BRAIN
SCIENTIFIC COMMENTARY

# Towards a coherent view of network hyperexcitability in Alzheimer's disease

**This scientific commentary refers to 'Neuronal synchrony abnormalities associated with subclinical epileptiform activity in early-onset Alzheimer's disease' by Ranasinghe *et al.* (https://doi.org/10.1093/brain/awab442).**

A major challenge for the development of novel therapies for Alzheimer's disease is the heterogeneity in clinical phenotypes and in rates of cognitive and functional decline across individuals. This heterogeneity necessitates large sample sizes for clinical trials to be sufficiently powered to detect treatment effects. It also poses a risk for premature dismissal of therapies that may be highly effective in specific subgroups of patients with Alzheimer's disease but that fail to show an overall benefit in a broader study population where the effect is washed out. Understanding and controlling for disease heterogeneity is therefore vital to improving our success rate in clinical trials. In this issue of *Brain*, Ranasinghe and co-workers[1] examine resting-state measures of network hyperexcitability in Alzheimer's disease, a feature that may have important implications for understanding clinical heterogeneity in future therapeutic trials.

Multiple lines of evidence, from rodents to humans, across various study modalities, have provided strong support for the idea that network dysconnectivity and hyperexcitability are intrinsic and important features of Alzheimer's disease[2,3] (Fig. 1). Studies in rodent genetic models have shown that network hyperexcitability arises early in the disease course, is closely linked to amyloid and tau pathology by a feedforward mechanism and independently contributes to cognitive dysfunction. Seizures and epileptiform activity are a classic manifestation of network hyperexcitability, and many rodent genetic models of Alzheimer's disease spontaneously develop clinical seizures and epileptiform discharges.[4] Treatment with anti-seizure medications reduces network hyperexcitability and improves cognitive function in these animals.[5]

In humans, Alzheimer's disease is also associated with an increased risk of seizures, with up to 15–20% of patients affected. Seizures are associated not only with an earlier onset of cognitive decline but also with more rapid disease progression.[4] Even among those individuals with Alzheimer's disease without seizures, recent studies have shown that 20–40% have epileptiform discharges that can be detected on scalp EEG and/or MEG recordings, and this 'epileptiform phenotype' may also be associated with accelerated cognitive decline.[6,7]

The results from the recent Levetiracetam for Alzheimer's Disease-Associated Network Hyperexcitability (LEV-AD) trial highlight the potential significance of accounting for the epileptiform phenotype of Alzheimer's disease in clinical trials.[8] LEV-AD was a small phase 2a randomized, double-blind, placebo-controlled crossover study of low-dose levetiracetam (LEV) in the early clinical stages of Alzheimer's disease (mild cognitive impairment or mild dementia). All participants had biomarker-confirmed Alzheimer's disease by CSF or amyloid PET imaging. The primary outcome measure was improvement in executive function based on the NIH EXAMINER composite score, while secondary outcome measures included improvement in additional measures of executive function, global cognitive function, disability and behaviour. Ultimately, LEV-AD was a negative study; the overall study population showed no significant change in any of the primary or secondary outcome measures with LEV compared with placebo.

However, a unique feature of LEV-AD was that prior to treatment, all participants underwent neurophysiological characterization with overnight scalp EEG and 1-h MEG, to identify those with the epileptiform phenotype. Stratification of the study results based on those with the epileptiform phenotype (AD-EPI+) versus those without (AD-EPI−) revealed that AD-EPI+ had significantly improved performance on executive function and spatial memory tasks with LEV compared with placebo, while AD-EPI− had no improvement with LEV on any measure. While these results require validation in a larger study population, they provide a hint that stratification based on the epileptiform phenotype in Alzheimer's disease could be important, particularly for developing targeted therapies to reduce network hyperexcitability.

The epileptiform phenotype of Alzheimer's disease is currently defined by the presence of epileptiform discharges on scalp EEG or MEG recordings. Epileptiform discharges are the best characterized clinical biomarker of epilepsy and network hyperexcitability, although they are a labour-intensive and subjective biomarker. These brief (<200 ms), paroxysmal electrical abnormalities are identified by their distinct morphology relative to the background activity. This process requires thorough visual review of an EEG/MEG recording by trained neurophysiologists, is subjective in nature and has limited inter-rater reliability. Computational algorithms that can automatically identify epileptiform discharges on EEG may address these shortcomings in the future but currently require substantial human supervision due to high false-positive rates.

Particularly in Alzheimer's disease, epileptiform discharges are also a poorly sensitive and temporally inconsistent biomarker for network hyperexcitability. Among those with Alzheimer's disease and clinical seizures, only 50% have epileptiform discharges visible on scalp EEG.[6] Among those with Alzheimer's disease without seizures but with the epileptiform phenotype, a 24-h scalp EEG recording typically contains 10 or fewer epileptiform discharges,[6,7] which

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may create a floor effect, making these discharges a suboptimal biomarker for assessing target engagement in a therapeutic trial. Consequently, the development of more objective and quantitative biomarkers of network hyperexcitability in Alzheimer's disease could be helpful, particularly as targets in clinical trials.

This was the motivation for the study by Ranasinghe and colleagues. Here, they used resting-state, source space reconstructed MEG recordings to calculate global imaginary coherence, a measure of the similarity in oscillatory activity between a given brain region and the rest of the brain at a specific frequency band. In a previous study, the authors had found that individuals with Alzheimer's disease have localized abnormalities in alpha and delta/theta imaginary coherence relative to age-matched healthy controls, and that these synchronization abnormalities were associated with tau and amyloid deposition, as well as with cognitive function as indexed by the MMSE.[9] In this study, the authors combined and extended their prior lines of research on hyperexcitability and synchrony changes in Alzheimer's disease by examining the frequency- and region-specific differences in imaginary coherence between AD-EPI+ and AD-EPI− groups who were mildly to moderately impaired, in addition to healthy age-matched controls. They found that AD-EPI+ had regional patterns of reduced imaginary coherence in the alpha band (8–12 Hz) and increased imaginary coherence in the delta-theta band (2–8 Hz), compared with AD-EPI−. Logistic regression models using region- and frequency-specific imaginary coherence features accurately discriminated between AD-EPI+ and AD-EPI− groups.

A prior study by the same group (which included 54% of participants from the current study) had reported accelerated rates of decline in global cognition and executive function in AD-EPI+ compared with AD-EPI−.[7] The authors replicated their prior findings in this study's larger cohort and then examined the relationship between network synchrony measures and global cognitive decline. Using a principal component analysis to capture the variance of imaginary coherence across their study population, they found that the first two principal components accounted for 47% of the variance in MMSE decline across their population. A regression model using the first two principal components also showed a significant association between these components and longitudinal change in MMSE score.

The novel and most important contribution of the work by Ranasinghe *et al.* is thus the identification of abnormalities in imaginary coherence as a potential resting-state biomarker of network hyperexcitability, as indexed by the presence or absence of epileptiform discharges. Placed in broader context, their work is coherent with multiple other experimental modalities that have revealed abnormalities in functional connectivity and network hyperexcitability in Alzheimer's disease (Fig. 1) and further demonstrates how these findings may be related to one another as well as to amyloid and tau deposition.

Yet, there are some questions that remain with regards to the relationship between network synchrony measures, the epileptiform phenotype and cognitive decline in Alzheimer's disease. While imaginary coherence features accurately discriminated between AD-EPI+ and AD-EPI−, the authors found no clear spatial relationship between the location of epileptiform discharges and the regional pattern of network synchrony abnormalities in AD-EPI+. The pattern of network synchrony differences between AD-EPI+ and AD-EPI− was also curiously distinct from the pattern of synchrony differences between the Alzheimer's disease group as a whole and healthy controls. In addition, the relationship between the frequency of epileptiform discharges and the degree of network synchrony abnormality in AD-EPI+ remains to be determined, as does the importance of arousal state, as imaginary coherence was measured in the awake resting-state, while the majority of epileptiform abnormalities in Alzheimer's disease occur during sleep.[6,7]

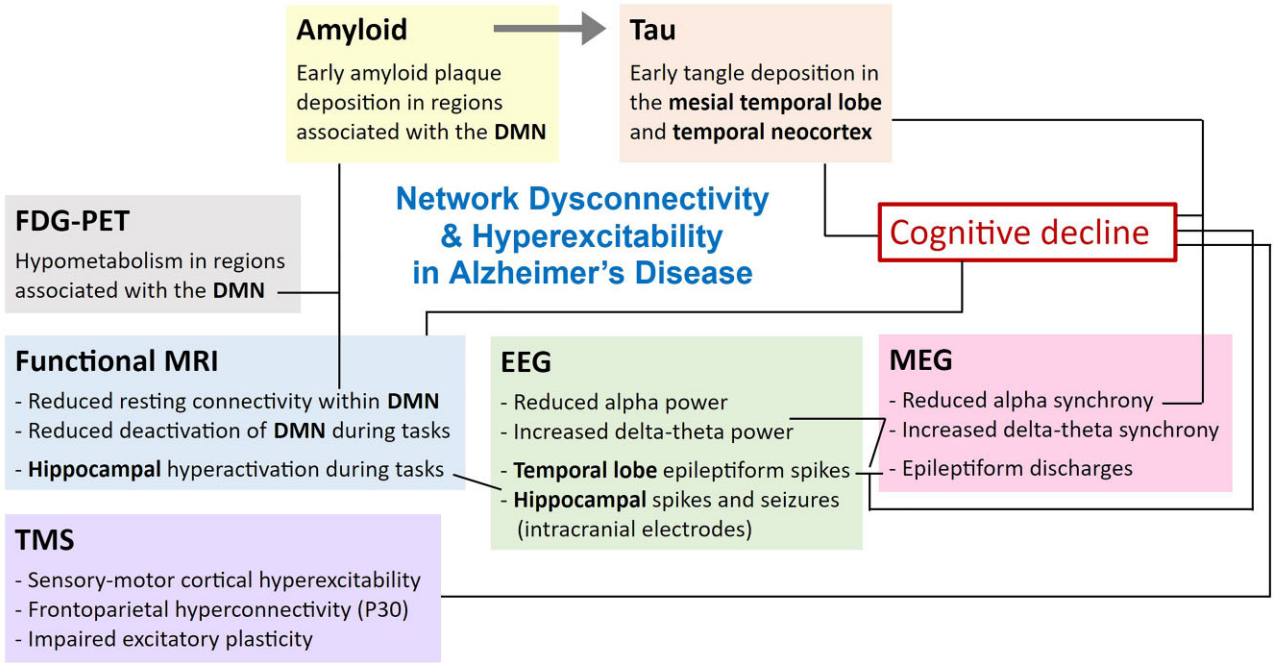


**Figure 1 Multiple experimental modalities have provided evidence of network dysconnectivity and hyperexcitability in patients with Alzheimer's disease**. This schematic highlights how the findings from these modalities are related to one another, as well as to Alzheimer's disease pathology and cognitive decline.

Replication of these findings in a larger cohort will be needed, particularly as the reliability of several measures of MEG/EEG connectivity, including imaginary coherence, remains in question. Another important consideration is that over 90% of the Alzheimer's disease group in this study had early-onset Alzheimer's disease (median age of onset ~54 years), and it is unclear how these findings will translate to a more typical, late-onset Alzheimer's disease population.

The study by Ranasinghe *et al.* identifies a potential biomarker that, if validated, could greatly facilitate targeted recruitment for future clinical trials of therapeutics aimed at modulating network hyperexcitability in Alzheimer's disease. Network synchrony measures also have the potential to function as dynamic biomarkers that could be used to assess target engagement in the same trials. Prior studies have provided some evidence that acute treatment with LEV normalizes resting-state network abnormalities in Alzheimer's disease.[10] Demonstration from the LEV-AD study that chronic treatment with LEV results in normalization of imaginary coherence abnormalities, which in turn correlates with improvement in executive function, would provide an important validation of this measure as a meaningful and dynamic estimate of network hyperexcitability in Alzheimer's disease.

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## Competing interests

The authors report no competing interests.

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