Publishable Summary

This deliverable reports on the continued modeling efforts from WP5 with respect to 1) the value of quantitative and regional information from amyloid PET imaging, 2) sub-types of early Alzheimer's disease pathways, and 3) the effects of amyloid pathology in cognitive performance across the disease spectrum.

In short, analyses reported in this document allow for the following observations:

- Quantitative PET imaging has improved statistical power in longitudinal studies compared to standard static imaging measurements

- Regional amyloid PET information can be more sensitive in earlier stages of the disease, both to establish emerging pathology and to understand early relationships with other disease biomarkers

- CSF and PET measurements of amyloid pathology may bring complementary information, and the order of biomarker abnormality might provide further information on disease pathways

- A non-negligible proportion of the population might accumulate tau beyond agerelated increases before amyloid accumulates, representing an alternative pathway to AD

- Dynamic PET imaging provides additional information on blood flow, which seems to provide valuable information in predicting future cognitive decline even in cognitively healthy individuals

- Resting-state fMRI can be used to determine cognitive reserve, which helps explain resilience to AD-pathology and better model disease-related decline

- The phenomenon of super-aging is not only observable by above-average cognitive performance, but indeed accompanied by resistance to AD pathology

- Multi-modal disease signatures can be determined by machine learning, and amyloid PET seems to provide the most information at the MCI stage

The scientific work performed by this WP has been made possible by the efforts in collecting external data in the previous years of the project, and many of the results reported in this document have previously been presented in international scientific conferences.

Both final and preliminary results in this document will serve the AMYPAD project in two ways: first, by continuing to inform WP4 on individual profiles that can be identified within Parent Cohorts and used for recruitment into AMYPAD PNHS; second, by supporting the ongoing modeling work of collaborating projects and providing current and future trials with valuable insight into the best practices for modeling amyloid accumulation and its effects on the disease course accurately and robustly in an early population.

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