Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Alzheimer's Disease: A Search for Broken Links

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Review of He et al. (http://www.jneurosci.org/cgi/content/full/28/18/4756)

Amnesia is the most well known symptom of Alzheimer's disease (AD), and typically the earliest to be noticed, but the disease is soon accompanied by a range of disparate cognitive disruptions such as in linguistic and visuospatial abilities and in overall executive function (Perry and Hodges, 1999). Neuropathologically, AD is defined by the occurrence of neurofibrillary tangles, predominantly in the medial temporal lobe, and by amyloid aggregations distributed across the cerebral cortex. Structural magnetic resonance imaging (MRI) reveals medial temporal lobe atrophy, but the same Alzheimer's patients exhibit hypometabolism in temporoparietal and retrosplenial association cortices. It is therefore still unclear whether early stages of the disease can be localized to the medial temporal lobe or whether the disease is distributed across the cortex from its onset. Even if AD pathology is initially localized, its progression may reflect a stereotyped and sequential breakdown in the interactions between affected and unaffected brain regions. The contention between localizationist and connectionist theories of brain (dys)function is at least as old as modern neuroscience, and is unlikely to be resolved soon. However, the analysis of structural connectivity patterns in neuroimaging data of a progressive disease such as AD might provide a better understanding of the interaction between the local and global neural disturbances underlying the diverse symptoms of AD.

Recent neuroimaging work has demonstrated a variety of alterations in interregional communication in AD. Analysis of low-frequency fluctuations in functional MRI data of patients at risk for AD has revealed a distributed loss of connectivity, especially in the long-range connections between association cortices and prefrontal areas (Sorg et al., 2007). A network analysis of electroencephalographic data showed an increase in the average communication distance between brain regions in patients with AD (Stam et al., 2007). Those recent findings in functional data lend novel support to the conception of AD as a type of disconnection syndrome (Morrison et al., 1986). Now, in a recent issue of *The Journal of Neuroscience*, He et al. (2008) have presented the first comparison of anatomical connectivity in early-stage AD patients and in healthy controls (He et al., 2008).

Although the link between cortical network architecture and cortical activity has been extensively investigated, our understanding of this large-scale structure–function relationship is still in its infancy (Fox and Raichle, 2007). This is mainly because of the lack of reliable data concerning the underlying connection architecture of the human brain. Tract-tracing methods cannot be applied in humans, and so anatomical connectivity is typically inferred from primates via uncertain homologies, or is derived from diffusion tensor imaging, which is based on the idea that fiber tracts distort the microscale diffusion of water in the brain. Although diffusion imaging and tractography have shown great promise, the spatial resolution at which images are obtained and the variability in results from different tractographic techniques are limitations that still need to be overcome.

In their study, He et al. (2008) instead used an innovative morphometric technique to infer anatomical connectivity: correlation patterns in cortical thickness. The assumption underlying this technique is that two cortical areas are likely to be anatomically connected if, after controlling for other factors, their thickness covaries across subjects. If thickness correlations are produced by shared trophic influences or are caused by activity-dependent plasticity [as has been argued for gray matter density correlations (Mechelli et al., 2005)], then the inference from thickness correlations to anatomical connectivity is probably well founded.

The authors first calculated cortical thickness correlation matrices for both groups of subjects. These data revealed both weakening and strengthening in negative and positive thickness correlations, depending on the region. Consistent with previous functional and behavioral studies, the interhemispheric couplings were found to be weaker in AD patients. Additionally, many of the strongest increases in

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thickness correlations that occurred in AD involved regions contained in the "default-mode" network, a set of regions that is prominently functionally and metabolically affected in early AD (Sorg et al., 2007; Buckner et al., 2008). The authors could not determine definitively whether these correlations resulted from changes in anatomical connectivity or whether they reflected the fact that these regions shared a common predisposition to AD-related thinning. It is also possible that both explanations could be correct: local cell death, diminished synaptic activity, and weaker interregional coupling could well form a mutually reinforcing atrophic cycle.

Going beyond a simple analysis of individual interregional connections, He et al. (2008) performed a network analysis on the data. The thickness correlation maps for healthy and clinical groups were thresholded to produce binary matrices that could be interpreted as maps of interregional anatomical linkage and could then be analyzed using graph theory. In graph theory, a graph (or network) is a set of nodes linked by edges. In large-scale cortical networks, the nodes typically represent distinct cortical regions and the edges represent interregional pathways. To characterize a given node in a network, one might measure its degree (the number of nodes to which it is directly linked), the path length to another node (the number of edges in the shortest path between those two nodes), its clustering coefficient (the proportion of its neighbor pairs that are directly linked to one another, forming a triangle), and its betweenness centrality (the proportion of shortest paths in the network that pass through the node). Based on these individual node measures, one can then define properties of the entire network structure (i.e., the entire cerebral cortex) and classify networks based on their overall properties.

The large-scale connection networks of healthy brains are believed to belong to the category of "small-world networks." This type of network shows a balance of connections so that there is high average clustering in the network combined with a relatively short distance between nodes; small-world networks are suspected to be highly effective in terms of information processing. He et al. (2008) found that, although both AD and control networks could be classified as small-world, the clustering coefficients and the average path length between nodes was larger in the AD group. The authors suggest that the small-world networks of the AD patients are less optimal, but this claim is difficult to evaluate in the absence of a specification of the objective toward which large-scale brain networks are being optimized.

In AD patients, the superior temporal gyrus and angular gyrus had significantly decreased nodal centrality. These regions were found by He et al. (2008) to have extremely high centrality in the networks of healthy subjects, and this is presumably a reflection of the long-range connections that they maintain with frontal cortex, which enable them to fulfill their roles in attentional orienting (Goldman-Rakic, 1988). The finding that the interlobar connectivity they mediate is disrupted in early-stage AD provides a potential explanation for the fact that attentional deficits are typically the disease's first postamnesic cognitive symptoms (Perry and Hodges, 1999).

This study by He et al. (2008) applies a promising new methodology for structural connectivity analysis, and one which can readily be extended to existing morphological datasets for other clinical populations. Supporting the idea that disconnection plays a major role in AD, the authors described prominent network alterations in the patients, which correspond in many instances to the alterations observed in functional imaging studies (Sorg et al., 2007; Stam et al., 2007). There are nevertheless some aspects of their methodology that could be strengthened, and some results that remain open to interpretation. Cortical thickness correlations are used as a basis for inference concerning anatomical connectivity, but the basis for this inference is uncertain, because these thickness correlations may also be produced by other factors, such as genetic influences that are shared across regions. Additionally, it is difficult to know whether cortical thickness correlations bear the same relationship to connectivity in the control group as they do in the AD group, in which progressive atrophy is occurring.

As in any clinical study, choices had to be made to ensure fair comparisons across clinical and control groups. In this study, to compare connectivity across AD patients and healthy subjects, thickness correlations were thresholded so as to equalize the number of binary connections present in the networks for each group. If the AD population does in fact have sparser anatomical connectivity than the control population, then adjusting the thresholds to equalize sparsity in the two groups might introduce a bias into intergroup comparisons. Future studies should combine connectivity estimates gathered from thickness correlations, from diffusion tensor imaging tractography, and from functional measures (such as interregional coherence in neuroimaging signals), in search of convergent results.

It seems likely that the behavioral symptoms of Alzheimer's disease result from insult to local neural areas as well as to large-scale neural communication networks (Perry and Hodges, 1999; Buckner et al., 2008). The study of cortical thickness patterns has already aided us in understanding the progression of AD-related atrophy, and the analysis of correlations in cortical thickness now provides a window into changes in the underlying anatomical connectivity.

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