ALZHEIMER DISEASE

Functional connectivity changes show similar trajectories in autosomal dominant and sporadic Alzheimer disease

The general consensus is that Alzheimer disease (AD) therapies are likely to be most beneficial when administered in the early stages of the disorder. In patients with sporadic AD, however, the disease process tends to be well advanced before the clinical signs emerge, and responses to treatment are difficult to monitor in an objective manner. According to new research by Beau Ances and colleagues, autosomal dominant AD (ADAD) seems to follow a similar disease trajectory to sporadic AD—at least in terms of changes in resting-state functional brain connectivity—and might, therefore, provide valuable insights into AD pathogenesis and treatment.

“The idea is that if we understand what is happening in ADAD, we may be able to translate our understanding to what’s happening in sporadic AD,” explains Ances. “That’s a big assumption—Randall Bateman and colleagues had a paper that showed the time courses of these diseases, but they have never taken the two groups together and looked at a biomarker to see if they progress in the same manner.”

ADAD can be caused by autosomal dominant mutations in any one of three genes: amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*). Carriers of these mutations are almost certain to develop AD, and the age of onset can often be predicted by analysing the patient’s family history.

Ances and colleagues recruited 79 individuals from families with ADAD (23 mutation-positive with AD, 31 mutation-positive but cognitively normal, and 25 mutation-negative and cognitively normal), and 444 patients with sporadic late-onset AD (LOAD). The results of resting-state functional connectivity MRI were correlated with dementia severity, as measured on the Clinical Dementia Rating (CDR) scale, in all participants, and also with estimated years from symptom onset (EYO) in the ADAD cohort.

Mean DMN functional connectivity composite score as a function of degree of cognitive impairment, as assessed by the Clinical Dementia Rating scale. Image courtesy of B. M. Ances.

“Brain areas that oscillate together form networks together, and we can look at a lot of these different networks of the brain just by having the individual lie quietly in the scanner,” says Ances. “One area that’s been heavily studied, and seems to be very affected in AD, is the default mode network (DMN)—the ‘daydreaming area’ of the brain.”

The researchers found that functional connectivity in several resting-state networks (RSNs), including the DMN, was reduced in parallel with rising CDR scores. Importantly, the patterns and trajectories of connectivity changes were similar between the ADAD and the LOAD cohort, suggesting that ADAD could be an appropriate model for sporadic AD.

The EYO-based analysis in patients with ADAD indicated that alterations in functional connectivity preceded the onset of clinical symptoms. As Ances points out, however, these are unlikely to be the earliest changes in AD: “changes in amyloid are seen 10–15 years, and tau 10 years, before age of onset, but resting-state functional connectivity changes are observed, at most, 5 years before age of onset.” He suggests that functional connectivity, if used as a biomarker, is likely to be most sensitive in patients with mild cognitive impairment.

These findings raise the possibility that functional connectivity within the DMN and other RSNs could provide a ‘read-out’ in clinical trials to assess the effects of new therapies in patients with AD. In addition, this MRI technique might aid the identification of preclinical AD in patients who are already undergoing clinical assessment for other neurological conditions. “Resting-state functional connectivity can easily be added to the common MRI sequence,” says Ances. “It only takes 10–15 min to do, and doesn’t require an individual to do any tasks.”

Alterations in functional connectivity might also inform the development of new treatment strategies for AD. The networks that exhibit these changes could themselves be prime targets for neuromodulatory therapies, as well as providing broader insights into the underlying disease mechanisms.

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Original article Thomas, J. B. *et al.* Functional connectivity in autosomal dominant and late-onset Alzheimer disease. *JAMA Neurol.* doi:10.1001/jamaneuro.2014.1654

Further reading Bateman, R. J. *et al.* Clinical and biomarker changes in dominantly inherited Alzheimer’s disease. *N. Engl. J. Med.* 367, 795–804 (2012) | Zhang, D. & Raichle, M. E. Disease and the brain’s dark energy. *Nat. Rev. Neurol.* 6, 15–28 (2010)