Deciphering neurodegeneration

A paradigm shift from focality to connectivity

Peter Bede, MD, PhD

Correspondence to Dr. Bede: bedep@tcd.ie

Neurology® 2017;89:1758–1759

"Wet or dry" is the fundamental dichotomy of biomarker research, referring to biofluid vs imaging-based approaches. Biomarker development in neurodegeneration has gained unprecedented momentum in recent years. Despite the substantial diagnostic advantages of molecular PET and biofluid markers, accurate prognostic indicators and sensitive monitoring markers are urgently required both for clinical trial designs and individualized patient care.

In this issue of *Neurology*®, Filippi et al.[1] present an MRI-based neuroimaging study that examines disease-specific connectivity alterations in early-onset Alzheimer disease and behavioral variant frontotemporal dementia. Patients with suspected neurodegenerative syndromes typically undergo MRI to rule out alternative pathologies that could mimic neurodegenerative processes. The obvious question is whether these data could be utilized for other purposes, such as a monitoring marker in a clinical trial or learning about network integrity. This article demonstrates that the answer is yes. The originality of the study stems from its reliance on quantitative network–based analyses of magnetic resonance (MR) data at a time when PET ligand development and CSF biomarker studies dominate the field of diagnosis. Moreover, the practical advantages of MR-based biomarkers include the widespread availability of MRI scanners, noninvasive data acquisition, and established strategies for cross-platform data harmonization. The authors used 3T-derived MRI connectivity data, which has the benefit of being a readily available technology.

Filippi et al. explore 2 main themes, both of which have pragmatic implications to clinical neurology; one is the long-awaited transition from qualitative image interpretation to quantitative imaging and the other is a shift from evaluating focal pathology to the assessment of network integrity.

Quantitative imaging benefits from the wealth of spatially coded data that are acquired during a routine MRI scan. In a clinical setting, the image is all too often only visually inspected and qualitatively interpreted. This is in sharp contrast with quantitative research MR protocols, where disease-, phenotype-, and genotype- specific patterns of degeneration are reliably captured. The role of quantitative imaging is not merely descriptive; it also provides pathophysiologic insights into neurodegenerative processes. Longitudinal studies in particular have the potential to decipher spatial patterns of pathologic spread, elucidate presymptomatic changes, and verify emerging hypotheses of prion-like molecular mechanisms.[2] Beyond contrasts with healthy controls, Filippi et al. highlight the value of quantitative imaging in their comparative study of 2 neurodegenerative conditions.

More important, Filippi et al. signal a shift from evaluating focal pathology to the assessment of network integrity. This is an important trend in the field of quantitative imaging, which offers better clinic-radiologic correlations and is particularly useful in dementia syndromes, where specific neuropsychological deficits are driven by selective network failure. Traditionally, separate whole-brain analyses are performed for gray and white matter metrics to identify disease-associated anatomic foci. However, direct correlations between focal MRI metrics and neuropsychological measures may be contentious: cognitive and behavioral functions are mediated by multisynaptic, frontostriatal, and cortico-thalamic networks that have multiple cortical components and project through specific white matter tracts.[3] The notion of selective anatomic vulnerability[4] is increasingly replaced by syndrome-specific network vulnerability.[5] As the concepts of network-wise degeneration,[6] circuit-specific vulnerability,[7] and disease progression along structural connectivity patterns[8] are increasingly recognized, novel imaging tools are required to provide validated network-integrity metrics.

Filippi et al. demonstrate the value of a network-based approach in their comparative study of Alzheimer disease and frontotemporal dementia. Our conventional, focal MRI indices, such as cortical thickness, basal ganglia volumes, white matter fractional anisotropy, and radial diffusivity, are now complemented by an array of network measures, such as nodal strength, local efficiency, clustering coefficient, and internodal path length. It remains to be seen how sensitive these indices are in diagnostic, monitoring,

See page 1764

From the Quantitative Neuroimaging Group, Academic Unit of Neurology, Trinity College Dublin, Ireland.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the author, if any, are provided at the end of the editorial.

and prognostic applications, but they enrich our armamentarium of imaging tools.

Another important aspect of this study is the comparison of the connectivity patterns of 2 clinically diagnosed neurodegenerative conditions. Descriptive imaging studies often characterize changes in a single patient group in comparison to healthy controls. From a diagnostic perspective, however, the question is seldom whether an individual is healthy or not, but rather whether the MRI data are more consistent with one neurodegenerative condition than another. Once discriminatory connectivity signatures are established and associated with a specific pathology, these may later be utilized in automated machine-learning algorithms to provide diagnostic probabilities. In addition to potential diagnostic applications,[9] connectivity metrics have already been proposed as accurate prognostic indicators.[10]

One of the most interesting aspects of connectivity-based studies is the interpretation of hyperconnectivity. Decreased functional connectivity, i.e., hypoconnectivity, may be regarded as a natural corollary of neurodegeneration. Increased connectivity, however, is also often observed in neurodegeneration, and may be interpreted as a compensatory mechanism, failure of inhibitory circuits, or other possible explanations. Filippi et al.[1] elegantly illustrate and discuss the coexistence of network-wise hypoconnectivity and hyperconnectivity. Similarly to structural studies,[4] it is conceivable that unaffected, resilient networks and networks exhibiting hyperconnectivity are just as specific to a given condition as disintegrating, hypoconnected networks.

The study by Filippi et al. illustrates the rich potential contribution of quantitative network imaging in neurodegenerative diseases. Connectivity-based instruments are likely to supersede their current academic role to be developed into viable clinical applications. Connectomics therefore remains an exciting interface of clinical neurology, neuropathology, and radiology, a veritable treasure chest of neuroimaging tools capable of characterizing dynamic pathologic changes in vivo.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

Peter Bede is supported by the Health Research Board (HRB–Ireland; HRB EIA-2017-019), the Irish Institute of Clinical Neuroscience (IICN)–Novartis Ireland Research Grant, the Iris O'Brien Foundation, the Perrigo Clinician-Scientist Research Fellowship, and the Research Motor Neuron (RMN–Ireland) Foundation. The author's sponsors had no role in writing of this report or influence on the opinions expressed herein. Go to Neurology.org for full disclosures.

REFERENCES

1. Filippi M, Basaia S, Canu E, et al. Brain network connectivity differs in early-onset neurodegenerative dementia. Neurology 2017;89:1764–1772.
2. Jucker M, Walker LC. Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. Nature 2013;501:45–51.
3. O'Callaghan C, Bertoux M, Hornberger M. Beyond and below the cortex: the contribution of striatal dysfunction to cognition and behaviour in neurodegeneration. J Neurol Neurosurg Psychiatry 2014;85:371–378.
4. Bede P, Iyer PM, Schuster C, et al. The selective anatomical vulnerability of ALS: "disease-defining" and "disease-defying" brain regions. Amyotroph Lateral Scler Frontotemporal Degener 2016;17:561–570.
5. Guo CC, Tan R, Hodges JR, Hu X, Sami S, Hornberger M. Network-selective vulnerability of the human cerebellum to Alzheimer's disease and frontotemporal dementia. Brain 2016;139:1527–1538.
6. Ahmed RM, Devenney EM, Irish M, et al. Neuronal network disintegration: common pathways linking neurodegenerative diseases. J Neurol Neurosurg Psychiatry 2016;87:1234–1241.
7. Warren JD, Rohrer JD, Schott JM, Fox NC, Hardy J, Rossor MN. Molecular nexopathies: a new paradigm of neurodegenerative disease. Trends Neurosci 2013;36:561–569.
8. Verstraete E, Veldink JH, van den Berg LH, van den Heuvel MP. Structural brain network imaging shows expanding disconnection of the motor system in amyotrophic lateral sclerosis. Hum Brain Mapp 2014;35:1351–1361.
9. Welsh RC, Jelsone-Swain LM, Foerster BR. The utility of independent component analysis and machine learning in the identification of the amyotrophic lateral sclerosis diseased brain. Front Hum Neurosci 2013;7:251.
10. van der Burgh HK, Schmidt R, Westeneng HJ, de Reus MA, van den Berg LH, van den Heuvel MP. Deep learning predictions of survival based on MRI in amyotrophic lateral sclerosis. NeuroImage Clin 2017;13:361–369.