# **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			METHOD				
The most common type of dementia			<b>1. Pr</b>	e-processing	2. Clustering		
Degrade cognition, memory	5	<ul><li>There is no available treatment for AD</li><li>Needs for early diagnosis and treatment</li></ul>	From ADNI MCI patients (n = 359)	Freesufer	$\begin{bmatrix} Choose number of cluster \\ Data matrix (subjects x features) \\ \begin{bmatrix} 2 & 3 & 4 & 5 & 6 \end{bmatrix}$		
Decline in the ability to perform daily activities		AD is suggested to be a heterogeneous disorder		Ace Volume $\rightarrow$ 310 brain features	$ \begin{array}{c} & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & $		
Plasma proteins are suggested to be		With differences in developing patterns of brain atrophy	MRI I I-weighted MP-RAGE				
promising candidate for diagnosis of AD		ightarrow developing diagnostic methods and personalized					
Convenience in sample collection	Alzheimer's	treatments for AD			Cluster 1 Cluster 2 Cluster 3 Cluster n		
<ul> <li>Minimal invasion and cost</li> </ul>	disease	Limited number of researches focus on early stage		+ Cognitive tests:	Bank     Feature Names       2     Right Cateral Ventrick Volume       3     Lift Cateral Ventrick Volume       4     Right Cateral Ventrick Volume       5     Right Advents Volume       6     Right Nemplates Sport Frontal Volume       8     CV Volume       9     Balls Mark Volume		
Time-effectiveness		of AD: MCI (Mild cognitive impairment)	191 plasma proteins	MMSE, CDR, FAQ, ADAS-Cog13	10       Righ Heinsplere Road Moder Fordal Volume         12       July Heinsplere Road Moder Fordal Volume         13       Light Heinsplere Road Moder Fordal Volume         14       Light Heinsplere Road Moder Fordal Volume         15       Light Heinsplere Road Moder Fordal Volume         16       Light Heinsplere Road Volume         17       Right Heinsplere Road Volume         18       Light Heinsplere Road Volume         19       Light Heinsplere Road Volume         10       Light Heinsplere Road Volume         16       Light Heinsplere Road Volume         17       Light Heinsplere Road Volume         18       Light Heinsplere Road Volume         19       Light Heinsplere Road Volume         10       Light Heinsplere Ro		

### **OBJECTIVES:**

**CIMILR 2D visualization** 

- 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

## RESULTS

B

### **1)** Clustering analysis results



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

- **Feature Names** Rank Left Hemisphere Superior Frontal Volume
  - Left Hemisphere Superior Frontal Thickness
  - Right Hemisphere Isthmus Cingulate Mean Curvature
  - Right Hemisphere Lateral Orbitofrontal Mean Curvature
  - Left Hemisphere Lateral Occipital Volume
  - Left Hemisphere Entorhinal Volume
  - Right Hemisphere Transverse Temporal Area
  - Right Hemisphere Precentral Mean Curvature
  - Right Hemisphere Rostral Anterior Cingulate Area
  - Left Hemisphere Superior Temporal Area
  - Left Hemisphere Precuneus Mean Curvature
  - Left Hemisphere Frontal Pole Mean Curvature
    - Left Hemisphere Entorhinal Area
  - Left Hemisphere Rostral Middle Frontal Mean Curvature
    - **Right Hemisphere Inferior Parietal Area**
    - Right Hemisphere Middle Temporal Area

- Cluster 1 Cluster 2 🛨 Cluster 3 🐥 Cluster 4



### 2) Cluster comparison

A LH Superior Frontal Volume	1.89e+04	1.621e+04	2.209e+04	1.854e+04
LH Superior Frontal Thickness	2.346	2.37	2.496	2.545
RH Isthmus Cingulate Mean Curvature	0.13	0.1286	0.1275	0.1292
RH Lateral Orbito Frontal Mean Curvature	0.1406	0.1437	0.1387	0.1394
LH Lateral Occipital Volume	1.067e+04	9.083e+03	1.208e+04	1.004e+04
LH Entorhinal Volume	1.949e+03	1.494e+03	2.018e+03	1.86e+03
RH Transverse Temporal Area	329.1	293.1	350.3	297.8
RH Precentral Mean Curvature	0.1113	0.1146	0.1113	0.1079
RH Rostral Anterior Cingulate Area	612.8	466.2	669.6	531.0
LH Superior Temporal Area	3.951e+03	3.354e+03	4.21e+03	3.598e+03
LH Precuneus Mean Curvature	0.1307	0.1328	0.1306	0.1269
LH Frontal Pole Mean Curvature	0.1638	0.1705	0.1643	0.1668
LH Entorhinal Area	479.3	374.4	461.5	430.7
LH Rostral Middle Frontal Mean Curvature	0.1376	0.143	0.1387	0.1376
RH Inferior Parietal Area	5.155e+03	4.238e+03	5.444e+03	4.629e+03
RH Middle Temporal Area	3.374e+03	2.782e+03	3.592e+03	3.055e+03
RH Cuneus Mean Curvature	0.1436	0.1468	0.142	0.1408
RH Parahippocampal Thickness	2.359	2.399	2.531	2.592
LH Lingual Volume	5.758e+03	5.069e+03	6.597e+03	5.47e+03
RH Insula Mean Curvature	0.1234	0.1254	0.1222	0.1215

#### 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

Alpha-2-Macroglobulin (A2Macro) (mg/mL)	0.05661	0.07852	0.03407	0.07102
Adiponectin (ug/mL)	0.7564	0.8249	0.6925	0.7742
Brain-Derived Neurotrophic Factor (BDNF) (ng/mL)	0.163	0.3423	0.2782	0.3411
B Lymphocyte Chemoattractant (BLC) (pg/ml)	1.453	1.444	1.449	1.41
Brain Natriuretic Peptide (BNP) (pg/ml)	3.044	3.114	2.912	2.983
Calcitonin (pg/mL)	1.029	0.9539	1.054	0.985
CD40 Ligand (CD40-L) (ng/mL)	-0.7248	-0.5549	-0.5383	-0.5618
Chromogranin-A (CgA) (ng/mL)	2.721	2.632	2.618	2.631
Creatine Kinase-MB (CK-MB) (ng/mL)	-0.3818	-0.5229	-0.4314	-0.4651
Cortisol (Cortisol) (ng/ml)	2.177	2.162	2.149	2.129
Epithelial-Derived Neutrophil-Activating (ENA) (ng/mL)	-0.2369	-0.05327	-0.1433	-0.02735
Fatty Acid-Binding Protein- heart (FABP) (ng/mL)	0.6192	0.5406	0.4892	0.4542
Factor VII (ng/mL)	2.744	2.768	2.75	2.807
FASLG Receptor (FAS) (ng/mL)	1.075	1.04	1.032	1.041
Ferritin (FRTN) (ng/mL)	2.082	1.886	2.108	1.895
Follicle-Stimulating Hormone (FSH) (mIU/mL)	0.9695	1.438	0.872	1.314
Growth-Regulated alpha protein (GRO-alph) (pg/mL)	2.597	2.716	2.705	2.701
Haptoglobin (mg/mL)	0.05988	0.2847	0.07621	0.1744
Hepatocyte Growth Factor (HGF) (ng/mL)	0.614	0.6063	0.5887	0.5775
Immunoglobulin A (IgA) (mg/mL)	0.637	0.6222	0.6195	0.5646
Interleukin-18 (IL-18) (pg/mL)	2.434	2.37	2.407	2.419
Leptin (ng/mL)	0.7989	1.107	0.8068	1.024
Luteinizing Hormone (LH) (mIU/mL)	0.5702	0.9057	0.4664	0.8201
Monokine Induced by Gamma Interferon (MI) (pg/ml)	3.541	3.561	3.454	3.493
Myoglobin (ng/mL)	1.377	1.292	1.303	1.252
eutrophil Gelatinase-Associated Lipocal (NGAL) (ng/ml)	2.459	2.416	2.433	2.4
Osteopontin (ng/ml)	1.368	1.331	1.259	1.273
Prostatic Acid Phosphatase (PAP) (ng/mL)	-0.6889	-0.7864	-0.6992	-0.7363
onary and Activation-Regulated Chemo (PARC) (ng/mL)	2.038	2.08	2.012	2.009
Platelet-Derived Growth Factor BB (PDGF-BB) (pg/ml)	3.053	3.212	3.164	3.221
I-Cell-Specific Protein RANTES (RANTES) (ng/mL)	0.9302	1.119	1.055	1.09
Resistin (ng/mi)	0.5094	0.4865	0.4574	0.4437
Sortinn (ng/mL)	0.7453	0.780	0.7334	0.708
	1.747	1.70	1.775	1.///
Trofoil Eactor 2 (TEE2) (ug/ml)	0.5252	-0.1475	0.4036	-0.0240
Thromhomodulin (TM) (ng/ml)	-0.8001	-0.0017	-0.894	-0.8322
Filmon Necrosis Factor Pecentor Like 2 (TNEP2) (ng/ml)	0.8117	0.0095	0.0921	0.040
	2 126	2.42	2 204	2 291
Transthyretin (TTR) (mg/dl)	2 552	2.42	2.204	2.231
Vascular Endothelial Growth Factor (VEGE) (pg/ml.)	2.804	2.814	2.756	2.797
Glv	423.9	431.2	399.9	440.5
His	104.9	97.31	104.1	104.9
lle	88.06	79.02	89.03	83.7
Lys	356.8	330.5	355.1	370.0
Met	31.85	29.61	31.84	31.18
Trp	73.06	67.28	73.37	70.29
Val	292.7	275.8	303.8	289.6
Creatinine	109.4	96.03	100.4	94.81
Sarcosine	1.627	1.477	1.512	1.457
Spermidine	0.2252	0.2045	0.2157	0.2016
	c1 TheRest	c2 TheRest	C3 TheRest	CA TheRest

protein characteristics. The heatmap colors indicate the p-values, the annotation numbers indicate the mean values of each features or plasma protein

Apo C-I	-0.16	-0.023	-0.14	-0.016	-0.11	0.074	0.12	-0.15	0.06	0.042	0.083	0.044	0.063	0.31	-0.11	0.14	-0.12	0.012	-0.15	-0.084
FABP	0.01	-0.1	-0.064	-0.14	-0.0059	-0.087	0.049	0.072	0.044	-0.038	0.12	0.11	0.052	-0.047	-0.14	0.00072	-0.047	-0.33	-0.14	-0.24
NGAL	0.05	0.066	0.084	-0.0032	0.013	-0.15	-0.057	0.087	0.047	-0.052	0.32	0.013	0.1	0.04	-0.045	-0.02	0.042	0.02	0.17	-0.077
NFL	-0.022	-0.07	-0.23	-0.25	0.062	0.1	-0.021	-0.00085	-0.17	-0.13	-0.14	-0.18	-0.12	0.048	-0.15	-0.13	-0.16	-0.45	-0.14	-0.13
SDMA	-0.073	-0.1	-0.017	-0.14	0.042	-0.087	0.025	0.2	0.13	0.1	0.031	-0.042	0.11	-0.048	-0.13	-0.036	-0.028	-0.3	-0.0031	-0.12
2Macro	-0.3	-0.1	-0.011	-0.0074	-0.043	0.096	0.21	0.059	0.092	-0.21	-0.14	0.11	0.094	-0.056	0.015	-0.022	-0.18	0.012	-0.0086	0.12
Apo C-I	-0.018	-0.24	-0.17	-0.09	-0.11	-0.28	-0.077	-0.056	-0.1	-0.032	-0.13	-0.14	-0.015	-0.36	-0.02	0.11	0.12	-0.092	-0.15	-0.18
BNP	-0.045	0.053	0.038	0.11	0.13	0.13	-0.075	0.0053	0.13	0.088	-0.011	-0.00028	0.32	0.005	0.01	0.07	-0.057	-0.047	0.083	0.19
CgA	0.14	0.098	0.31	0.061	-0.035	-0.1	0.2	-0.021	-0.11	-0.12	0.0086	-0.0069	0.091	-0.076	-0.065	-0.08	0.15	-0.044	0.0029	-0.0079
ENA	0.071	-0.16	0.2	0.0057	-0.039	-0.14	-0.22	-0.31	-0.29	-0.17	0.12	0.057	0.099	0.11	-0.011	0.055	-0.049	0.16	0.22	-0.2
FABP	0.095	0.057	0.015	-0.063	-0.016	-0.25	0.31	0.1	-0.032	0.15	0.038	0.0043	0.17	-0.0054	0.063	0.022	-0.032	-0.14	0.073	0.0089
FRTN	-0.26	-0.041	-0.01	0.21	-0.032	-0.13	-0.13	0.00011	0.099	0.027	0.028	-0.083	0.21	0.34	0.2	0.069	-0.26	-0.061	0.13	0.23
ΤM	0.0072	0.21	0.13	0.0027	0.087	0.096	0.33	0.078	0.089	0.15	-0.058	-0.056	0.088	-0.11	0.017	0.068	-0.015	0.027	0.024	0.038
Glu	0.076	0.16	-0.15	0.038	0.068	0.24	0.061	0.21	0.35	0.28	0.094	0.029	0.0076	0.2	0.062	-0.028	0.01	0.25	0.06	0.12
His	0.049	0.056	-0.029	-0.08	-0.054	0.0036	0.043	0.069	0.046	0.041	0.065	0.015	0.11	0.015	-0.12	-0.012	-0.0034	0.32	0.18	0.008
lle	-0.062	0.2	-0.034	0.16	0.077	0.07	0.11	0.081	0.19	0.18	0.055	0.15	0.09	0.21	-0.04	-0.17	0.015	0.31	0.12	0.17
Met	0.12	0.23	0.054	0.16	0.023	0.086	0.074	0.15	0.15	0.14	0.087	0.097	0.036	0.14	-0.13	-0.13	0.01	0.31	0.3	-0.013
Irp	-0.12	0.14	-0.072	0.01	-0.005	0.11	0.12	0.11	0.10	-0.025	0.14	0.037	0.15	0.085	0.062	-0.020	-0.0014	0.54	0.20	0.19
vai	-0.031	0.17	-0.12	0.17	0.055	0.12	0.027	0.10	0.14	0.17	0.12	0.15	0.14	0.55	0.05	-0.077	0.039	0.25	0.039	0.21
2Macro	-0.054	-0.21	-0.14	-0.3	0.024	0.11	0.16	-0.079	-0.0039	-0.051	-0.026	-0.15	-0.055	0.046	-0.06	-0.079	-0.16	-0.061	0.087	0.058
citonin	0.2	0.18	0.069	0.18	-0.062	0.1	0.18	0.18	0.27	0.16	0.17	0.033	0.12	0.033	-0.071	0.02	0.17	0.18	0.0098	0.34
ctor VII	0.0099	-0.026	0.023	-0.17	-0.027	0.046	0.33	-0.012	0.093	0.08	0.23	0.098	0.0059	0.1	-0.22	0.1	0.0048	0.0086	0.0046	0.0091
FAS	-0.025	0.066	-0.0089	-0.055	-0.047	-0.34	0.025	0.17	0.022	-0.046	-0.079	-0.02	-0.083	-0.0097	0.032	-0.012	0.0034	-0.072	0.065	0.22
oglobin	0.096	-0.023	-0.14	-0.13	-0.15	0.16	0.12	-0.0031	0.18	0.11	-0.16	-0.18	0.076	0.31	-0.16	0.11	-0.15	-0.027	0.18	-0.14
PAP	0.09	-0.24	-0.11	0.047	0.07	-0.098	-0.032	0.027	-0.063	0.33	-0.12	-0.13	0.15	0.2	0.23	0.089	-0.074	0.049	-0.081	0.0056
SHBG	0.06	0.05	0.068	0.08	-0.14	-0.041	-0.1	-0.18	-0.16	-0.2	-0.13	0.056	-0.15	-0.19	-0.016	-0.36	0.05	-0.065	0.12	-0.057
TNFR2	0.11	-0.099	0.056	-0.093	0.036	-0.23	0.059	0.0058	-0.034	0.061	-0.064	0.066	-0.11	0.055	-0.046	-0.13	0.042	-0.3	0.019	0.022
Glu	-0.028	0.016	0.043	0.02	0.16	0.019	0.075	0.18	0.034	0.048	-0.16	0.17	0.033	-0.092	-0.054	-0.092	0.054	0.093	-0.15	0.34
Gly	-0.17	0.078	0.068	-0.056	-0.027	0.04	0.065	-0.091	0.051	-0.089	-0.088	0.037	-0.22	-0.091	-0.15	-0.25	-0.33	0.021	0.15	-0.045
onectin	-0.057	-0.33	-0.013	-0.12	0.042	-0.14	0.3	-0.0088	-0.12	0.043	-0.075	-0.077	0.13	0.066	-0.048	-0.069	-0.12	0.0077	-0.16	0.02
FABP	0.057	0.047	0.035	0.19	-0.064	0.032	-0.11	-0.36	-0.16	-0.16	0.0098	-0.2	0.08	-0.2	-0.23	0.091	0.011	-0.053	-0.084	-0.059
IL-18	-0.12	0.093	0.043	-0.05	0.0032	0.0038	0.028	-0.22	-0.15	-0.11	-0.0085	-0.17	-0.032	-0.11	-0.0097	-0.21	-0.34	-0.038	-0.2	0.033
NGAL	-0.14	-0.13	-0.079	0.0085	-0.2	-0.17	0.014	-0.36	-0.052	-0.032	0.11	-0.11	0.19	-0.12	0.051	0.12	-0.062	-0.14	-0.073	-0.087
esistin	-0.11	0.047	0.0057	0.063	-0.27	-0.12	-0.1	-0.34	-0.22	-0.021	0.037	-0.054	0.1	-0.16	-0.088	-0.013	0.022	-0.074	-0.04	-0.12
NFL	-0.13	-0.0074	0.049	-0.027	0.17	-0.084	0.072	-0.27	-0.22	-0.13	0.029	-0.16	0.17	0.036	-0.49	-0.034	-0.18	-0.025	-0.31	0.067
midine	-0.19	-0.2	-0.17	-0.23	-0.18	-0.24	-0.07	-0.32	0.027	-0.083	-0.048	-0.21	0.022	-0.21	0.16	-0.012	-0.13	-0.068	-0.063	-0.11
SDMA	0.037	-0.028	0.04	-0.096	-0.099	-0.018	-0.065	-0.27	-0.23	-0.087	0.056	-0.23	0.16	-0.23	-0.36	-0.0078	-0.042	0.11	-0.053	-0.099
	LH Superior Frontal Vol	uperior Frontal Thickness	mus Cingulate Meancurv	l Orbito Frontal Meancurv	LH Lateral Occipital Vol	LH Entorhinal Vol	ransverse Temporal Area	RH Precentral Meancurv	I Anterior Cingulate Area	H Superior Temporal Area	LH Precuneus Meancurv	LH Frontal Pole Meancurv	LH Entorhinal Area	Middle Frontal Meancurv	RH Inferior Parietal Area	RH Middle Temporal Area	RH Cuneus Meancurv	ahippocampal Thickness	LH Lingual Vol	RH Insula Meancurv

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	Cluster 2	Cluster 3	Cluster 4
	(n = 133)	(n = 77)	(n = 67)	(n = 82)
sMCI	68	33	40	51
cCMI	65	44	27	31
Age	76.43 ± 6.65	77.23 ±	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	$26.92 \pm 1.84$	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	$3.07 \pm 3.8$



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

## 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

# CONTACTS

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ADAS  $19.11 \pm 6.07$   $20.64 \pm 7$  $19 \pm 6.62$ 16.86 ± 6.21

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

## RESULTS

#### There are 04 distinct clusters:

- C1 oldest group but has had mild atrophy and moderate progression 3
- 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 4. 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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