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ALZHEIMER DISEASE

Altered functional connectivity in preclinical dementia

Several investigations of the brain's intrinsic connectivity networks have described notable loss of intrinsic connectivity in older people with and without dementia. Two new studies elucidate the complex involvement of amyloid-β (Aβ) in age-related alterations within the default mode network (DMN) and other large-scale networks.

Hyun Kook Lim and colleagues sought to uncover the potential effects of Aβ on intrinsic connectivity in the early preclinical phase of Alzheimer disease (AD), before overt symptoms of dementia manifest. A thorough understanding of how and when Aβ affects networks in the brain might reveal valuable information about the slow, insidious onset of AD.

Lim and co-workers recruited 56 participants aged over 60 who had no cognitive impairment, as defined by scores within normal limits on the Mini Mental State Examination. These participants then underwent PET scans with the ^{11}C-PIB radiotracer, which selectively binds to Aβ deposits. Using *a priori* determined cut-off values for ^{11}C-PIB uptake, the investigators split the group of healthy participants into Aβ+ and Aβ– subgroups.

Functional MRI (fMRI) scans were then conducted in all participants, and the investigators applied previously defined maps to delineate the DMN, salience network and central executive network.

Although the groups had similar performance on a range of cognitive tasks, the Aβ+ participants showed decreased connectivity in the central executive network relative to the Aβ– group. Integrity of salience network connectivity did not differ between the groups. Unexpectedly, connectivity in the DMN was increased in Aβ+ participants. This effect seems inconsistent with previous studies, which have found reduced connectivity in patients with mild cognitive impairment or AD.

Lim and colleagues argue that their data might indicate an important consequence of early Aβ deposition. Their results are largely consistent with data from animal models, which have demonstrated that high levels of Aβ in the brain disrupt synaptic activity, but moderate levels can enhance functional connectivity.

Longitudinal studies will be necessary to fully uncover how the DMN changes with age, and a recent study by Matthew Brier and co-workers highlights the importance of carefully designing these studies with respect to participant recruitment.

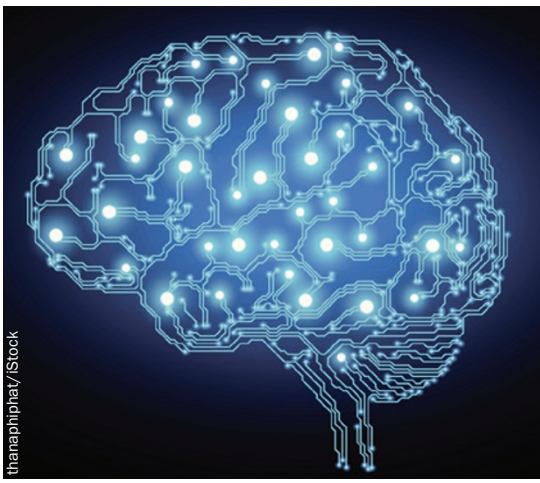
"One of the critical problems in the ageing and dementia field is the accurate attribution of changes in brain function and behaviour to healthy ageing or disease," explains Brier. Given the long prodromal phase associated with AD, Brier continues, it is possible for previous studies that investigated functional connectivity to have convoluted the effects of healthy ageing with the effects of preclinical dementia.

Brier and colleagues drew participants between the ages of 45 and 95 from a community-based study conducted by the Knight AD Research Center at Washington University in St Louis, MO, USA. The investigators measured levels of Aβ in the cerebrospinal fluid (CSF) of cognitively normal participants, and identified 200 typical individuals (Aβ–) and 97 patients with abnormally low levels of Aβ in CSF, which suggests retention of this peptide in the brain (Aβ+).

All participants then underwent fMRI scans, and the researchers fitted a multivariate regression model to the resting-state connectivity data, including age and Aβ status as variables of interest.

In the Aβ+ participants, connectivity in several clusters within the DMN negatively correlated with age, but these relationships were substantially attenuated in the Aβ– individuals.

To further explore the effects of age and Aβ on resting-state networks, the investigators calculated composite scores reflecting overall connectivity within five separate networks. These scores were then analysed with an additional sample of similarly aged people.



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Connectivity within the dorsal attention network was significantly lower in older participants than in younger participants, and this effect was not mediated by Aβ status. The analysis of the composite scores also reaffirmed the results of the regression model: connectivity in the DMN was significantly reduced in Aβ+ participants, but not in those who were Aβ–. The other networks investigated, including the salience network, were not affected by age.

"The results of this study are extremely relevant to ongoing research that seeks to identify the earliest effects of neurodegenerative disease on brain networks," concludes Brier. "It will be impossible to identify the earliest effects of disease if the control group is contaminated with unrecognized disease." Therefore, future studies of large-scale networks in older people should account for Aβ status.

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Original articles Lim, H. K. *et al.* Regional amyloid burden and intrinsic connectivity networks in cognitively normal elderly subjects. *Brain* doi:10.1093/brain/awu271 | Brier, M. R. *et al.* Unrecognized preclinical Alzheimer disease confounds rs-fcMRI studies of normal aging. *Neurology* doi: 10.1212/WNL.0000000000000939

Further reading Lyall, D. M. *et al.* Are APOE ε genotype and TOMM40 poly-T repeat length associations with cognitive ageing mediated by brain white matter tract integrity? *Transl. Psychiatry* **4**, e449 (2014)