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Mapping Neurodegenerative Disease Onset and Progression

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Brain networks have been of long-standing interest to neurodegeneration researchers, including but not limited to investigators focusing on conventional prion diseases, which are known to propagate along neural pathways. Tools for human network mapping, however, remained inadequate, limiting our understanding of human brain network architecture and preventing clinical research applications. Until recently, neuropathological studies were the only viable approach to mapping disease onset and progression in humans but required large autopsy cohorts and laborious methods for whole-brain sectioning and staining. Despite important advantages, postmortem studies cannot address in vivo, physiological, or longitudinal questions and have limited potential to explore early-stage disease except for the most common disorders. Emerging in vivo network-based neuroimaging strategies have begun to address these issues, providing data that complement the neuropathological tradition. Overall, findings to date highlight several fundamental principles of neurodegenerative disease anatomy and pathogenesis, as well as some enduring mysteries. These principles and mysteries provide a road map for future research.

Neurodegenerative diseases are united by the inexorable and targeted spread of misfolded disease protein inclusions, gliosis, and synaptic and neuronal loss. Clinical symptoms and deficits, which coalesce into recognizable syndromes, reflect the topography of neurodegeneration rather than the identity of the aggregating disease protein. Indeed, each protein is associated with a handful of distinct clinical syndromes. Uncertainty surrounds which specific aspects of each proteinopathy (i.e., "disease") drive that protein to select its unique anatomy in an individual patient. It has become clear, however, that the ultimate spatial patterning of disease is linked to the healthy brain's connectional architecture or "connectome."

When discussing neurodegenerative conditions, it is critical to disambiguate terms that refer to the clinical syndrome from terms that describe the underlying neuropathological entity giving rise to that syndrome. Throughout this review, I use "syndrome" when describing a named constellation of symptoms and deficits. Examples include "behavioral variant frontotemporal dementia" (bvFTD), "Alzheimer's disease (AD)-type dementia" or "corticobasal syndrome." In contrast, I use "disease" to refer to a histopathological entity that might be

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found at autopsy in a patient showing a neurodegenerative syndrome during life. Examples of disease terms include frontotemporal lobar degeneration (FTLD) with TAR DNA-binding protein 43 (TDP-43) immunoreactive inclusions (FTLD-TDP) Type A, Alzheimer's disease, or corticobasal degeneration, a subtype of FTLD with tau immunoreactive inclusions (FTLD-tau). In short, syndromes reflect *where* the damaging pathological process is, whereas disease terms describe *what* the pathological process is. Table 1 details the clinical syndromes used to illustrate key principles throughout this review. Because the frontotemporal dementia (FTD), Alzheimer-type dementia, and amyotrophic lateral sclerosis (ALS) syndromes have been particularly well-studied from a human network perspective, these disorders receive more attention here than several other equally important and related disorders.

The need to separate clinical syndromic from neuropathologic terms stems from how few one-to-one correspondences exist between syndrome and disease. These imperfect clinicopathological correlations give rise to two related concepts, "clinicoanatomical convergence" and "phenotypic diversity," which receive extensive consideration in the sections that follow.

NETWORK DEGENERATION: HISTORICAL METHODS, OBSERVATIONS, AND LIMITATIONS

The stereotypical patterns of neurodegenerative disease onset and progression have long stimulated ideas about a link to neuronal networks (Pearson et al. 1985; Saper et al. 1987; Braak and Braak 1991; Weintraub and Mesulam 1996). The connectedness among degenerating regions was inferred from axonal tracer studies performed in laboratory mammals, chiefly rodents and primates, and engendered diverse mechanistic hypotheses ranging from spreading prions (Prusiner 1984) to transported toxins (Saper et al. 1987), disrupted growth factors (Salehi et al. 2006), and unknown pathogens (Braak et al. 2003b). Despite these seminal perspectives, for decades neurodegenerative disease anatomy was viewed through oversimplified frameworks, divided into focal versus diffuse or subcortical versus cortical. The notion that each disorder represents a network-based degeneration flows naturally, however, from careful, comprehensive postmortem neuropathological localization and staging studies (Steele et al. 1964; Brun and Gustafson 1978; Braak and Braak 1991). The great advantage of these approaches, which often used whole-brain or whole-hemisphere sectioning and staining, was and remains their capacity to resolve cellular details in patients with defined molecular pathological lesions. Early neuropathological hallmarks could therefore be identified in asymptomatic or prodromal individuals to render a detailed picture of onset and progression. The need to collect and process many brains, each requiring substantial resources, limited the use of these methods to a few laboratories. And, although the approach proved spectacularly successful for prevalent aging-related diseases like AD and Lewy body disease (LBD), it can rarely capture preclinical stages of FTLD, ALS, and other diseases too rare to be encountered by chance even in large autopsy series.

The dawn of human brain mapping in the late 1980s, made possible by brain-wide, voxelwise statistical methods, slowly gave rise to an era in which neurodegeneration researchers could determine disease topographies in vivo without narrow a priori hypotheses. This shift enabled validation of established patterns (such as that in AD) but was most impactful for less common disorders, such as FTD (Rosen et al. 2002), for which ideas about anatomical onset and progression had been difficult to derive from postmortem data. Network-sensitive imaging approaches emerged in the mid-1990s (Biswal et al. 1995; Fox and Raichle 2007) and provided a means for visualizing network organization and degeneration in living humans (Greicius et al. 2003, 2004; Seeley et al. 2009). Around that time, complementary in vitro and animal model studies had begun to explore mechanisms of network-based dysfunction and disease protein spread. A strong tide of empirical data now supports the notion that misfolded disease protein conformers undergo prion-like spread within and between neurons and across synapses

Table 1. Neuroanatomy of onset and progression in the major neurodegenerative syndromes

Syndrome	Prodromal symptom(s)	Presenting symptom(s)	Onset neuron(s)	Onset region(s)	Target network	Known or candidate downstream networks	Most likely neuropathological diagnosis	Spreading protein	Differential diagnosis
AD-type dementia	Depression, sleep disturbance, anxiety	Episodic memory loss	NE 5HT Layer II stellate pyramidal	LC DRN ERC	DMN	ECN Language DAN	AD	Tau Aβ*	LBD FTLD-TDP HS Mixed
lvPPA	Word-finding difficulty	Hesitant speech Word finding difficulties	Unknown	Dominant AG, TPJ	Posterior language	DMN	AD	Tau Aβ*	FTLD-TDP
PCA	Unknown	Visual changes Navigation	Meynert cell	CalcCtx Lat occipital	1° and 2° visual	DMN	AD	Tau Aβ*	LBD
bvFTD	Job loss "Midlife crisis"	Apathy Disinhibition Compulsivity	VEN Fork cell	ACC, FI	Salience	ECN SAN	FTLD-TDP FTLD-tau	TDP-43* Tau	FTLD-FUS AD
svPPA	Word-finding difficulty	Loss of word/object meaning	Unknown	Tpole	SAN	Salience	FTLD-TDP	TDP-43*	FTLD-tau
nfvPPA	Speech difficulty	Nonfluent aphasia	Unknown	IFGo	Anterior language	Posterior language	FTLD-tau	Tau	FTLD-TDP
CBS	Unknown	Loss of limb control	Unknown	Premotor cortex	Dorsal perirolandic	ECN Language	FTLD-tau	Tau	AD FTLD-TDP
PSP-S	Apathy, mental rigidity	Falls	Unknown	rMT	rMT network	Dorsal perirolandic	PSP	Tau	CBD
ALS	Fasiculations, atrophy	Weakness	UMN LMN	1° MC AH	Pyramidal motor	ECN Salience	ALS-TDP	TDP-43*	ALS-FUS ALS-SOD
CJD	Variable	Variable	Unknown	Variable	Variable	Variable	CJD	PrP^{Sc}	-

Asterisk acknowledges lingering uncertainty about whether the indicated protein spreads along axonal pathways.

1° MC, primary motor cortex; 5-HT, 5-hydroxytryptamine; ACC, anterior cingulate cortex; AD, Alzheimer's disease; AH, anterior horn; ALS, amyotrophic lateral sclerosis; AG, angular gyrus; bvFTD, behavioral variant frontotemporal dementia; CalcCtx; calcarine cortex; CBS, corticobasal syndrome; CJD, Creutzfeldt–Jacob Disease; DAN, dorsal attention network; DMN, default mode network; DRN, dorsal raphe nucleus; ECN, executive-control network; ERC, entorhinal cortex; FI, frontoinsula; FTLD, frontotemporal lobar degeneration; FUS, fused in sarcoma; IFGo, inferior frontal gyrus, opercular part; LBD, Lewy body disease; LC, locus ceruleus; LMN, lower motor neuron; NE, norepinephrine; PrP^{Sc}, prion protein scrapie; PSP, progressive supranuclear palsy; rMT, rostral midbrain tegmentum; SAN, semantic-appraisal network; SOD, superoxide dismutase; TDP-43, transactive response DNA-binding protein 43 kDa; Tpole, temporal pole; TPJ, temporoparietal junction; UMN, upper motor neuron; VEN, von Economo neuron.

(Frost and Diamond 2010; Goedert et al. 2010; Prusiner 2012). Most recently, structural, functional, and molecular neuroimaging studies have been combined to replicate the stereotypical spread of AD pathological hallmarks (Choo et al. 2007; Whitwell et al. 2007; Thal et al. 2014; Johnson et al. 2016). Emerging positron emission tomography (PET) ligands for pathological forms of the tau protein may enable similar characterizations for the non-AD tauopathies, such as FTLD-tau, at least during their symptomatic phases. Molecular probes for α-synuclein, TDP-43, and other disease proteins remain an important target for development.

HUMAN BRAIN NETWORK MAPPING: THE METHODS

Structural and functional connectivity analyses noninvasively map healthy large-scale networks in vivo (Greicius et al. 2003; Damoiseaux et al. 2006; Fox and Raichle 2007; Biswal et al. 2010) and can detect network connectivity changes in living patients (Greicius et al. 2004; Zhou et al. 2010). The following paragraphs provide a brief overview of the major network-sensitive structural and functional magnetic resonance–based neuroimaging methods.

Intrinsic Connectivity

With task-free functional magnetic resonance imaging (tf-fMRI), researchers can now identify functional intrinsic connectivity networks (ICNs) derived from temporally synchronous, spatially distributed, spontaneous low-frequency (<0.1 Hz) blood oxygen level–dependent (BOLD) signal fluctuations (Biswal et al. 1995; Raichle et al. 2001; Fox et al. 2005; Fox and Raichle 2007). These ICNs, which may represent functional connections spanning multiple synapses, represent a conserved and robust form of organized macroscopic brain activity. Compared to conventional task-based fMRI studies, tf-fMRI is free of performance confounds, making it easier to apply and interpret in cognitively impaired populations. To derive ICNs, seed-based analyses determine correlations among low-frequency BOLD fluctuations of a seed region with the rest of the brain (Biswal et al. 1995). Other approaches, such as independent component analysis and clustering methods, take advantage of multiple simultaneous brain interactions to identify brain networks (Beckmann et al. 2005; Yeo et al. 2011). Ongoing efforts seek to characterize temporal dynamics of ICNs and elucidate possible causal relationships (see reviews by Krajcovicova et al. 2014 and Dennis and Thompson 2014). Synchronization across neuronal assemblies can likewise be computed from task-free electro- or magneto-encephalography data.

Structural Covariance

Coordinated variations in brain structure across subjects have been used as measures of the association between regions to construct large-scale "structural covariance networks" (Mechelli et al. 2005; Lerch et al. 2006; He et al. 2008; Seeley et al. 2009). This approach, which may use gray matter volume or cortical thickness data, relies on the assumption that structural covariance reflects a shared trophic influence during development or ongoing co-trophism conferred by synaptic coupling across regions. Mean gray matter volume or thickness of a region of interest is used to conduct a whole-brain voxel-wise regression across subjects to identify those voxels (or regions or vertices) whose magnitude is correlated with the region of interest. Other analytic approaches, such as independent component analysis and clustering, can likewise be used to derive structural covariance networks.

Structural Connectivity

The term "structural connectivity" most strictly refers to the axonal connections between neurons or brain regions. Although axonal connectivity remains beyond the resolution of current neuroimaging techniques, the integrity of medium to large fiber tracts can be assessed in vivo using diffusion-weighted imaging methods, which map the diffusion of water molecules and rely on the principle that diffusion is restricted by tissue structure (Le Bihan et al. 1992), especially within highly ordered white

matter tracts. Region of interest analysis or data-driven voxel-based analysis allows estimation of group differences in fiber tract integrity or associations with cognitive functioning. Fiber tracking between specific region pairs can further be performed (Mori et al. 1999; Mori and Zhang 2006).

Connectomics

The term "connectome" refers to a comprehensive map of the brain's neural connections (Sporns et al. 2005), whether the connections are defined on structural (MRI/diffusion) or functional (fMRI, electroencephalogram [EEG], magnetoencephalography [MEG]) grounds. By modeling networks as graphs (brain regions as nodes and node-to-node connections as edges), graph theoretical analyses offer a flexible and quantitative approach for characterizing brain network topology. Several graph theoretical metrics quantify brain network "hubs" (i.e., regions with high degree centrality) (Sporns et al. 2007; van den Heuvel and Sporns 2011; Zuo et al. 2012; Crossley et al. 2013), whereas other metrics, such as clustering coefficient and path length, emphasize modularity or efficiency of communication. "Connectomics," then, refers to the science of brain connectivity.

NEURODEGENERATIVE DISEASE: UNIFYING ANATOMICAL PRINCIPLES

This section introduces the key concepts of neurodegenerative disease onset and progression. In my view, the most critical unanswered questions in neurodegenerative disease research regard these two issues. In addition, I discuss two interrelated neurodegenerative disease phenomena: clinicoanatomical convergence and phenotypic diversity. Any comprehensive model of disease onset and progression must account for these observations, which cut across this class of human illness.

Onset

Patients with each neurodegenerative syndrome emerge from an incipient preclinical stage during which symptoms remain absent or subtle and the lesion remains restricted to just one or few brain regions and only to the most susceptible cells and microcircuits within the affected regions. This focal onset manifests as cell-type-specific disease protein aggregation followed by quantifiable neuronal dropout (Hyman et al. 1984; Graveland et al. 1985; Seeley et al. 2006; Kim et al. 2012).

Progression

What anatomical principles govern the relentless spatiotemporal progression of each disease? Postmortem and in vivo neuroimaging studies suggest that the pattern of regional injury reflects a network-based landscape (Fig. 1), arguing against the notion that disease spreads across the cortical mantle via spatial contiguity (Steele et al. 1964; Brun and Gustafson 1978; Saper et al. 1987; Braak and Braak 1991; Greicius et al. 2004; Buckner et al. 2005; Seeley et al. 2009). But what factors govern how disease spreads from the onset node(s) to downstream regions within and beyond the target network? At least three onset-progression scenarios should be considered (Fig. 2).

1. Unifocal (or simultaneous oligofocal) onset with connectional spread. In this scenario, the later-affected regions are determined entirely by the axonal connections of the most vulnerable cells within the onset region(s).
2. Staggered multifocal onset without connectional spread. Here, anatomical progression reflects independent, temporally staggered eruptions of disease within multiple (not necessarily interconnected) regions. In this way, progression is connectivity-independent and generated by a graded hierarchy of regional and/or cellular vulnerabilities to some diffusely expressed pathogenic process.
3. Combined unifocal and staggered multifocal onset with connectional spread. In this model, which blends aspects of the previous two, disease progression reflects not only the connectivity of the initial onset regions but also the emergence of later but independent on-

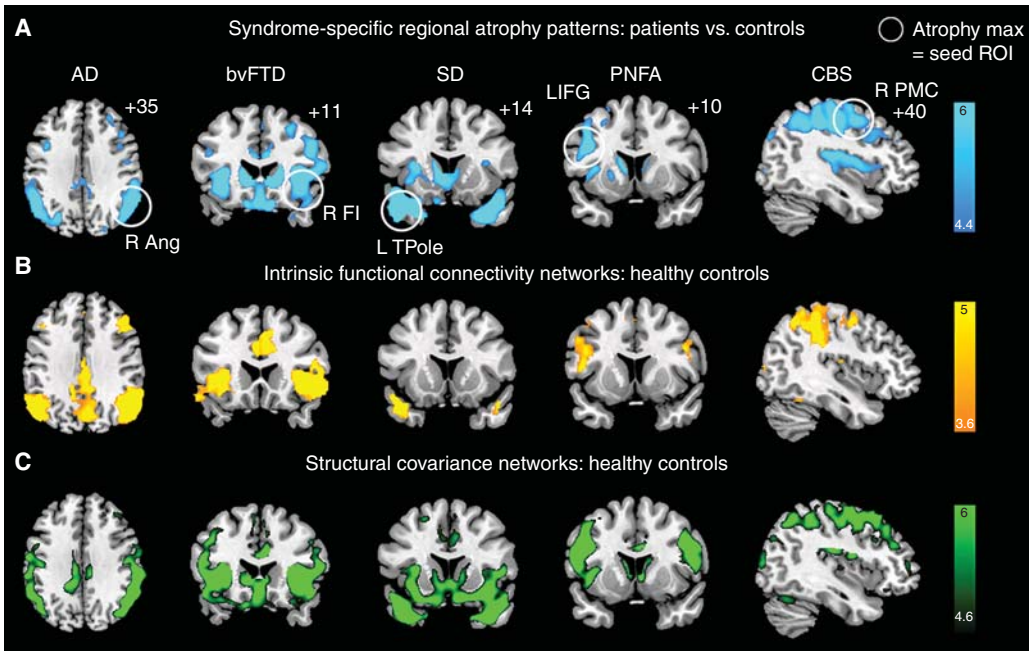

Figure 1. Neurodegenerative syndromes reflect degeneration within large-scale networks. (*A*) Five clinical neurodegeneration syndromes showed distinct atrophy patterns, with atrophy maxima highlighted with white circles. Regions circled in *A* were used as seed regions of interest (ROIs) for task-free functional magnetic resonance imaging (fMRI) analysis (*B*) and structural covariance mapping (*C*) in healthy controls. Both approaches showed that the connectivity of the healthy brain mirrored the five atrophy patterns. These data showed that each syndrome was anatomically linked to a specific large-scale network that could be detailed in the healthy brain with connectivity-based methods. (Reproduced, with permission, from Seeley 2016, © 2016 Oxford University Press; www.oup.com.)

set sites and the connections of affected neurons within those later-affected sites.

Clinicoanatomical Convergence

Clinicoanatomical convergence describes the observation that most clinical syndromes can be caused by at least a few and often several underlying pathological entities. For example, patients with bvFTD may be found to have any one of at least 15 different underlying pathological diagnoses, spanning three FTLD major molecular classes (FTLD with tau, TDP-43, or FUS immunoreactive inclusions) and AD. The key question is whether convergence occurs at the network, regional, or neuronal level (Fig. 3). In other words, distinct proteinopathies could converge at the network level by targeting disease-specific nodes within the same syndrome-associated network. In this scenario, neuroimaging studies might improve antemortem pathological predictions by detecting disease-specific atrophy signatures (within the syndromic network). Alternatively, convergence could occur at the regional or even neuronal level, in which case methods capturing brain structure or function would fail to discriminate between diseases, and alternative approaches, such as molecular imaging or fluid biomarkers linked to the disease proteins themselves, would be required.

Phenotypic Diversity

Phenotypic diversity refers to the observation that the same histopathological entity (i.e., disease) may be associated with several distinct clinical syndromes, reflecting distinct regional degeneration patterns (Fig. 4). For example,

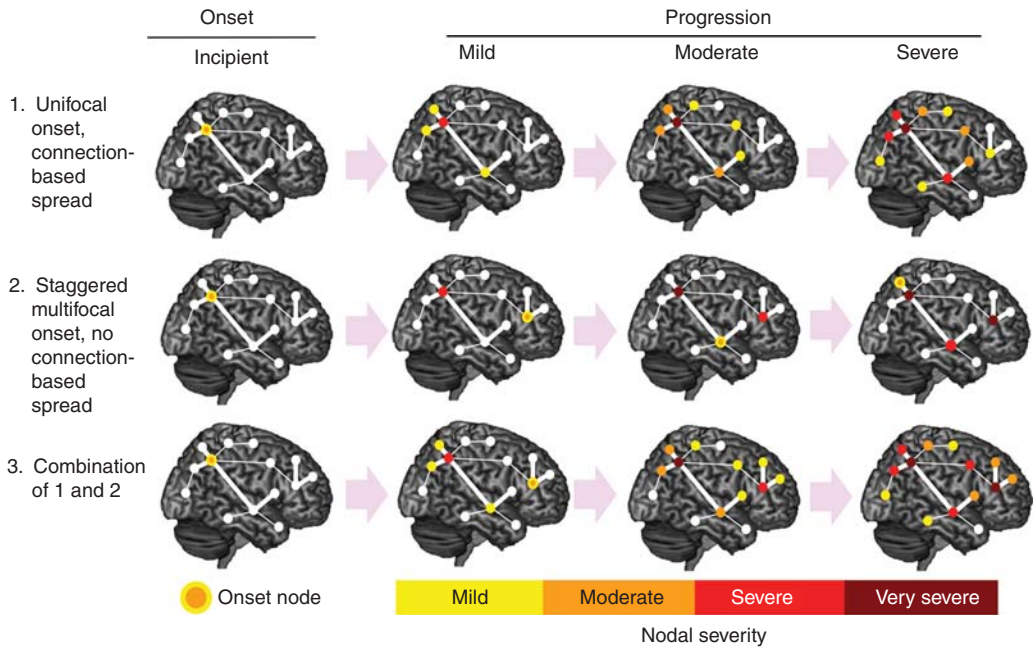

Figure 2. Neurodegenerative disease onset and progression. What is the relationship between disease onset and progression? After a first locus of onset, progression to other regions could involve (1) connectivity-based spread alone, (2) secondary sites of onset within or outside the target network, or (3) a combination of these models. (Reproduced, with permission, from Seeley 2016, © 2016 Oxford University Press; www.oup.com.)

Pick's disease, a subtype of FTLD-tau, may present with bvFTD, semantic variant primary progressive aphasia, nonfluent variant primary progressive aphasia, or corticobasal syndrome, based on the targeted regional epicenter and its network-based affiliations. This observation suggests either that (1) each disease protein maintains a certain nonrandom variability with regard to where it first aggregates in an individual brain or that (2) neuropathological taxonomy remains inadequately specified and that further characterization (i.e., "splitting") of the tau protein found in Pick's disease will, extending the example, reveal different forms of posttranslationally modified or misfolded tau in each of the syndromic presentations of Pick's disease. Such hypothetical subtypes of a given single disease protein are often conceptualized as conformer "strains" (Sanders et al. 2014). To explain phenotypic diversity entirely, the tau protein strain recognized pathologically as Pick's disease would have to be further divided into Pick-type "substrains," one for each of the syndromic presentations of Pick's disease.

Based on these unifying neurodegeneration principles, I will discuss disease onset regions and cell types in more detail. I will review neuroimaging data that inform competing models of disease progression. I will relate competing concepts of onset and spread to clinicoanatomical convergence and phenotypic diversity. Finally, I will consider the most important frontiers in selective vulnerability and network imaging.

MODELING ONSET: WHERE AND HOW DOES DISEASE BEGIN?

Evidence to Date

How does each neurodegenerative disease select its initial target or targets? This question remains an enduring mystery for every illness, and merely identifying the early targets has proven challenging enough. For AD and LBD,

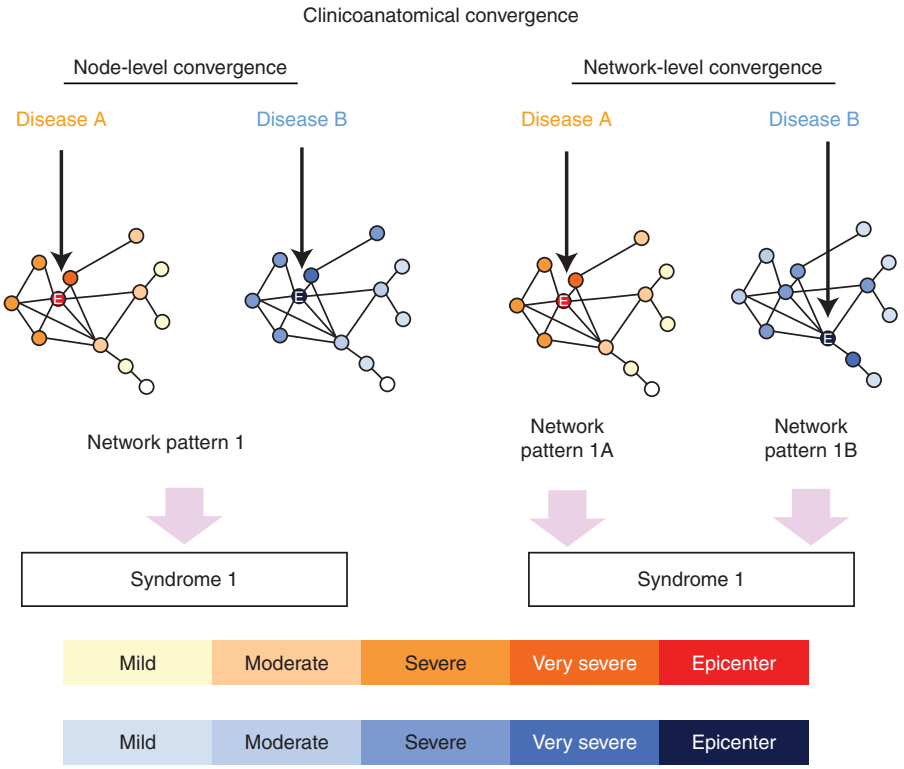

Figure 3. Clinicoanatomical convergence may occur at the neuronal, nodal, or network levels. Diseases that cause each syndrome may converge at multiple levels to create the syndrome. Convergence at the level of specific neuronal types (not shown) or even specific network nodes (*left*) would be expected to create nearly identical patterns of network impairment. Alternatively, convergence could occur at the level of the overall network (*right*), with each disease targeting different nodes but, nonetheless, manifesting as the same (or nearly the same) syndrome. Circles represent network nodes (brain regions), lines represent edges (connections between two nodes), and shorter edges indicate tighter connections between node pairs. Color shading indicates the severity of predicted regional impairment based on the onset nodes ("epicenters") indicated by arrows. (Reproduced, with permission, from Seeley 2016, © 2016 Oxford University Press; www.oup.com.)

early neuronal targets have been identified through cross-sectional postmortem studies that have included patients at all stages of the disease process, from asymptomatic to prodromal to full-blown symptomatic and even end-stage (Braak et al. 1993, 2004). Regional-level observations made with this approach have been well-supported by longitudinal imaging studies in living individuals. For example, studies following older individuals from health to mild memory impairment and later AD-type dementia show early tau deposition and atrophy in the entorhinal cortex (Killiany et al. 2002; Jack et al. 2004; Varon et al. 2011; Johnson et al. 2016), consistent with classical postmortem studies (Braak and Braak 1991; Braak et al. 1993). Johnson et al. (2016) found that tau deposition extends beyond the medial temporal lobe only in patients with cortical β-amyloid deposition. On the other hand, in vivo brain imaging lacks the regional subnuclear and neuronal subtype resolution required to provide a complete picture. This limitation is well-illustrated by AD and Parkinson's disease, in which the earliest brain neuronal protein aggregates are now understood to emerge in brainstem nuclei that are difficult to resolve with conventional MRI or PET: the locus coeruleus and dorsal ra-

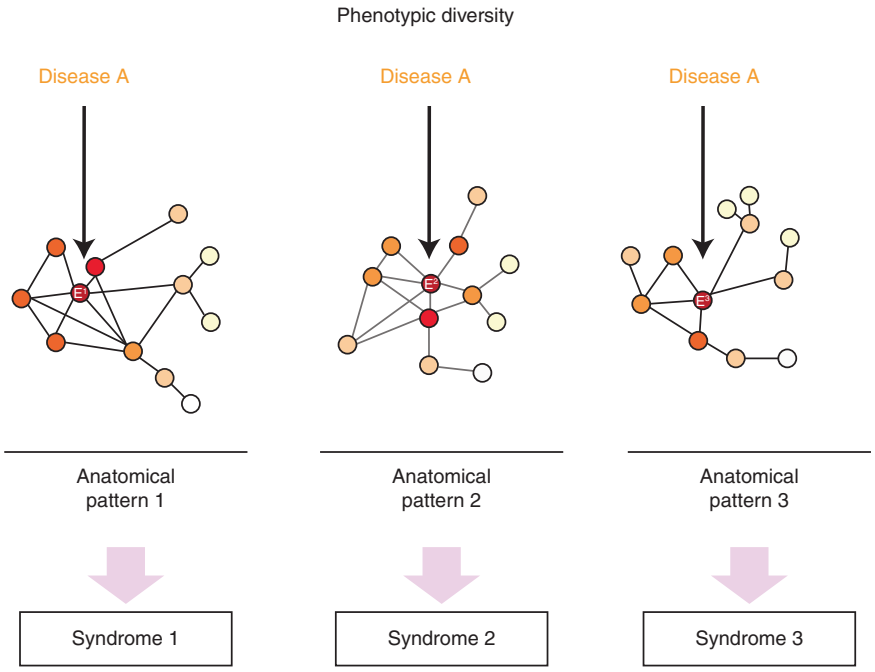

Figure 4. Phenotypic diversity suggests that most diseases can produce multiple clinical syndromes, reflecting a small portfolio of candidate onset regions ("epicenters," E). The heterogeneity of clinical manifestations for each disease is illustrated here at the network level, where onset within epicenters (E^1, E^2, or E^3) that anchor distinct networks gives rise to three different clinicoanatomical presentations. Network depictions follow Figure 3.

phe in AD (Bondareff et al. 1981; Grinberg et al. 2009; Braak and Del Tredici 2012) and the dorsal motor nucleus of the vagus nerve in LBD (Braak et al. 2003a). In LBD, the process may begin even more peripherally, in the olfactory mucosa and enteric nervous system. For less common diseases, like FTLD, determining early neuronal subtype selectivity has been even more difficult because of the diversity of FTD syndromes and the scarcity of postmortem materials from patients with asymptomatic or prodromal disease. The few laudable attempts to derive distinct stages using cross-sectional materials have not been able to include individuals with presymptomatic disease (Brettschneider et al. 2014; Irwin et al. 2016). Furthermore, because each FTLD pathological subtype produces diverse clinical phenotypes, it would be difficult to interpret presymptomatic FTLD materials even if they became available. One remarkable exception comes from a patient who died of brainstem lymphoma but was astutely noted to harbor premanifest Pick's disease (Miki et al. 2014), with Pick bodies and other Pick-type tau inclusions in an anterior cingulate-frontoinsular pattern that almost perfectly matches the early bvFTD regional vulnerability profile (Seeley et al. 2008).

How, then, can brain imaging studies in symptomatic patients inform our understanding of disease onset? Regions showing the greatest atrophy during symptomatic disease may or may not represent the sites of initial injury, but recent neuroimaging studies support an emerging model for generating hypotheses about where each syndrome begins before it spreads. Having established that each neurodegenerative syndrome is linked to a specific network (Fig. 3) (Seeley et al. 2009), my colleagues and I, led by Juan (Helen) Zhou, showed that each syndrome-associated brain network contains a vulnerable "epicenter" (or epicenters), whose

connectivity in health mirrors—and may template—the spatial patterning of each syndrome (Zhou et al. 2012). These epicenters bear close relationships to the early clinical and anatomical deficits that define each syndrome. For instance, in bvFTD the identified epicenters in the right frontoinsula and pregenual anterior cingulate cortex are known for their co-activation as part of a "salience network" for homeostatic behavioral guidance (Seeley et al. 2011) and harbor a unique class of large, bipolar projection neurons, called von Economo neurons, that may represent the initial target in bvFTD (Seeley et al. 2006; Kim et al. 2012). Identifying an epicenter, as defined above, does not prove that this epicenter represents the site of initial injury; nonetheless, there is a striking overlap between regions of peak atrophy and those that serve as epicenters (Zhou et al. 2012).

Despite the scarcity of postmortem materials representing presymptomatic FTLD, structural and functional imaging has begun to provide insights into presymptomatic inherited FTD. In the first large study of this kind, carriers of FTLD-causing microtubule-associated protein tau (*MAPT*) or progranulin (*GRN*) mutations showed fractional anisotropy reductions in the right uncinate fasciculus and decreased functional connectivity between key salience network hubs, the anterior mid-cingulate cortex and frontoinsula, compared with noncarriers (Dopper et al. 2013). More recently, using region of interest–based structural MRI, researchers have identified sites presumed to reflect incipient atrophy in each of the three major FTD-causing mutations (*MAPT*, *GRN*, and *C9ORF72*) (Rohrer et al. 2015). Converging with findings from patients with symptomatic bvFTD and with the bvFTD epicenters identified by Zhou and colleagues (Zhou et al. 2012), Rohrer et al. identified the insula as a region showing atrophy among the youngest mutation carriers when examining all three genetic subgroups together. Although the insula appeared to degenerate first in a *GRN* mutation carrier subset analysis, other regions showed even earlier deficits in *MAPT* (hippocampus) and *C9ORF72* (thalamus) carriers, as predicted by the atrophy seen in symptomatic mutation carriers (Whitwell et al. 2009a,b; Mahoney et al. 2012; Sha et al. 2012). These important studies, however, share several methodological limitations. In presymptomatic FTD gene carriers, we have no way to predict which of the several associated clinical syndromes will later emerge; in this way, group-level results likely represent a blend of preclinical syndromic patterns, as well as the known anatomical heterogeneity within each syndrome. Studies of preclinical inherited FTD may also generalize weakly to sporadic FTD, considering the diversity of genetic mechanisms and the known anatomical differences seen in patients with inherited versus sporadic FTD. Finally, it remains uncertain whether the observed gray matter volume deficits represent incipient degeneration in early adulthood or an abnormal developmental trajectory that has yet to be traced back to its origins.

Relationship to Clinicoanatomical Convergence and Phenotypic Diversity

Does clinicoanatomical convergence reflect onset within the same vulnerable neuron population or within different neuronal constituents of the same region or network? To address this question requires that we study all relevant levels, in a single syndrome, as caused by multiple diseases. For example, does bvFTD begin in the von Economo neurons whether the syndrome is caused by FTLD-tau, TDP-43, or FUS? Some studies have provided clues toward this cell-type-level convergence on the von Economo neurons (Seeley et al. 2006; Kim et al. 2012; Santillo et al. 2013; Santillo and Englund 2014), but the studies needed to fully resolve the issue have yet to be performed.

Principles of disease onset should also be viewed in light of phenotypic diversity. For example, although most patients with underlying AD present with early memory loss, a significant minority presents with a nonamnestic syndrome (Snowden et al. 2007). Patients with nonfamilial early-onset AD (EOAD, defined as onset $<$65 years in most studies) show a mix of cognitive deficits, often beginning with attentional or executive impairment (Frisoni et al. 2007; Koedam et al. 2010). Focal syndromes

such as posterior cortical atrophy (PCA), characterized by predominant visuospatial and visuoperceptual deficits (Crutch et al. 2012) and the logopenic variant of primary progressive aphasia (lvPPA), a progressive disorder of language (Gorno-Tempini et al. 2008), are also strongly linked to AD pathology. The factors driving this phenotypic diversity are not well understood but could reflect an internal hierarchy or "pecking order" of vulnerability that differs between individual patients based on their genetic backgrounds, life experiences, region-specific stressors (trauma, seizures, vascular malformations, etc.), or developmental anomalies (Rogalski et al. 2013).

Lingering Questions and Uncertainties

Many key questions remain within the general concept of disease onset. How many cell types and/or brain regions undergo independent (sometimes referred to as "cell autonomous") onsets? What is the hierarchy of neuron-type vulnerabilities for each disease? Does this order vary across individuals? Does onset occur within neurons, glia, or both? Can cells undergo a "reversible onset," such as protein aggregation and dysfunction, but then revert to a healthy state? Does protein misfolding and aggregation begin only within a select and finite group of cell types/brain regions for each protein, or, alternatively, does this homeostatically controlled process pervade the aging brain but remain in check in all but that protein's short list of onset cells/regions, which are somehow ill-equipped to manage the quality control process?

MODELING PROGRESSION: HOW DOES DISEASE MOVE BEYOND THE CELLS AND REGIONS WHERE IT BEGINS?

Evidence to Date

That each neurodegenerative syndrome reflects a large-scale network breakdown has now been established through data that converge across diseases, methods, and research groups. Early network-based imaging support for this principle came from studies of AD-type dementia, which features an anatomical profile strongly linked to the default mode network (Greicius et al. 2003, 2004; Buckner et al. 2008). Next, it was shown that AD and four distinct FTD syndromes are each associated with atrophy reflecting a healthy human intrinsic connectivity and structural covariance network (Fig. 1) (Seeley et al. 2009). But how does disease progress from the onset stage to render a network-based spatial pattern? At least four disease-general hypotheses have been put forth and can be summarized as (1) "nodal stress," in which regions subject to heavy network traffic (i.e., "hubs") undergo activity-related "wear and tear" that gives rise to or worsens disease (Buckner et al. 2009; Saxena and Caroni 2011); (2) "transneuronal spread," in which some toxic agent propagates along network connections, perhaps through "prion-like" templated conformational change (Prusiner 1984; Baker et al. 1994; Ridley et al. 2006; Walker et al. 2006; Frost et al. 2009; Frost and Diamond 2010; Lee et al. 2010; Jucker and Walker 2011); (3) "trophic failure," in which disruption of network connectivity undermines internodal trophic factor support, accelerating disease within nodes lacking collateral trophic sources (Appel 1981; Salehi et al. 2006); and (4) "shared vulnerability," in which networked regions feature a common gene or protein expression signature (Richiardi et al. 2015) that confers relatively disease-specific susceptibility, evenly distributed throughout the network. These nonmutually exclusive candidate network degeneration mechanisms make competing predictions about how healthy network architecture should influence disease-associated regional vulnerability. Although "network degeneration" is often understood to mean "network-based spread," only the "transneuronal spread" model proposes that progression represents physical spreading of a pathological process along axons connecting individual neurons.

To date, most efforts to investigate mechanisms of disease progression have relied on cross-sectional data. In the study by Zhou and coworkers (2012), we identified epicenters whose normal connectivity profiles most resembled the syndrome-associated atrophy patterns, as described above. We then used graph

theoretical analyses in healthy subjects to show that regions with higher total connectional flow and, more consistently, shorter functional paths to the epicenters showed greater syndrome-associated vulnerability. The relationship between regional network "traffic" and vulnerability suggests that activity-dependent mechanisms, such as oxidative stress, local extracellular milieu fluctuations, or glia-dependent phenomena might influence regional vulnerability; this influence might be a key factor in determining sites of initial or secondary onset. Because nodes with shorter connectional paths to an epicenter also showed greater vulnerability, it appears that "connectional closeness" is another key vulnerability factor, an observation most parsimoniously explained by physical, transsynaptic spreading of a toxic agent. Epicenter infiltration by disease may provide privileged but graded and connectivity-driven access across the network that determines where the disease will arrive next. Predictions made by the trophic factor insufficiency hypothesis were not consistent with our data. Although a shared gene or protein expression profile across networked regions may influence sites of onset, our findings were difficult to reconcile with predictions made by the "shared expression" model. We further examined connectivity-vulnerability relationships within the "off-target" networks to determine how nodal characteristics influence downstream vulnerability. Here, overwhelmingly, the evidence supported the transneuronal spread model. In summary, the findings best fit a model in which initial vulnerability may in part reflect a node's centrality (i.e., "hubness") within the target network, whereas downstream vulnerability within and beyond the target network more closely relates to a node's connectional proximity to the most vulnerable epicenters.

In AD, innovative studies have begun to link regional connectivity profiles to hallmark AD molecular lesions, which can now be localized in vivo with molecular PET imaging, and disease progression. In a study describing an "epidemic spreading model," the investigators considered axonal propagation of amyloid protein along the healthy structural connectome and regional clearance mechanisms. The model was able to explain roughly 50% of the variance in measured amyloid deposition on amyloid PET (Iturria-Medina et al. 2014) based on the connectional model, supporting the general hypothesis that regional amyloid deposition in part reflects the connectional distance from specific outbreak regions, which may lie in the anterior paramedian and posterior cingulate cortices. In AD, clearly, progression models need to account for two stages of the illness, one in which amyloid-β deposition is a key factor and another in which intraneuronal tau spreading takes over and drives the clinical and anatomical deficit pattern. In a recent longitudinal study of prodromal AD and AD-type dementia, the healthy brain's structural connectome was used to predict the progression of regional atrophy by modeling progression as simple diffusion along fiber tracts (Raj et al. 2015). This model makes no assumptions about where the diffusive process begins, a feature that may allow the model to accommodate the known heterogeneity in onset sites across patients.

Relationship to Clinicoanatomical Convergence and Phenotypic Diversity

How do emerging principles of disease progression relate to clinicoanatomical convergence? If progression is driven by connectional spread, then brain-wide anatomical convergence could merely reflect a shared population of onset neurons. Alternatively, distinct onset sites within the same network could, via connectional spread, produce convergent involvement of the overall network. In other words, there may be alternative anatomical pathways to the same syndrome. A particularly clear example of this notion comes from bvFTD. In the subset of patients who carry the *C9ORF72* hexanucleotide repeat expansion, salience network dysfunction resembles that seen in sporadic bvFTD, but the loss of network integrity is linked to a strategic lesion of the medial pulvinar thalamus (Lee et al. 2014). This mechanism of network breakdown differs from that seen in sporadic bvFTD, where the salience network is disrupted by early involvement of anterior cingulate and frontoinsular cortices. Thus, in bvFTD, the clinical def-

icits may reflect disruption of the same network by damage to distinct onset nodes.

The phenotypic diversity produced by AD raises the question of whether each clinical AD variant can be linked to a distinct large-scale network or onset site. A recent study tested this hypothesis by assessing intrinsic functional connectivity in healthy subjects, seeding regions commonly or specifically atrophied in early-onset AD, lvPPA, or posterior cortical atrophy (Lehmann et al. 2013). The investigators found that the connectivity maps derived from commonly atrophied regions of interest resembled the default mode network, which was affected in all AD variants, whereas seeding regions specifically atrophied in each AD variant revealed distinct, syndrome-specific connectivity patterns in the healthy brain. These findings indicate that the syndrome-specific neurodegenerative patterns in AD variants are driven by the involvement of specific networks outside the default mode network. One might predict that spread into these distinct networks reflects differences in the precise localization of onset in the three variants; where exactly (in which regions and neuronal subtypes) these syndromes begin remains uncertain, but meticulous neuroanatomical studies suggest that PCA may begin with neurofibrillary tangle formation and neuronal loss within large, long-range projection neurons in the primary visual cortex, such as the layer 5 Meynert cells (Hof et al. 1997).

Lingering Questions and Uncertainties

Many questions about the mechanisms of disease progression remain unanswered, and many of those questions are daunting. Considering the three hypothetical progression scenarios (Fig. 2), what is the balance between connection-based spread versus secondary sites of onset? Does spread within the local microcircuitry occur via contiguity (such as release of disease protein by dying cells and uptake by others), or is it governed by axo-dendritic (or dendro-dendritic) synapses? What better predicts disease progression: a patient's current, "personalized" (i.e., diseased) connectome, that patient's premorbid connectome, or a normative connectome from young or older subjects? How do genetic risk factors interact with the connectome to influence disease progression? Resolving these questions may help to facilitate development of individualized treatment and prevention trials.

FUTURE DIRECTIONS

To aid in the search for treatments, connectivity-based neuroimaging methods will need to detect early disease in individuals or track progression over time. For most sporadic diseases, presymptomatic detection remains a distant reality because either the right tools are lacking or the disease is too infrequent to facilitate large-scale population screening without a sensitive and affordable test. Efforts to monitor disease with connectivity metrics have, so far, been limited, with most evidence coming from cross-sectional correlations with disease severity (Zhang et al. 2010; Zhou et al. 2010). One longitudinal study showed reduced intrinsic connectivity in the posterior default mode network and increased connectivity in anterior and ventral default mode subnetworks in AD compared to healthy controls at baseline (Damoiseaux et al. 2012). At follow-up, patients showed worsening connectivity across all default mode subsystems, consistent with a network-based degeneration model in which disease first spreads from its "epicenters" to interconnected nodes within the target network (Zhou et al. 2012). An alternative model based on diffusion within the white matter architecture (i.e., structural connectome) showed that the model could predict progression in subjects with mild cognitive impairment and AD-type dementia (Raj et al. 2015). Systematic collection and analysis of multicenter multimodal imaging and biomarker data, including functional and structural connectivity metrics, will be required to assess the value of imaging biomarkers for diagnosis, prognosis, and disease monitoring.

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