Disintegrating Brain Networks: from Syndromes to Molecular Neuropathies

Jason D. Warren,1,* Jonathan D. Rohrer,1 and John Hardy2

1Dementia Research Centre, Department of Neurodegenerative Disease
2Reta Lila Weston Laboratories and Departments of Molecular Neuroscience
University College London Institute of Neurology, London WC1N 3BG, UK
*Correspondence: jason.warren@ucl.ac.uk
DOI 10.1016/j.neuron.2012.03.006
Open access under CC BY license.

In this issue of Neuron, Raj et al. (2012) and Zhou et al. (2012) use graph theory to suggest that neurodegenerative diseases spread diffusively via intrinsic brain networks. These studies provide a powerful model for understanding and predicting disease-specific profiles of neurodegeneration.

Neurodegenerative brain diseases are collectively characterized by two core features: abnormal protein deposition and distinctive profiles of damage across the brain and over time (Frisoni et al., 2010; Rohrer et al., 2011). If we understood in detail how proteinopathies translate to clinical phenotypes, we might anticipate and perhaps prevent the devastating impact of these diseases. While we have recognized for some time that spatiotemporal brain atrophy profiles track neuropathological patterns of disease evolution (Frisoni et al., 2010), we have lacked a principled framework for understanding and predicting the profiles observed. The brain is composed of neural networks and graph theory.

to fully understand how neural tissue changes in the minutes and hours after learning. Thus, molecular and optical imaging are perhaps most suited to understand how these compartments change in the living organism.

The present work, along with previous studies (Blumenfeld-Katzir et al., 2011; Lerch et al., 2011) combining imaging and histology, provides valuable insights into the types of structural changes that can be detected on different timescales with noninvasive MRI. For instance, 5 days of training in the water maze task increased the volume of the hippocampus, as measured with MRI, and produced a correlated increase in GAP-43, a marker for neuronal process remodeling (Lerch et al., 2011). In another study using 5 days of training with the same task, changes in diffusion MRI parameters were related to increases in GFAP, synaptophysin, and myelin basic protein (MBP) (Blumenfeld-Katzir et al., 2011). The time frame of these studies allows for slower remodeling mechanisms like dendritic sprouting or gliogenesis to occur (Figure 1). Such mechanisms could contribute to the structural brain changes detected using MRI in humans with long-term learning (Draganski et al., 2004; Scholz et al., 2009).

Sagi and colleagues’ results provide us with an important reminder that the brain is an extremely dynamic structure. This study used a focused period of video game playing, but presumably many of the learning experiences we undergo throughout our lives produce similar effects in task-relevant regions of our brains. The findings therefore have more general implications for human neuroimaging. Many studies that employ the standard imaging methods used here assume that human brain structure is relatively static, at least on short timescales. However, we must remember that we are merely looking at snapshots of an organ that is in a constant state of flux, and these new findings demonstrate that even the relatively crude technique of MRI is sensitive to this rapid structural change.

REFERENCES

Blumenfeld-Katzir, T., Pasternak, O., Dagan, M., and Assaf, Y. (2011). PLoS ONE 6, e20678.
Chklovskii, D.B., Schikorski, T., and Stevens, C.F. (2002). Neuron 34, 341–347.
Draganski, B., Gaser, C., Busch, V., Schlaug, G., Bogdahn, U., and May, A. (2004). Nature 427, 311–312.
Fu, M., and Zuo, Y. (2011). Trends Neurosci. 34, 177–187.
Lerch, J.P., Yiu, A.P., Martinez-Canabal, A., Pekar, T., Bohbot, V.D., Frankland, P.W., Henkelman, R.M., Josselyn, S.A., and Sled, J.G. (2011). Neuroimage 54, 2088–2095.
MacVicar, B.A., Feighan, D., Brown, A., and Ransohoff, B. (2002). Glia 37, 114–123.
Maguire, E.A., Gadian, D.G., Johnsrude, I.S., Good, C.D., Ashburner, J., Frackowiak, R.S., and Frith, C.D. (2000). Proc. Natl. Acad. Sci. USA 97, 4398–4403.
Sagi, Y., Tavor, I., Hofstetter, S., Tzur-Moryosef, S., Blumenfeld-Katzir, T., and Assaf, Y. (2012). Neuron 73, this issue, 1195–1203.
Scholz, J., Klein, M.C., Behrens, T.E., and Johansen-Berg, H. (2009). Nat. Neurosci. 12, 1370–1371.
Skucas, V.A., Mathews, I.B., Yang, J., Cheng, Q., Treister, A., Duffy, A.M., Verkman, A.S., Hempstead, B.L., Wood, M.A., Binder, D.K., and Scharfman, H.E. (2011). J. Neurosci. 31, 6392–6397.
Sykova, E., and Nicholson, C. (2008). Physiol. Rev. 88, 1277–1340.
Zhao, C., Deng, W., and Gage, F.H. (2008). Cell 132, 645–660.
provides a methodology for representing and analyzing those networks (Bullmore and Sporns, 2009). Work in animal models has demonstrated a correspondence between mathematically derived network characteristics and the hierarchical and distributed architectures of neuroanatomy (Modha and Singh, 2010). Network-level analysis is an ideal approach to understanding neurodegenerative diseases, due both to the fundamentally coherent and distributed nature of the underlying pathological processes and the failure of conventional approaches to adequately explain the distinctive phenomenology of these diseases. However, the potential clinical value of network-based approaches remains largely unrealized.

Two papers in this issue of Neuron (Raj et al., 2012; Zhou et al., 2012) take us further toward this goal, by applying the methods of graph theory to quantify and predict network disintegration in a range of neurodegenerative diseases. These papers capitalize on two key recent insights: the expression of neurodegeneration within specific, distributed, intrinsic brain networks (Zhou et al., 2010) and the propensity of culprit proteins to “template” further protein aggregation and spread of disease along neural pathways (Hardy, 2005; de Calignon et al., 2012). Raj et al. (2012) model network diffusion based on tractography data in the healthy brain and derive robust spatial eigenmodes that correspond closely to atrophy profiles observed in Alzheimer’s disease and frontotemporal dementia; their model makes no prior assumptions about selective neuronal vulnerabilities or protein-specific factors. Zhou et al. (2012) show that common neurodegeneration syndromes seed distinctive connectivity structures derived using task-free fMRI in the healthy brain: their data suggest that the neurodegenerative process spreads primarily between neurons according to the functional proximity of specific brain regions acting as critical hub-like “epicenters,” rather than various alternative candidate mechanisms. Both papers agree that transsynaptic diffusion plays a core role in the spread of neurodegenerative pathologies, and together they provide a succinct framework for characterizing network disintegration in these diseases. For clinical neurologists and molecular biologists, these elegant and sophisticated studies hold a strong intuitive appeal. That being said, the studies raise many issues as they resolve. So where do we go from here? Viewed critically, these two studies are directed chiefly toward the “deep phenotyping” of neurodegenerative syndromes: the mapping between clinical profiles and permissive brain architectures. Less widely pursued has been the reverse mapping, from specific molecular pathologies via network breakdown to clinical disease; yet accurate prediction and tracking of molecular pathology from phenotype will be essential for the rational application of specific protein-targeting therapies. As Raj et al. (2012) and Zhou et al. (2012) point out, large-scale connectivity approaches have yet to settle such fundamental issues as the basis for initial targeting of particular brain regions by neurodegenerative pathologies, the role of protein-specific mechanisms in disease evolution and (perhaps most problematically of all) the typically wide variation in phenotypic expression among individuals with a particular molecular diagnosis. On the other hand, we already know that particular canonical syndromes can be produced by genetic mutations with radically different group-level brain atrophy profiles (Rohrer et al., 2011; see Figure 1). A complete network account of neurodegeneration will need to resolve such apparently paradoxical observations. In our view, progress is likely to depend on incorporating molecular pathological “minutiae” (Raj et al., 2012) into existing network models.

One way forward may be to assess patterns of network breakdown that segregate according to the morphology of network elements rather than networks in their neuroanatomical entirety. The idea that particular network components may be differentially vulnerable to neuropathological processes is implicit in the work of Zhou et al. (2012) and compatible with the results of Raj et al. (2012). Intrinsic brain connectivity and transsynaptic disease spread may be overarching principles, while within damaged networks, proteinopathies may operate via subsidiary mechanisms such as those delineated by Zhou et al. (2012) to produce specific profiles of network...
breakdown. Recent rapid progress in characterizing genetic and histopathological substrates of the frontotemporal dementias has enabled, for the first time, a more or less complete analysis of these diseases in molecular terms. Such analyses suggest that specific clinicoanatomical signatures of proteinopathies can be identified (Rohrer et al., 2010, 2011; Whitwell et al., 2012). In particular, there appears to be a partitioning between pathologies that produce largely symmetrical versus strongly asymmetrical cerebral degeneration and between pathologies that produce relatively localized versus widespread degeneration at a given disease stage. Although the common sporadic neurodegenerative diseases are the ultimate targets of genetic proteinopathies meanwhile constitute crucial test cases. Rather than focusing on the selective vulnerability of network nodes to extinction under sociological and ecological events (Saavedra et al., 2011) may help generate models for the selective targeting of the epicenters identified by Zhou et al. (2012). In addition, the power of anatomical signatures can be achieved; these are likely to inform our understanding of network organization. Models of human semantic processing, for example, make relatively specific predictions about permissive network architecture in semantic dementia (Lambon Ralph et al., 2010). Similar arguments favor the use of task-based as well as task-free fMRI to characterize damaged networks. Empirical longitudinal data on the evolution of network disintegration are sorely needed in order to determine the validity of predictive models (Raj et al., 2012). Finally, clinical neurologists and neuroradiologists, by identifying the sometimes counterintuitive (e.g., highly asymmetric) profiles thrown up by particular neurodegenerative diseases, can help inform and constrain the search for candidate mechanisms to explain such profiles. The power and beauty of data such as those presented by Raj et al. (2012) and Zhou et al. (2012) will be fully realized if we can move beyond syndromic disease maps to a taxonomy of protein-based network degenerations: “molecular neuropathies.”

ACKNOWLEDGMENTS

We thank Professor Nick Fox for helpful discussion. This work was undertaken at UCLH/UCL, which received a proportion of funding from the Department of Health’s NIHR Biomedical Research Centres funding scheme. The Dementia Research Centre is an Alzheimer’s Research UK Co-ordinating Centre. The authors are also funded by the Medical Research Council UK and by the Wellcome Trust. J.D.W. is supported by a Wellcome Trust Senior Clinical Fellowship (Grant No 091673/Z/10/Z).

REFERENCES

Bullmore, E., and Sporns, O. (2009). Nat. Rev. Neurosci. 10, 186–198.

de Calignon, A., Polidoro, M., Suárez-Calvet, M., William, C., Adamowicz, D.H., Kopeikina, K.J., Pitstick, R., Sahara, N., Ashe, K.H., Carlson, G.A., et al. (2012). Neuron 73, 685–697.

Frisoni, G.B., Fox, N.C., Jack, C.R., Jr., Scheltens, P., and Thompson, P.M. (2010). Nat. Rev. Neurol. 6, 67–77.

Hardy, J. (2005). Biochem. Soc. Trans. 33, 578–581.

Lambon Ralph, M.A., Sage, K., Jones, R.W., and Mayberry, E.J. (2010). Proc. Natl. Acad. Sci. USA 107, 2717–2722.

Modha, D.S., and Singh, R. (2010). Proc. Natl. Acad. Sci. USA 107, 13485–13490.

Piscopo, P., Rivabene, R., Adduci, A., Mallozzi, C., Malvezzi-Campeggi, L., Crestini, A., and Confalonieri, A. (2010). Neurochem. Int. 57, 893–898.

Raj, A., Kuceyeski, A., and Weiner, M.W. (2012). Neuron 73, this issue, 1204–1215.

Roberts, G.W., Nash, M., Ince, P.G., Royston, M.C., and Gentleman, S.M. (1993). Neuroreport 4, 7–9.

Rohrer, J.D., Geser, F., Zhou, J., Gennatas, E.D., Sidhu, M., Trojanowski, J.Q., de Silva, R., Warrington, E., et al. (2011). Brain 134, 2565–2581.

Saavedra, S., Stouffer, D.B., Uzzi, B., and Bascompte, J. (2011). Nature 479, 233–235.

Whitwell, J.L., Weigand, S.D., Boeve, B.F., Senjem, M.L., Gunter, J.L., de Jesus-Hernandez, M., Rutherford, N.J., Baker, M., Knopman, D.S., Wszolek, Z.K., et al. (2012). Brain 135, 794–806.

Zhou, J., Greicius, M.D., Gennatas, E.D., Growdon, M.E., Jang, J.Y., Rabinovici, G.D., Kramer, J.H., Weiner, M., Miller, B.L., and Seeley, W.W. (2010). Brain 133, 1532–1547.