Defaulting on the default network: Increased risk for dementia

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The past decade of cognitive neuroscience and neuroimaging research has yielded several critical insights into the organization of the human brain, in particular, the existence of multiple large-scale functional networks. Several of these networks map easily onto conventional notions regarding brain–behavior relationships, such as intrinsic networks subserving motor, sensory, and language function. Perhaps the least intuitive network and arguably the most salient for the study of dementia is a set of brain regions, including the posterior cingulate, precuneus, lateral parietal, lateral temporal, and medial prefrontal cortices, collectively known as the default mode network (DMN). This nomenclature arose from the initial observation in PET studies that these regions show the greatest activity during the resting or “default” state, and demonstrate a marked decrease in activity during cognitive tasks involving externally directed attention.1,2 Multiple fMRI studies, during both cognitive tasks and resting state, have confirmed strong intercorrelations among the DMN cortical regions, as well as functional connectivity with the hippocampus and related structures within medial temporal lobe. The DMN is known to subserve a number of key memory processes, including episodic encoding and retrieval, autobiographical and metamemory processes, as well as other complex cognitive constructs, including moral decision-making and “theory of mind.”

In this issue of Neurology®, Petrella et al.3 report that DMN connectivity was significantly lower in a group of patients with mild cognitive impairment (MCI) who subsequently progressed to a diagnosis of Alzheimer disease (AD) over a period of 2–3 years, compared to patients with MCI who did not decline. Importantly, the study also demonstrated that DMN connectivity provided additional information in predicting the likelihood of progression among the patients with MCI, above and beyond age, Mini-Mental State Examination score, and gray matter volume at baseline. Interestingly, DMN connectivity did not remain a significant predictor when delayed recall memory performance was included in the model, suggesting that DMN connectivity may reflect the integrity of episodic memory systems. Indeed, previous studies across the MCI/AD spectrum have reported associations between DMN connectivity as measured with fMRI and memory performance assessed outside of the scanner.4,5 Notably, the patients with MCI who progressed to AD in the current study also performed significantly worse on the face–name associative memory task that was performed in the MRI scanner at baseline.3

Greicius and colleagues6 first noted DMN alterations during the resting state in patients with mild AD compared to age-matched controls, manifesting as decreased functional connectivity between the posterior cingulate/precuneus and the hippocampus. Subsequently, several groups have reported DMN disruption in MCI,3,e1-e3 in subjects at genetic risk for AD, e4-e6 and, most recently, in clinically normal older subjects with occult amyloid deposition.e7,e8

The anatomic overlap between amyloid deposition and the DMN has been previously noted.e7,8 Both CSF and PET amyloid imaging studies suggest that the subset of amnestic MCI subjects who are amyloid-positive, typically ranging from 50% to 70%, have a much higher likelihood of rapid progression to clinical dementia, consistent with AD.e9,e10 Therefore, it is possible that the disruption of the DMN in the subjects with MCI who were destined to decline to AD dementia in the study of Petrella et al.3 is a marker for the subset of patients with MCI who harbor amyloid pathology. Future longitudinal studies in MCI, including multiple neuroimaging modalities such as PET amyloid imaging...
and functional connectivity MRI, should shed light on these relationships.

What is functional connectivity MRI (fc-MRI) actually measuring? fc-MRI estimates the coherence in the neural activity across brain regions by measuring patterns of synchronous fluctuations in the blood oxygenation level–dependent (BOLD) magnetic resonance (MR) signal. These analyses involve a number of data processing steps, including extracting the BOLD signal time course for specific voxels in the brain image and computing the correlation between these signal fluctuations and those of other brain regions. Accumulating evidence suggests that the intrinsic correlations estimated by fc-MRI are sufficiently constrained by known anatomic connections to use resting-state fc-MRI as a noninvasive probe of integrity of neuronal systems. fc-MRI studies in young healthy subjects have demonstrated at least 7 other major functional networks, including motor, visual, dorsal attention, and frontoparietal control network, in addition to the DMN.

fc-MRI methodology is attractive as a potential biomarker in AD for a number of reasons. MRI scanners with standard sequences to measure BOLD signal are widely available. fc-MRI is noninvasive (does not use any injected contrast agents) and can be repeated multiple times over the course of a longitudinal natural history study or a clinical trial. In addition, the acquisition time of a typical resting-state fc-MRI scan is relatively short (approximately 5 to 8 minutes) and several types of analytic software to preprocess and analyze the data are freely available on the Internet. Moreover, effective pooling of data across different scanner platforms and centers has recently been demonstrated. Taken together, this positions resting-state fc-MRI as a powerful tool for assessing the integrity of functional brain networks in healthy subjects across the lifespan, as well as in neurologic and psychiatric patient populations. Indeed, impaired DMN connectivity has already been demonstrated in a range of neurologic and psychiatric conditions, including frontotemporal dementia, epilepsy, schizophrenia, autism, and late-life depression (for review, see Greicius). One recent study demonstrated that 5 different neurodegenerative syndromes caused a specific pattern of regional atrophy corresponding to 5 distinct intrinsic functional connectivity networks. Collectively, these findings suggest that fc-MRI may one day prove useful in differential diagnosis at very early stages of neurodegenerative disease, ideally prior to irreversible neuronal loss.

In the study of Petrella and colleagues, DMN connectivity was measured during an associative memory fMRI task, whereas the majority of studies in MCI and AD have investigated connectivity during the resting state in the absence of a cognitive task. Although we know that DMN strength during the resting state is somewhat higher while healthy volunteers had their eyes open vs eyes closed, the DMN remains detectable during sleep and even under anesthesia. It remains unclear whether the state of the subject or any specific cognitive task demands will significantly affect the diagnostic or predictive utility of these measures in patient populations, but it is possible that the predictive value of fc-MRI in the Petrella et al. study was enhanced with the use of a memory task known to engage the DMN. There are obvious advantages to measuring integrity of functional networks such as the DMN during the resting state, as opposed to during the performance of a cognitive task, for MCI and AD clinical trials, as this would obviate the need for specialized stimulus presentation equipment, making this technology more widely applicable, and also allow longitudinal functional monitoring of patients who may become too impaired to perform complex cognitive tasks.

Petrella et al. used an independent component analysis (ICA) approach, which is “data driven,” meaning that spatiotemporal characteristics of the functional networks are identified during the analysis without any predetermined regions of interest or hypothesis-driven identification of networks. The ICA approach generates a number of component maps comprised of voxels with significantly correlated time courses. A subset of these component maps correspond to networks, such as the motor network, visual network, and the DMN, but often additional analyses are required to determine the goodness of fit of a given component with a previously identified network. Another analytic approach for fc-MRI has been termed seed-based analysis or seed region of interest analysis, in which the BOLD MR signal, after appropriate preprocessing, is sampled from a predetermined “seed” region in the brain. The MR signal time course from this seed region is then correlated with every voxel in the brain, yielding an estimate of the synchronization between the MR signal fluctuations within the seed region and other brain regions. If one chooses the posterior cingulate cortex, which is known to be a major hub in the DMN, as a seed region, the resulting connectivity map will typically yield the classic pattern of the DMN. While both ICA and seed-based techniques have distinct strengths, they are believed to capture the same functional networks, and likely yield similar results in detecting AD-related alterations in brain connectivity.

A number of questions remain to be elucidated with future research. What is the natural trajectory of decline of DMN connectivity over the course of pre-
clinical and prodromal AD? Are these measures sufficiently sensitive and specific enough to predict future progression for an individual patient? Will DMN connectivity prove to be a sensitive surrogate marker of pharmacologic effects in clinical trials? There are very limited reliability data with these techniques in older adults or patient populations to date, but multicenter studies such as the Alzheimer’s Disease Neuroimaging Initiative and the Dominantly Inherited Alzheimer Network are beginning to incorporate resting-state fMRI into their standard protocols.

Jack and colleagues\textsuperscript{15} recently proposed a hypothetical model for the cascade of biomarkers for AD. This model posits that amyloid-\(\beta\) accumulation (assessed by CSF assays or PET amyloid imaging) is followed later by synaptic dysfunction (assessed by FDG-PET) and neuronal loss (assessed by volumetric MRI), all occurring prior to the onset of dementia. Although further validation studies are clearly needed regarding the reliability and sensitivity of fc-MRI techniques in assessing AD, the study by Petrella et al.\textsuperscript{3} represents an important step forward in adding fc-MRI to the list of biomarkers to track progression in the earliest stages of AD, and ultimately in detecting response to therapeutic intervention in early AD clinical trials.

**DISCLOSURE**

Dr. Van Dijk reports no disclosures. Dr. Sperling serves on a scientific advisory board for Link Pharmaceuticals; serves on the editorial board of *Alzheimer's Disease and Associated Disorders*; serves as a consultant for Elan Corporation, Janssen, Bristol-Myers Squibb, and Pfizer Inc.; and receives research support from Elan Corporation, Janssen, Bristol-Myers Squibb, the NIH/NIA (R01AG027435 [PI] and P01AG036694 [PI]), the Alzheimer’s Association, Anonymous Foundation, and the American Health Assistance Foundation.

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