Machine Learning-based Individual Assessment of Cortical Atrophy Pattern in Alzheimer's Disease Spectrum: Development of the Classifier and Longitudinal Evaluation

Jin San Lee,[1-3,*] Changsoo Kim,[4,*] Jeong-Hyeon Shin,[5,*] Hanna Cho,[7] Dae-seock Shin,[8] Nakyoung Kim,[8] Hee Jin Kim,[1,2] Yeshin Kim,[1,2] Samuel N. Lockhart,[9,10] Duk L. Na,[1,2,11] Sang Won Seo,[1,2,11,12,†] Joon-Kyung Seong[5,6,†]

[1]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 06351, Korea

[2]Neuroscience Center, Samsung Medical Center 06351, Seoul, Korea

[3]Department of Neurology, Kyung Hee University Hospital, Seoul, Korea

[4]Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, South Korea

[5]Department of Bio-convergence Engineering, [6]School of Biomedical Engineering, Korea University, Seoul, Korea

[7]Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

[8]MIDAS Information Technology Co., Ltd.

[9]Department of Internal Medicine, Section on Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA

[10]Department of Internal Medicine, Division of Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA

[11]Department of Health Sciences and Technology, [12]Clinical Research Design and Evaluation,

SAIHST, Sungkyunkwan University, Seoul 06351, Korea

* These authors contributed equally as first authors of the paper.

† These authors contributed equally as corresponding authors of the paper.

Corresponding author 1: Joon-Kyung Seong, PhD

School of Biomedical Engineering, Korea University, 145, Anam-ro, Anam-dong 5-ga, Seongbuk-gu, Seoul 02841, Korea.

Tel: +82-2-3290-5660, Fax: +82-2-921-6434, E-mail address: jkseong@korea.ac.kr

Corresponding author 2: Sang Won Seo, MD, PhD

Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Kangnam-ku, Seoul 06351, Korea

Tel: +82-2-3410-1233, Fax: +82-2-3410-0052, E-mail address: sangwonseo@empal.com

Supplementary data: Supplementary Table 1 and Supplementary Figure 1

Supplementary Table 1 Comparison of results of the AD-specific atrophy similarity and neuropsychological tests during their years of follow-up in patients with aMCI and AD

	Patients with aMCI			Patients with AD			*p*-value
	Total	**Non-converters**	**Converters**	**Total**	**Slow-decliners**	**Fast-decliners**	
AD-specific atrophy similarity							
Baseline	41.1 (8.7)	39.4 (7.5)	44.7 (10.0)	48.9 (10.6)	43.9 (9.5)	54.4 (9.1)	a, b
1st year follow-up	44.0 (9.9)	40.9 (7.6)	49.9 (11.2)	51.5 (11.0)	45.9 (10.0)	57.6 (8.9)	a, b
3rd year follow-up				53.9 (12.0)	47.5 (10.6)	60.9 (9.5)	b
Neuropsychological tests							
Baseline							
N	79	53 (67.1)	26 (32.9)	27	14 (51.9)	13 (48.1)	
Attention	9.3 (2.3)	9.5 (2.3)	9.0 (2.1)	8.1 (1.4)	7.7 (1.5)	8.6 (1.0)	
Language	20.9 (3.5)	21.4 (3.2)	19.8 (4.1)	18.3 (4.7)	18.1 (4.7)	18.5 (4.9)	
Visuospatial	30.1 (6.1)	31.3 (4.2)	27.7 (8.4)	27.0 (10.9)	29.6 (9.2)	24.1 (12.1)	
Memory	51.3 (16.5)	56.6 (14.9)	40.8 (14.6)	29.4 (11.6)	32.5 (12.4)	26.1 (10.1)	a
Frontal/executive	36.7 (10.0)	38.5 (9.2)	33.0 (10.7)	36.5 (11.1)	38.4 (11.9)	34.5 (10.2)	a
SNSB-D total	149.7 (26.0)	157.8 (20.6)	133.2 (28.4)	119.4 (28.3)	126.4 (29.4)	111.8 (26.0)	a
MMSE	26.4 (2.4)	27.0 (1.9)	25.4 (3.0)	21.4 (3.1)	21.1 (3.0)	21.7 (3.3)	a
CDR	0.5 (0.1)	0.5 (0.2)	0.5 (0.0)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)	a
CDR-SB	1.2 (0.8)	1.0 (0.8)	1.6 (0.8)	4.7 (1.8)	4.4 (1.4)	5.0 (2.2)	a
1st year follow-up							
N	66	43 (65.2)	23 (34.8)	25	13 (52.0)	12 (48.0)	
Attention	8.9 (2.1)	9.4 (1.9)	7.9 (2.3)	8.0 (1.9)	7.9 (2.2)	8.1 (1.6)	
Language	20.6 (4.0)	21.2 (3.8)	18.8 (4.3)	16.9 (5.4)	17.9 (4.8)	15.8 (6.0)	b
Visuospatial	29.2 (7.5)	30.7 (5.6)	25.0 (10.4)	25.4 (11.1)	29.8 (7.6)	20.7 (12.6)	b
Memory	49.3 (18.1)	52.7 (17.4)	39.8 (17.5)	28.0 (12.4)	32.5 (12.5)	23.1 (10.7)	b
Frontal/executive	37.7 (11.5)	40.4 (9.5)	30.2 (13.9)	34.7 (11.7)	39.4 (8.6)	29.7 (12.9)	a, b
SNSB-D total	145.5 (29.9)	152.7 (26.1)	128.6 (32.4)	113.0 (33.1)	127.4 (26.0)	97.4 (33.8)	a, b
MMSE	25.3 (3.9)	26.8 (2.5)	22.3 (4.4)	19.9 (4.0)	20.7 (2.8)	19.1 (4.9)	a
CDR	0.6 (0.3)	0.5 (0.1)	0.7 (0.4)	0.9 (0.5)	0.8 (0.3)	1.1 (0.5)	a, b
CDR-SB	2.1 (1.8)	1.3 (0.9)	3.5 (2.1)	5.7 (2.6)	4.7 (1.8)	6.7 (2.9)	a, b
3rd year follow-up							
N				27	14 (51.9)	13 (48.1)	
Attention				6.4 (2.7)	7.3 (1.8)	5.5 (3.3)	
Language				12.9 (7.4)	16.3 (5.6)	9.2 (7.6)	b
Visuospatial				17.6 (14.4)	24.5 (11.5)	10.2 (13.9)	b

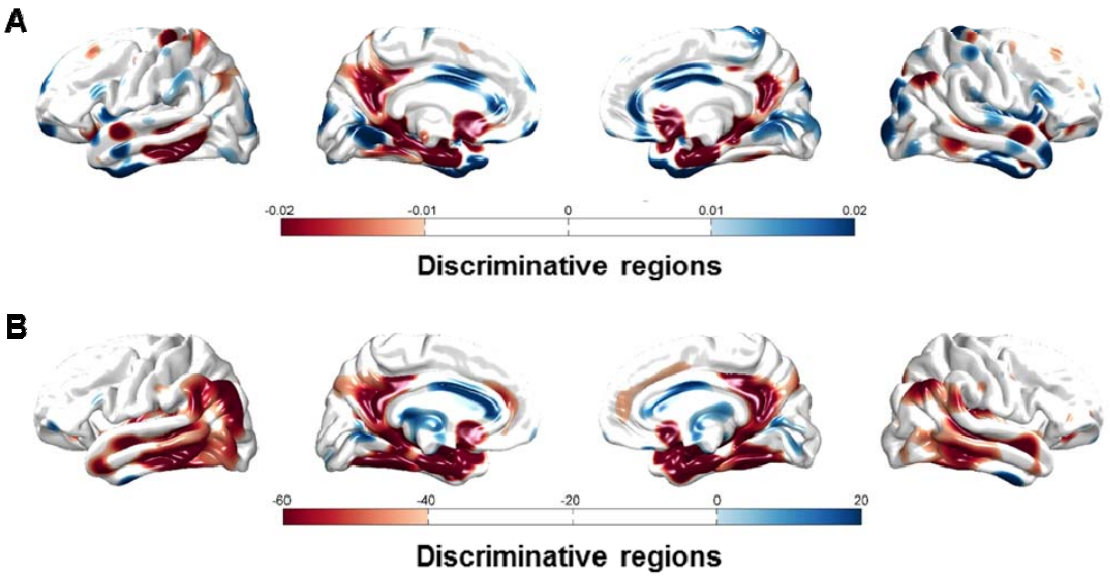
Memory	21.0 (13.5)	28.5 (11.8)	12.9 (10.6)	[b]
Frontal/executive	26.3 (15.4)	35.6 (10.1)	16.2 (13.8)	[b]
SNSB-D total	84.1 (48.7)	112.2 (32.2)	53.9 (45.8)	[b]
MMSE	15.9 (6.5)	18.9 (4.5)	12.5 (6.9)	[b]
CDR	1.6 (0.8)	1.0 (0.4)	2.2 (0.6)	[b]
CDR-SB	9.3 (4.2)	6.1 (2.4)	12.6 (2.9)	[b]

Values are mean (SD) or N (%). Age and education were included as covariates for analyses of covariance, in comparison of the AD-specific atrophy similarity and neuropsychological test performances among the groups.

[a] $p < 0.05$ with Bonferroni's post hoc analyses comparing non-converters and converters in patients with aMCI.

[b] $p < 0.05$ with Bonferroni's post hoc analyses comparing slow- and fast-decliners in patients with AD.

Abbreviations: N = number; SD = standard deviation; AD = Alzheimer's disease; aMCI = amnestic mild cognitive impairment; SNSB-D = Seoul Neuropsychological Screening Battery-Dementia version; MMSE = mini-mental state examination; CDR = Clinical Dementia Rating; CDR-SB = Clinical Dementia Rating sum of boxes.



Supplementary Figure 1 Comparison of the discriminative regions between the (A) PCA/LDA- and (B) SVM-based methods. Color intensities in the figure represent discriminative power in AD classification. In the case of the linear SVM, the value of the *i*-th component of the vector *v* that is orthogonal to the separating hyperplane represents the contribution of the component to classification. The discriminative regions for both classifiers are consistent with each other.

PCA = principal component analysis; LDA = linear discriminant analysis; SVM = support vector machine; AD = Alzheimer's disease.