. This property of the PCC may be relevant when considering why Alzheimer's disease appears to target the DMN and how Alzheimer's disease might spread across the DMN.

MULTIMODAL AND LONGITUDINAL APPROACHES

Given the abundance of evidence across several disciplines, there is little question that Alzheimer's disease and many other neurodegenerative diseases progress along large-scale distributed networks. The more pressing question is *how* do these disorders spread across networks? Answering this question may provide novel approaches to treating these diseases. One compelling possibility is that the mechanism of spread is similar, and therefore a single new approach to preventing or slowing progression may be applicable across several neurodegenerative diseases. In the imaging realm, recent and ongoing efforts are underway to get at the 'how' of network-based neurodegeneration. Such studies may leverage multiple imaging modalities or longitudinal study designs or, ideally, both.

Two recent multimodal studies have used graph theoretical approaches to test various models of how neurodegenerative diseases spread along a network. Zhou *et al*. [53▪▪] combined structural imaging in demented patients with resting-state fMRI in healthy controls to test theories of network spread. Their analysis was most consistent with a transneuronal spread of neurodegeneration from initial disease epicenters to directly connected neighboring nodes. Raj *et al*. [54▪▪] landed on a similar conclusion using a different approach. Here, whole-brain structural connectivity maps, derived from DTI tractography of healthy controls, were compared with VBM atrophy maps of Alzheimer's disease and bvFTD. A graph theoretical analysis was applied and again supportive of a transneuronal spread of neurodegeneration. Although already compelling, this type of multimodal, graph theoretical approach should prove even more informative when applied to multimodal, longitudinal data acquired in patients moving from health into the mild and later stages of a dementia.

The Alzheimer's disease Neuroimaging Initiative (ADNI) study has provided a wealth of longitudinal, multimodal data on hundreds of healthy older controls, MCI patients, and Alzheimer's disease patients [55▪]. In keeping with earlier work [56,57], several ADNI studies have now shown longitudinal changes in DMN regions like the medial temporal lobes and PCC as patients progress into Alzheimer's disease and through its later stages [12,58]. Similar work with the ADNI FDG PET data has found that MCI and Alzheimer's disease patients show progressive loss of metabolism in the core DMN regions like the PCC, lateral parietal cortex, and medial temporal lobes [59▪▪]. The true potential for ADNI to inform the network-based hypothesis of neurodegeneration, however, remains untapped. The continuation of ADNI into ADNI2 expands the scope of imaging so that in addition to the structural MRI, FDG PET, and amyloid PET data acquired at most sites, some sites will also be acquiring DTI data

and an independent (unfortunately) set of sites will be adding resting-state fMRI. Previous work comparing independent datasets has shown that all modalities tend to converge on the DMN [19]. In ADNI2, the combination of connectivity-based imaging measures with PET and structural data acquired longitudinally in the same patients should allow for more explicit testing of the network-based neurodegeneration hypothesis in Alzheimer's disease.

CONCLUSION

Neuroimaging has already contributed significantly to our understanding of neurodegenerative diseases and their progression along brain networks. Continued advances in imaging acquisition and analysis techniques should allow for increasingly powerful tools to study brain networks. Submillimeter human brain imaging now provides a means of examining functional activation changes at the level of specific cortical layers [60,61]. Similar advances in DTI technology are beginning to allow for estimation of finer tracts, like the perforant pathway, connecting medial temporal lobe subfields [62▪,63]. Functional and structural connectivity maps at this degree of spatial resolution should ultimately deliver layer-specific connectivity maps allowing us to track the layer-specific spread of disorder in Alzheimer's disease [2]. Translational imaging is another domain in which the field is advancing quickly. Resting-state functional connectivity maps have been reliably characterized in nonhuman primates [64,65], rats [66,67], and mice [68]. The ability to image functional connectivity in mouse models of Alzheimer's disease and in humans with Alzheimer's disease should help speed the translation of promising animal work into clinical trials.

Finally, although amyloid imaging with PIB constitutes a momentous advance in Alzheimer's disease imaging, it has also served to highlight the poor correlation between amyloid plaques and neuronal dysfunction. Although there are large areas of overlap between the DMN and maps of PIB deposition [19], there are also glaring mismatches. The hippocampus and medial temporal lobes are key nodes in the DMN [32] and are among the earliest sites of tau disorder [2], but are notably plaque free in the early stages of Alzheimer's disease. Conversely, the caudate tends to be functionally spared early in the course of sporadic and familial Alzheimer's disease, but PIB imaging (backed by postmortem findings) shows robust, early plaque deposition in the caudate [69]. In MCI patients, some frontal lobe regions show a positive correlation between PIB deposition and FDG PET metabolism [70], raising the intriguing possibility that plaque deposition in regions like the caudate and frontal lobes is protective, whereas regions like the entorhinal cortex that are slow to develop plaques are quick to show dysfunction. In-vivo PET tracers specific to tau disorder have shown promise in preclinical studies [71,72▪▪] and would enable important advances in a host of diseases that feature tau disorder, including Alzheimer's disease, bvFTD, and PSP. Tau is the pathologic agent most tightly linked to brain network dysfunction in Alzheimer's disease [73], it is capable of transneuronal spread [74], and its association with microtubules in axons suggests a critical role in connectivity. The ability to image tau disorder and brain network connectivity in the same patients would represent a critical bridge between molecular and systems neuroscience.

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Conflicts of interest

M.D.G. has been paid for consulting by Genetech, Pfizer and Perceptive. D.L.K. has no conflicts of interest to declare.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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Along with Raj *et al.* [54▪▪], the first example of using graph theoretical measures, applied here to a whole-brain functional connectivity map, to characterize the spread of neurodegenerative disease. Four competing models of network-based neurodegeneration are outlined and explicitly tested.

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