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Functional brain network disruption in cognitively unimpaired autosomal dominant Alzheimer's disease: a magnetoencephalography study

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Background

- Understanding the nature and onset of neurophysiological changes, and selective vulnerability of hub regions, in Alzheimer's disease (AD) patients may be useful for early diagnosis, prognosis and intervention in the future[1-3].
- Prior studies in sporadic AD proposed an activity dependent degeneration and suggest that excitation-inhibition (E-I) imbalance contribute to observed functional brain network changes [4-7], but the precise neurophysiological changes occuring in the preclinical stage remain unknown[8-13].

Aim

To increase insight on neurophysiological alterations in cognitively unimpaired subjects with autosomal dominant AD, 'a true early-stage of Alzheimer's disease', using robust measures that also reflect E-I balance[4-7].

Methods

High spatial resolution source-space magnetoencephalography (MEG) during rest in 11 cognitively unimpaired individuals with autosomal dominant AD (carrying pathogenic mutations in the *APP* and *PSEN1* genes) and a 1:3 matched control group.

Quantitative MEG measures: spectral power, and functional connectivity (FC) in different frequency bands on whole-brain and regional level. Specific vulnerability of hubs was investigated using the hub disruption index (HDI).

Results

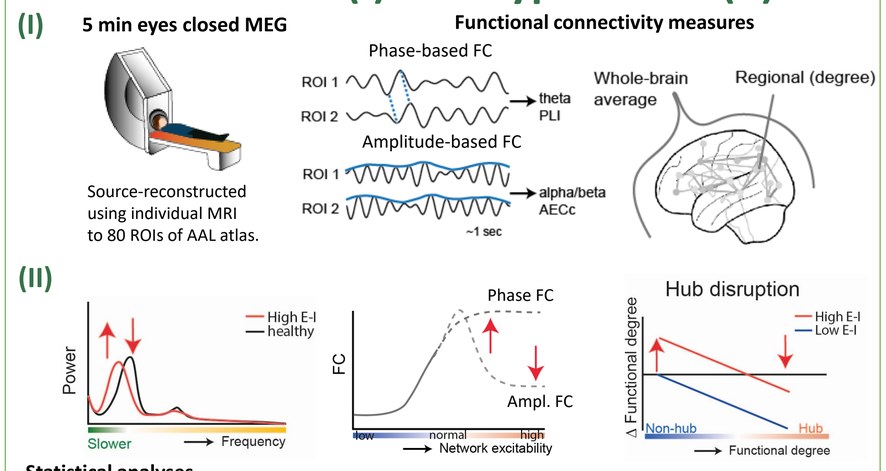
Mutation carriers present:

- Spectral slowing, *i.e.* significantly higher widespread relative theta (4 – 8 Hz) power, lower posterior peak frequency and occipital alpha 2 (10 – 13 Hz) power compared to controls.
- Lower whole-brain average (amplitude-based) FC in the alpha (8 – 13 Hz) and beta (13 – 30 Hz) bands, predominantly in parieto-temporal hub regions.
- Both decreased (phase-based) FC in hubs and increased (phase-based) FC in "non-hubs" in the theta band.

Conclusions

Neurophysiological alterations present before cognitive impairment in individuals with autosomal dominant AD. The changes are comparable to those observed in clinical stages of sporadic AD, and fit with the activity dependent degeneration hypothesis.

Methods (I) and hypotheses (II)



Statistical analyses

- Whole-brain differences: Wilcoxon matched-pairs signed rank sum test, sign: $p < .05$
- Regional differences: Paired-sample permutation test (2000 permutation), corrected by maximal statistic
- HDI: Linear regression analyses

PLI, Phase Lag Index; AECc, Amplitude Envelope correlation corrected for volume conduction; ROI, region of interest; E-I, excitation-inhibition balance,

Subject demographics

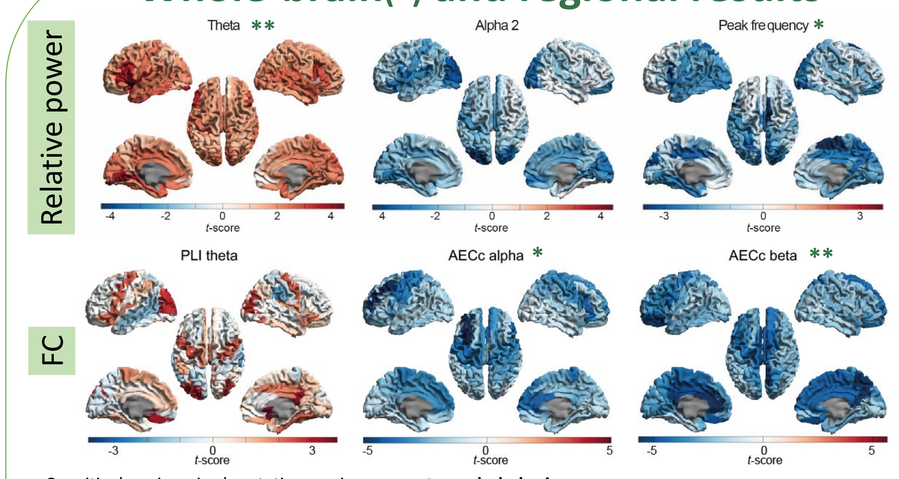
	Mutation carriers (n = 11)	Controls (n = 33)
Age (y)	49 [20 – 61]	49 [20 – 62]
Female/Male (n)	8/3	24/9
***PSEN1/APP* (n)**	9/2	-
Education (Verhage)	6 [5 – 7]	6 [1 – 7]
MMSE	29 [27 – 30] (n = 11)	27 [27 – 30] (n = 7)
EYBSO (y)	1 [-16 – 22]	

Median [min – max]. MMSE, mini-mental state examination; EYBSO, estimated years before symptom onset

Hub locations

	PLI theta		AECc alpha		AECc beta	
	Controls	**Mutation carriers**	**Controls**	**Mutation carriers**	**Controls**	**Mutation carriers**
Hub #1	Temporal_Mid_L	Precentral_L	Fusiform_R	Fusiform_L	Parietal_Inf_R	Angular_L
Hub #2	Temporal_Pole_Mid_L	Olfactory_L	Hippocampus_R	Temporal_Inf_R	Angular_R	Parietal_Inf_R
Hub #3	Angular_L	Fusiform_R	Angular_R	Temporal_Mid_R	Parietal_Inf_L	SupraMarginal_L

Whole-brain(*) and regional results

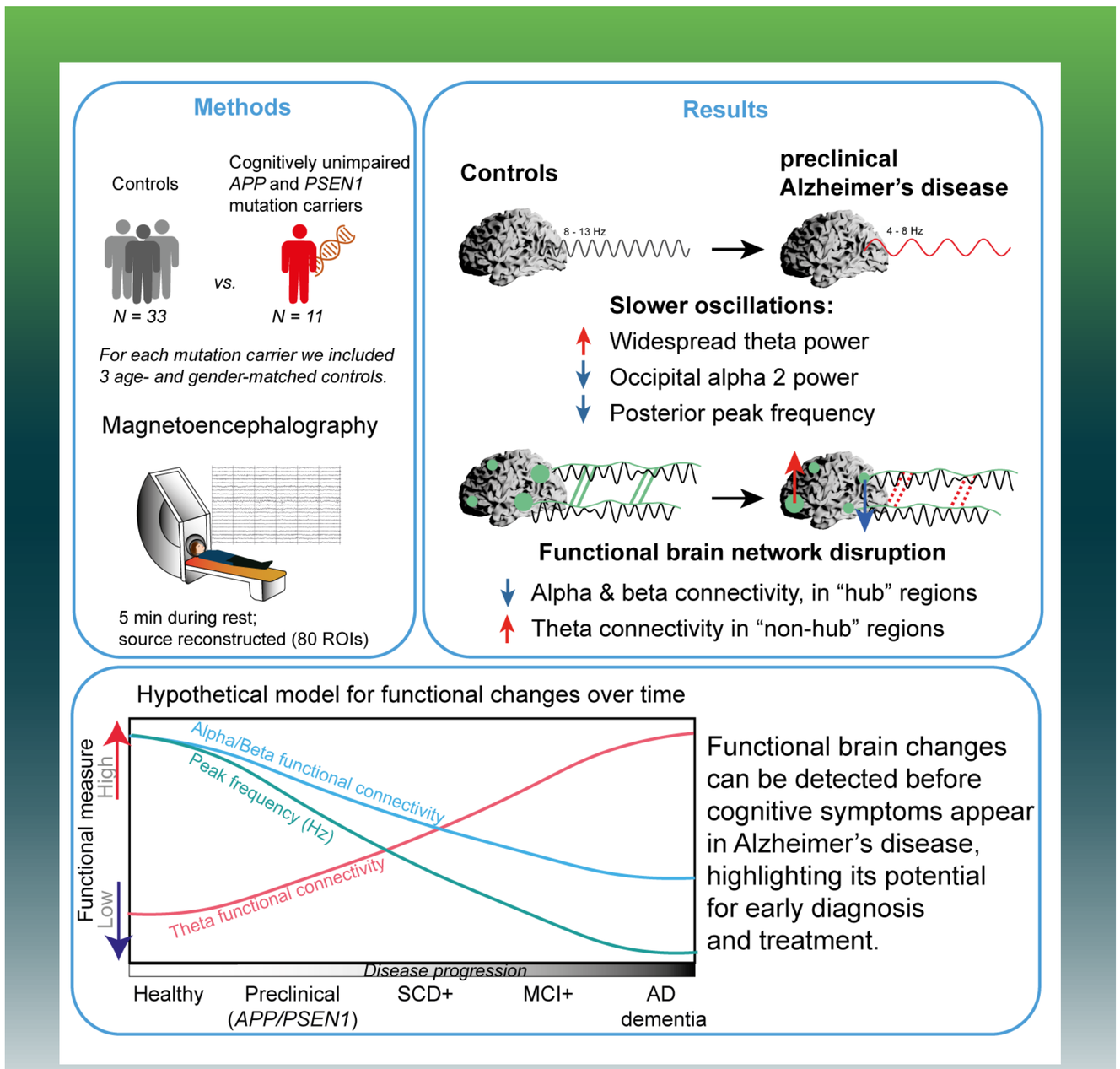


Cognitively unimpaired mutation carriers present on **whole-brain average:**

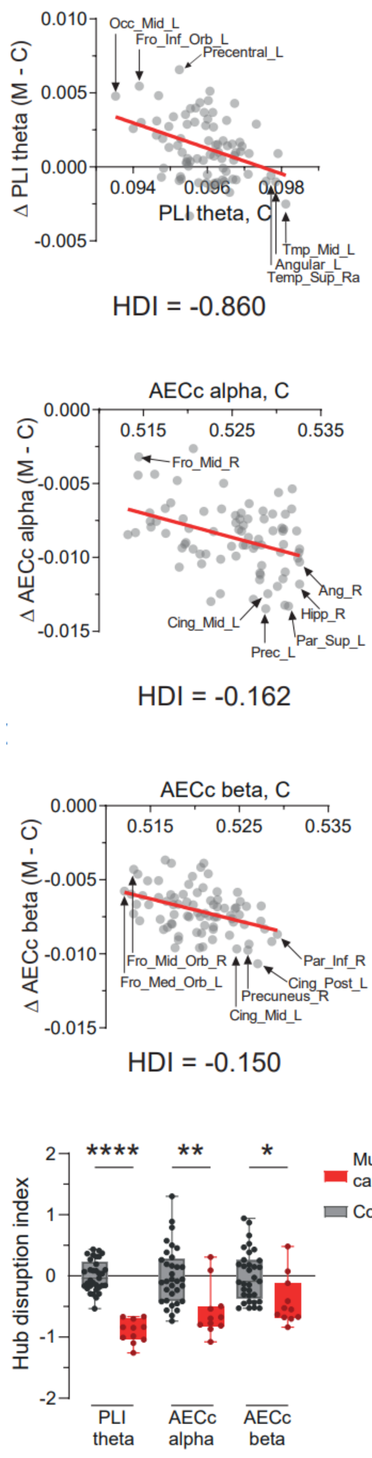
- Power: lower relative theta power ($p < .01$) and peak frequency ($p < .05$),
- FC: lower alpha ($p < .05$) and beta ($p < .01$) band FC compared to controls

Significant **regional differences** between mutation carriers and controls after multiple comparisons correction:

- Power: **theta** in insula, lingual gyrus, triangular frontal inferior (L) and sup. motor area (R); **alpha 2** in sup occipital cortex (L)
- FC: **AECc alpha** in mid- and inferior-frontal gyrus (L/R), **AECc beta** in *n* = 23 ROIs including frontocentral and anterior-posterior cortices (L/R), and precuneus (R)



Hub disruption index results



Cognitively unimpaired mutation carriers exhibit degree-dependent functional connectivity changes, with a preferential disruption of connectivity in temporoparietal hub regions as well as an increase in connectivity in anterior "non-hub" regions.

HDI, hub disruption index; M, mutation carriers; C, controls

Relevance & Future studies

- The findings do not suggest a biphasic change but points towards progressive neurophysiological alterations across the AD continuum
- An abnormal E-I ratio and activity dependent disruption may underlie the observed alterations already in a preclinical stage of the disease.
- **Future studies** are required to firmly establish the underlying cause of neurophysiological alterations, using more direct measures of E-I.
- Timely detecting and intervening with abnormal neurophysiological activity and E-I balance offers potential early diagnostic or prognostic tools and an alternative, noninvasive treatment target.

References

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