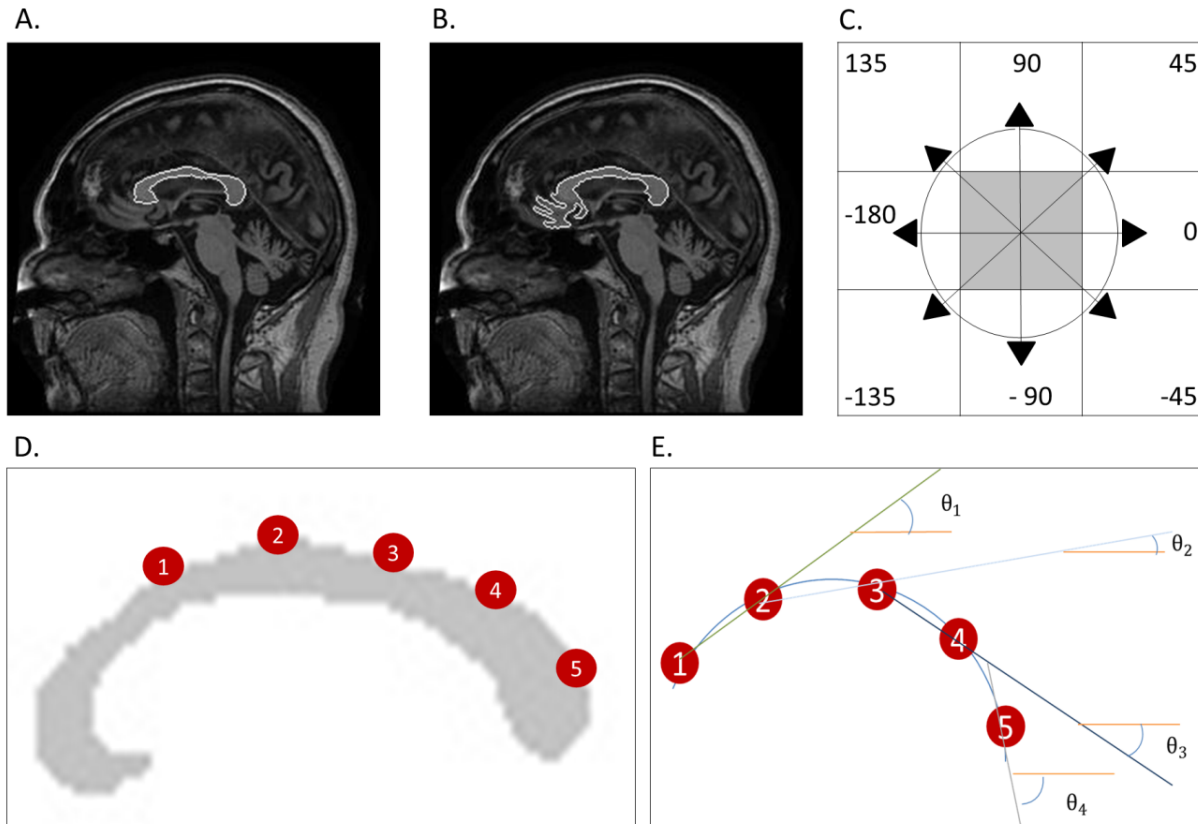


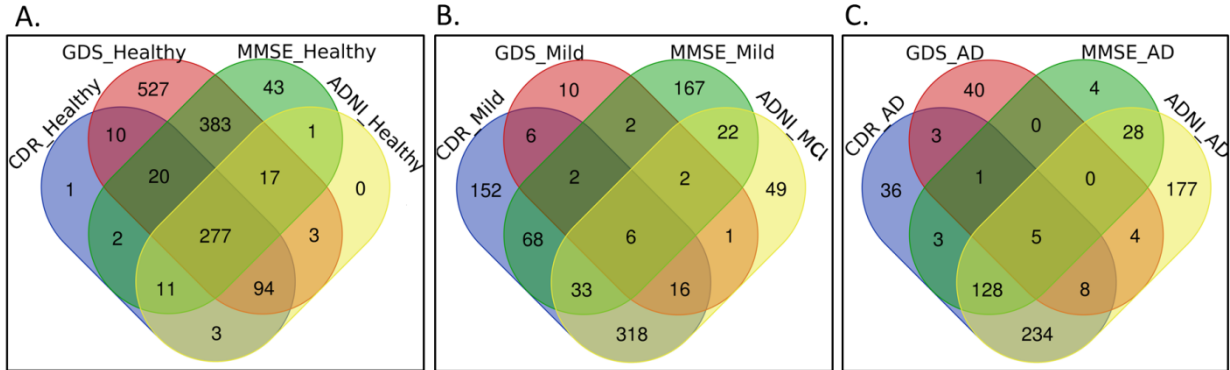
Supplementary Material

Corpus Callosum Atrophy in Detection of Mild and Moderate Alzheimer's Disease Using Brain Magnetic Resonance Image Processing and Machine Learning Techniques

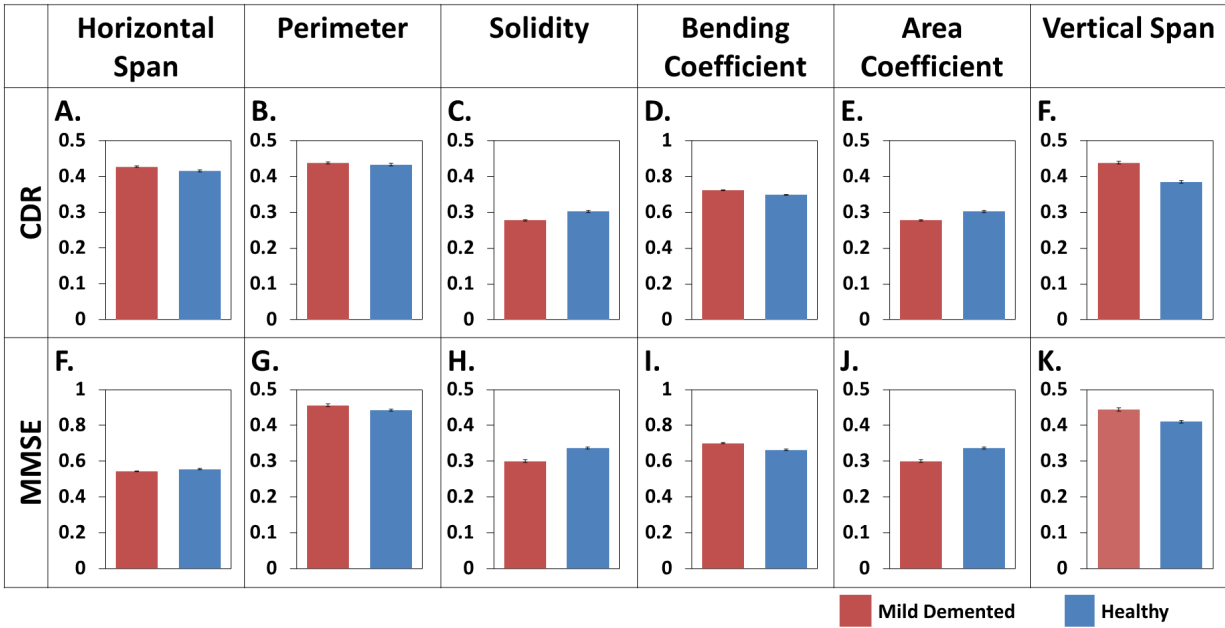
Supplementary Figure 1. Algorithm of automatic corpus callosum (CC) detection. Panel A and B are sample mid sagittal images of native CC and a non-native CC, respectively. Panel C shows a pixel (gray one) can have its immediate neighbor at 8 possible directions with angle (in degree) assigned. Panel D shows a subpart of the walk along the boundary of a segmented region with the corresponding change in angle ($\theta_1, \theta_2, \theta_3, \theta_4$) along the traversal across the boundary (E). Cumulative change in angle through the walk is calculated to get the series which represent the region of interest (CC).



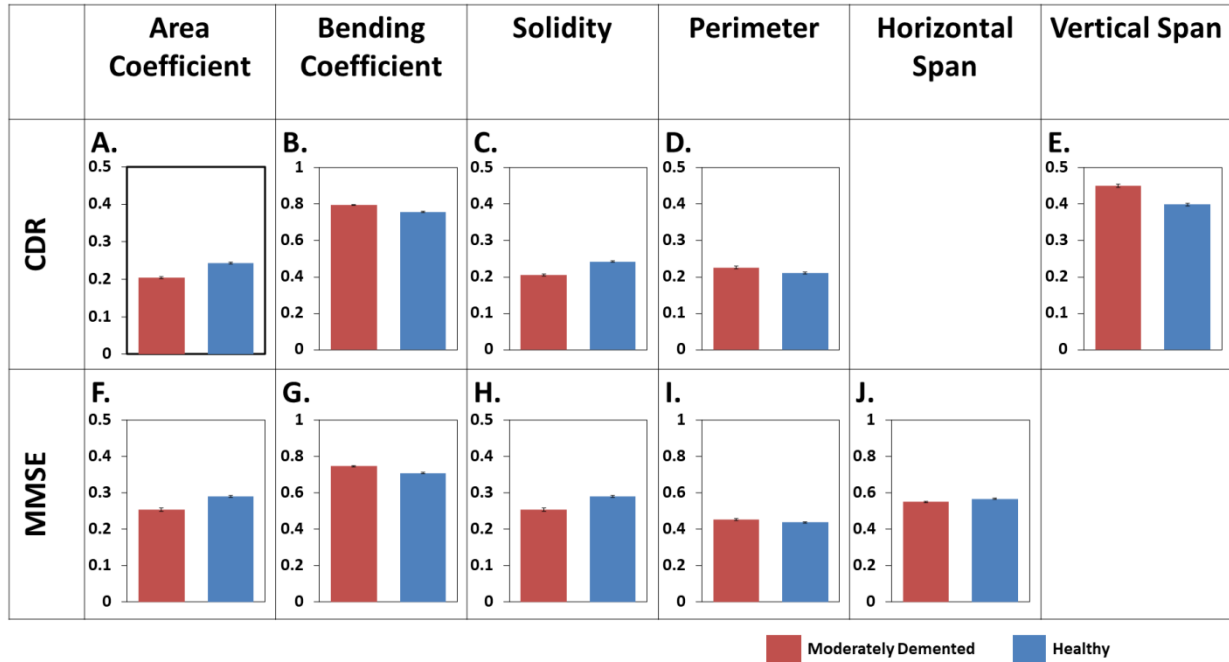
Supplementary Figure 2. Comparison of the datasets. Panel A provides the overlap and intersection of samples categorized as healthy. Panel B shows comparison of mild groups from CDR, GDS, and MMSE with MCI group of ADNI categorization. C) Comparison of moderate and severe groups of CDR, GDS, and MMSE with AD control group of ADNI.



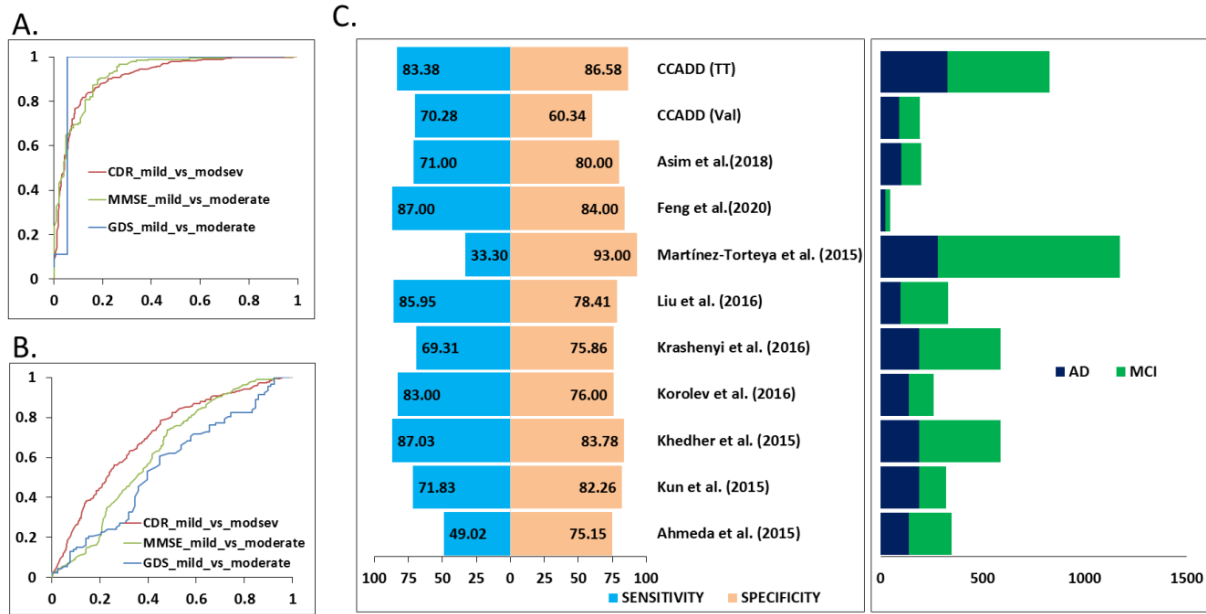
Supplementary Figure 3. Comparison of average ratio of significantly different corpus callosum (CC) features between healthy and mild demented samples. Features were calculated and normalized with respect to the convex hull of the CC. Average values are compared between mild (red) demented and healthy (blue) control sample categorized by CDR and MMSE, respectively.



Supplementary Figure 4. Comparison of average ratio of significantly different corpus callosum (CC) features between healthy and moderately demented samples. Features were calculated and normalized with respect to the convex hull of the CC. Average values are compared between moderately (red) demented and healthy (blue) control sample categorized by CDR and MMSE, respectively.



Supplementary Figure 5. Benchmarking results for test and validation datasets and comparison of the performance. Panels A and B show the receiver operating characteristics (ROC) curves via plotting the sensitivity and 1-specificity values obtained for classification of test sets and validation set respectively using the CDR, GDS, and MMSE categorization based progressively (moderate and severe) and mild demented groups. Panel C plots the sensitivity and specificity values (left side) of our method, CCADD (corpus callosum based Alzheimer's disease detection) obtained for differentiating progressively demented and only mild demented patients. 'TT' and 'Val' signify training-testing and validation cohorts. Corresponding dataset sizes of the AD and MCI cohorts are plotted at the right side.



Supplementary Table 1. Classification criteria of different clinical scoring methods

Classified Groups	Scoring Values		
	CDR	MMSE	GDS
Healthy	=0	≥24	<4
Mild	=0.5	≥19, ≤23	=4
Moderate	=1	≥10, ≤18	>4, ≤6
Severe	≥2	≤9	>6

Supplementary Table 2. List of all and common significantly distinguishable features of corpus callosum used in SVM classification

Features	CDR		MMSE		GDS		ADNI	
	Mild	Moderate	Mild	Moderate	Mild	Moderate	MCI	AD
Convex Hull Area	*		**				*	
Area	*	**	**	**		*	**	**
Area coefficient	**	**	**	**		*	**	**
Perimeter			**	**	*		**	
Perimeter Coefficient		**						**
Centroid x-coordinate		*	**	**	**	**		**
Centroid y-coordinate			**	**	**	**		**
Major Axis Length	**		**	*			**	
Minor Axis Length	**	**	**				*	**
Horizontal Maximum Distance	**		**	**	**			**
Vertical Maximum Distance	**	**	**			*	**	**
Inner Horizontal Maximum Distance	**						*	
Inner Vertical Maximum Distance	**	**	**			*	**	**
Eccentricity	*	**	**					**
Orientation	**	**	**	*		*	*	**
Bending Coefficient	**	**	**	**		*	**	**
Tangent mean	**	**					**	**
Tangent SD	**			*			**	
Binary threshold	**	**	**	**	**	**	**	**
Average intensity	**	**	**	**	**		**	**
Max Intensity	**	**	**		**	**	**	**
Min Intensity	**	**	**	**	*	**	**	**
Mean Intensity	**	**	**	**	**	**	**	**
Equivalent Diameter	**	**	**	**		**	*	**
Solidity	**	**	**	**		*	**	**
Extent	**	**	**	**			**	**
Boundary Left Top			**	**				**
Boundary Right Bottom	**	**	**			*	**	**

*p<0.05; **<0.01

Supplementary Table 3. Data distribution (mid sagittal slice) in different category of different clinical scoring methods

	Alzheimer's disease detection scoring functions							
	CDR		MMSE		GDS		ADNI	
	Models	Samples	Models	Samples	Models	Samples	Models	Samples
Train Test Dataset	Mild versus Healthy	MC: 1,955	Mild versus Healthy	MC: 944	Mild versus Healthy	MC: 94	MCI versus Healthy	MCI: 1,331
		HC: 1,310		HC: 1,603		HC: 395		HC: 1,426
	Moderate versus Healthy	MoC: 1,152	Moderate versus Healthy	MoC: 508	Moderate versus Healthy	MoC: 92		
		HC: 1,310		HC: 1,603		HC: 395		
	Severe versus Healthy	SC: 339	Severe versus Healthy	SC: n.a.	Severe versus Healthy	SC: n.a.		
		HC: 1,310		HC: n.a.		HC: n.a.		
	All Demented versus Healthy	DC: 3,446	All Demented versus Healthy	DC: 1,452	All Demented versus Healthy	DC: 186	AD versus Healthy	AD: 2,090
		HC: 1,310		HC: 1,603		HC: 395		HC: 1,426
Validation Dataset	Mild versus Healthy	MC: 387	Mild versus Healthy	MC: 388	Mild versus Healthy	MC: 92	MCI versus Healthy	MCI: 317
		HC: 554		HC: 1,057		HC: 358		HC: 276
	Moderate versus Healthy	MoC: 291	Moderate versus Healthy	MoC: 279	Moderate versus Healthy	MoC: 78		
		HC: 554		HC: 1,057		HC: 358		
	Severe versus Healthy	SC: 120	Severe versus Healthy	SC: n.a.	Severe versus Healthy	SC: n.a.		
		HC: 554		HC: n.a.		HC: n.a.		
	All Demented versus Healthy	DC: 798	All Demented versus Healthy	DC: 667	All Demented versus Healthy	DC: 170	AD versus Healthy	AD: 590
		HC: 554		HC: 1,057		HC: 358		HC: 276

MC, mild cohort; MoC, moderate cohort; SC, severe cohort, HC, healthy cohort, MCI, mild cognitive impairment, AD, Alzheimer's disease

Supplementary Table 4. Comparison of performance between SVM and RF.

Categorization scheme	Classification group	Methods	Accuracy (%)	Sensitivity (%)	Specificity (%)
ADNI	MCI versus Healthy	SVM	86.93	81.58	91.93
		RF	82.43	81.89	82.93
	AD versus Healthy	SVM	93.60	95.45	90.88
		RF	87.36	85.99	89.31
CDR	Mild versus Healthy	SVM	87.75	94.37	77.86
		RF	86.22	84.45	90.53
	Moderate versus Healthy	SVM	89.02	91.74	86.64
		RF	86.82	83.06	90.61
	Severe versus Healthy	SVM	97.87	94.03	98.85
		RF	91.52	93.88	91.10
GDS	Mild versus Healthy	SVM	93.81	83.33	96.20
		RF	87.76	100.00	85.71
	Moderate versus Healthy	SVM	96.91	94.44	97.47
		RF	86.73	92.86	85.71
MMSE	Mild versus Healthy	SVM	87.20	82.45	90.00
		RF	83.14	86.00	81.94
	Moderate versus Healthy	SVM	93.82	84.16	96.88
		RF	87.94	91.18	87.32

Supplementary Table 5. Benchmarking results of the validation datasets using the best Train models.

Validation dataset (Mild versus Healthy); Scoring function CDR													
<i>TRAIN Model (MC: one or multiple slices from patient having CDR=0.5 and HC: one or multiple slices from patient having CDR=0 Ratio: 1:5)</i>													
Demented	Healthy	Probability threshold	TP	TN	FP	FN	Accuracy	TPR (Sensitivity)	TNR (Specificity)	NPV	Precision	F1 score	MCC
387	554	0	387	0	554	0	41.13	1.00	0.00	0.41	0.59	0.58	0.40
387	554	0.1	380	158	396	7	57.17	0.98	0.29	0.49	0.96	0.65	0.35
387	554	0.2	374	229	325	13	64.08	0.97	0.41	0.54	0.95	0.69	0.43
387	554	0.3	364	281	273	23	68.54	0.94	0.51	0.57	0.92	0.71	0.47
387	554	0.4	353	319	235	34	71.41	0.91	0.58	0.60	0.90	0.72	0.50
387	554	0.5	341	349	205	46	73.33	0.88	0.63	0.62	0.88	0.73	0.51
387	554	0.6	321	370	184	66	73.43	0.83	0.67	0.64	0.85	0.72	0.49
387	554	0.7	293	400	154	94	73.65	0.76	0.72	0.66	0.81	0.70	0.47
387	554	0.8	257	434	120	130	73.43	0.66	0.78	0.68	0.77	0.67	0.45
387	554	0.9	195	480	74	192	71.73	0.50	0.87	0.72	0.71	0.59	0.40
387	554	1	0	554	0	387	58.87	0.00	1.00	0.75	0.59	0.00	0.38
Validation dataset (Moderate versus Healthy); Scoring function CDR													
<i>TRAIN Model (MoC: one or multiple slices from patient having CDR=1 and HC: one or multiple slices from patient having CDR=0 Ratio: 1:5)</i>													
291	554	0	291	0	554	0	34.44	1.00	0.00	0.34	0.66	0.51	0.46
291	554	0.1	277	259	295	14	63.43	0.95	0.47	0.48	0.95	0.64	0.43
291	554	0.2	260	329	225	31	69.70	0.89	0.59	0.54	0.91	0.67	0.47
291	554	0.3	247	372	182	44	73.25	0.85	0.67	0.58	0.89	0.69	0.49
291	554	0.4	229	428	126	62	77.75	0.79	0.77	0.65	0.87	0.71	0.54
291	554	0.5	209	457	97	82	78.82	0.72	0.82	0.68	0.85	0.70	0.54
291	554	0.6	193	468	86	98	78.22	0.66	0.84	0.69	0.83	0.68	0.51
291	554	0.7	175	487	67	116	78.34	0.60	0.88	0.72	0.81	0.66	0.50
291	554	0.8	154	503	51	137	77.75	0.53	0.91	0.75	0.79	0.62	0.48
291	554	0.9	120	523	31	171	76.09	0.41	0.94	0.79	0.75	0.54	0.44
291	554	1	0	554	0	291	65.56	0.00	1.00	0.86	0.66	0.00	0.45
Validation dataset (Severe versus Healthy); Scoring function CDR													
<i>TRAIN Model (SC: one or multiple slices from patient having CDR ≥ 2 and HC: one or multiple slices from patient having CDR=0 Ratio: 1:5)</i>													
120	554	0	120	0	554	0	17.80	1.00	0.00	0.18	0.82	0.30	0.60
120	554	0.1	108	405	149	12	76.11	0.90	0.73	0.42	0.97	0.57	0.50
120	554	0.2	102	448	106	18	81.60	0.85	0.81	0.49	0.96	0.62	0.55
120	554	0.3	96	465	89	24	83.23	0.80	0.84	0.52	0.95	0.63	0.55
120	554	0.4	88	486	68	32	85.16	0.73	0.88	0.56	0.94	0.64	0.55
120	554	0.5	84	507	47	36	87.69	0.70	0.92	0.64	0.93	0.67	0.59
120	554	0.6	80	520	34	40	89.02	0.67	0.94	0.70	0.93	0.68	0.62

120	554	0.7	72	534	20	48	89.91	0.60	0.96	0.78	0.92	0.68	0.63
120	554	0.8	64	545	9	56	90.36	0.53	0.98	0.88	0.91	0.66	0.64
120	554	0.9	54	549	5	66	89.47	0.45	0.99	0.92	0.89	0.60	0.60
120	554	1	0	554	0	120	82.20	0.00	1.00	0.98	0.82	0.00	0.56
Validation dataset (Mild versus Healthy); Scoring function GDS													
<i>TRAIN Model (MC: one or multiple slices from patient having GDS = 4 and HC: one or multiple slices from patient having GDS < 4 Ratio: 1:5)</i>													
92	358	0	92	0	358	0	20.44	1.00	0.00	0.20	0.80	0.34	0.16
92	358	0.1	67	242	116	25	68.67	0.73	0.68	0.37	0.91	0.49	0.33
92	358	0.2	48	249	109	44	66.00	0.52	0.70	0.31	0.85	0.39	0.18
92	358	0.3	36	316	42	56	78.22	0.39	0.88	0.46	0.85	0.42	0.29
92	358	0.4	29	326	32	63	78.89	0.32	0.91	0.48	0.84	0.38	0.27
92	358	0.5	23	327	31	69	77.78	0.25	0.91	0.43	0.83	0.32	0.20
92	358	0.6	20	340	18	72	80.00	0.22	0.95	0.53	0.83	0.31	0.24
92	358	0.7	13	344	14	79	79.33	0.14	0.96	0.48	0.81	0.22	0.17
92	358	0.8	0	358	0	92	79.56	0.00	1.00	1.00	0.80	0.00	0.16
92	358	0.9	0	358	0	92	79.56	0.00	1.00	1.00	0.80	0.00	0.16
92	358	1	0	358	0	92	79.56	0.00	1.00	1.00	0.80	0.00	0.16
Validation dataset (Moderate versus Healthy); Scoring function GDS													
<i>TRAIN Model (MoC: one or multiple slices from patient having 4<GDS≤6 and HC: one or multiple slices from patient having GDS < 4 Ratio: 1:5)</i>													
78	358	0	78	0	358	0	17.89	1.00	0.00	0.18	0.82	0.30	0.31
78	358	0.1	67	167	191	11	53.67	0.86	0.47	0.26	0.94	0.40	0.25
78	358	0.2	59	240	118	19	68.58	0.76	0.67	0.33	0.93	0.46	0.33
78	358	0.3	46	268	90	32	72.02	0.59	0.75	0.34	0.89	0.43	0.28
78	358	0.4	38	299	59	40	77.29	0.49	0.84	0.39	0.88	0.43	0.30
78	358	0.5	34	312	46	44	79.36	0.44	0.87	0.43	0.88	0.43	0.30
78	358	0.6	30	320	38	48	80.28	0.38	0.89	0.44	0.87	0.41	0.29
78	358	0.7	26	327	31	52	80.96	0.33	0.91	0.46	0.86	0.39	0.28
78	358	0.8	23	336	22	55	82.34	0.29	0.94	0.51	0.86	0.37	0.29
78	358	0.9	16	349	9	62	83.72	0.21	0.97	0.64	0.85	0.31	0.30
78	358	1	0	358	0	78	82.11	0.00	1.00	1.00	0.82	0.00	0.18
Validation dataset (Mild versus Healthy); Scoring function MMSE													
<i>TRAIN Model (MC: one or multiple slices from patient having 19≤MMSE≤23 and HC: one or multiple slices from patient having MMSE ≥ 24 Ratio: 1:5)</i>													
388	1,057	0	388	0	1057	0	26.85	1.00	0.00	0.27	0.73	0.42	0.19
388	1,057	0.1	353	233	824	35	40.55	0.91	0.22	0.30	0.87	0.45	0.15
388	1,057	0.2	316	392	665	72	49.00	0.81	0.37	0.32	0.84	0.46	0.18
388	1,057	0.3	276	520	537	112	55.09	0.71	0.49	0.34	0.82	0.46	0.18
388	1,057	0.4	241	620	437	147	59.58	0.62	0.59	0.36	0.81	0.45	0.18
388	1,057	0.5	208	732	325	180	65.05	0.54	0.69	0.39	0.80	0.45	0.21

388	1,057	0.6	179	806	251	209	68.17	0.46	0.76	0.42	0.79	0.44	0.22
388	1,057	0.7	144	854	203	244	69.07	0.37	0.81	0.41	0.78	0.39	0.19
388	1,057	0.8	113	909	148	275	70.73	0.29	0.86	0.43	0.77	0.35	0.17
388	1,057	0.9	65	992	65	323	73.15	0.17	0.94	0.50	0.75	0.25	0.16
388	1,057	1	0	1057	0	388	73.15	0.00	1.00	0.58	0.73	0.00	0.19
Validation dataset (Moderate versus Healthy); Scoring function MMSE													
<i>TRAIN Model (MoC: one or multiple slices from patient having $10 \leq MMSE \leq 18$ and HC: one or multiple slices from patient having $MMSE \geq 24$ Ratio: 1:5)</i>													
279	1,057	0	279	0	1057	0	20.88	1.00	0.00	0.21	0.79	0.35	0.40
279	1,057	0.1	242	501	556	37	55.61	0.87	0.47	0.30	0.93	0.45	0.28
279	1,057	0.2	202	727	330	77	69.54	0.72	0.69	0.38	0.90	0.50	0.34
279	1,057	0.3	183	828	229	96	75.67	0.66	0.78	0.44	0.90	0.53	0.39
279	1,057	0.4	167	868	189	112	77.47	0.60	0.82	0.47	0.89	0.53	0.39
279	1,057	0.5	150	901	156	129	78.67	0.54	0.85	0.49	0.87	0.51	0.38
279	1,057	0.6	138	931	126	141	80.01	0.49	0.88	0.52	0.87	0.51	0.38
279	1,057	0.7	124	976	81	155	82.34	0.44	0.92	0.60	0.86	0.51	0.41
279	1,057	0.8	118	984	73	161	82.49	0.42	0.93	0.62	0.86	0.50	0.41
279	1,057	0.9	90	1010	47	189	82.34	0.32	0.96	0.66	0.84	0.43	0.37
279	1,057	1	0	1057	0	279	79.12	0.00	1.00	0.76	0.79	0.00	0.35
Validation dataset (MCI versus Healthy); ADNI Grouping													
<i>TRAIN Model (MC: one or multiple slices from patient diagnosed as MCI and HC: one or multiple slices from subject diagnosed as normal healthy Ratio: 1:5)</i>													
317	276	0	317	0	276	0	53.46	1.00	0.00	0.53		0.70	
317	276	0.1	305	57	219	12	61.05	0.96	0.21	0.58	0.83	0.73	0.26
317	276	0.2	298	86	190	19	64.76	0.94	0.31	0.61	0.82	0.74	0.33
317	276	0.3	284	92	184	33	63.41	0.90	0.33	0.61	0.74	0.72	0.28
317	276	0.4	271	114	162	46	64.92	0.85	0.41	0.63	0.71	0.72	0.30
317	276	0.5	242	153	123	75	66.61	0.76	0.55	0.66	0.67	0.71	0.33
317	276	0.6	194	188	88	123	64.42	0.61	0.68	0.69	0.60	0.65	0.29
317	276	0.7	169	204	72	148	62.90	0.53	0.74	0.70	0.58	0.61	0.28
317	276	0.8	138	219	57	179	60.20	0.44	0.79	0.71	0.55	0.54	0.24
317	276	0.9	99	237	39	218	56.66	0.31	0.86	0.72	0.52	0.44	0.20
317	276	1	0	276	0	317	46.54	0.00	1.00	0.79	0.47	0.00	0.23
Validation dataset (AD versus Healthy); ADNI Grouping													
<i>TRAIN Model (AD: one or multiple slices from patient diagnosed as AD and HC: one or multiple slices from subject diagnosed as normal healthy Ratio: 1:5)</i>													
590	276	0	590	0	276	0	68.13	1.00	0.00	0.68		0.81	
590	276	0.1	566	97	179	24	76.56	0.96	0.35	0.76	0.80	0.85	0.42
590	276	0.2	545	149	127	45	80.14	0.92	0.54	0.81	0.77	0.86	0.52
590	276	0.3	530	171	105	60	80.95	0.90	0.62	0.83	0.74	0.87	0.55
590	276	0.4	516	177	99	74	80.02	0.87	0.64	0.84	0.71	0.86	0.53
590	276	0.5	497	190	86	93	79.33	0.84	0.69	0.85	0.67	0.85	0.53

590	276	0.6	469	205	71	121	77.83	0.79	0.74	0.87	0.63	0.83	0.52
590	276	0.7	423	220	56	167	74.25	0.72	0.80	0.88	0.57	0.79	0.48
590	276	0.8	385	236	40	205	71.71	0.65	0.86	0.91	0.54	0.76	0.47
590	276	0.9	309	255	21	281	65.13	0.52	0.92	0.94	0.48	0.67	0.43
590	276	1	0	276	0	590	31.87	0.00	1.00	0.94	0.32	0.00	0.40