Quantitative Markers for Neuropsychiatric Disease: Give It a Rest[1]

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See also the article by Chen et al in this issue.

Nearly 20 years have passed since the first descriptions of human functional neuroimaging (1–3), yet routine clinical applications of functional magnetic resonance (MR) imaging remain limited. Although the use of functional MR imaging in presurgical planning is now well established and other applications such as localization of a cortical disease like epileptigenic foci, are growing at a steady pace, realizing the broader promise of functional MR imaging as a diagnostic tool for diseases of cognitive function remains a work in progress. It is upon this stage that the work of Chen et al (4) enters.

Their work is based on the remarkable and unanticipated discovery by Biswal and colleagues (5) that low-frequency fluctuations in hemodynamic-based functional signals (including those seen by using standard gradient-echo blood oxygen level–dependent sequences) show significant temporal correlation across functionally connected but spatially distributed regions in the brain. Extended over the ensuing years, investigators have shown that a broad range of functional neural networks—such as those involved in sensory processing (6), memory (7), attention (8), chronic pain processing (9), and even the systems invoked when the brain spends time off task (the so-called default mode network) (10)—can be identified by looking for the correlation in resting functional MR imaging signals across different brain regions. In fact, resting correlations have been found to replicate the same networks typically found in task activation studies (11). While the neurophysiology underlying the connectivity patterns in resting-state low-frequency oscillations (typically, 0.1 Hz or about six times per minute) remains to be elucidated, a remarkable degree of information can be gleaned about the complex orchestration of brain activity across a broad array of cognitive activities, even as subjects do little more than lie still in the MR system for typically less than 10 minutes (only 6 minutes in the Chen et al study).

The simplicity of data acquisition (standard gradient-echo echo-planar whole-brain image acquisition sequences were repeated every 2 seconds or so for several minutes, and subjects were given little instruction other than to hold still) belies the complexity of the structure of the captured data. With data sets on the order of 0.5×10^5 voxels and between two and 300 time points, we have the opportunity to look across nearly 100 million four-dimensional points in space and time for correlations that can serve to inform us of the overall state of functional health in the brain. Not surprisingly, given the richness of the data, a wide range of approaches has been used to analyze resting functional MR imaging signals. At times, it seems as if the number of different approaches rivals the density of the data itself! Most commonly, investigators interrogate their data on the basis of seed regions, which are regions of interest defined in anatomic areas of functional relevance (the hippocampus for investigation of memory networks), by asking the questions of where, and to what extent, other brain areas are correlated in time with the signal fluctuations seen in the seed region. Those areas that show signal fluctuation highly correlated with the MR imaging signal within the seed region are then assumed to be functionally connected, and the location and degree of correlation between the seed region and these other regions can be mapped, quantified, and compared across groups or within groups over time.

An increasingly common alternative to seed-based methods are so-called data-driven approaches, which include methods such as independent component analysis. These techniques pose a more open-ended question: where throughout the brain are there regions

whose signals look alike? Grouping together brain regions whose functional MR imaging time courses look most alike while allowing other distributed regions to assemble on the basis of their own related time courses forms the basis for the determination of multiple functional networks from a single data set, all without the investigator using any a priori anatomic or functional knowledge. By allowing the data, rather than investigator-chosen seed regions, to determine who is alike, these methods are used not only to identify known sensory or cognitive networks in a remarkably robust fashion, but also to suggest new neural components of known networks and indeed other entire networks whose functions are as yet poorly understood. Together with seed-based approaches, these and related methods are now widely used in the cognitive neurosciences to investigate functional connectivity and brain networks in healthy subjects, as well as in translational research to study sensory and cognitive network abnormalities in a wide range of neurodegenerative, affective, and psychotic disorders.

A final class of methods takes an even more holistic perspective in the interrogation of resting-state functional MR imaging data. In these methods, researchers measure the correlation between every pair of pixels (or regions) across the whole brain and look for patterns in the subsequent correlation matrix, which is quite large. Data of this nature have been used to investigate the interconnectedness of cortical regions and identify characteristics of these whole-brain correlations that show small-world properties like hubs, which are central nodes of high interconnectedness (12). A particularly active area of research into basic human brain connectional anatomy focuses on relating such functional connectivity maps to maps defined by anatomic measures of connectivity, such as those derived from diffusion imaging (13,14), where similar but not identical features have been found. The emerging field of human connectomics, which has been embraced by the National Institutes of Health newly initiated Human Connectome Project *(http://www.humanconnectome.org/consortia)*, is one such effort to bring together an integrated view of both functional and structural connectivity of the human brain.

Chen et al (4) used a variant of this approach to resting-state functional MR imaging connectivity analysis, but they used it to address a different set of questions: rather than characterize normal brain patterns of interconnectedness across broad populations, Chen et al ask how these global patterns might vary by disease state and if they can in fact be used as specific diagnostic biomarkers with which to classify individual patients into appropriate categories. To investigate this question, Chen and colleagues focused on a small cohort of patients with early-stage Alzheimer disease (AD), another cohort with mild cognitive impairment (MCI) with amnesic features, and a third group of age-matched control subjects without apparent cognitive impairment (referred to as cognitively normal [CN] subjects). Rather than measure the correlations between every voxel in the image space, to simplify analysis and improve statistical power they parcellated the cortex into 116 anatomically defined regions, averaged the MR imaging time series across the multiple voxels encompassing these regions, and cross-correlated each region to the other 115 regions for all subjects. They then interrogated the results in a stepwise fashion: First, they compared patients with AD with those without AD (the MCI and CN groups). Then, they used a similar method to compare the MCI and CN groups.

The overall results of this study are encouraging. Classification of patients with AD against the pool of patients with MCI and the CN subjects yielded an overall accuracy of 82% (85% sensitivity, 80% specificity). Comparison of patients with MCI and CN subjects was even more successful, resulting in an accuracy of 91% (93% sensitivity, 90% specificity). Also of note, the global indexes of connectivity showed significant correlation against two important behavioral measures known to be affected in AD, the Mini-Mental State Examination score and the Rey Auditory Verbal Learning Test delayed recall score. This result supports the claim of Chen et al that the resting-state data reflect underlying cognitive status.

Recently, there has been major interest in the identification of biomarkers of early cognitive impairment that may be used to predict subsequent conversion to AD; the data acquired by Chen et al suggest that resting-state functional MR imaging may offer another image-based method to complement promising results arising from quantitative morphometric analysis of anatomic MR images, such as those from recent analyses of the Alzheimer's Disease Neuroimaging Initiative (ADNI) trial (15–17). Although it is not appropriate to directly compare the results from the large-scale multicenter ADNI trial with the results from the small sample analyzed by Chen et al, the findings of Chen et al, along with supportive data from other researchers who used resting-state MR imaging to investigate network abnormalities in patients with AD (18) (see also references in Chen et al), suggest that these methods may indeed be used to sensitively detect connectional abnormalities associated with incipient dementia, even in individual subjects.

Two important issues are left unresolved by the existing data. First, the most important results of the ADNI trial suggest that not only can quantitative morphometry be used to discriminate between patients with AD, those with MCI, and control subjects, it can be used to predict which patients with MCI will subsequently go on to have AD. Unfortunately, the existing ADNI data set did not routinely include resting-state functional MR imaging data. Thus, new longitudinal data will be required to address, in a prospective way, the predictive capability of resting-state functional MR imaging data. Of course, resting-state functional MR imaging data would not need to be used exclusively to make this determination—that is, data could be used as components in models that combine structural neuroimaging and other variables with high predictive power. For instance, existing data already suggest that combined biomarkers, such as quantitative morphometric MR imaging and cerebrospinal fluid β-amyloid, perform better in terms of their predictive capabilities than if they were used individually (19). In addition, it may well be that resting-state data serve primarily as

a complement to other biomarkers analyzed in an integrative manner, such that together they yield sufficient predictive accuracy to enable one to make prognostic and therapeutic decisions. The latter, of course, presently remains broadly in the future for patients with AD, though we hope it is the near future.

Second, the specific analytic pathway taken by Chen et al may or may not represent an optimal algorithm as a predictive biomarker. For example, the use of anatomic cortical parcellation to reduce the dimensionality of the primary voxelwise data, as performed in the Chen et al study, may indeed provide the requisite functional segregation for successful network analysis. On the other hand, it may not, as we continue to learn more about the often distinctive characteristics of functionally defined cortical modules versus anatomically defined cortical modules. Likewise, the stepwise analysis strategy used by Chen et al is likely to require some modification for prospective analysis. Nevertheless, the work they present here certainly highlights the promise of the underlying data to probe key characteristics of the functional connectome and its dysregulation in the setting of AD in a real-world patient-oriented setting.

More broadly, the use of resting-state functional MR imaging, again likely combined with quantitative MR morphometry and potentially other noninvasive imaging metrics such as MR spectroscopy and/or neurochemical markers from combined MR imaging and positron emission tomography, should offer substantial improvements over our current ability to evaluate and care for patients with a neuropsychiatric illness. The forthcoming arrival of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, and the inevitable confusion and discord associated with this report, should emphasize in unmistakable fashion for our community the need for clear quantitative means with which to assess the mental status and underlying brain function of patients with behavioral disorders. Despite 40 years of research indicating the promise of our tomographic imaging methods to provide these measures, such metrics are not yet routinely available in clinical practice. However, the promising results of the ADNI trial and the current work by Chen et al, as well as other similar trials in patients with a variety of behavioral illnesses, suggest that we may finally be close to achieving this long-held goal. Despite the complexity of the analytic strategies and of the human connectome itself, the elegance of the underlying physiologic observations of Biswal et al (5), and the simplicity of collecting such compelling functional data with today's instruments and examination protocols, as shown here by Chen et al, makes a compelling case that resting-state functional MR examinations will appreciably improve our ability to contribute meaningfully to the care of patients with mental illness, with profound consequences for their health and well-being.

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