Awareness of cognitive decline through the continuum of Alzheimer's disease and its association to APOE-ϵ4 and amyloid load

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Background: Anosognosia is a common symptom of Alzheimer's disease (AD) dementia. However, the trajectory of the awareness of cognitive decline (ACD) across the predementia phases remains unclear. This study aimed to outline ACD changes through the entire course of AD, and study the impact of APOE-ε4 genotype and amyloid load on the ACD evolution.

Method: We included 1280 subjects (7403 visits) from ADNI cohort, aged from 55 to 91 (M=73.7). They are progressors from cognitively-normal and MCI stages, but also subjects with stable MCI and AD. ACD was measured as the subject-informant discrepancy on the Everyday cognition (ECog). Using a non-linear Bayesian mixed-effects model (Schiratti et al., 2015, NIPS), we recombined the short-term individual measurements into a long-term progression of ACD. This allows to map the individual visits onto a common disease timeline, so that the real ages are reparametrized into comparable physiological ages. From each individual trajectory, we extracted the physiological age of (i) maximum hypernosognosia, (ii) accurate awareness, and (iii) anosognosia - whose value corresponded to the upper 20th percentile cut-off (normalized discrepancy of 0.3). These ages were correlated to the number of ε4 alleles and amyloid status (Aβ+ and Aβ-) on PET or CSF.

Result: An early phase of hypernosognosia (subject's > informant's ECog) preceded a gradual decrease in ACD, eventually leading to a clear anosognosia (Figure 1, with 100 bootstrapped runs). Unawareness started on average 5 years before diagnosis. APOE-ε4 carriers reached the peak of hypernosognosia and the anosognosia cut-off earlier than the non-carriers (all $p<.001$; Figure 2). Aβ+ subjects reached the peak of hypernosognosia later than Aβ-, but their ACD started to decline earlier (all $p<.05$; Figure 3).

Conclusion: The role of cognitive complaints and low ACD in AD is currently highly debated. Our study showed that both are associated with AD pathology, being two conditions that occur in temporal succession. This has strong implications in terms of timely and accurate diagnosis, and in patients' treatment. Further analyses may study the longitudinal trajectory of ACD in relation to additional AD features, such as brain atrophy and metabolism, especially in the predementia phases.

Figure 1

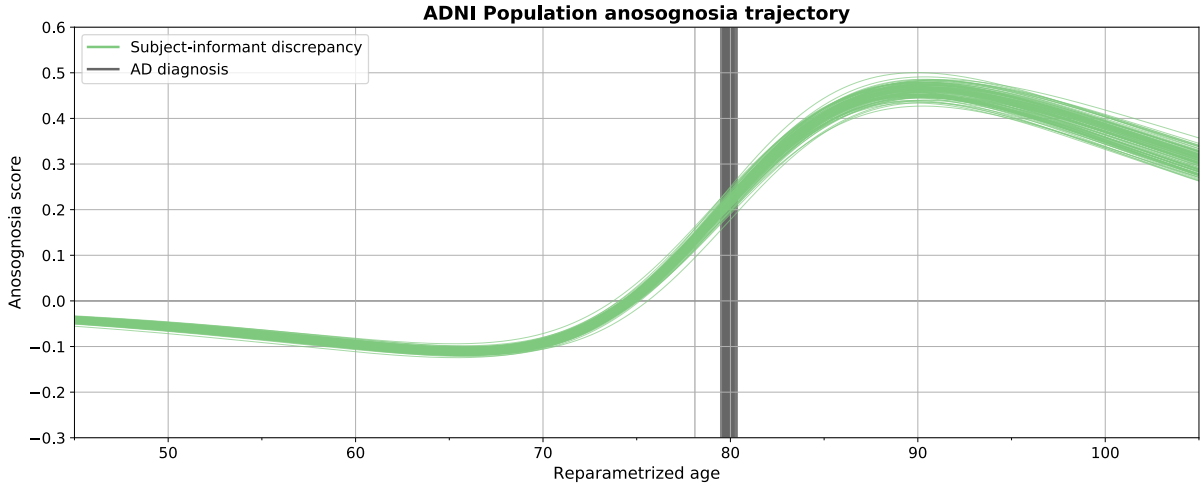

Figure 2

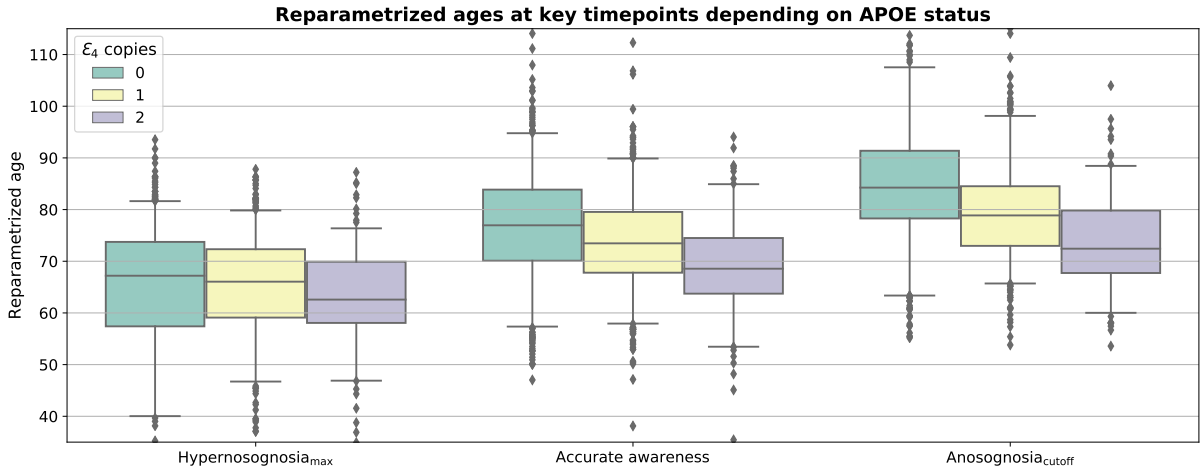

Figure 3