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Supplemental information

Subtyping of mild cognitive impairment using a deep learning model based on brain atrophy patterns

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Supplementary Figures

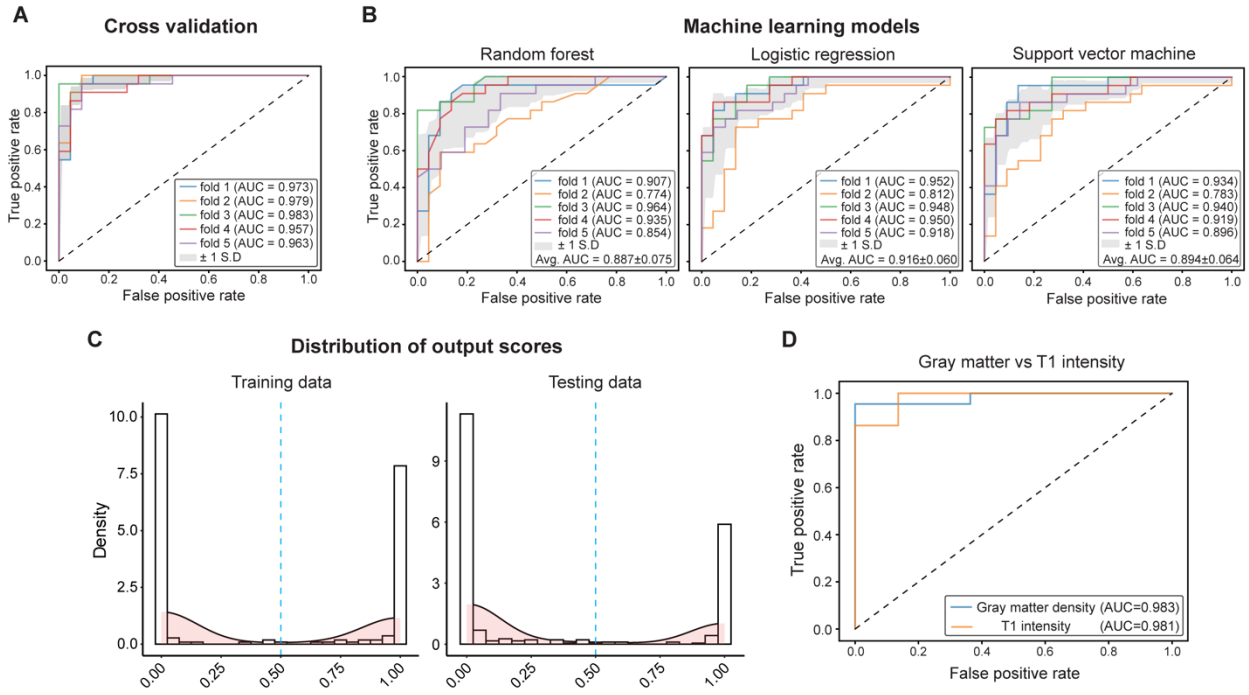

Figure S1. Validation for the performance of the proposed deep learning model, Related to Figure 1. (**A**) ROC curves for the proposed deep learning model obtained in each cross-validation fold. Comparison of ROC curves obtained in each cross-validation fold revealed consistent performance of the proposed deep learning model during the training phase. (**B**) The performance of the proposed deep learning model was compared to that obtained in standard machine learning models, including: Support vector machine, Random forest, and Logistic regression. Shown are ROC curves for each model in each cross-validation fold. All 3 models achieved lower performance than the proposed deep learning model during the training phase. (**C**) The distribution of output scores is shown in the training data in the task of differentiating AD and CN subjects and testing data in the task of dividing MCI subjects into subgroups. The blue dashed lines indicate cut-off of 0.5. (**D**) Comparison of ROC curves obtained when using GM density and T1 intensity values revealed similar performance, but the accuracy of the model based on T1 intensity was lower (T1 intensity=88.5%, GM density=93.75%). Abbreviations: ROC=receiver operating characteristic, AUC=area under the curve, S. D=standard deviation, AD=Alzheimer's disease, CN=cognitively normal, MCI=mild cognitive impairment, GM=gray matter.

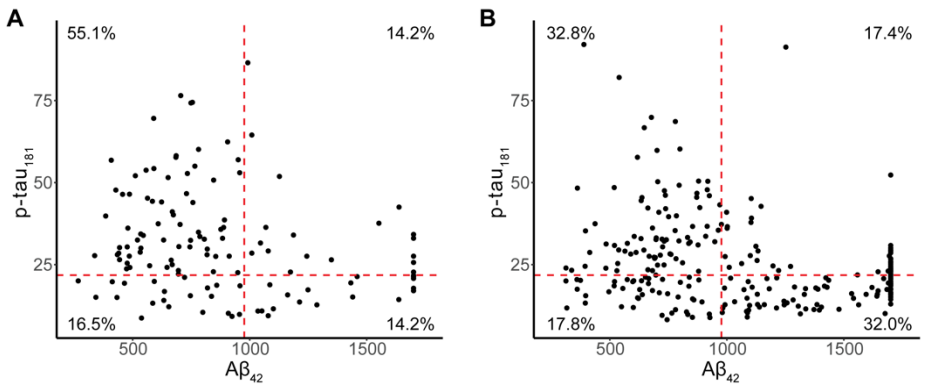

Figure S2. Distributions of CSF biomarker levels in the MCI subgroups, Related to Figure 2. The concordance between CSF Aβ_{42}, and CSF p-tau$_{181}$ levels is shown in the MCI-AD (**A**) and MCI-CN (**B**) subgroups. The red dashed lines indicate a-priori cut-off points used in the CSF biomarkers. The percentages indicate proportions of subjects falling in each quadrant. Abbreviations: AD=Alzheimer's disease, CN=Cognitively normal, MCI=mild cognitive impairment, CSF= cerebrospinal fluid.

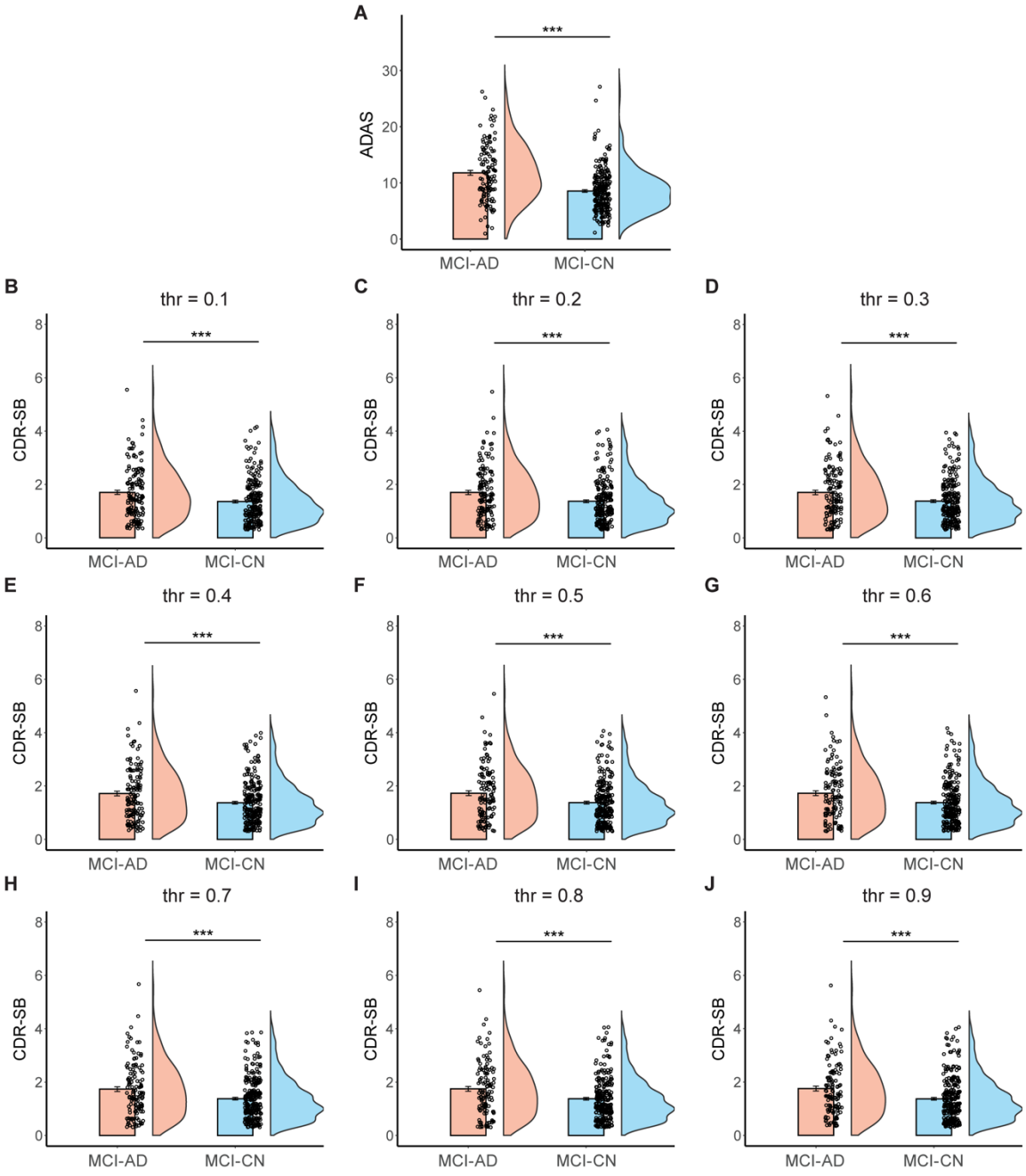

Figure S3. Comparison of cognition between the MCI subgroups, Related to Figure 2. (**A**) Bar plots show ADAS score in the MCI-AD and MCI-CN subgroups. (**B** to **J**) Threshold values used to assign class labels were manipulated to investigate the effect of threshold criteria on MCI subgroup classification, with the default threshold being 0.5 as the cut-off point. In each step, suprathreshold cases are assigned the label MCI-AD, while subthreshold cases are assigned the label MCI-CN. The manipulation of threshold had relatively little effect on group differences, assessed here with CDR-SB scores. Bars represent the mean ± SE. Abbreviations: AD=Alzheimer's disease, CN=Cognitively normal, MCI=mild cognitive impairment, ADAS=Alzheimer's disease assessment scale. CDR-SB=clinical dementia rating sum of boxes. ***p<0.001.

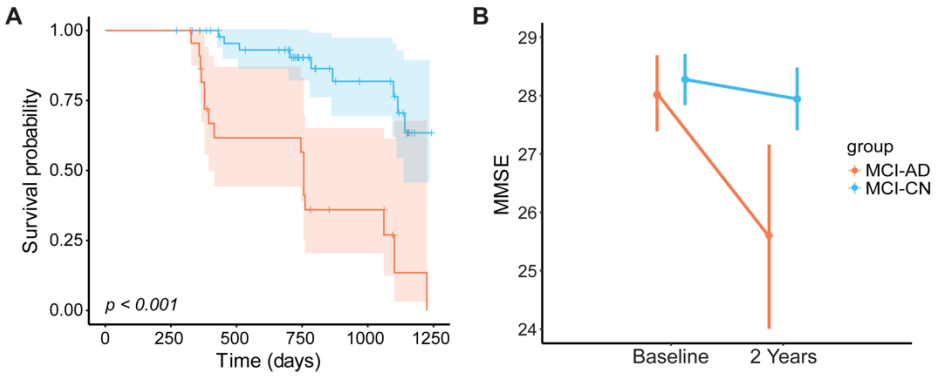

Figure S4. Longitudinal comparison of the model-based MCI subgroups in an independent cohort, Related to Figure 5. (**A**) Kaplan-Meier plots depicting disease-free survival in the MCI-AD and MCI-CN subgroups as found in an independent dataset (OASIS-3). The MCI-CN group showed significantly different disease-free survival over time (log-rank test). Shaded areas depict confidence intervals (**B**) Longitudinal changes in MMSE scores, displayed by the two MCI subgroups, tested with a RM-ANOVA. Abbreviations: AD=Alzheimer's disease, CN=cognitively normal, MCI=mild cognitive impairment, MMSE=mini-mental state exam, RM-ANOVA=repeated measures analysis of variance.

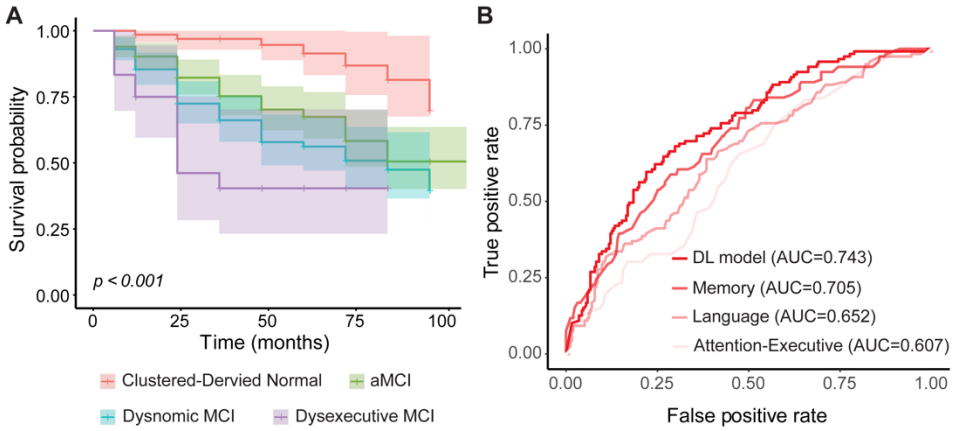

Figure S5. Neuropsychological subtyping approaches in the prediction of progression from MCI to AD, Related to Figure 6. (**A**) Kaplan-Meier curves show disease-free survival for 4 neuropsychological subtypes of MCI: aMCI, Dysnomic MCI, Dysexecutive MCI, and Clustered-Derived Normal. Log-rank test was used to find significant differences among the 4 MCI subtypes (Posthoc test; aMCI vs Dysnomic MCI: p=0.618, Dysnomic MCI vs Dysexecutive MCI: p=0.529). (**B**) ROC curve was used to display the best predictor of progression to AD using cognitive domain scores (Memory, Language, and Attention-Executive function) in comparison to a model based on GM density. Abbreviations: AD=Alzheimer's disease, MCI=mild cognitive impairment, ROC= receiver operating characteristic, GM=gray matter.

Supplementary Tables

Table S1. Demographics of the OASIS dataset, Related to Figure 5

	n	Age	Gender, female	CDR global	MMSE
MCI	78	73.38 (6.4)	35 (44.87%)	0.5 (0)	28.21 (1.63)

Continuous variables are presented as means with SDs and categorical variables are presented as % in parentheses. Abbreviations: MCI=mild cognitive impairment. N=number of subjects, CDR=clinical dementia rating global, MMSE=mini-mental state exam, SD=standard deviation.

Table S2. Group comparisons, Related to STAR Methods.

Variable	Group	Mean difference	95 % CI		P value
			Lower Bound	Upper Bound	
CDR-SB	CN (A−T−) vs AD (A+T+)	-4.57	-4.89	-4.24	< 0.001
	MCI vs AD (A+T+)	-3.08	-3.34	-2.82	<0.001
	MCI vs CN (A−T−)	1.48	1.22	1.75	<0.001
ADAS	CN (A−T−) vs AD (A+T+)	-15.00	-16.55	-13.47	<0.001
	MCI vs AD (A+T+)	-12.34	-13.56	-11.11	<0.001
	MCI vs CN (A−T−)	2.67	1.43	3.91	<0.001
CSF Aβ_{42}	CN (A−T−) vs AD (A+T+)	856.96	741.99	971.93	<0.001
	MCI vs AD (A+T+)	389.43	297.33	481.54	<0.001
	MCI vs CN (A−T−)	-467.53	-559.96	-375.10	<0.001
CSF p-tau$_{181}$	CN (A−T−) vs AD (A+T+)	-24.02	-28.32	-19.71	<0.001
	MCI vs AD (A+T+)	-12.82	-16.27	-9.37	<0.001
	MCI vs CN (A−T−)	11.20	7.74	14.66	<0.001

Post-hoc comparisons using Tukey's HSD. Abbreviations: CI=Confidence interval, AD=Alzheimer's disease, CN=cognitively normal, MCI=mild cognitive impairment, CDR-SB=clinical dementia rating sum of boxes, ADAS=Alzheimer's disease assessment scale, Aβ_{42}=beta-amyloid42, p-tau$_{181}$=phosphorylated-tau181.

Table S3. Demographics for subtypes based on neuropsychological assessments, Related to Figure 6.

	Dysnomic MCI	aMCI	Dysexecutive MCI	Clustered-Derived Normal
n	140	137	26	71
Memory				
RAVLT delayed recall	3.6 (3.2)	2.3 (2.1)	3.1 (2.9)	9.7 (3.0)
RAVLT recognition	11.0 (3.4)	9.8 (2.8)	9.6 (2.4)	14.2 (1.1)
Attention-Executive function				
TMT part A	46.5 (9.0)	30.3 (6.1)	81.6 (23.3)	28.1 (6.4)
TMT part B	122.6 (57.8)	93 (44.3)	197.7 (72.2)	81.3 (41.8)
Language				
Boston naming test	25.2 (4.5)	27.9 (1.7)	24.0 (4.2)	28.1 (1.5)
Animals fluency	15.6 (4.1)	18.6 (4.0)	12.1 (4.0)	22.8 (4.5)

Continuous variables are presented as means with SDs. Abbreviations: MCI=mild cognitive impairment. N=number of subjects, RAVLT= Rey auditory verbal learning test, TMT=trail making test, SD=standard deviation.