NEURODEGENERATION

Connectomics of neurodegeneration

Misfolded protein aggregates are a classical hallmark of many neurodegenerative diseases. By combining a mouse model of misfolded protein injection and a brain network model of misfolded protein diffusion, a study now finds a strong link between the stereotypical spreading patterns of neurodegeneration, protein expression and anatomical connectivity.

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Why does neurodegeneration progress so slowly but, at the same time, generate such remarkably consistent and predictable patterns? This question has kept scientists busy for over a century, and its answer could hold the key to treating neurodegenerative disease. Many neurodegenerative disorders, including Alzheimer's disease, Parkinsons's disease and amyotrophic lateral sclerosis, are associated with the accumulation of misfolded proteins in the brain[1]. While their clinical symptoms may vary, at the molecular level, these disorders share the common biophysical features of pathogenic protein nucleation, templating, aggregation and spread[2]. A growing body of evidence suggests that the connectome, the wiring diagram of the brain, could play a major role in spreading misfolded proteins across the brain and explain the stereotypical patterns of neurodegeneration[3]. However, there is currently no technology to interrogate connectome-based spreading in the living human brain in vivo.

In this issue of *Nature Neuroscience*, Henderson et al.[4] combined quantitative pathology mapping of mouse brains—injected with misfolded α-synuclein (α-syn)—with network diffusion modeling to understand the spatiotemporal progression of pathological α-syn in Parkinson's disease. They found that the pattern of misfolded α-syn is correlated with two intrinsic features of the brain: anatomical connectivity and α-syn expression (Fig. 1). These results are an important step toward quantitative, predictive brain network modeling in Parkinson's disease.

Parkinson's disease is a progressive neurodegenerative disorder associated with a gradual decline of motor function that affects more than six million people worldwide. Its clinical manifestations—shaking, rigidity and slowness of movement—are a reflection of the death of neurons in the substantia nigra, a basal ganglia structure in the ventral midbrain[5]. This cell death is associated with the build-up of Lewy bodies, abnormal aggregates of the presynaptic protein α-syn (ref. [6]). From histopathological observations of hundreds of Parkinson's brains, we know that Lewy body pathology is not restricted to the substantia nigra but spreads across the brain in highly stereotypical patterns: pathological α-syn accumulates first in the dorsal motor nucleus and the anterior olfactory nucleus from where the pathology spreads to the brainstem and ultimately to the entire neocortex[7]. Understanding how misfolded α-syn proteins multiply, aggregate and spread could point toward new strategies to slow down or stop disease progression[8].

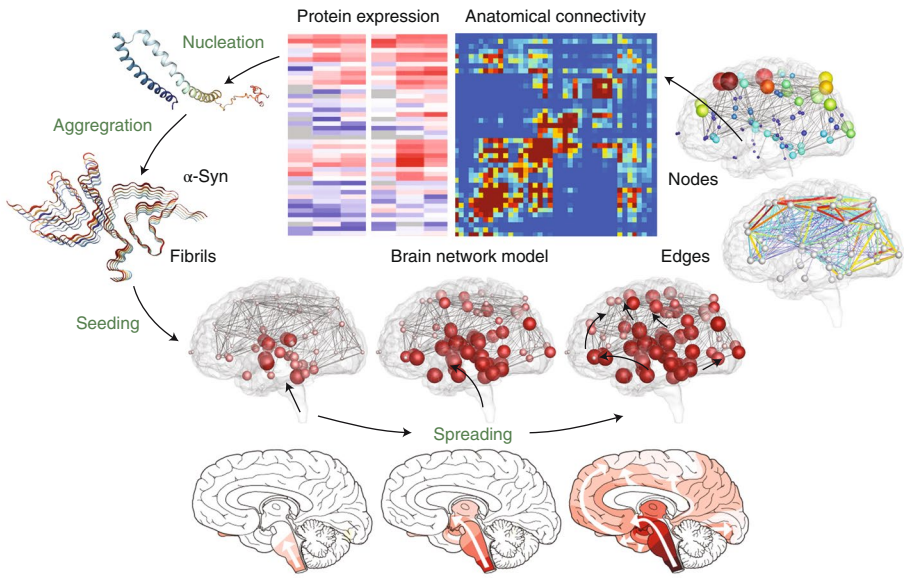

Fig. 1 | Network modeling of neurodegeneration. Neurodegenerative diseases are characterized by the aggregation of misfolded protein in the brain. At the molecular level (left), protein misfolding is associated with nucleation, templating and aggregation into progressively larger aggregates. At the whole-brain level (right), misfolded proteins spread across the brain in consistent and predictable patterns that follow the brain's connectome. Brain network models can integrate protein expression and anatomical connectivity to predict the stereotypical spreading pattern of misfolded α-syn in Parkinson's disease (bottom).

To experimentally quantify the spatiotemporal pattern of α-syn pathology, Henderson et al.[4] injected three-month-old mice with α-syn preformed fibrils, waited one, three and six months after injection, and then quantified α-syn pathology using a survey approach. At an unprecedented spatial resolution, they characterized the degree of pathology in 172 regions across five coronal slices and created concentration maps to illustrate the spreading pattern. Each brain region displayed a distinct and dynamic spreading profile with its own characteristic timeline of initiation and progression. Strikingly, regions with a direct anatomical connection to the injection site displayed a higher degree of pathology than remotely connected regions.

To computationally quantify the correlation between anatomic connectivity and pathological spreading, Henderson et al.[4] created a network diffusion model based on connectivity maps of the Allen Brain Institute mouse brain. This model represents the individual brain regions through 116 nodes and their connections through connectivity-weighted directed edges. In the initial model, pathological α-syn was hypothesized to travel retrogradely within the network, proportional to the density of axonal connections. Notably, with only one mechanism, anatomical connectivity, and one free parameter, timing of spread, this model already explained much of the experimentally observed pathological α-syn spread. To explain the remaining difference between experiment and simulation, the authors consulted the local α-syn expression levels. In a clever improvement of the model, they weighted diffusion by α-syn expression and created the first brain network model that directly correlates spreading of misfolded protein to two intrinsic features of the brain, anatomical connectivity and protein expression.

The most innovative aspect of this study is that it establishes, calibrates and validates a new technology, protein-expression-weighted brain network modeling, to understand, explain and predict pathological protein spreading in neurodegenerative disease (Fig. 1). Properly calibrated and validated, such models are powerful tools to quickly elaborate what-if scenarios and answer fundamental questions of pathological spread[9]: What are the underlying mechanisms of protein pathogenesis? Is spreading driven by extracellular diffusion or intracellular transport? Do misfolded proteins propagate retrogradely or anterogradely? How do protein expression levels modulate pathogenesis? Brain network modeling encodes the answers to these questions in the adjacency matrix, a matrix with 116 rows and columns, one for each brain region. Its diagonal terms tell us how well a region is connected, and its off-diagonal terms characterize its connectivity to all other regions[10]. We can virtually probe potential spreading mechanisms—quickly and efficiently—by weighting the entries of this matrix, by distance, by connectivity or both[11], by matrix transposition, or by weighting by individual protein expression levels[4]. Or we can identify vulnerable brain regions by virtually probing different seeding locations to identify central spreading hubs[12]. In essence, brain network models can rapidly test different hypotheses of spreading patterns, timing, directionality and vulnerability.

A wave of recent research has begun to validate network diffusion models using patterns of tissue atrophy rather than protein pathology since atrophy patterns are readily available from magnetic resonance imaging[13]. Yet what is truly new and notable about the study by Henderson et al.[4] —and unique to studying pathogenic protein spreading in mice—is the direct assessment of the pathogenic protein itself, the availability of directional connectivity, and the precise control of the injection site and timing. However, in view of the fast developments in neuroimaging and the rapid growth of public databases like the Human Connectome Project or the Alzheimer's Disease Neuroimaging Initiative, it seems reasonable to expect that we will soon have access to longitudinal human disease data to validate network diffusion models for neurodegeneration in humans.

The concept of linear network diffusion is compelling and powerful, but, at the same time, oversimplifies a disease process as complex as that of Parkinson's disease. Indeed, Henderson et al.[4] acknowledge this limitation, and improve the fit of their model by weighting diffusivity by protein expression levels. However, selectively increasing or decreasing network diffusion is a rather ad hoc and phenomenological approach. Instead, we could combine global modeling of network diffusion[13] with local modeling of aggregation kinetics[14]. In fact, this would result in a mechanistic multiscale model in which the concentrations and aggregate sizes of misfolded proteins emerge naturally, dynamically and independently at each node and propagate across the network through its connectivity-weighted edges[15].

What is most compelling about Henderson et al.'s network analysis of pathological α-syn spread in mice is that the underlying paradigm naturally generalizes to other pathological proteins and to humans. For example, a recent study used a similar network model to simulate amyloid-β pathology and found a good agreement with the amyloid-β patterns in positron emission tomography scans from hundreds of brains at different stages of Alzheimer's disease[12]. Undoubtedly, network modeling of neurodegeneration is quick and easy: simulating the spatiotemporal evolution of aggregate size distributions, biomarker curves and infection times across the human brain throughout a period of 30 years takes less than ten seconds on a standard laptop computer. This 30-year interval between the first evidence of protein aggregation, neuronal death, tissue atrophy and clinical symptoms presents a window of opportunity for therapeutic intervention. Computational simulations can provide mechanistic insight into the precise interplay, sequence and timeline of these neurodegenerative events[9].

At present, there is no cure for neurodegenerative disease. Current treatment strategies focus primarily on managing symptoms: active immunization or injection of monoclonal antibodies that target α-syn can decrease pathogenic α-syn spread, increase neuronal protection and slow disease progression in mice, and the first immunotherapies that target α-syn have passed stage I clinical trials in humans[8]. At a practical level, testable, quantitative, predictive network models of protein spreading can guide these new therapeutic approaches, for example, by promoting protein clearance and blocking protein aggregation at the network nodes or by modulating intercellular spreading and synaptic transport along the network edges. Fueled by the growing availability of public databases for healthy and diseased human brains, new in vivo imaging techniques, and new analysis tools inspired by machine learning, there is hope that pre-symptomatic therapies to slow down neurodegeneration could become a reality in the near future. Combining longitudinal experimental and computational analyses of pathological protein spread is an important first step in this direction. ❐

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Competing interests

The author declares no competing interests.