Fujifilm and National Center of Neurology and Psychiatry announce positive study results of Fujifilm's AI technology predicting mild cognitive impairment conversion to Alzheimer's disease

- Study published in *npj Digital Medicine*, a high quality Nature Portfolio journal, cites 88% accuracy

TOKYO, April 13, 2022 —FUJIFILM Corporation (Head Office: Minato-ku, Tokyo; President and CEO, Representative Director: Teiichi Goto) and National Center of Neurology and Psychiatry (location: Kodaira City, Tokyo; President: Kazuyuki Nakagome) announce positive study results of Fujifilm's new AI technology (hereinafter "AI Technology for AD Progression Prediction") to predict whether patients with mild cognitive impairment (MCI) will progress to Alzheimer's disease (AD) within two years. The AI Technology for AD Progression Prediction*1 has an 88%*2 accuracy rate, which was published*3 on April 12 in *npj Digital Medicine,* a high quality Nature Portfolio journal.

The AI Technology for AD Progression Prediction was developed by Fujifilm based on its advanced image recognition technologies and machine learning expertise.

Following the successful study results, Fujifilm and the National Center of Neurology and Psychiatry will further verify the technology, with the aim of applying it to a stratification of patients in clinical trials for treatment of AD.

Key points of the research outcomes

- Fujifilm used its advanced image recognition technologies accumulated in the fields of photography and healthcare, to establish an AI technology that predicts the progression from MCI to AD with a high accuracy, even with limited learning data. The AI Technology for AD Progression Prediction makes predictions using multimodal information such as MRI images and cognitive test scores.
- Fujifilm and National Center of Neurology and Psychiatry research group*4 applied AI Technology for AD Progression Prediction to two databases of different-cohort patient groups (North Americans and Japanese), and confirmed that the accuracy for predicting MCI conversion to AD was about 84-88%. They verified that the AI Technology for AD Progression Prediction has a high generalizability.

<Background>

There are currently about 55 million dementia patients throughout the world. Moreover, as the population ages, the number is predicted to increase to approximately 139 million by the year 2050. AD, which is a type of dementia, is the most common cause of dementia, and this trend is predicted to continue.

In the development of new drugs for AD in recent years, many clinical trials of MCI patients have been conducted to observe amyloid-β presence, which is the major causal substance of AD and begins accumulating prior to onset of AD. However, most clinical trials have not been successful, and it is difficult to prove statistically significant differences. One of the reasons is that the percentage of patients who progress from MCI to AD within two years is less than 20%*5 and many MCI patients remain unchanged even if they receive placebo. Under these circumstances, Fujifilm and National Center of Neurology and Psychiatry believes that the AI Technology for AD Progression Prediction would address the issue and contribute to evaluate the efficacy of drug candidates accurately.

<Content of research>

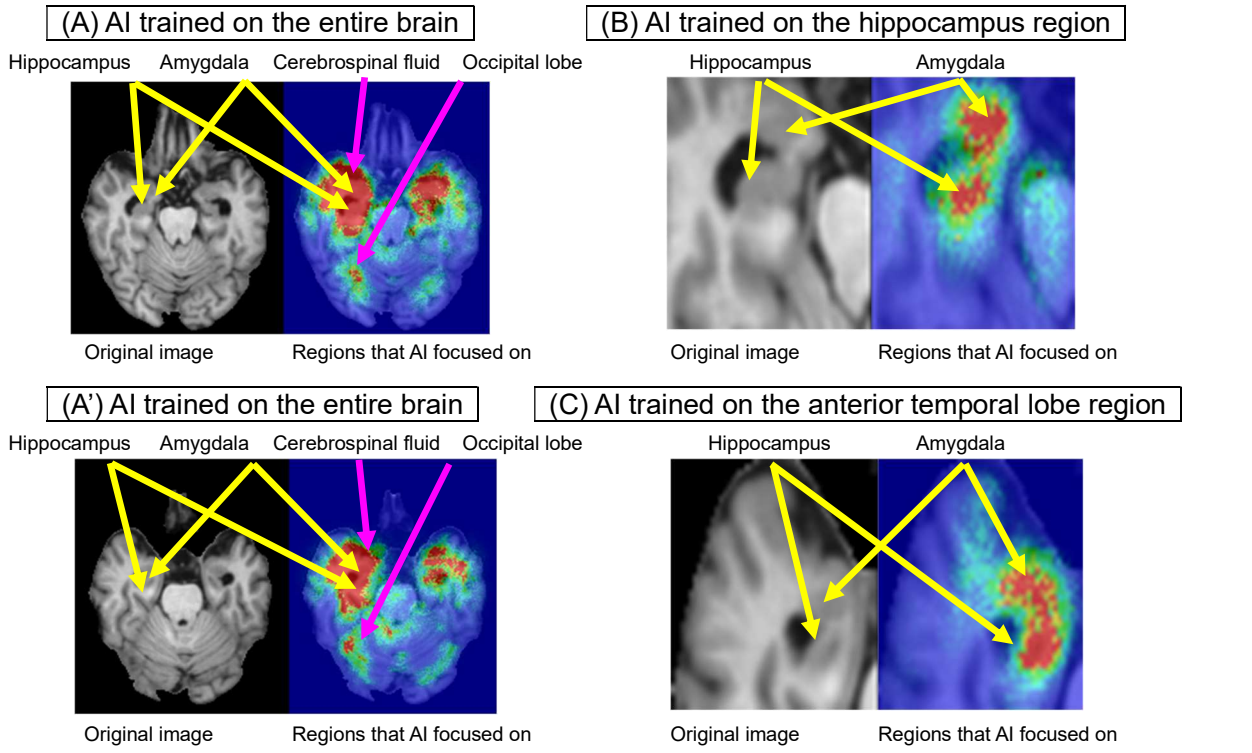
Numerous research has been reported in recent years indicating that the accuracy of image recognition is enhanced by deep learning technology. In addition, accurate predictions require a large dataset of images, however the open database of NA-ADNI*6, the world's largest AD research project, only has images of about 1,000 MCI patients. Generally, establishing deep learning technology requires over 10 million images in the research of object recognition. To overcome this limitation, Fujifilm built

AI Technology for AD Progression Prediction, by targeting specific areas inside the brain that are strongly correlated with the progression of AD.

[Establishment of technology]

- Fujifilm used its advanced image recognition technologies accumulated in the fields of photography and healthcare, and focused on ① the hippocampus and ② the anterior temporal lobe, respectively, identified the regions from the three-dimensional MRI brain images that are considered to be strongly correlated with the progression of AD.
- Fujifilm used deep learning to extract detailed atrophy patterns from the described two regions, and calculated them as the image features*7. AI focused even more on the atrophy patterns in the hippocampus and the amygdala regions which are important regions for AD diagnosis in radiographic image interpretation, and then predicted the progression to AD from those patterns (Fig. 1).
- NA-ADNI's MCI patient data was used as the training data. In addition to the described image features extracted from the specific regions that are considered to be strongly correlated with the progression to AD, other clinical information such as cognitive test scores were also used.

<Figure 1> Detailed atrophy patterns that AI focused on predicting the progression to AD (the three-dimensional MRI images)



Red: High-level of focus, Blue: Low-level of focus

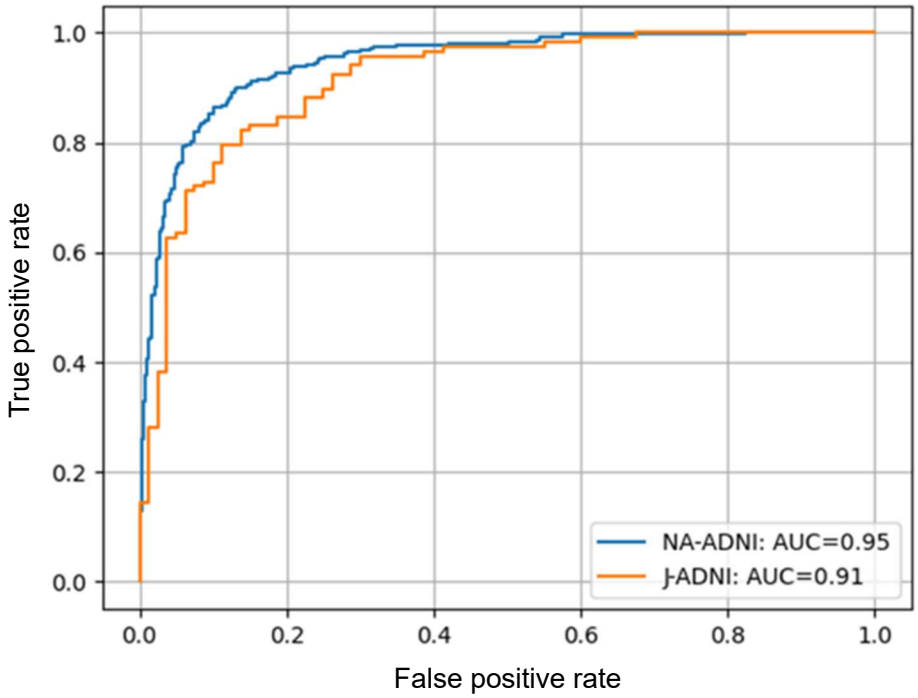
- AI trained on the entire brain (Fig. 1-A and A') focused not only on the hippocampus and the amygdala that are strongly correlated with the progression to AD, but also the cerebrospinal fluid and the occipital lobe that are not strongly correlated.
- AI trained on the regions of the hippocampus (Fig. 1-B) and the anterior temporal lobe (Fig. 1-C) focused even more on the detailed atrophy patterns seen in the hippocampus and amygdala regions, and was more effective to predict MCI conversion to AD than the AI trained on the entire brain.
- By excluding the regions which have lower correlation with AD progression, the effects of individual differences were reduced based on the deep learning with limited data and a high prediction accuracy was achieved.

[Verification of technology]

- Fujifilm and National Center of Neurology and Psychiatry predicted whether patients would progress from MCI to AD within two years with the AI Technology for AD Progression Prediction. Objective evaluation of the technology's prediction accuracy was conducted by applying the AI Technology for AD Progression Prediction to the databases not only of NA-ADNI but also of J-ADNI*8 that is completely unknown to AI.

・Accuracy in predicting whether patients would progress to AD from MCI was 88% for NA-ADNI and 84% for J-ADNI.
・AUC*9, which is an important evaluation index of AI, was 0.95 for NA-ADNI and 0.91 for J-ADNI (Fig. 2).

<Figure 2>　ROC curve*10 showing the evaluation results in NA-ADNI and J-ADNI



The AUC (area under the ROC curve) that was calculated from the ROC curve was 0.95 for NA-ADNI, and 0.91 for J-ADNI. Since the maximum value of AUC is 1, the results showed that the progression to AD was predicted with a high accuracy in both NA-ADNI and J-ADNI.

From the above, the AI Technology for AD Progression Prediction was verified to have a high generalizability and can predict which patients would progress from MCI to AD with a high accuracy, even for subjects from different cohorts.

<Future developments>

Fujifilm and National Center of Neurology and Psychiatry will apply the AI technology to the patient stratification, using its prediction results on the clinical trial data, and verify the technology's usefulness even further. Specifically, they will predict the speed of the patients' progression to AD, and investigate the possibility of improving the clinical trial's success rate by ① excluding the patients who do not progress to AD from the clinical trial, and ② reducing the gap in the distribution of progression speed between the control group and the treatment group. Moreover, they will aim to apply the AI Technology for new clinical trials prospectively.

The organizations will also apply the algorithm of the AI Technology to the brain images and clinical data of diverse mental and neural diseases. It is expected that these activities will lead to predicting the prognosis and response to treatment, and can play an important role in promoting personalized medicine.

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*1 The AI technology isn't intended to perform diagnosis, treatment or prevention of AD or other diseases.

*2 Accuracy, an evaluation indexes of AI, is a numerical value indicating how well the prediction result matches the true value.

*3 Published paper

Name of paper:	A high generalizability machine learning framework for predicting the progression of Alzheimer's disease using limited data
Name of author(s):	Caihua Wang, Yuanzhong Li, Yukihiro Tsuboshita, Takuya Sakurai, Tsubasa Goto, Hiroyuki Yamaguchi, Yuichi Yamashita, Atsushi Sekiguchi, Hisateru Tachimori and for Alzheimer's Disease Neuroimaging Initiative
Journal published in:	*npj Digital Medicine* (a high-quality Nature Portfolio journal)
URL:	https://www.nature.com/articles/s41746-022-00577-x
doi:	10.1038/s41746-022-00577-x

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*5 Practice Guideline Update Summary: Mild Cognitive Impairment. (Petersen, R. C., et al. Neurology 16, 126-135 (2018))

*6 The world's largest research project for developing methods of predicting the onset of AD and confirming the effects of treatment drugs. ADNI is the abbreviation of the Alzheimer's Disease Neuroimaging Initiative, and the research comprising mostly North American people is noted as NA (North American)-ADNI.

*7 Quantified information of image patterns which play important roles for predicting AD progression.

*8 Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) was launched in 2008, aiming at conducting a longitudinal workup of a standardized neuroimaging, biomarker and clinico-psychological surveys.

*9 The area under a receiver operating characteristic (ROC) curve, abbreviated as AUC. The AUC is a robust overall measure to evaluate the performance of score predictors because its calculation relies on the complete ROC curve and thus involves all possible prediction thresholds. If the value of AUC is 1, it means the AI can make perfect predictions (true positive rate: 100% and false positive rate: 0%). On the other hand, if the AI output is completely random, the value of AUC will be 0.5.

*10 Receiving Operating Characteristic (ROC) curves are bidimensional graphs commonly used to evaluate and compare the performance of predictors. ROC plots nicely show the sensitivity/specificity trade-off of a predictor for all possible prediction thresholds, thus allowing the ranking and selection of predictors according to specific user needs that often are associated with differential error costs and accuracy demands.

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