

Atrophy network mapping of transdiagnostic cognitive and neuropsychiatric symptoms

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Glossary

Functional connectivity Distributed regions across the brain that show correlations in the time course of spontaneous activity. These regions form networks thought to underlie specific cognitive, sensory and behavioural functions.

Cortical Thickness An estimate of the thickness of the grey matter in the cerebral cortex, calculated as the distance between the boundary of grey and white matter and the pial surface.

Lesion Network Mapping Lesions in different regions of the brain in patients with the same symptom are mapped to functional or structural networks

Default mode network The most recognizable and studied functional brain network. Distributed regions include the posterior cingulate cortex, medial prefrontal cortex and angular gyrus that show correlated temporal activity. The network has been repeatedly implicated in Alzheimer's disease.

Network nodes Brain regions whose connections to each other define a structural or functional network. Nodes vary in the number and importance of their connections within a network.

One of the most significant challenges in diagnosis and monitoring of Alzheimer's disease, as well as biomarker and treatment development, is the considerable heterogeneity in clinical presentation and pathology observed across individuals. In this issue, Tetreault et al., introduce a new technique aimed at finding underlying patterns within this heterogeneity by mapping clinical, cognitive and neuropsychiatric symptoms to large-scale brain networks.

A decade ago, Seely et al.,'s (2009) landmark paper provided evidence of meaningful patterns of syndrome-specific atrophy across five neurodegenerative dementias. Syndromes refer to the broad diagnostic categories of neurodegenerative dementias, such a behavioural-variant frontotemporal dementia or corticobasal syndrome. The peak region of cortical atrophy across groups, with the same clinical syndrome, was used as a seed in functional connectivity analysis in cognitively normal individuals.

Healthy functional connectomes closely resembled the patterns of atrophy observed in the clinical syndromes, being both distinct from each other and reflecting known, domain-specific, functional networks that mirrored the principal deficit in each syndrome. For example, Alzheimer's disease was associated with episodic memory deficits and atrophy within medial temporal and posterior cingulate regions, while semantic dementia patients had typical word and object finding difficulties associated with prominent left temporal pole atrophy. Later, work by Zhou et al., (2012) clarified the mechanisms by which atrophy may spread through functional networks, namely via transneuronal spread of pathology in high use, high vulnerability network nodes. While a critical step in formalising the importance of large-scale distributed brain networks underlying dementia syndromes, these studies stopped short of identifying brain networks associated with specific *symptoms*. This is important for two reasons. Firstly, within clinical syndromes, there is significant heterogeneity in the symptoms presented by individual patients. Symptoms include both cognitive deficits, such as memory impairment, and neuropsychiatric problems such as hallucinations or delusions. Secondly, the same symptom may occur across clinical syndromes, suggesting the underlying molecular pathology alone cannot account for the clinical phenotype (Husain, 2017; Pievani, Filippini, Van Den Heuvel, Cappa, & Frisoni, 2014).

The development of lesion network mapping sought to understand one of the most heterogeneous clinical populations, ischaemic stroke patients. Stroke patients present a complex challenge to cognitive neurology, and our understanding of brain-behavior mapping, because patients with the same symptom can have damage in different, even non-overlapping regions (Fox, 2018). Lesion network mapping sought to reconcile this heterogeneity, positing that the same symptom arises because the damage has occurred somewhere within a distributed, large-scale, symptom-specific network (Fox, 2018). Lesion network mapping has been successfully applied to the identification of functional networks underlying complex symptoms from memory deficits to delusions, auditory hallucinations and, disorders of volition, familiarity and agency (Fox, 2018).

In this issue, Tetreault et al., introduce a new method, atrophy network mapping, that applies the logic of lesion network mapping to a clinical syndrome associated with

more diffuse brain damage, namely Alzheimer's disease. In doing this they make a significant advance on the work of Seeley et al., (2009) investigating both syndrome and *symptom* specific brain networks. Tetreault et al., first defined individual atrophy maps by comparing each AD patient with a group level cortical thickness map of cognitively normal individuals (see Figure 1.1). Unsurprisingly, they showed significant heterogeneity in the pattern of atrophy across individuals, with a maximum of 42% of patients showing overlapping atrophy in any single region. Next, they used the individual atrophy maps as seeds in a functional connectivity analysis of 1000 healthy functional connectomes from an openly available dataset (Figure 1.3). The technique produced an 'atrophy network map' for each individual, representing the regions of the brain (determined on a voxelwise basis) that were functionally connected to their atrophied map. Here, they demonstrated the underlying pattern uniting this heterogeneous AD group, with all patients showing connectivity to the same large-scale network that includes mesial temporal regions, the precuneus and the angular gyrus, and resembled the default mode network (see Figure 1.4). The group atrophy network map replicated previous work implicating these regions in network neurodegeneration in AD (Seeley et al., 2009; Zhou et al., 2012). Importantly, Tetreault et al., used a discovery and test replication dataset (330 AD patients in total), and several control analyses to validate their findings. As proof of concept, atrophy network mapping successfully identified 100% of clinically diagnosed AD patients from cognitively normal individuals despite their considerable neuroanatomical differences. In itself, this is not a major advance, many imaging techniques and analysis methods (Cuingnet et al., 2011) have successfully classified clinically diagnosed AD individuals from cognitively normal controls - including at the individual level, and in spite of the heterogeneity (Cho, Seong, Jeong, & Shin, 2012). Where Tetreault et al., do make a significant advance is in relating specific cognitive and neuropsychiatric symptoms, memory and delusions respectively, to underlying large-scale functional networks.

Using performance in the auditory verbal learning task (AVLT) to assess memory and the presence of delusions in the six months preceding MRI scan, Tetreault et al., compared the atrophy network maps across patients with and without memory deficits and with and without delusions. Voxelwise t-tests and regression were used to find the peak regions associated with presence of delusions and memory performance

across atrophy network maps, generating a peak region of interest for each symptom (Figure 1.5). Functional connectivity between each peak seed and the single subject atrophy maps were then extracted from the healthy functional connectome (Figure 1.6). The analysis generated an average functional connectivity score for each patient and each symptom. Functional connectivity of the delusion atrophy network was significantly higher in patients with delusions than patients without delusions. Functional connectivity of the memory atrophy network was significantly negatively correlated with memory performance in the AVLT. Here, results should be taken with a pinch of salt. There is a degree of circularity in defining the peak region for functional connectivity analysis using memory scores, and the presence of delusions, and then testing whether functional connectivity is associated with these symptoms. The correlation may be inflated and replication in an independent dataset is necessary (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009). Nevertheless, the authors go on to show a striking similarity between the symptom-specific atrophy network maps and lesion network maps (Figure 1.7) obtained in patients with focal lesions that lends credence to the idea that large-scale network disruption may underlie these transdiagnostic symptoms. The finding has important implications for understanding how the same symptoms can arise from very different pathologies and how distinct, reproducible brain networks underlie clinical phenotypes. Given the heterogeneity of symptoms within the same clinical syndrome the most promising management of complex neurological disorders, from focal lesions to dementia syndromes, will require treatment of individual symptoms (Husain, 2017).

The authors briefly speculate mechanisms underlying neurodegeneration of large-scale, symptom and syndrome specific functional networks, positing the effects of diaschisis or global network dysfunction. A number of questions remain as to how and why structural changes spread within a network defined from the spontaneous correlated activity of distributed regions. Do these regions require physical connections for the spread of pathology to occur (Torok, Maia, Powell, Pandya, & Raj, 2018) or does disruption to coherent activity result in cortical thinning due to underutilization within the distributed network? The work generates a number of questions and future lines of research, whilst providing a promising new analytical method. What underlies the observed neuroanatomical variability across patients? While disruption to the same large-scale functional network explains both syndrome

and symptom specific network atrophy, what causes variability in the network nodes affected in a given individual? At the group level, network nodes that are highly metabolically active and serve as epicentres (i.e. heavily connected to all other network nodes) are particularly vulnerable to pathological dysfunction and are likely to be the initial target of disease (van den Heuvel & Sporns, 2013; Zhou et al., 2012). There is some evidence that network epicentres vary across individuals, providing different regions of vulnerability for the initial pathological target (Torok et al., 2018). Perhaps the stage of disease is an important factor and the progression of atrophy within the network might explain the observed heterogeneity (a limitation of cross-sectional designs, acknowledged by the authors). Further complicating the picture is the background cerebrovascular burden, itself a risk factor for AD, which likely accelerates atrophy and may differentially impact regions of the network (for example by targeting deeper regions perfused by small vessels). With the majority of AD cases showing evidence of mixed pathology (most commonly cerebral small vessel disease) future studies would benefit from careful control of cerebrovascular risk and small vessel disease pathology.

Heterogeneity is often averaged out at a group-level, but this may obscure important patterns relating clinical and neuroanatomical variability. Tetreault et al., provide a promising method of finding signal within this noise.

The author reports no competing interests.

References

- Cho, Y., Seong, J.-K., Jeong, Y., & Shin, S. Y. (2012). Individual subject classification for Alzheimer's disease based on incremental learning using a spatial frequency representation of cortical thickness data. *NeuroImage*, 59(3), 2217–2230. <https://doi.org/10.1016/j.neuroimage.2011.09.085>
- Cuingnet, R., Gerardin, E., Tessieras, J., Auzias, G., Lehéricy, S., Habert, M. O., ... Colliot, O. (2011). Automatic classification of patients with Alzheimer's disease from structural MRI: A comparison of ten methods using the ADNI database. *NeuroImage*. <https://doi.org/10.1016/j.neuroimage.2010.06.013>
- Fox, M. D. (2018). Mapping symptoms to brain networks with the human

- connectome. *New England Journal of Medicine*.
<https://doi.org/10.1056/NEJMra1706158>
- Husain, M. (2017). Transdiagnostic neurology: Neuropsychiatric symptoms in neurodegenerative diseases. *Brain*. <https://doi.org/10.1093/brain/awx115>
- Kriegeskorte, N., Simmons, W. K., Bellgowan, P. S. F., & Baker, C. I. (2009). Circular analysis in systems neuroscience: the dangers of double dipping. *Nature Neuroscience*, 12(5), 535–40. <https://doi.org/10.1038/nn.2303>
- Pievani, M., Filippini, N., Van Den Heuvel, M. P., Cappa, S. F., & Frisoni, G. B. (2014). Brain connectivity in neurodegenerative diseases - From phenotype to proteinopathy. *Nature Reviews Neurology*.
<https://doi.org/10.1038/nrneurol.2014.178>
- Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L., & Greicius, M. D. (2009). Neurodegenerative diseases target large-scale human brain networks. *Neuron*, 62(1), 42–52. <https://doi.org/10.1016/j.neuron.2009.03.024>
- Torok, J., Maia, P. D., Powell, F., Pandya, S., & Raj, A. (2018). A method for inferring regional origins of neurodegeneration. *Brain*.
<https://doi.org/10.1093/brain/awx371>
- van den Heuvel, M. P., & Sporns, O. Network hubs in the human brain. , 17 *Trends in Cognitive Sciences* § (2013).
- Zhou, J., Gennatas, E. D., Kramer, J. H., Miller, B. L., & Seeley, W. W. (2012). Predicting regional neurodegeneration from the healthy brain functional connectome. *Neuron*, 73(6), 1216–1227.
<https://doi.org/10.1016/j.neuron.2012.03.004>

Figure title and legend

Figure 1. *Illustrative figure of the main steps in atrophy network mapping of clinical, cognitive and neuropsychiatric symptoms (does not represent real data). 1.1 Cortical thickness is estimated in cognitively normal (CN) controls. 1.2 Cortical thickness in each patient is compared to the CN control group to estimate individual patient atrophy patterns, controlling for age and sex. 1.3 Binarised individual atrophy maps are used as seeds in functional connectivity analysis in a large, normative dataset of healthy controls to produce individual patient atrophy network maps. 1.4 Atrophy networks maps overlap across patients and are specific to the clinical syndrome. 1.5 To estimate symptom-specific atrophy,*

the peak regions associated with a specific symptom are estimated voxelwise in the atrophy network maps. Correlation plot illustrates relationship between functional connectivity and the neuropsychiatric symptom measure in the peak region. 1.6 Functional connectivity between this peak region and the rest of the brain produces a cognitive and neuropsychiatric symptom-specific atrophy network map. 1.7 Symptom-specific atrophy network maps show a high degree of overlap with lesion network maps obtained in focal lesion patients with the same symptoms, showing transdiagnostic utility of the method.