ALZHEIMER DISEASE

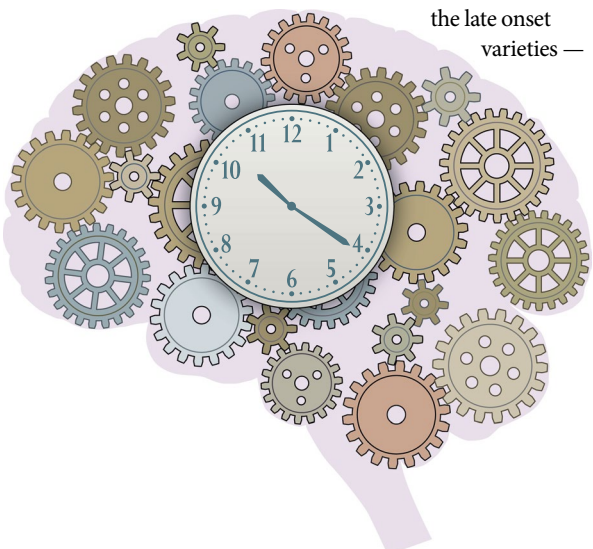
Neuroimaging model predicts time of symptom onset in sporadic AD

> Sporadic AD might not be as sporadic as the name suggests

Changes detected with structural and functional MRI can be used to forecast the number of years until sporadic Alzheimer disease (AD) symptom onset, according to a new study published in *Brain*. Investigators used imaging features in the healthy descendants of individuals with sporadic AD to build a model capable of predicting the age of dementia onset in populations at risk of AD.

AD has a long preclinical stage in which changes in brain structure and function gradually occur without cognitive symptoms. In people with autosomal dominant forms of AD, symptom onset occurs at around the same age across generations. By contrast, estimation of the timing of progression to disease is difficult in those with sporadic AD.

In a new study, a team led by Sylvia Villeneuve and Jacob W. Vogel investigated whether the partial heritability of sporadic AD could enable the prediction of disease onset from MRI data. "We were struck by evidence that AD — even the late onset varieties — seems to be somewhat heritable," remarks Vogel. "Ageing and parental history of AD are two of the strongest risk factors for developing AD, and with the Presymptomatic Evaluation of Novel Treatment of Alzheimer's Disease (PREVENT-AD) cohort, we had a unique opportunity to examine the interaction between these two risk factors."



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The researchers examined MRI data from 255 cognitively normal individuals from the PREVENT-AD cohort who had at least one parent who had been clinically diagnosed with sporadic AD. They used the difference between the parent's age of dementia onset and the participant's current age as an estimate for the number of years until symptom onset, and examined whether any correlation existed between this value and the structural and functional brain features present in each individual.

"We used a machine-learning approach to test whether we can use brain properties such as grey matter volume and whole-brain resting state functional connectivity to predict a person's expected age of dementia onset," explains Villeneuve.

Villeneuve and colleagues found that a low estimated time to disease onset was associated with a loss of grey matter volume and changes in functional connectivity in many of the same regions that are known to undergo changes in AD. The team then used these imaging features to train a model to predict the age of disease onset from MRI data in other individuals.

The researchers first tested their model in a separate subset of the PREVENT-AD cohort that had not been examined in the initial machine-learning phase, and found that the model could predict the estimated years to disease onset. However, the actual age of dementia onset was unknown in these individuals as they had not yet converted to clinical AD. "To surmount this issue, we attempted to replicate our results in another off-site sample (the Alzheimer's Disease Neuroimaging Initiative (ADNI)) that collected the same types of MRI data," says Vogel.

The team tested their model on data from 26 individuals in the ADNI cohort who eventually converted to mild cognitive impairment or AD, and for whom MRI data was available prior to AD symptom onset. Interestingly, the model could successfully predict the number of years to symptom onset in these individuals, even after adjusting for age. In addition, the team found that their neuroimaging model outperformed a second similar model that had been trained with only traditionally used clinical measures, including cognition, demographics, genetics and imaging.

"Our results suggest that changes in the structural and functional properties of certain brain regions might be able to provide information as to when an at-risk person might start showing symptoms of AD," remarks Vogel. "These findings re-inforce the idea that sporadic AD might not be as sporadic as the name suggests, but progresses similarly in genetically alike individuals across generations."

Charlotte Ridler

ORIGINAL ARTICLE Vogel, J. W. et al. Brain properties predict proximity to symptom onset in sporadic Alzheimer's disease. *Brain*. https://doi.org/10.1093/brain/awy093 (2018)
FURTHER READING Elahi, F. M. & Miller, B. L. A clinicopathological approach to the diagnosis of dementia. *Nat. Rev. Neurol.* **13**, 457–476 (2017)