REVEALING THE HETEROGENEITY OF PLASMA PROTEIN AND COGNITIVE TRAJECTORY AMONG MILD COGNITIVE IMPAIRMENT PATIENTS BY CLUSTERING OF BRAIN ATROPHY FEATURES

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INTRODUCTION

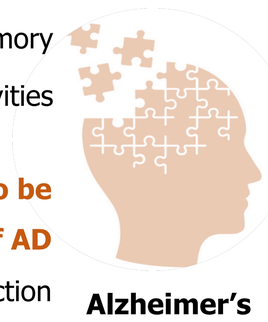
The most common type of dementia

- Degrade cognition, memory

Decline in the ability to perform daily activities

Plasma proteins are suggested to be promising candidate for diagnosis of AD

- Convenience in sample collection
- Minimal invasion and cost
- Time-effectiveness



Alzheimer's disease

There is no available treatment for AD

➢ Needs for early diagnosis and treatment

AD is suggested to be a heterogeneous disorder

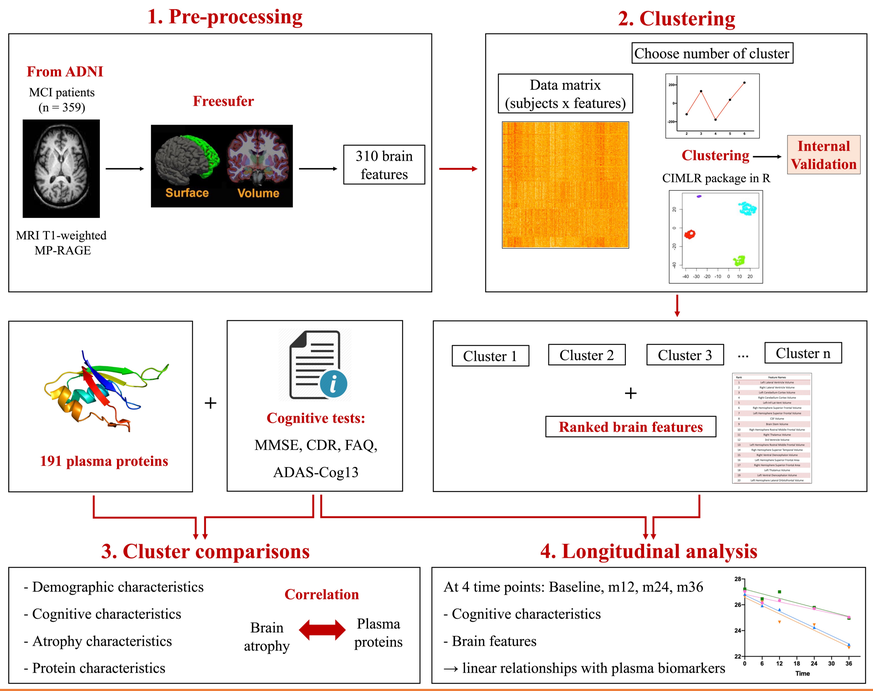
With differences in developing patterns of brain atrophy → developing diagnostic methods and personalized treatments for AD

➢ **Limited** number of researches focus on early stage of AD: **MCI** (Mild cognitive impairment)

OBJECTIVES:

- Utilizing clustering analysis to study the heterogeneities in MCI stage
- Investigate the brain atrophy and plasma protein characteristics among clusters
- Longitudinal analysis on cognitive characteristics of each clusters

METHOD



RESULTS

1) Clustering analysis results

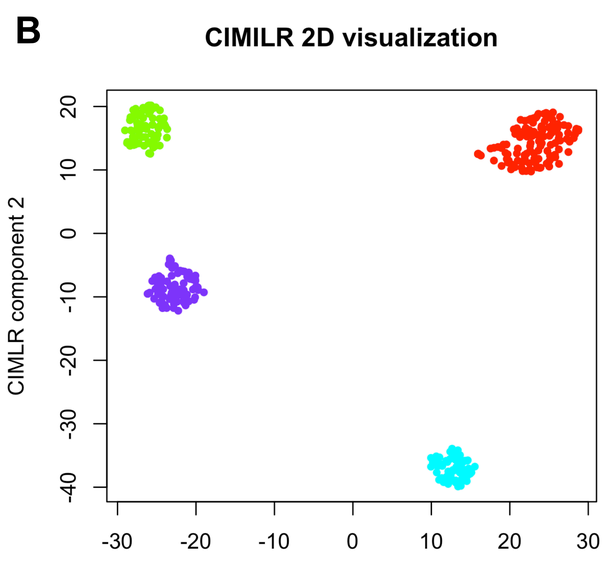


Figure 1: Visualization of the 4 clusters was retrieved by CIMLR

Table 1: Top 20 structural brain features were retrieved by CIMLR

Rank	Feature Names
1	Left Hemisphere Superior Frontal Volume
2	Left Hemisphere Superior Frontal Thickness
3	Right Hemisphere Isthmus Cingulate Mean Curvature
4	Right Hemisphere Lateral Orbitofrontal Mean Curvature
5	Left Hemisphere Lateral Occipital Volume
6	Left Hemisphere Entorhinal Volume
7	Right Hemisphere Transverse Temporal Area
8	Right Hemisphere Precentral Mean Curvature
9	Right Hemisphere Rostral Anterior Cingulate Area
10	Left Hemisphere Superior Temporal Area
11	Left Hemisphere Precuneus Mean Curvature
12	Left Hemisphere Frontal Pole Mean Curvature
13	Left Hemisphere Entorhinal Area
14	Left Hemisphere Rostral Middle Frontal Mean Curvature
15	Right Hemisphere Inferior Parietal Area
16	Right Hemisphere Middle Temporal Area
17	Right Hemisphere Cuneus Mean Curvature
18	Right Hemisphere Parahippocampal Thickness
19	Left Hemisphere Lingual Volume
20	Right Hemisphere Insula Mean Curvature

2) Cluster comparison

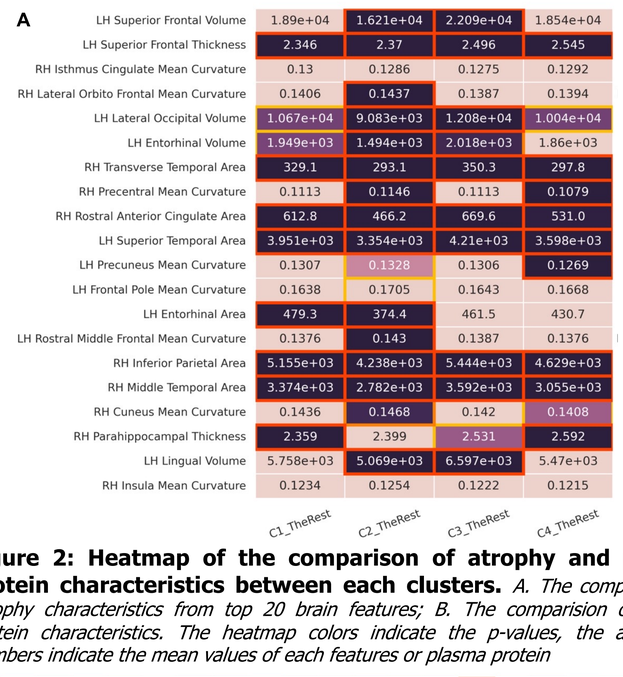


Figure 2: Heatmap of the comparison of atrophy and plasma protein characteristics between each clusters. *A. The comparision of atrophy characteristics from top 20 brain features; B. The comparision of plasma protein characteristics. The heatmap colors indicate the p-values, the annotation numbers indicate the mean values of each features or plasma protein*

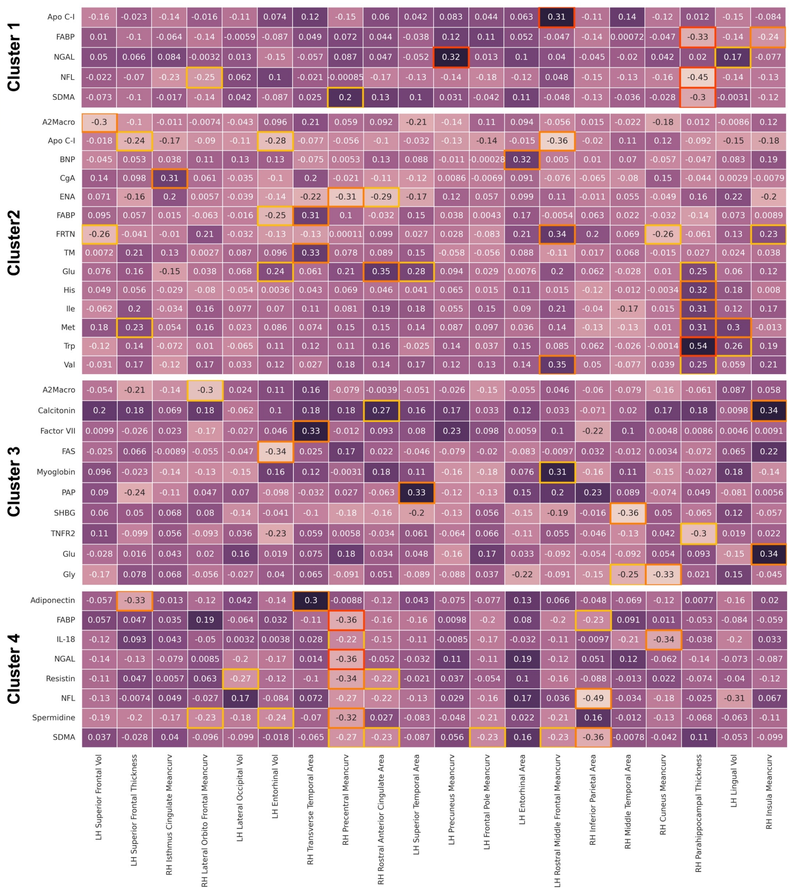


Figure 3: Heatmap of the correlation between top 20 brain features and plasma protein of each clusters using Spearman correlation. *A. The correlation of Cluster 1; B. The correlation of Cluster 2; C. The correlation of Cluster 3; D. The correlation of cluster 4. The heatmap colors and the annotation numbers indicate the Rho values*

3) Longitudinal analysis

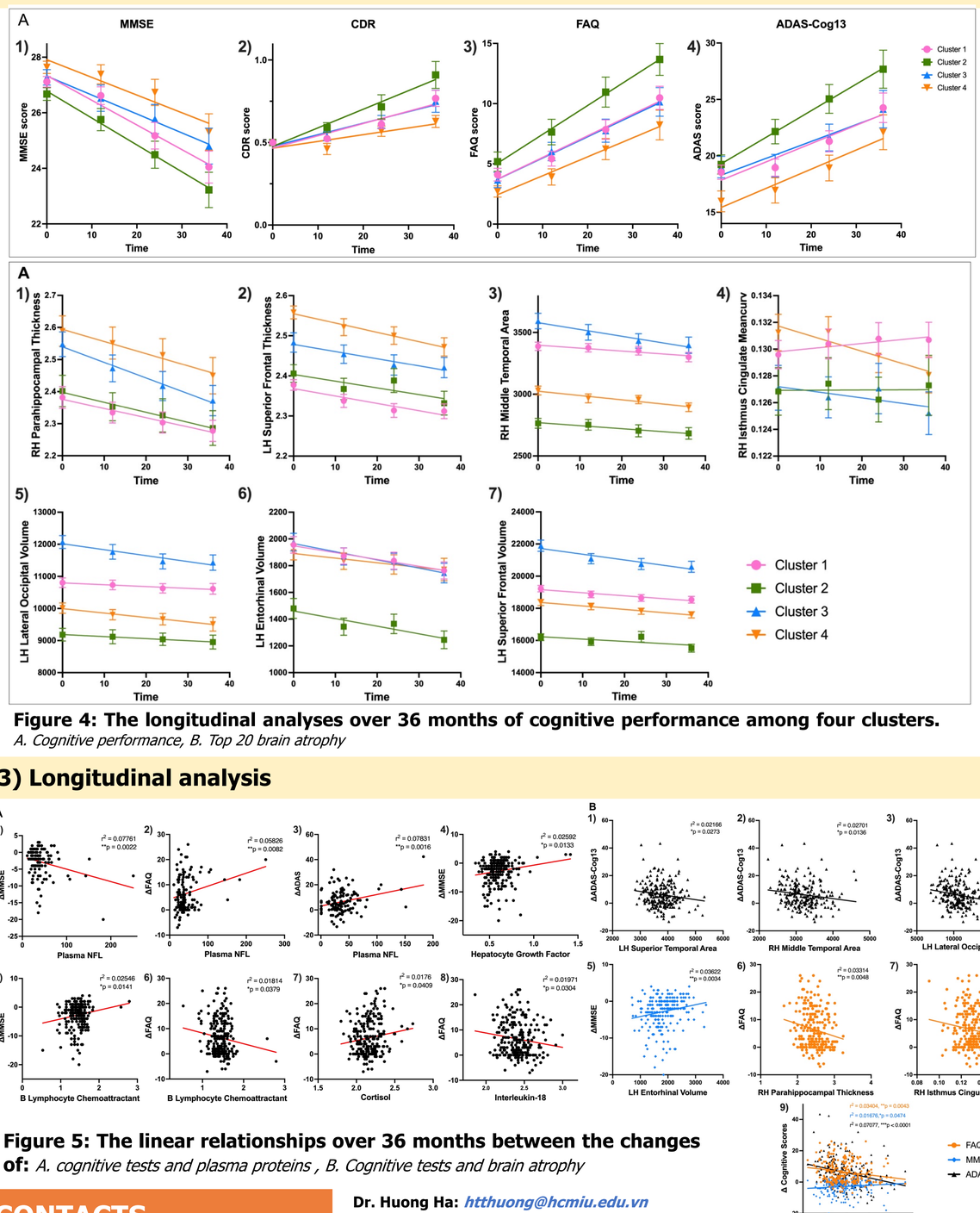


Figure 4: The longitudinal analyses over 36 months of cognitive performance among four clusters. *A. Cognitive performance, B. Top 20 brain atrophy*

Table 2: Comparison of demographic and cognitive characteristics among clusters. *Data is illustrated as mean ± standard deviation or number/number. cMCI = converted Mild cognitive impairment, sMCI = stable Mild cognitive impairment, MMSE = Mini-Mental State Examination, CDR = Clinical Dementia Rating, FAQ = Functional Activities Questionnaire, ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale test*

	Cluster 1 (n = 133)	Cluster 2 (n = 77)	Cluster 3 (n = 67)	Cluster 4 (n = 82)
sMCI	68	33	40	51
cCMI	65	44	27	31
Age	76.43 ± 6.65	77.23 ± 6.95	72.06 ± 7.2	72 ± 7.11
Sex (M/F)	116/17	24/53	56/8	30/52
MMSE	26.98 ± 1.75	26.58 ± 1.59	26.92 ± 1.84	27.32 ± 1.83
CDR	0.5	0.5	0.5	0.5
FAQ	4.25 ± 4.84	4.75 ± 5.09	3.49 ± 3.95	3.07 ± 3.8
ADAS	19.11 ± 6.07	20.64 ± 7	19 ± 6.62	16.86 ± 6.21

3) Longitudinal analysis

Figure 5: The linear relationships over 36 months between the changes of: *A. cognitive tests and plasma proteins , B. Cognitive tests and brain atrophy*

RESULTS

There are 04 distinct clusters:

- C1 oldest group but has had mild atrophy and moderate progression
- C2 highest risk for aggressive MCI progression
- C3 has mild atrophy that shared similar patterns with C1
- C4 is the healthiest group during longitudinal tracking, with the mildest Parahippocampal atrophy, which was found to be positively correlated with cognitive impairment and amino acid levels.

The longitudinal analysis suggested prognostic markers of aggressive progression of MCI:

- Hepatocyte Growth Factor: a marker for slow cognitive impairment
- Neurofilament Light Polypeptide and Cortisol: prognosis markers for aggressive MCI progression

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