

MRI-Based Alzheimer's Disease-Resemblance Atrophy Index in the Detection of Preclinical and Prodromal Alzheimer's Disease

Wanting Liu

Chinese University of Hong Kong

Lisa Wing Chi Au

Chinese University of Hong Kong

Jill Abrigo

Chinese University of Hong Kong

Yishan Luo

BrainNow Research Institute

Adrian Wong

Chinese University of Hong Kong

Bonnie Yin Ka Lam

Chinese University of Hong Kong

Xiang Fan

Chinese University of Hong Kong

Pauline Wing Lam Kwan

Chinese University of Hong Kong

Hon Wing Ma

Chinese University of Hong Kong

Anthea Yee Tung Ng

Chinese University of Hong Kong

Sirong Chen

Hong Kong Sanatorium & Hospital

Eric Yim Lung Leung

Hong Kong Sanatorium & Hospital

Chi Lai Ho

Hong Kong Sanatorium & Hospital

Simon Ho Man Wong

Medheath Diagnostic MRI Centre

Winnie CW Chu

Chinese University of Hong Kong

Ho Ko

Chinese University of Hong Kong

Alexander Yuk Lun Lau (✉ alexlau@cuhk.edu.hk)

Chinese University of Hong Kong <https://orcid.org/0000-0002-5933-9290>

Lin Shi

Chinese University of Hong Kong

Vincent Chung Tong Mok

Chinese University of Hong Kong

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Abstract

Background: We aimed to validate the performance of an MRI-based machine learning derived Alzheimer's Disease-resemblance atrophy index (AD-RAI) in detecting preclinical and prodromal AD.

Methods: A total of 62 subjects (mild cognitive impairment [MCI]=25, cognitively unimpaired [CU]=37) underwent MRI, ^{11}C - PIB, and ^{18}F -T807 PET. We investigated the performance of AD-RAI at the pre-specified cutoff of ≥ 0.5 in detecting preclinical and prodromal AD and compared its performance with that of visual and volumetric hippocampal measures.

Results: AD-RAI achieved the best metrics among all subjects (sensitivity 0.73, specificity 0.91, accuracy 87.10%) and among MCI subgroup (sensitivity 0.91, specificity 0.79, accuracy 84.00%) in detecting A+T+ subjects over other measures. Among CU subgroup, hippocampal volume (sensitivity 0.75, specificity 0.88, accuracy 86.49%) achieved a higher sensitivity than AD-RAI (sensitivity 0.25, specificity 0.97, accuracy 89.19%) in detecting preclinical AD.

Conclusions: AD-RAI aids the detection of early AD, in particular at the prodromal stage.

Background

Detection of subjects at risk of developing dementia associated with Alzheimer's disease (AD) and intervention at the early stage provides the greatest opportunity in reducing the increasing dementia burden associated with AD, which is the commonest cause for dementia worldwide. The latest 2018 National Institute on Aging and Alzheimer's Association (NIA-AA) research framework defined AD biologically by the presence of 2 core pathologic molecular biomarkers, beta-amyloid (A+) and neurofibrillary tau (T+), rather than by the presence of cognitive impairment (1). With this definition, subjects harboring A+T+ may exhibit a continuum of severity of cognitive impairment, ranging from cognitively unimpaired (CU) (i.e. preclinical AD), to mild cognitive impairment (MCI) (i.e. prodromal AD), to dementia (i.e. AD with dementia). The evolution from preclinical to prodromal AD, or from prodromal AD to AD with dementia may take several years and this slow transition provides an excellent window to implement strategies that may prevent conversion to dementia.

This shift in paradigm (i.e. from reliance on clinical symptoms to molecular biomarkers, from focusing on dementia to pre-dementia stage) makes having an accurate *in-vivo* method in detecting AD biomarkers to be of great importance. At present, accurate *in-vivo* detection of beta-amyloid and neurofibrillary tau is feasible with positron emission tomography (PET) and cerebrospinal fluid (CSF) analysis. Studies comparing antemortem amyloid and tau PET and CSF analysis of beta-amyloid₁₋₄₂ and phosphorylated tau showed excellent correlation with post-mortem amyloid and tau burden (2-4). Both PET and/or CSF are currently considered as the gold standard *in-vivo* diagnostic tests for preclinical and prodromal AD.

Apart from beta-amyloid and neurofibrillary tau, the 2018 NIA-AA research framework also considers neurodegeneration (N) as another biomarker for AD (1). However, neurodegeneration is considered a

downward and relatively more advanced event in the biological cascade of AD progression and is also non-specific, as many other brain diseases may also cause neurodegeneration. Neurodegeneration in AD is currently captured *in-vivo* by Fluorodeoxyglucose (FDG) PET hypometabolism, CSF total-tau, and atrophy on magnetic resonance imaging (MRI). Despite being considered as an advanced event in the biological cascade of AD, previous studies suggested that subtle yet characteristic pattern of neurodegeneration could still be detected by FDG PET, CSF total -tau, or MRI at the preclinical or prodromal stage of AD (5-8). Moreover, subjects with A+T+(N)+ are at higher risk of future cognitive decline than those with A+T+(N)- (9, 10). Hence, detection of characteristic pattern of neurodegeneration may have a role in the detection or prognostication for preclinical and prodromal AD.

Pattern of brain atrophy associated with AD is more prominent in the medial temporal lobe (e.g. hippocampus) initially, and then spread throughout the entire temporal lobe, parietal lobe, and frontal lobe (5, 8, 11). Medial temporal lobe atrophy (MTA) or hippocampal volume (HV) as determined by MRI is the commonest imaging biomarker used for the diagnosis of AD with dementia or as a prognostic biomarker predicting conversion from MCI to AD with dementia (12, 13). With the advancement of MRI-based automated brain segmentation tools, global and regional brain volumes (e.g. HV) can now be quantified accurately, reliably, easily, and quickly. In addition, several studies attempted to combine multi-region brain atrophy features on MRI in the form of a single severity index as derived from machine learning method and investigated its accuracy in predicting risk of conversion from CU to MCI or from MCI to AD with dementia at an individual-level (14-19). We recently showed that an MRI-based machine learning derived AD-resemblance atrophy index (AD-RAI) had the best prognostic performance over other regional volumetric measures in predicting conversion from CU to MCI and from MCI to AD with dementia using subjects from the AD neuroimaging initiatives (ADNI) (19). This index indicates the similarity in atrophy pattern between the subject's brain and those with AD with dementia. It ranges from 0 to 1.0 and value closer to 1 implies greater similarity. The optimal AD-RAI cutoff of differentiating converters from non-converters derived from subjects recruited from ADNI was ≥ 0.5 (19).

In this study, we aimed to validate the performance of AD-RAI at the cutoff of ≥ 0.5 obtained from the derivation study (19) in the detection of preclinical and prodromal AD among MCI and CU subjects recruited from another prospective cohort, and to compare its performance with that of traditional MRI-based measures, namely visual MTA rating and HV measures.

Methods

Participants

Participants of this study were recruited from an on-going CU-SEEDS (The Chinese University of Hong Kong - Screening for Early Alzheimer's Disease) study, which aimed to validate biomarkers (e.g. retinal imaging, brain MRI, plasma) for detection of AD. The study aimed to initially recruit 100 subjects (40 CU, 40 MCI, 20 mild AD with dementia) from the community and Cognitive Disorder Clinic of the Prince of Wales Hospital, Hong Kong SAR. Inclusion criteria were (1) Chinese ethnicity; (2) age between 50 to 80-

year-old; and (3) a primary language of Cantonese. Exclusion criteria were (1) known diagnosis of non-AD dementia; (2) known history of stroke, parkinsonism, major psychiatric disease, or any significant neurological diseases (e.g. brain tumor); and/or (3) contraindication for MRI/PET. An experienced dementia specialist (L.W.C.A.) examined all potential subjects for eligibility of this study.

Syndromal staging of cognitive continuum

We defined CU and MCI according to the 2018 NIA-AA research framework (1). We used the Chinese Abbreviated Memory Inventory (CAMI) to define the presence of memory complaints(20). Subjects having one or more “Yes” to the 5 questions in CAMI were classified as having subjective memory complaints. We performed Hong Kong List Learning Test (HKLLT) (21) and the Hong Kong version of Montreal Cognitive Assessment (HK-MoCA) (22) for all subjects. We defined MCI as the presence of subjective memory complaints that represented a decline from baseline, objective memory impairment as defined by a z-score adjusted by age in Trial 4 (i.e. 10 min-delayed recall) of HKLLT of ≤ -1 standard deviation (SD) (23), and the cognitive impairment has no major impact in daily function as defined by a clinical dementia rating scale (CDR) of ≤ 0.5 . We defined CU as having a z-score adjusted by age in Trial 4 of HKLLT $> -1SD$ and a CDR of 0. All participants provided written informed consent and this study was approved by the local ethics committee.

MRI

MRI was performed at Prince of Wales Hospital using a 3.0 Tesla scanner (Achieva TX; Philips Medical Systems, Best, Netherlands). The scanning protocol included a 3D T1-weighted MPRAGE sequence acquired at a resolution of 1.1mmx1.1mmx1.2mm which was used for visual assessment and volumetric analysis, as well as standard T2-weighted and FLAIR sequences to assess for other structural abnormalities including strategic infarcts and significant white matter hyperintensities.

PET

We performed ^{11}C -PIB and ^{18}F -T807 PET/CT to quantify beta-amyloid and tau deposition, respectively at the Department of Nuclear Medicine & PET of Hong Kong Sanatorium & Hospital, Hong Kong SAR. All subjects received ^{11}C -PIB intravenously and were scanned at 35 min post injection. Within one week, they underwent ^{18}F -T807 PET/CT at 85 min post IV injection. ^{11}C -PIB and ^{18}F -T807 uptake were quantified by the “global cortical to cerebellum Standard Uptake Value ratio (SUVR)”. The calculation of SUVR included 13 target regions of interest contoured automatically: frontal gyrus, gyrus rectus, lateral temporal lobe, medial temporal lobe, posterior cingulate gyrus, precuneus, putamen, thalamus, superior parietal lobe, occipital lobe, head of the caudate, cerebellar vermis and brainstem.

We defined A+ if (1) increased ^{11}C -PIB uptake was visually observed in regions known to have beta-amyloid deposits in patients with AD dementia, e.g. frontal lobe, parietal lobe, lateral temporal lobe, posterior cingulate, precuneus and/or caudate; and/or (2) global retention ≥ 1.42 . We defined T+ if (1) increased ^{18}F -T807 uptake was visually observed in regions known to have tau deposits in AD dementia,

e.g. medial temporal lobe, inferior and middle temporal lobe, medial and lateral parietal lobe, occipital and frontal lobe (24); and/or (2) SUVR ≥ 1.14 . CU and MCI subjects who had A+T+ were diagnosed as having preclinical and prodromal AD, respectively (1). All PET imaging data was interpreted by an experienced nuclear medicine specialist (E.Y.L.L.) who was blinded to subjects' cognitive and structural imaging data.

Visual ratings of MTA

An experienced neuroradiologist (J.A.) rated MTA using Scheltens's scale (25). 10 individuals were randomly selected and rated again by the same neuroradiologist to obtain intra-rater reliability. We took the average of the left and right MTA scores as the final MTA score. We used the cutoff of ≥ 1 to define prodromal AD (26). We also explored the performance using other pre-specified cutoffs (i.e. ≥ 1.5 (27, 28) and age-adjusted: 1.5 for <75-year-old, and 2 for ≥ 75 -year-old (29)) which have been used for the diagnosis of AD at the dementia stage.

MRI post-processing

All the MRIs were processed using AccuBrain[®] IV 1.1 (BrainNow Medical Technology Company Ltd.) that performs brain structure and tissue segmentation and quantification using 3D T1-weighted MR image (30). We used the summation of the volume of both sides in milliliter (mL) as the final raw HV. Accubrain[®] also generated the hippocampal fraction (HF) (bilateral absolute HV/intracranial volume). AccuBrain[®] also generated AD-RAI to indicate the similarity in atrophy pattern between the subject's brain and those with AD with dementia (ranging from 0 to 1.0).

We investigated the performance of AD-RAI in detecting subjects with A+T+ using an index of ≥ 0.5 , as obtained from the derivation study that was found to be the optimal cutoff in differentiating between "converters" and "stable" using ADNI database(19). Note that in our derivation study, we did not obtain the optimal cutoffs of HV and HF in differentiating between "converters" and "stable". In order to compare AD-RAI with conventional imaging measures (i.e. HV and HF) in detecting A+T+ subjects in the present validation study, we further generated receiving operating curve (ROC) among all subjects and among MCI and CU subgroups for the differentiation between "converters" and "stable" subjects. The derived optimal cutoffs were as follows: all subjects - HV: 6.44mL, HF: 0.42%, MCI subjects - HV: 6.07mL, HF: 0.41%, and CU subjects - HV: 6.64mL, HF: 0.44%. The performance metrics (sensitivity, specificity, positive predictive values, negative predictive values, accuracy) using the optimal cutoffs of AD-RAI, HV, and HF in differentiating converters and stable subjects from ADNI database can be found in supplemental material (Appendix I to III). We also compared pre-specified cutoffs (HV: 5.91mL, HF: 0.39%) used for the detection of AD with dementia (30). MRI of the 10 individuals who were randomly selected for evaluation of intra-rater reliability for visual MTA rating were processed again by AccuBrain[®] to test/re-test precision of the tool in generating HV, HF, and AD-RAI.

Statistical analyses

Continuous variables were presented as means (SD), whilst categorical variables were presented as numbers (percentage). The p-values representing the group difference were derived from independent-samples t-test. Intra-rater reliability was assessed with the weighted Cohen's kappa test (31). Sensitivity and specificity with 95% confidence intervals (CI), positive and negative prediction values (PPV, NPV), and accuracy were employed to evaluate the performance of different measures in the identification of A+T+ subjects. We also explored the metrics of various imaging measures in the detection of A+ with or without T+ (i.e. Alzheimer's continuum). Statistical analyses were performed using SPSS version 25.0 for IOS.

Results

We recruited 62 patients altogether, 25 had MCI and 37 subjects were CU (Table 1). Intra-rater reliability for visual MTA rating showed a weighted Kappa of 0.74. The test/re-test precision of AccuBrain® in generating repeated measures was perfect (i.e. 100%) for AD-RAI, HV, and HF. Among all recruited subjects, 15 subjects (24.2%) were A+T+. Number (percentage) of subjects who were A+T+ among MCI and CU were 11 (44%) and 4 (10.8%), respectively.

Table 1. Demographic and clinical characteristics of subjects

	All subjects (n=62)	MCI subgroup (n=25)	CU subgroup (n=37)	P- value
Age (years), mean (SD)	66.77 ± 7.10	69.80 ± 6.49	64.73 ± 6.83	0.005*
Male (n [%])	26 (41.9)	11 (44.0)	15 (40.5)	0.791
Education (years), mean (SD)	9.32 ± 4.41	8.64 ± 4.64	9.78 ± 4.26	0.321
HK-MoCA, mean (SD)	24.28 ± 4.80	20.76 ± 4.70	26.72 ± 3.06	< 0.001*
HKLLT z-score in Trial 4, mean (SD)	-0.51 ± 1.22	-1.72 ± 0.59	0.31 ± 0.76	< 0.001*
A+T+ (n [%])	15 (24.2)	11 (44.0)	4 (10.8)	0.006*
A+T- (n [%])	3 (4.8)	2 (8.0)	1 (2.7)	0.348

MCI=mild cognitive impairment; CU=cognitively unimpaired; MoCA=Hong Kong version of Montreal Cognitive Assessment; HKLLT=Hong Kong List Learning Test; A+T+=subjects harboring beta-amyloid and tau. The p-values represent the group difference in each variable between MCI subgroup and CU subgroup derived from independent-samples t-test. * represents significant difference between MCI subgroup and CU subgroup at p < 0.05.

Among all recruited subjects (Table 2a), AD-RAI (≥ 0.5) yielded the best sensitivity (0.73) and accuracy (87.10%) over other measures, as well as a high specificity of 0.91 in detecting AD (A+T+) subjects. HV (≤ 6.44 mL) yielded a fair sensitivity of 0.67, with a specificity of 0.85 and an accuracy of 80.65%. HF (\leq

0.42%) had the highest specificity of 1.00, yet with a very low sensitivity of 0.27. Sensitivity, specificity, and accuracy of MTA (≥ 1) were 0.53, 0.91, and 82.26%, respectively.

Table 2a. Performance metrics of AD-RAI, HV, HF and MTA among all subjects (n=62)

Measures	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value	Accuracy
AD-RAI (≥ 0.5)	0.73 (0.45-0.91)	0.91 (0.79-0.97)	73.33%	91.49%	87.10%
HV ($\leq 6.44\text{mL}$)	0.67 (0.39-0.87)	0.85 (0.71-0.93)	58.82%	88.89%	80.65%
HF ($\leq 0.42\%$)	0.27 (0.09-0.55)	1.00 (0.91-1.00)	100.00%	81.03%	82.26%
MTA (≥ 1)	0.53 (0.27-0.78)	0.91 (0.79-0.97)	66.67%	86.00%	82.26%

AD-RAI=Alzheimer's disease resemblance atrophy index; HV=hippocampal volume; HF=hippocampal fraction; MTA=medial temporal lobe atrophy; CI=confidence interval.

Among MCI subgroup (table 2b), AD-RAI (≥ 0.5) yielded the best metrics over other measures, with an excellent sensitivity of 0.91, acceptable specificity of 0.79, and an accuracy of 84.00% in detecting prodromal AD. HV ($\leq 6.07\text{mL}$) also yielded a high accuracy of 84.00%. Despite the specificity was high (1.00), the sensitivity was only fair (0.64). HF ($\leq 0.41\%$) yielded a very low sensitivity of 0.27, high specificity of 1.00, and an accuracy of 68.00%. Sensitivity, specificity, and accuracy of MTA (≥ 1) were 0.64, 0.79, and 72.00%, respectively.

Table 2b. Performance metrics of AD-RAI, HV, HF and MTA among MCI subgroup (n=25)

Measures	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value	Accuracy
AD-RAI (≥ 0.5)	0.91 (0.57- 1.00)	0.79 (0.49- 0.94)	76.92%	91.67%	84.00%
HV (\leq 6.07mL)	0.64 (0.32- 0.88)	1.00 (0.73- 1.00)	100.00%	78.78%	84.00%
HF (\leq 0.41%)	0.27 (0.07- 0.61)	1.00 (0.73- 1.00)	100.00%	63.63%	68.00%
MTA (≥ 1)	0.64 (0.32- 0.88)	0.79 (0.49- 0.94)	70.00%	73.33%	72.00%

AD-RAI=Alzheimer's disease resemblance atrophy index; HV=hippocampal volume; HF=hippocampal fraction; MTA=medial temporal lobe atrophy; MCI=mild cognitive impairment; CI=confidence interval.

Among CU subgroup (table 2c), AD-RAI yielded a fair sensitivity (0.5), a high specificity (0.97) and a high accuracy of 89.1% in detecting preclinical AD. HV (≤ 6.64 mL) yielded a higher sensitivity (0.75) than AD-RAI, along with a good specificity (0.88) and accuracy (86.49%). HF ($\leq 0.44\%$) and MTA (≥ 1) yielded metrics identical to that of AD-RAI.

Table 2c. Performance metrics of AD-RAI, HV, HF and MTA among CU subgroup (n=37)

Measures	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value	Accuracy
AD-RAI (≥ 0.5)	0.25 (0.01- 0.78)	0.97 (0.82- 1.00)	50.00%	91.43%	89.19%
HV (\leq 6.64mL)	0.75 (0.22- 0.99)	0.88 (0.71- 0.96)	42.86%	96.67%	86.49%
HF (\leq 0.44%)	0.25 (0.01- 0.78)	0.97 (0.82- 1.00)	50.00%	91.43%	89.19%
MTA (≥ 1)	0.25 (0.01- 0.78)	0.97 (0.82- 1.00)	50.00%	91.43%	89.19%

AD-RAI=Alzheimer's disease resemblance atrophy index; HV=hippocampal volume; HF=hippocampal fraction; MTA=medial temporal lobe atrophy; CU=cognitively unimpaired; CI=confidence interval.

Comparison of performance between other cutoffs can be found in Supplemental Material (Appendix IV and V). Overall, cutoffs used for detecting AD with dementia had lower sensitivity and higher specificity when compared with cutoffs used in the present cohort.

The metrics of various imaging measures in detecting subjects harboring A+ with or without T (i.e. A+T+ and A+T-) can be found in Supplemental Material (Appendix VI to VIII). Overall, taking account into all A+ subjects, almost all imaging measures had lower sensitivity and accuracy when compared to that among subjects harboring A+T+.

Discussion

In the present validation study, using the cutoff derived from the ADNI database (i.e. ≥ 0.5) (19), AD-RAI achieved the best performance (sensitivity 0.73, specificity 0.91, accuracy 87.10%) in identifying AD subjects (i.e. A+T+) when compared with HV measures (i.e. raw HV, HF) and visual MTA ratings among all subjects with either mild or no cognitive impairment. Among MCI subgroup, AD-RAI also yielded the best metrics when compared with other measures in detecting prodromal AD. Among CU subgroup, HV achieved a higher sensitivity than AD-RAI, while maintaining a good specificity and accuracy, in detecting preclinical AD. Overall, this study validated the performance of AD-RAI at the pre-specified cutoff of ≥ 0.5 in detecting early AD, in particular at the prodromal stage. HV may be useful in the detection of preclinical AD. To date, this is the first study exploring the performance of machine learning methods in detecting preclinical and prodromal AD as defined by the 2018 NIA-AA research framework, i.e. by the presence A+ and T+. Previous studies mainly investigated the ability of MRI-based machine learning methods in differentiating between converters and non-converters without knowledge of subjects' amyloid and tau status (14-18).

Although there is still no pharmacological treatment approved for preventing subjects with prodromal AD from progressing to AD with dementia, making a diagnosis of prodromal AD among subjects with MCI is at least important for recruiting prodromal AD subjects into preventive clinical trials. Recent trials for AD have shifted to targeting subjects from the dementia stage to the prodromal or even preclinical stage (32). Although PET or CSF analyses are now available to detect A+T+ at the early stage and have been used to recruit prodromal or preclinical AD subjects into clinical trials, availability of an easier method in detecting A+T+ subjects will help to reduce the cost of conducting clinical trials. Among MCI subjects, AD-RAI (≥ 0.5) achieved a high NPV of 91.67%, hence a "negative" AD-RAI will first help to rule out subjects without AD. For subjects with a "positive" AD-RAI, although the PPV was acceptable (76.92%), it will still be important to arrange further investigations (i.e. PET or CSF analyses) in order to confirm the diagnosis of prodromal AD and/or to quantify the amyloid/tau burden. Moreover, using MRI as an initial investigation in MCI is also useful in ruling out other common brain lesions, e.g. cerebral small vessel

disease (Figure i), or other rare yet potential reversible causes, e.g. normal pressure hydrocephalus, brain tumor.

Noteworthy is that among our 25 MCI subjects, only less than half of them (44%) had A+T+. This frequency is very similar to a meta-analysis showing that prevalence of amyloid positivity in MCI subjects at age of around 70-year-old (i.e. age similar to our MCI subjects) was around 50% (33). Overall, the prevalence of amyloid positivity ranges from about 30% at age 50-year-old to 60% at age 80-year-old in MCI subjects (33). This highlights the need of having additional tool to aid the detection of A+T+ among subjects presenting with MCI syndrome.

Among CU subjects, although AD-RAI obtained an excellent specificity (0.97) and accuracy (89.19%) in the detection of preclinical AD, its sensitivity was very low (0.25). In comparison, HV achieved a more balanced metrics (sensitivity 0.75, specificity 0.88, accuracy 86.49%) than AD-RAI in the detection of preclinical AD. A recent study also showed that HV measure had acceptable accuracy in predicting conversion from normal to MCI (34). Note that in our recent study (19), although AD-RAI achieved the best specificity (0.98) and accuracy (79.45%) over other measures, its sensitivity was also lower (0.39) than that of HV (0.70) (see Supplemental Material). Overall, the relative superiority of HV over AD-RAI is consistent with our current understanding on the temporal evolution of brain atrophy in AD, which is most apparent mainly in the hippocampus at the very early stage (e.g. preclinical stage), followed by spreading to other regions as disease progresses (e.g. prodromal stage). Hence, measure that focuses only at the hippocampus is probably more appropriate than AD-RAI at the preclinical stage, as multi-region atrophy is probably negligible at this stage. Given the very high NPV of HV (96.67%), it may be useful in ruling out AD among CU subjects. Confirmatory diagnostic test (e.g. PET, CSF analyses) can then be arranged for those with a “positive” HV. It must be stressed that given that there were only 4 A+T+ subjects among CU subgroup in the present study, a larger study is needed to confirm the validity of HV (or AD-RAI) in detecting preclinical AD subjects.

In this study, sensitivity of visual MTA rating in detecting AD at an early stage was low, which might partly be explained by the fact that the current visual grading has a floor effect (Figure ii). However, devising a finer visual scale may be challenging as detecting small volumetric change by human vision may not be possible and is also not reliable. Moreover, the intra-rater reliability is likely to be lower if a finer visual scale is used. Note that the current machined-based automated tool has a test/re-test precision of 100%.

Among subjects having A+ with or without T+, the imaging measures had poorer performance when compared to that among subjects having both A+T+. This is expected because brain atrophy is likely absent or negligible when only beta-amyloid is present. Therefore, assessing brain atrophy using MRI is unlikely to identify the earliest stage of the Alzheimer’s continuum, i.e. A+T-.

Limitations

A strength of our study was that all our subjects received comprehensive clinical and imaging assessment, including both amyloid and tau PET, hence allowing accurate classification on the cognitive,

amyloid, and tau status of each individual. However, the sample size was relatively small. Hence, a larger study is needed to confirm the results of this study, in particular those that were generated from the CU subgroup. Last, although ^{18}F -T807 PET is commonly used for *in-vivo* clinical research in AD, off-target ^{18}F -T807 bindings unrelated to tau in the basal ganglia (35, 36) or in some tau-negative conditions (37, 38) were reported. Note that in our study, we did not label subjects with ^{18}F -T807 uptake at basal ganglia as T+. Ideally, the performance of automatic volumetric segmentation tool needs to be validated against brain pathology.

Conclusions

The current study validated an MRI-based machine learning derived AD-RAI at the cutoff of ≥ 0.5 in the detection of early AD, in particular at the prodromal stage. Given the validity, reliability, and ease of use, AD-RAI may provide additional information in guiding physicians or researchers of selecting who should receive further confirmatory investigations for the diagnosis of early AD as defined by the presence of A+ and T+ among subjects with MCI.

Declarations

Ethics approval and consent to participate

This study protocol was approved by The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CUHK-NTEC CREC). The design and performance of the current study involving human subjects were clearly described in a research protocol. All participants completed informed consent in writing before participating the current study.

Consent for publication

Not applicable

Availability of data and materials

All datasets used or analyzed in the current study are available from the corresponding authors on reasonable request.

Competing interests

L.S. is the director of BrainNow Medical Technology Limited. Y.L. is now employed by BrainNow Medical Technology Limited. V.C.T.M. is the Chief Medical Advisor of BrainNow Medical Technology Limited. All other authors report no financial relationships with commercial interests.

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Author's contributions

Acquisition of clinical data (W.L., L.W.C.A., J.A.; P.W.L.K., H.W.M., A.Y.T.N., S.C., E.Y.L.L., C.L.H.), imaging and statistical analysis (Y.L., L.S., J.A. W.L.), manuscript preparation (W.L., V.C.T.M.), study conception and design (W.L., V.C.T.M., L.S., A.W.), technical assistance (A.W., B.Y.K.L., X.F., S.H.M.W., W.C.W.C., H.K., A.Y.L.L.), and study coordination (W.L., V.C.T.M., L.S., A.Y.L.L.). All authors read and approved the final manuscript.

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Authors' information

¹ Division of Neurology, Department of Medicine and Therapeutics, Therese Pei Fong Chow Research Centre for Prevention of Dementia, The Chinese University of Hong Kong, Hong Kong SAR, China. ² Gerald Choa Neuroscience Centre, Lui Che Woo Institute of Innovative Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China. ³ Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong SAR, China. ⁴ BrainNow Research Institute, Hong Kong Science and Technology Park, Hong Kong SAR, China. ⁵ Department of Nuclear Medicine & PET, Hong Kong Sanatorium & Hospital, Hong Kong SAR, China. ⁶ Medhealth Diagnostic MRI Centre, Hong Kong SAR, China. ⁷ Li Ka Shing Institute of Health Sciences; School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China.

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Figures

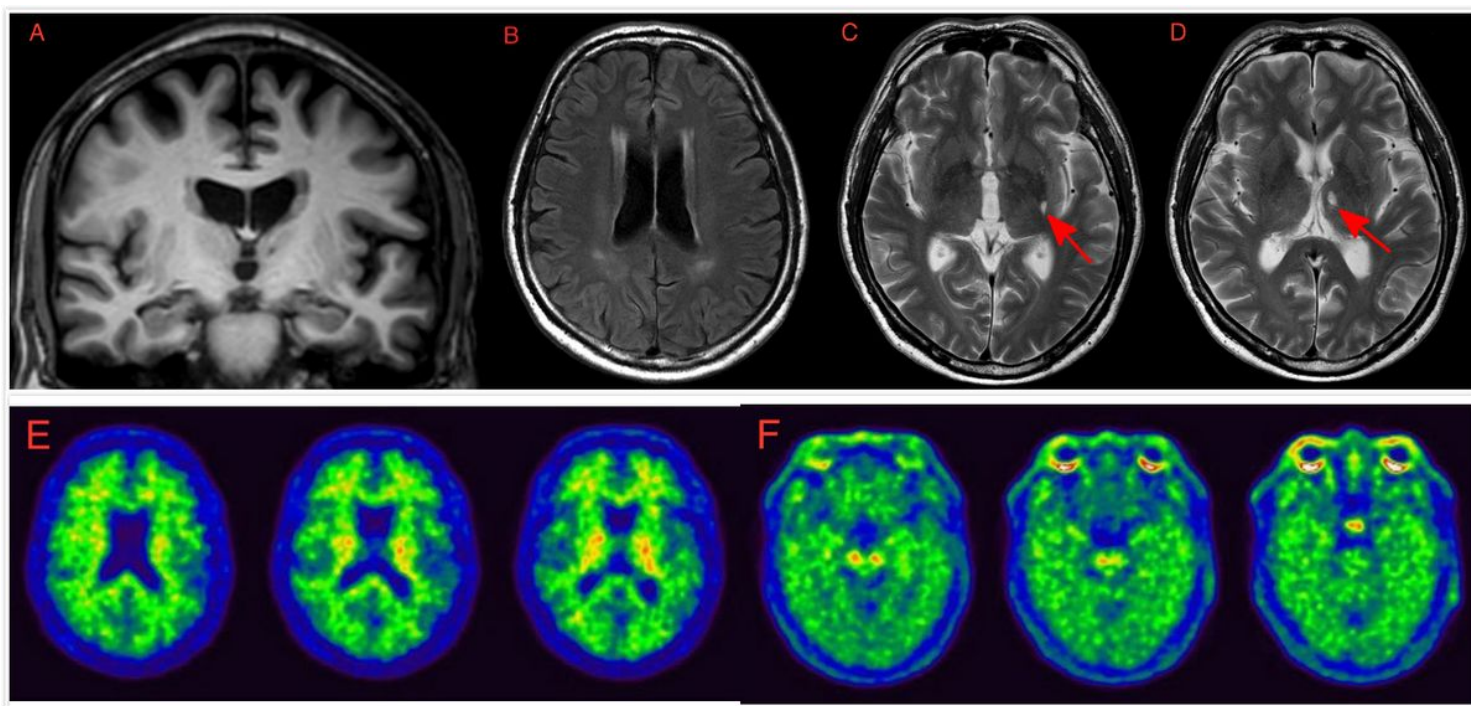


Figure 1

Clinical utility of AD-RAI in MCI subjects i. A 68-year-old man with 11 years of education had complaints of memory decline for over 3 years. Z-score in Trial 4 of HKLLT was -1.94 SD (≤ -1 SD, i.e. MCI). Visual MTA rating score on MRI was 1 (≥ 1), (A) which was suggestive of AD. However, HV measures yielded conflicting results, with HF of 0.47% ($> 0.41\%$) and raw HV of 7.38ml (> 6.07 ml) suggestive of non-AD. FLAIR and T2-weighted sequences showed periventricular white matter hyperintensity and two subcortical lacunes (red arrows) (B, C, D). AD-RAI was only 0.11 (< 0.5) also suggestive of non-AD. Subsequent PIB PET (E) and T807 PET (F) showed negative results (i.e. A-T), supporting the finding of AD-RAI. The MCI syndrome and mild MTA might be associated with cerebral SVD (i.e. vascular MCI associated with SVD).

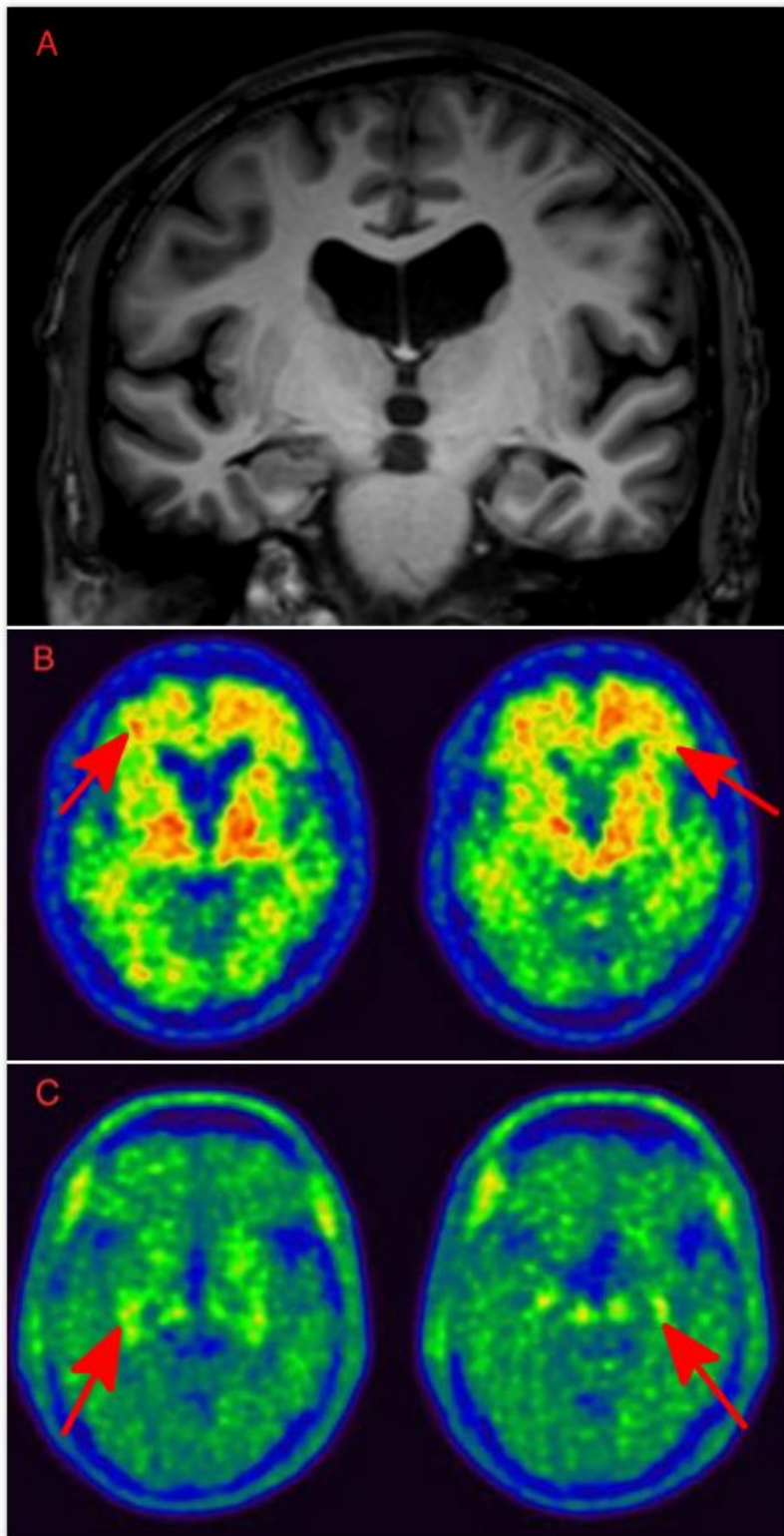


Figure 2

A 66-year-old man with 6-year education had complaints of impaired short-term memory for several years. Z-score in Trial 4 of HKLLT was -1.65 SD (≤ -1 SD, i.e. MCI). The average visual MTA rating score was 0.5 suggestive of non-AD (A). HV measures also suggested non-AD, with a normal raw HV of 7.38 mL (> 6.07 mL) and HF of 0.43% ($> 0.41\%$). However, AD-RAI was 0.74 (> 0.5) suggestive of AD. Subsequent PIB PET (B) and T807 PET (C) confirmed PIB and T807 retention, respectively (red arrows). The final

diagnosis of this subject was prodromal AD. Abbreviations: AD-RAI=Alzheimer's disease resemblance atrophy index; MCI=mild cognitive impairment; MTA=medial temporal lobe atrophy; HKLLT=Hong Kong List Learning Test; SD=standard deviation; MRI=magnetic resonance imaging; HV=hippocampal volume; HF=hippocampus fraction; PET=positron emission tomography; SVD=small vessel disease.

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