DEEP-LEARNING METHODS FOR ENRICHMENT OF ALZHEIMER'S DISEASE CLINICAL TRIALS USING MRI AND PET

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OBJECTIVES

Drug development trials aimed at modifying Alzheimer's disease (AD) increasingly look at recruitment of participants at early stages, preferably before symptomatic onset. This represents two challenges: firstly, participants may not significantly decline during the clinical trial period, vanishing the statistical effect of the evaluated treatment. This problem can be solved by recruiting a large number of participants; however, this leads to the second challenge: high trial running costs. This high cost limits the number of compounds that can be tested.

The process of recruiting participants that are likely to decline within a trial's observational period is commonly called *trial enrichment.* The standard approach for trial enrichment is to use biological and neuropsychiatric markers as criteria to include or exclude participants. Some of these criteria could be a mild cognitive impairment (MCI) diagnosis, a cognitive score above certain threshold, or be cognitive normal with a family history associated with the disease.

Here we present a neuroimage-driven deep-learning framework for trial enrichment that is able to differentiate participants with accelerated cognitive decline from those that remain cognitively stable within 24 months. Our aim is to develop a tool that will allow a clinical research or pharma organisation to recruit participants that are likely to decline within a trial's observational period.

METHODS

Two Siamese deep convolutional neural networks (DCNNs) were trained using whole-brain PET (AV45, FBB) and T1-weighted MRI images from the ADNI longitudinal database. MCI and cognitively normal (CN) participants were dichotomised into decliners and non-decliners based on if they were diagnosed with AD or not in future follow-ups respectively; within ADNI, time to AD conversion spanned from 6 months to 10 years. Cognitive decline was measured with the CDR-SB score. A sample of 206 participants (50% decliners) were randomly selected for training (70%) and evaluation (30%).

Table I. Participant demographics of the randomly selected participants from the ADNI cohort. Both training and evaluation (eval) demographics are shown.

	Set	Baseline diagnosis	Age	Sex (F/M)	CDR-SB	MMSE	Education	APOE4
Decliner	Train	MCI: N=48 CN: N=3	71 (7.49)	25/26	2 (1.14)	27.5 (1.96)	16 (2.7)	0: N=17 1: N=21 2: N=13
	Eval	MCI: N=21 CN: N=1	71 (7.03)	6/16	1.77 (0.9)	27.4 (1.43)	16 (2.1)	0: N=6 1: N=12 2: N=4
Stable	Train	MCI: N=24 CN: 32	71 (6.84)	26/30	0.52 (0.73)	28.5 (1.5)	15.9 (2.8)	0: N=37 1: N=18 2: N=1
	Eval	MCI: N=7 CN: N=8	68 (4.18)	8/7	0.33 (0.44)	28.5 (1.3)	16.4 (3.3)	0: N=10 1: N=4 2: N=1

RESULTS

When identifying decliners PET embeddings showed an accuracy score in the training and evaluation sets of 87% and 78%, respectively. Using MRI embeddings these scores were 70% and 69%, and for PET+MRI combined the scores were 86% and 84%. The standard composite SUVR threshold of >1.22 [Chen K, J Nucl Med. 2015] reached an accuracy of 79% (training) and 81% (evaluation).

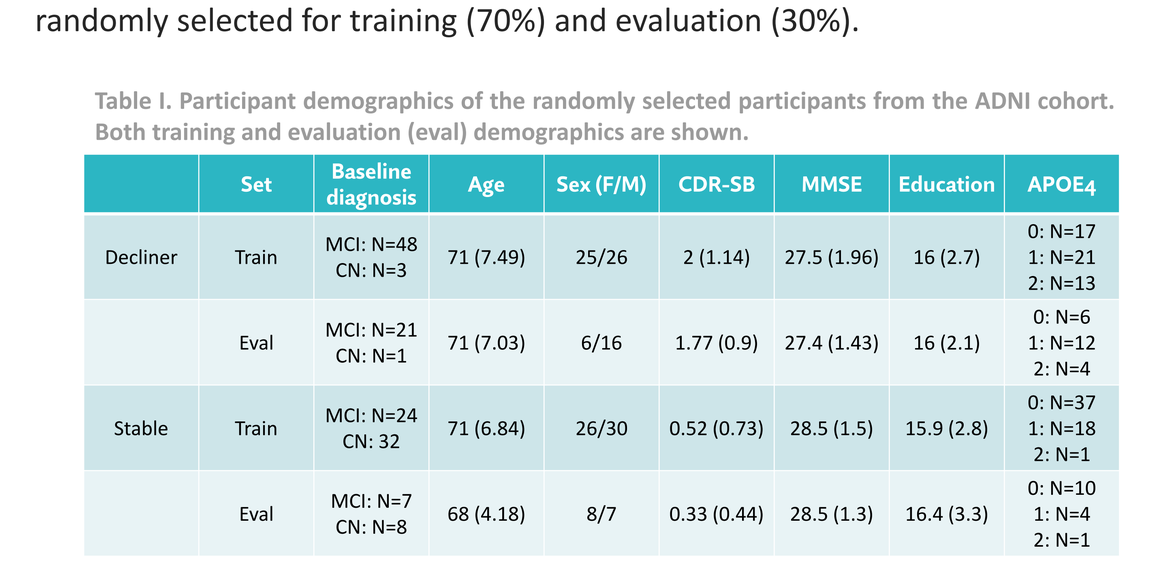
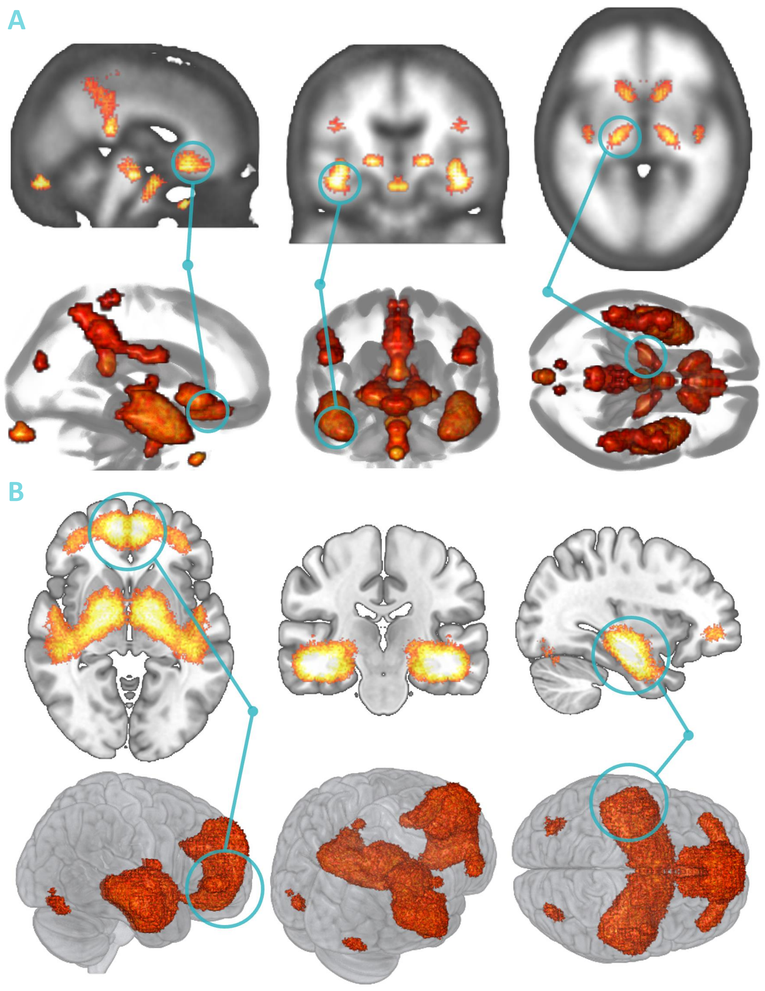


Figure 1. CDR-SB score differences between enriched and original baseline cohorts with a 20% rejection threshold at baseline. Top row: Cohort enrichment for MCI diagnosed participants, here our DCNN approach obtained a better cohort enrichment than the SUVR PET threshold. Bottom row: Cohort enrichment for the control group, here both DCNNs (MRI and PET) behave consistently when predicting decline in controls, however the SUVR approach failed to find the relationship.

RESULTS continued

When predicting decline in MCI, the DCNN-PET showed similar performance to the SUVR threshold, with an accuracy of 0.83 DCNN and 0.79 SUVR. However, when predicting cognitive decline in controls, only the DCNN embeddings correctly identified decliners using either PET or MRI. The SUVR threshold showed no association with cognitive decline in healthy controls (Figure 1).



The activation maps from the trained DCNNs (Figure 2), showed high gradients within brain regions associated with AD. For the PET images these regions were the Temporal, Parietal, Precuneal and Lower-Frontal cortices. We also found important contributions of subcortical regions in PET. For the MRI images, DCNN activation regions comprised the Temporal, Frontal cortices as well as Thalamic subcortices.

Figure 2. Activation maps from the trained Siamese DCNNs. A: Activation maps for the PET images. B: Activation maps for the structural MRIs.

IMPACT ON CLINICAL TRIALS

The results from the Aducanumab and Lecanemab clinical trials indicate that these new treatments are able to slow the rate of cognitive decline in AD. Particularly Lecanemab showed a clear dosage effect of slowing cognitive decline. Both compounds are the first approved disease modifying medication that have an impact in patients cognition. However, clinical trials that aim to follow the success of Lecanemab/Aducanumab still face the expensive costs that a large trial represents.

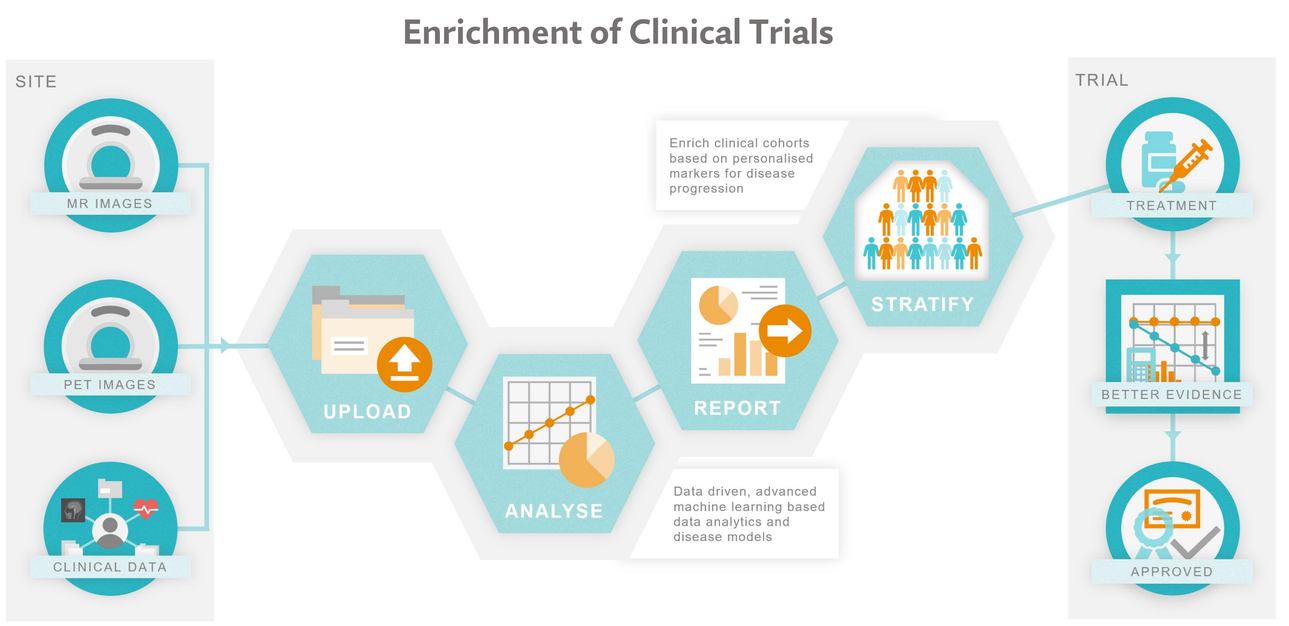


Figure 3. Cohort enrichment platform for clinical trials.

The high costs for trials is slowing the much-needed innovation to help AD patients. This cost can be reduced by an improved recruitment strategy that identifies participants that are more likely to benefit of an experimental treatment. Our future research efforts will be focused on developing a recruitment platform for clinical trials.

CONCLUSIONS

SUVR levels were associated with future cognitive decline in MCI but not in CN, while the DCNN embeddings were able to identify both groups. Deep-learning algorithms offer a reliable framework to predict cognitive decline in MCI and control participants using neuroimaging data only.

Future work will focus on combining clinical and neuroimaging data to further improve our results with the objective of building a recruitment platform that assist clinical trials.