AMYPAD
Amyloid imaging to prevent Alzheimer´s Disease

AMYPAD Deliverable 5.7

Final report on advanced disease modelling

Publishable Summary

This deliverable reports on the continued modeling efforts from WP5 with respect to 1) sub-types of spatial-temporal amyloid accumulation trajectories, 2) genetic risk underlying heterogeneity in AD, 3) methods for advanced computational and multi-modal analyses, and 4) the effects of amyloid pathology on disease progression.

In short, analyses reported in this document allow for the following observations:
- The Subtype and Stage Inference model has provided data-driven evidence for existence of three, rather than one, spatial-temporal trajectories of amyloid accumulation.
- These subtypes seem to be differentially related to risk factors, pathology and white matter hyperintensities.
- Polygenic Risk Scores (PRS) derived from Genome-wide association study (GWAS) genetic data of the EPAD cohort is differentially related to functional and structural connectivity.
- PRS is also related to different rates of accumulation in the AMYPAD PNHS affiliated PFACK cohort. This work is planned to be validated in a larger AMYPAD data-set and expanded based on the SuStaIn subtypes.

- Changes in structural and functional networks are more dynamic in the preclinical stages of AD than initially thought. Also, changes in these networks are highly dependent on each other.
- Deep learning approaches can be used to optimize selection of subjects into clinical trials. A Siamese neural network is a deep-learning (DL) method was applied to amyloid PET and T1-MRI images from the ADNIMERGE dataset, to obtain data-driven covariates associated with disease prediction, in our case the DL model is trained to detect participants who will decline from those that remain cognitively stable. The framework will be further validated with the integrated AMYPAD database.

- Cardiovascular risk and amyloid burden in AD signature regions were associated with increased cerebral blood flow in cognitively unimpaired individuals, which may reflect a vascular or inflammatory compensatory response to early amyloid accumulation.
- Regional amyloid PET better predicts subsequent tau accumulation than global measures.
- Quantitative amyloid PET predicts cognitive decline in initially cognitively unimpaired subjects. This is also highly influenced by known demographic and risk factors, i.e. sex, age, and APOE-ε4 carriership.

- Individual sensitivity to early amyloid accumulation may increase with higher education in stages of subjective cognitive decline, whereas in clinical stages higher education may support compensatory mechanisms against amyloid burden.

The scientific work performed by this WP in its last years has been made possible by the efforts in collecting external data and the collaborative data framework resulting from the AMYPAD Prognostic and Natural History study (PNHS) (PNHS) trial. Particularly, the ongoing integration and harmonization efforts of the PNHS-affiliated parent cohorts, allowed for most analyses reported in this deliverable to be based on data collected within the AMYPAD study. Many of the results reported in this document are submitted to scientific journals and have been or will be presented at international scientific conferences.

Together, the work presented in this deliverable will serve 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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