BRAIN COMMUNICATIONS

SCIENTIFIC COMMENTARY

Detecting early changes in Alzheimer's disease with graph theory

This scientific commentary refers to 'Single-subject grey matter network trajectories over the disease course of autosomal dominant Alzheimer disease', by Vermunt et al. (https://doi.org/10.1093/braincomms/fcaa102).

Alzheimer's disease has a long preclinical phase during which pathophysiological changes accumulate in the brain in the absence of clear cognitive symptoms. The order and rate of these changes can be estimated in mutation carriers of familial Alzheimer's disease, who have a predictable age of onset that can be used to assess the sequence of changes that eventually lead to dementia. This sequence has been shown to begin with decreases of amyloid in the cerebrospinal fluid 25 years before symptom onset, followed by Aβ deposition on positron emission tomography, increased concentrations of tau protein, brain atrophy and hypometabolism (Bateman *et al.*, 2012). However, it is currently unclear when brain network disruption emerges in this temporal sequence. This is important as brain connectivity is crucial for normal cognitive functioning and can potentially track the spread of pathological changes in Alzheimer's disease (Griffa *et al.*, 2013). In this issue of *Brain Communications*, Vermunt *et al.* (2020) address this knowledge gap and show compelling evidence that brain connectivity starts changing as early as 13 years before symptom onset in familial Alzheimer's disease. This evidence was obtained in a large cohort of individuals from the Dominantly Inherited Alzheimer Network (DIAN) by combining structural MRI with graph theory. After building grey matter covariance networks for each individual, the authors found that the earliest changes were located in the precuneus and that specific network measures correlated with relevant disease biomarkers such as amyloid accumulation, brain metabolism, cortical thickness and cognition. These findings open new opportunities for the application of brain connectivity measures as a non-invasive tool to improve the early diagnosis and track disease progression in Alzheimer's disease.

There is consistent evidence showing that, rather than relying on isolated brain areas, cognitive functions depend on the communication between interconnected regions across large-scale networks (Griffa *et al.*, 2013). Thus, studies assessing such interactions and networks are valuable for understanding conditions associated with cognitive decline and dementia such as Alzheimer's disease. In the past few years, the study of brain networks has been transformed by a mathematical approach based on graph theory, which represents the brain as a set of nodes connected by edges. This representation of the brain can be used to assess important measures that reflect its topological architecture such as short network paths or local clusters of connections (Mijalkov *et al.*, 2017). In the study by Vermunt *et al.* (2020), the authors applied a graph theory approach to study the network topology in mutation carriers of familial Alzheimer's disease. They found that the earliest network changes could be observed 13 years before disease onset and consisted of shorter network paths or more direct links between brain areas. These findings confirm previous reports of altered path lengths in the networks of patients with sporadic Alzheimer's disease and suggest that network paths could be used as early measures of network disruption in asymptomatic high-risk individuals. Another interesting finding is the fact that these changes were most prominent in the precuneus, an area that is known to play an important role as a brain hub, displaying a high number of connections to other brain regions. In addition, the precuneus is especially important for Alzheimer's disease because it overlaps with one the main sites of early amyloid accumulation (Palmqvist *et al.*, 2017) and belongs to a network with important memory functions known as the default-mode network (Bahk and Choi, 2018). The fact that the network paths were shorter in this particular region could be due to a compensatory mechanism by which the number of direct connections to other brain regions would increase in mutation carriers in order to withstand the

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effects of pathology, a phenomenon also known to occur in individuals with higher genetic risk for developing sporadic Alzheimer's disease (Bondi *et al.*, 2005).

Moreover, the authors found that the changes in the network paths were followed by a loss of small-world organization and reduced local clusters of connections, which are directly related since a small-world organization requires a high number of local clusters in the network in addition to a few short network paths. The fact that these measures were found to decrease together suggests that the brain networks of individuals who will eventually develop Alzheimer's disease become progressively more random over time, with more direct paths and less clusters, loosing their balance between global and local connectivity. These findings highlight the important role that network topology has in the development of Alzheimer's disease indicating that complex measures that combine information embedded in clusters and paths change earlier and are associated with other pathological changes such as amyloid deposition, brain hypometabolism and cognitive deficits. This was further confirmed by the author's additional results showing that simple network measures such as the degree and density, which basically reflect the number of connections in the network, changed later in the course of the disease and were closer to the symptom onset.

Thus, alterations of network topology could become an important biomarker for Alzheimer's disease and help understanding the underlying mechanisms that drive cognitive decline and dementia. This calls for studies assessing the biological meaning of topological measures and what they actually reflect in Alzheimer's disease. In particular, despite extremely valuable, it is currently unknown the exact underpinnings of networks built using correlations between grey matter areas, which Vermunt *et al.* used in their seminal study. A common interpretation is that these structural correlations result from some kind of brain connectivity such as the physical connectivity of white matter tracts or the functional connectivity of synchronous activation patterns (Alexander-Bloch *et al.*, 2013). In a previous study comparing white matter connections with structural correlations, it was found that ~40% of structural correlations overlap with white matter tracts (Gong *et al.*, 2012). In addition, a study comparing the spatial organization of clusters defined using structural correlations of grey matter or functional connectivity, found a striking spatial overlap between the two sets of clusters identified in the two different approaches (Kelly *et al.*, 2012). Altogether, this suggests that structural covariance might be associated with both white matter and functional connectivity but more studies are needed to further investigate this, particularly in patients with preclinical and clinical Alzheimer's disease.

In summary, the study by Vermunt *et al.* (2020) demonstrates that alterations of network topology may be a key feature of early stages of Alzheimer's disease and a plausible mechanism by which the whole brain networks become progressively more random over time. Identifying abnormalities within these networks may be useful in understanding how changes associated with amyloid and potentially tau pathology spread through interconnected brain areas, paving the way to cognitive decline. A key issue moving forward will be to investigate the exact neurobiological factors that drive the changes in the paths, clusters and small-world properties the authors have observed in their study as well as replicating their findings in independent samples.

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Competing interests

The authors report no competing interests.

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