AMYPAD
Amyloid imaging to prevent Alzheimer´s Disease

AMYPAD Deliverable 5.6

Final report on basic modelling

Publishable Summary

This deliverable reports on the final modeling efforts from WP5 with respect to 1) the amyloid accumulation process, 2) thresholds for abnormality in amyloid PET scans and 3) estimates of longitudinal change in amyloid burden from the AMYPAD Prognostic and Natural History study (PNHS) data-set. While the scientific work performed by this WP was previously made possible by the efforts in collecting external data, the current deliverable holds results from analyses performed using the AMYPAD DPMS and PNHS trials data. Many of these results will be presented in international scientific conferences.

In short, analyses reported in this document allow for the following observations:
- Quantification of flutemetamol and florbetaben PET scans with the Centiloid method yielded similar and robust findings across tracers, allowing for pooling of the data of the PNHS parent cohorts.

- In those cases expected to be stable over time (DPMS and PNHS), CL was found stable and robust to the choice of tracer and processing pipeline, with a longitudinal variability estimated around ~4-5 CL/year. This also suggests that a time interval of one year is not sufficient to detect a true underlying change in protein deposition between two scans one year apart.

- Within the PNHS data-set, a variability of ~3.3CL/year was observed. Thus, an annual increase in CL above this threshold would be considered true amyloid accumulation.
- Baseline CL can help identify subjects more likely to accumulate pathology, i.e. subjects in the so-called gray-zone show the highest accumulation rate. Also, baseline CL was significantly higher in cases that converted to amyloid-positivity based on visual read at follow-up.
- The selected method for quantification has a significant impact on the annual rates of change in amyloid pathology. This measured change in amyloid pathology was larger for SUVR compared with the fully quantitative methods (i.e. DVR and BPND), suggesting that SUVR might overestimate the actual change.

- Semi- and fully-quantitative PET measures (i.e. Centiloid vs BPND) perform similarly in predicting cognitive scores, even though kinetic models are more sensitive in measuring amyloid pathology. Not preferring kinetic modelling measures when predicting cognitive changes might be due to: 1) there are a high proportion of participants with low amyloid pathology; 2) decline in cognition is too far downstream the pathological cascade after the accumulation of amyloid; and 3) the lack of harmonization in BPND measures across sub-cohorts and tracer.

- The continuous discordance model was validated in the PNHS data-set, with CSF-over-PET imbalance being associated with APOE-ε4/ε4 genotype and greater attention impairments, while a PET-over-CSF imbalance being associated with greater memory impairments. In addition, CSF-over-PET imbalance was associated with greater cognitive decline over time. This suggests that a continuous index of amyloid CSF/PET imbalance might hold meaningful information on heterogeneous pathological trajectories from early stages of AD.

- Discordance between visual read and Centiloid quantification is associated with markers of pathology, and this leads to necessity to take these different discordances into account in research or clinical practice. This work will be expanded using longitudinal data.

The presented modeling work will provide valuable insight into the best practices for modeling amyloid accumulation accurately and robustly in an early population, which can support future clinical trial designs and possibly treatment monitoring in the near future. As such, the endeavors showcased in this deliverable have been done in close collaboration with the WP2 team and have supported the draft of a Biomarker Qualification Opinion document, supporting the use of quantitative amyloid PET in the clinical routine. Please see deliverable 5.9 for a detailed overview.

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