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Connectomics Sheds New Light on Alzheimer's Disease

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Rapid advances in brain imaging have stimulated studies worldwide on the network architecture of the living brain, revealing general organizational principles in functional systems and the fiber connections that support them. Connectomics, a relatively new field stimulated by revolutionary developments in neuroimaging, has opened up a new landscape of discovery in neuroscience and has led to major international initiatives, such as the Human Connectome Project (1) (http://www.humanconnectomeproject.org). Maps of brain connectivity are shedding light on some of the most tantalizing questions in neuroscience: how the brain is organized, how it develops, and how it changes in disease. Statistical data on connection patterns are also being assembled into large databases, making it feasible to search for factors that affect connectivity, from neurogenetic disorders to bipolar disorder and schizophrenia, from therapeutic interventions to single letter differences in the human genome.

As new methods emerge to assess brain connectivity, some research groups have begun to collect resting-state functional magnetic resonance imaging (rs-fMRI), diffusion-weighted imaging, and electroencephalography/magnetoencephalography to study the global breakdown of network integration in degenerative disease. Neuropsychologic deficits are often attributed to a disconnection between brain regions, sometimes producing a disconnection syndrome. The field of brain mapping has also evolved from reductionistic studies attempting to localize a brain dysfunction to a particular locus or structure in the brain to studies that examine the much more complex effects of disease, or experimental manipulations, on the connections or synchronization of activity throughout the brain.

Wang *et al.* (2) reported a highly innovative study revealing how brain networks break down in Alzheimer's disease (AD). They use rs-fMRI and graph theory, a branch of mathematics used to study networks, to understand how functional connectivity degrades in people with amnestic mild cognitive impairment (MCI). MCI is a syndrome that carries a vastly increased risk of AD; approximately 15% of people with amnestic MCI per year develop symptoms sufficient for a diagnosis of AD.

In their report, Wang *et al.* (2) used functional MRI to measure spontaneous, or so-called resting state, functional connectivity in the brain. To define a set of network nodes, they divide the cortical surface into 1024 regions and determine whether the time courses of activity are correlated between all pairs of such regions. In this kind of resting-state analysis, the activity of diverse brain regions is mapped, to infer functional connections between systems. The overall pattern of correlations may be broken down into statistical modes, including the default mode network (3), and other interacting systems whose properties can be manipulated experimentally. Wang *et al.* (2) took this approach further and studied

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correlations in functional signals within different frequency bands, using a wavelet transform method, to identify early signs of network failure in amnestic MCI.

The brain can be described as a graph, or network, in which predefined cortical regions are connected by links, or edges, that describe the strength of correlations in their functional activity. In the study by Wang *et al.* (2), the amnestic MCI group showed decreased functional connectivity overall; a variety of network descriptors were correlated with the severity of cognitive impairment, suggesting that the deterioration of functional coherence contributes to impairment in recall ability. These same network metrics also distinguished MCI subjects from normal controls with high specificity and sensitivity, suggesting that they may be advantageous for diagnosis and tracking of AD, even in a prodromal phase when symptoms are subtle. As the authors noted, network measures could be used, in the future, to supplement other biomarkers from imaging, cerebrospinal fluid, genomics, and proteomics to better understand how AD pathology evolves and perhaps even to assist with differential diagnosis.

The neural networks implicated by Wang *et al.* (2) are highly consistent with information gleaned from other imaging methods regarding the neuropathology of AD. The classical evolution of amyloid plaques and neurofibrillary tangles, hallmarks of AD that are documented in the highly cited work of (4), follows a relentless, spreading trajectory in the brain that is mirrored by a loss of neurons and their connections (Figure 1). The speed and trajectory of the spread differs in different patients, but the medial temporal circuitry of the hippocampus and entorhinal cortex are typically among the first to be involved, followed by parietal and limbic areas, and eventually frontal regions of the brain. Notably, the primary sensorimotor cortices are comparatively resistant to the effects of AD pathology, perhaps because of their high myelination levels, which may be protective. This progressive unraveling of brain integrity has been documented as a progressive wave of cortical thinning (5) and the dynamic spread of cerebral amyloid using positron emission tomography (PET) (6). One study showed that small-world measures of anatomical networks, computed from DTI, predicted future decline in people with mild cognitive impairment (7). Recent studies of familial AD also suggest an emerging wave of amyloid engulfing the brain decades before symptom onset. What makes these prodromal changes highly valuable is the fact that many of them occur well before overt cognitive symptoms become apparent.

Functional connectivity studies such as that of Wang *et al.* (2) lend insight and power to prior methods that have attempted to chart the spread of pathology. The current report also uses advanced mathematics to define new features for tracking and classification of brain disease. Wavelet methods and graph theory were once within the sole purview of pure mathematicians, but they now offer a remarkable way to sift through large and complex networks and home in on features that predict cognitive performance or clinical decline. Inevitably, the accumulation of pathology induces innumerable downstream changes in other brain systems not yet engulfed by pathology but reliant on functional connections with the impaired regions. If functional connectivity analyses can detect these system-wide changes, they will offer a powerful biomarker for earlier detection of AD and perhaps also for monitoring therapeutic effects. Evidence supporting a gradual disconnection process in AD has emerged from various techniques, including standard anatomical magnetic resonance imaging, electroencephalography, and PET. On diffusion-weighted magnetic resonance imaging, AD patients show a lower density of white matter association fibers in the cingulum, the splenium of the corpus callosum, and the superior longitudinal fasciculus. At the same time, interhemispheric functional synchronization also breaks down. Coherence studies by Wada *et al.* (8) found disturbed interhemispheric functional connectivity in AD, which has been linked to the disconnection syndrome observed clinically. PET studies also show reduced metabolism in a network of regions, with greater amyloid deposition in the

posterior cingulate, retrosplenial, and lateral parietal cortex (9). Functional magnetic resonance imaging also shows deactivated regions that overlap with medial parietal/posterior cingulate regions that show reduced resting metabolic activity in AD subjects, compared with normal elderly and young adults (10).

The use of connectomics to study brain disease is still in its infancy. Even the normal ranges of values for many network metrics, such as efficiency, clustering, and small-world properties, are not yet known. Work in large cohorts of developing and aging populations in our laboratories is attempting to define how such network measures change, and which markers are most reliable for defining changes, in terms robustness and ease of implementation across sites. As the field evolves from this stage of exuberant discovery to become a routine and integral component of clinical neuroimaging studies, we are likely to see efforts to harmonize analysis and acquisition methods across the world. This harmonization is currently being performed by large consortium efforts in neuroimaging genetics (e.g., the ENIGMA project, http://enigma.loni.ucla.edu; and ADNI, http://adni.loni.ucla.edu/). Such efforts will help us detect subtle factors, such as individual genetic polymorphisms, that affect brain connectivity. In the paper by Wang *et al.* (2), the appendix contains ample evidence to show that the effects are robust and do not depend on arbitrary choices in the analysis stream, such as the cortical regions used to define the network's nodes. This is in line with other technical efforts worldwide to determine how affected connectivity networks are by the protocols used to assess them. Data resolution, analysis methods, and scanner field strength all affect which kinds of connections are resolved. Recent studies show high-field imaging, at 7-Tesla, can pick up connectivity patterns generally consistent with lower-field scanners, but they also resolve additional connections and networks (11).

As the field of connectomics evolves, we are likely to see a new landscape of collaboration among scientists aiming to understand networks of diverse kinds, from brain networks to genetic networks, to dissect and infer patterns and principles guiding information processing in the human brain.

Acknowledgments

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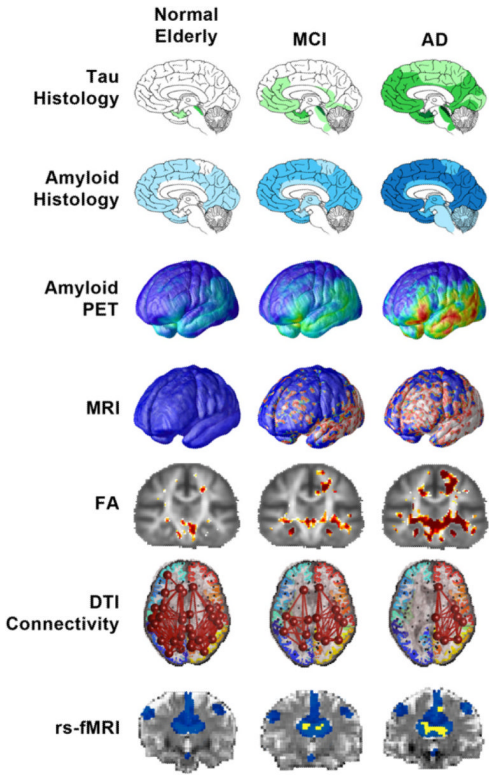

Figure 1.

A comparison of several imaging modalities, illustrating typical differences among normal, MCI, and Alzheimer's disease subjects. This is a summary figure only, based on data from different studies and adapted to illustrate regional similarities. Tau histology is plaque progression from the classical Braak stages of Alzheimer's disease. Darkening shades indicate greater tau deposition. Illustration is adapted from the following web site: http://cen.acs.org/articles/90/i27/Alzheimers-Prion-Connection.html. Amyloid histology is progression of amyloid plaque deposition, from Braak stages. Darkening shades indicate the typical patterns of amyloid plaques. Illustration is adapted from the following web site: http://cen.acs.org/articles/90/i27/Alzheimers-Prion-Connection.html. Amyloid PET projected mean [18F]FDDNP signal (DVR) can be calculated for various cognitive scores based on the empirical relationship of [18F]FDDNP signal to cognition in the subjects studied. Red colors denote regions in which greater [18F]FDDNP signal is predicted for people with lower cognitive Z scores based on a spatially varying model fitted at each cortical point. The parameterization of disease stages is based on cross-sectional data, but it is plausible that a comparable trajectory would be followed for each cognitive stage in an individual subject, albeit with variable timing across individuals. (Reproduced with permission from Braskie *et al.* (6). MRI maps show progressive gray matter reductions as Alzheimer's disease progresses. Variations in temporal, parietal, and ultimately frontal tissue are also linked with cognitive status. Less gray matter (white areas) is strongly correlated with poorer cognitive performance in all regions with prominent deficits. Linkages are detected most strongly in the left hemisphere medial temporoparietal zones. In FA, progressive white matter degeneration occurs in patients with early-stage mild cognitive impairment. Here the FA, a DTI measure of white matter integrity, decreases (red) as the disease progresses, suggesting a breakdown in neural fiber tract coherence. In DTI connectivity, with disease progression, primary connections between cortical regions are altered. When the networks are thresholded to show only highly connected nodes (known as the k-core), no nodes survive in the left hemisphere in Alzheimer's disease. (Image

reproduced with permission from Madelaine Daianu, Neda Jahanshad, Talia M. Nir, Emily Dennis, Arthur W. Toga, Clifford R. Jack Jr, Michael W. Weiner, Paul M. Thompson, and the Alzheimer's Disease Neuroimaging Initiative [2012]): Analyzing the structural k-core of brain connectivity networks in normal aging and Alzheimer's disease. MICCAI NIBAD 2012. In rs-fMRI, blue voxels represent the DMN. Yellow voxels show clusters of decreased FC compared with controls. (Image is an artist's interpretation adapted with permission from Binnewijzend *et al.* Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging. 2012;33:2018–2028). DMN, default mode network; DTI, ; DVR, ; FA, fractional anisotropy of diffusion; FC, functional connectivity; FDDNP, ; MCI, mild cognitive impairment; PET, positron emission tomography; rs-fMRI, resting-state functional magnetic resonance imaging.