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Timing and order of pathological events in Alzheimer's disease: focus on the trajectory of the awareness of cognitive decline

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Objectives

We built an Alzheimer's disease (AD) Course Map depicting the timing and order of the pathological events occurring during AD progression, with a particular focus on the evolution of the awareness of cognitive decline (ACD).

Methods

We included 373 ADNI participants with positive markers of amyloid and tau (A+T+), and 145 A-T-cognitively-normal controls.

The AD Course Map was built by including measures of global cognition (MMSE), episodic memory (RAVLT), autonomy (FAQ), self- and informant-reported ratings of cognitive functioning (E-Cog), brain metabolism, hippocampal volume. An Awareness of Cognitive Decline Index (ACDI) was computed as the subject-informant discrepancy in the E-Cog score. All measures were normalized between 0 (normal) and 1 (abnormal). We used a non-linear Bayesian mixed-effects model in the Leaspy software (<https://gitlab.com/icm-institute/aramislab/leaspy/>).

Results

Our model identified the following temporal sequence of events in AD (see Figure): the episodic memory was the first measure to become abnormal in A+T+ subjects (i.e. different from controls), followed by autonomy, study-partner's E-Cog score, brain metabolism and MMSE, hippocampal volume, and finally subject's E-Cog score (this latter occurring around 3 years after the diagnosis of dementia).

The ACDI had a non-linear evolution: the subject initially experiences cognitive complaints but his/her ACD soon decreases, eventually constituting a clear anosognosia.

Conclusions

The study of ACD in AD is a piece of the larger understanding of the pre-dementia phases. The presence of an informant is useful to identify the first signs of the disease and anticipate the diagnosis.

