Selection of amyloid positive pre-symptomatic subjects using automatic analysis of neuropsychological and MRI data for cost effective inclusion procedures in clinical trials

Manon Ansart, Stéphane Epelbaum, Olivier Colliot, Didier Dormont, Bruno Dubois, Harald Hampel, Stanley Durrleman

Selection of amyloid positive pre-symptomatic subjects using automatic analysis of neuropsychological and MRI data for cost effective inclusion procedures in clinical trials

Manon Ansart, MSc[1,2], Stéphane Epelbaum, MD, PhD[1,2,3], Olivier Colliot, PhD[1,2,3,4], Didier Dormont, MD[1,2,4], Bruno Dubois, Prof., MD[1,3], Harald Hampel, Prof., MD, PhD[1,3,5], Stanley Durrleman, PhD[2,1], for the ADNI, and the INSIGHT study group

[1] Sorbonne Universités, UPMC Univ Paris 06, Inserm, CNRS, Institut du cerveau et la moelle (ICM) - Hôpital de la Pitié-Salpêtrière, Boulevard de l'hôpital, F-75013, Paris, France
[2] Inria Paris, Aramis project-team, 75013, Paris, France
[3] AP-HP, Hôpital de la Pitié-Salpêtrière, Department of Neurology, Institut de la Mémoire et de la Maladie d'Alzheimer (IM2A), F-75013, Paris, France
[4] AP-HP, Hôpital de la Pitié-Salpêtrière, Department of Neuroradiology, F-75013, Paris, France
[5] AXA Research Fund & UPMC Chair, Paris, France

Background

Drug development in Alzheimer's Disease (AD) targets mostly the mechanisms of amyloid plaques formation. AD clinical trials now aim to test such drugs in pre-symptomatic at risk subjects, thus raising the need to form cohorts of pre-symptomatic amyloid positive (Aβ+) subjects. Recruitment of such subjects is often based on the analysis of a PET scan with amyloid ligands in subjective memory complainers, with an average of only 1 of 3 subjects being amyloid positive. To reduce the cost of the recruitment procedures, we propose a pre-screening phase based on the automatic analysis of neuropsychological and structural imaging data. We propose to use machine learning techniques to identify a sub-set of subjects with a much higher prevalence of amyloid positive cases (Figure 1). This pre-selection comes with a higher number of subjects to pre-screen, but results overall in a reduction of recruitment cost.

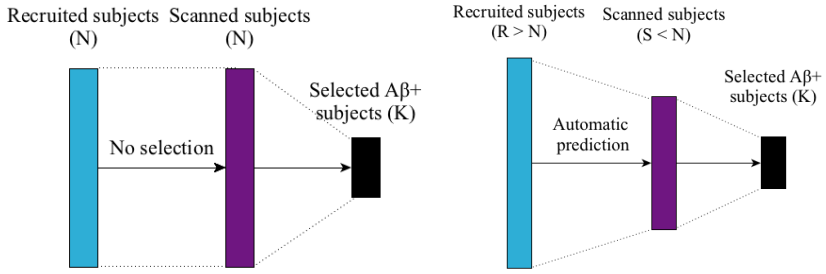

Figure 1: Current (left) and proposed (right) process for Aβ+ subject selection

Methods

The prediction of Aβ+ subjects is made training a classifier, namely a Random Forest, based on socio-demographic, genetic information and cognitive assessments. The performances are measured using the area under the ROC curve (AUC) and the cost for recruiting 100 subjects. To compute the minimal cost, a value of S (number of subjects to be scanned) and R (number of subjects to be recruited) is computed for each point on the ROC curve to create a S vs R curve where each point is associated to a cost based on the hypothesis that a subject recruitment (with cognitive scores and APOE genotype) costs 100€, an MRI 400€ and a PET scan 1000€.
The number and depth of the Random Forest trees are automatically tuned. Cross-validation using 50 random-splits is used, thereby guarantying that tested subjects have not been used for training. The 50 splits give 50 outcomes used to compute the average outcome, standard deviation (std), and then t-tests.

We validate our method on 3 cohorts: INSIGHT, ADNI-CN, ADNI-MCI. INSIGHT is a monocentric cohort following cognitively normal (CN) subjects with a subjective memory complaint (SMC). 318 subjects with an AV45 PET scan are available. We also use 431 CN subjects and 596 MCI subjects from ADNI with amyloid status assessed by AV45 PET scan or CSF biomarkers in the absence of PET scan.

Genetic (APOE alleles) and socio-demographic information (age, gender, education), and a battery of cognitive assessments are used as inputs. MRI is available for all subjects. Percentages of average cortical thicknesses in 72 regions of interest are computed using FreeSurfer. The hippocampal volume is computed using FreeSurfer for ADNI and in-house SACHA software for INSIGHT.

Results

Table 1: Results on the different cohorts and comparison with the estimated initial costs for recruiting K=100 amyloid positive subjects

	Current method	**Proposed method**				
Dataset	**Estimated current cost in €**	**% of AUC (std)**	**Subjects to be recruited**	**Subjects to be scanned**	**New cost in € (std)**	**Estimated savings in €**
INSIGHT (27.7% Aβ+)	397,499 (N=361)	68.0 (5.4)	995	196	295,560 (58,123)	101,939
ADNI-CN (37.6% Aβ+)	292,654 (N=266)	69.1 (4.0)	599	175	234,591 (23,106)	58,063
ADNI-MCI (62.9% Aβ+)	174,828 (N=159)	83.8 (2.1)	248	111	136,205 (3,678)	38,623

All validation cohorts (Table 1) show a significant cost reduction when recruiting 100 subjects ($p<0.001$). Our method combining multiple measures yields better results than using a single measure. The prediction using APOE genotype only is the best univariate one (Table 2 line 2), but yields significantly lower AUC than the multivariate model ($p<0.001$ for INSIGHT).
The neuropsychological assessments give significantly lower AUC than the selected MRI variables (Table 2 lines 1 and 3, $p<0.001$).

Table 2: Results in different experimental conditions

	% of AUC on the INSIGHT cohort (std)	**% of AUC on the ADNI-CN cohort (std)**	**% of AUC on the ADNI-MCI cohort (std)**
Proposed approach	68.0 (5.4)	69.1 (4.0)	83.8 (2.1)
APOE	63.7 (4.6)	62.1 (3.5)	75.1 (2.9)
Using MRI	59.8 (5.0)	61.3 (4.4)	80.8 (3.2)
After correction for age	68.5 (5.0)	67.7 (3.9)	80.9 (2.4)
With longitudinal variations	NA	71.7 (8.3)	87.7 (4.8)
Learned on ADNI-CN (MRI)	57.8 (7.2)	NA	NA

The impact of longitudinal measurements is evaluated by including the rate of change of cognitive scores (using a 12-month visit) in the inputs. The results (Table 2 line 5) show an increase in the AUC for ADNI-CN ($p<0.05$) and for ADNI-MCI ($p<0.001$).

The Aβ+ subjects are older than the Aβ− subjects, especially in ADNI. After correcting data values for age using linear regression, the performance of the classifier (Table 2 line 4) does not decrease significantly for ADNI-CN ($p>0.05$), but does for ADNI-MCI ($p<0.001$). The new cost for ADNI-MCI (141,221 ±4,391€) is still significantly better than the estimated recruitment cost with confirmatory PET scan for all subjects ($p<0.001$). Our method thus captures patterns associated with amyloid formation and not only with age as a risk factor for amyloidosis.
Finally, the classifier is trained on the socio-demographic, genetic and MRI features on ADNI-CN and tested on INSIGHT (Table 2 line 6). There is a 2-point decrease in AUC compared to training on the same data, i.e. INSIGHT, which is not significant ($p>0.1$). Our method therefore generalizes well when the classifier is trained on one cohort and validated on an independent one.

Conclusions

We proposed a method to automatically select pre-symptomatic subjects likely to be Aβ+ based on multimodal data analysis and machine learning techniques. It leads to a significant cost decrease when creating cohorts of such subjects, compared to the current method, consisting in scanning all potential subjects. It is also significantly better than each measure used individually. Our results are significantly better when cognitive assessments (especially their rate of change in longitudinal assessments) are used rather than MRI features. Those results might be improved by using a more extensive set of measures extracted from the images.