

BRIEF COMMUNICATION

Predicting long-term clinical stability in amyloid-positive subjects by FDG-PET

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Introduction

The development and design of prevention trials in Alzheimer's disease (AD) implies ethical and societal challenges for the research and clinical community.¹ Accurate screening of participants is crucial for optimizing trial effectiveness, duration, costs, and outcome

Abstract

Imaging biomarkers can be used to screen participants for Alzheimer's disease clinical trials. To test the predictive values in clinical progression of neuropathology change (amyloid-PET) or brain metabolism as neurodegeneration biomarker ([¹⁸F]FDG-PET), we evaluated data from $N = 268$ healthy controls and $N = 519$ mild cognitive impairment subjects. Despite being a significant risk factor, amyloid positivity was not associated with clinical progression in the majority ($\geq 60\%$) of subjects. Notably, a negative [¹⁸F]FDG-PET scan at baseline strongly predicted clinical stability with high negative predictive values (>0.80) for both groups. We suggest [¹⁸F]FDG-PET brain metabolism or other neurodegeneration measures should be coupled to amyloid-PET to exclude clinically stable individuals from clinical trials.

evaluation. Recently, the measure of brain amyloid burden by PET has fueled the design of prevention trials in AD, enabling the screening of amyloid positivity in healthy controls (HC) and in subjects with mild cognitive impairment (MCI).² To date, about 42.9% and 66.7% of ongoing and starting clinical trials (phase II/phase III and phase III) enrolling HC or subjects

with MCI, respectively, adopt amyloid-PET for screening (data retrieved from www.clinicaltrials.gov on 17 April 2018). It is expected that up to 4800 HC and 9763 MCI amyloid-positive subjects between 50 and 90 years of age will be enrolled in ongoing or starting clinical trials by 2024 (see Table S1).

A screening strategy based on the only evidence for amyloid positivity might nonetheless lead to inclusion of a considerable proportion of clinically stable subjects, especially in the older individuals.³ Additionally, the association between amyloid positivity and a diagnosis of dementia due to AD becomes weaker with aging,^{4,5} and autopsy evidence for significant amyloid deposition is also observed in aged brains of people without *ante-mortem* neurological deficits.⁶ All the above suggests that amyloid positivity does not necessarily imply future progression to clinical dementia.^{3,7} Identification and exclusion of subjects who are not on the trajectory to dementia is a critical requirement for the implementation of effective clinical trials. The inclusion of biomarkers of neurodegeneration could represent a valuable strategy to enhance enrollment accuracy by excluding subjects with a high likelihood of remaining cognitively stable notwithstanding a significant amyloid burden.³ [18F]FDG-PET measure of brain glucose metabolism is considered a sensitive marker of ongoing neurodegeneration/synaptic dysfunction, also preceding atrophy, with high accuracy in the early detection and staging of AD,^{8,9} especially when coupled with optimized analytical methods.¹⁰ The aim of the present study was to evaluate whether [18F]FDG-PET brain hypometabolism, as an early marker of neurodegeneration, and in the context of established amyloid positivity, would support the identification of subjects either clinically stable or on a trajectory to dementia, with a subsequent impact on screening accuracy for clinical trials.

We compared two different biomarker screening strategies including (1) only amyloid-PET status (Standard Strategy) or (2) amyloid-PET positivity plus [18F]FDG-PET brain hypometabolism status (Enriched Strategy) for the identifications of HC and subjects with MCI who could better benefit from putative treatments.

Methods

Participants

Data source

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The

primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. All subjects gave written informed consent, in accordance to the Declaration of Helsinki. The study was approved by local institutional ethics committees at each site. For up-to-date information, see www.adni-info.org.

Standard strategy test sample

Participants were retrieved from the ADNI database. Inclusion criteria were: (1) HC or MCI diagnosis at baseline; (2) Availability of amyloid-PET, either [11C]PiB-PET or [18F]Florbetapir-PET; (3) clinical follow-up of at least 3 months. These criteria led to the selection of $N = 269$ HC and $N = 518$ MCI subjects with, respectively, 44.79 ± 20.5 and 39.0 ± 22.7 months of follow-up (see Table 1).

Enriched strategy test sample

We here considered a subset of the subjects included in the Standard Strategy Test sample (see above), namely subjects with (1) amyloid-PET positivity and (2) available [18F]FDG-PET scan at baseline (within 6 months from the amyloid-PET scan). These criteria resulted in the selection of $N = 73$ HC and $N = 259$ subjects with MCI, with, respectively, 42.76 ± 23.23 and 34.45 ± 21.98 months of follow-up (see Table 1).

PET images preprocessing and analysis

Amyloid-PET

To establish amyloid positivity (Amy+ vs. Amy-), we compared the neocortical composite scores provided by ADNI^{11,12} with previously validated cut-off positivity thresholds, that is above 1.11 for [18F]Florbetapir-PET and 1.5 for [11C]PiB-PET.^{11,12}

[18F]FDG-PET

Raw [18F]FDG-PET images were downloaded from ADNI and preprocessed to obtain a single NIFTI file containing the last 15 min of PET acquisition. [18F]FDG-PET data analysis followed a well-validated single-subject scanner-independent Statistical Parametric Mapping (SPM) procedure, including spatial normalization with a custom template and statistical comparison to a large group of HC, covarying for age.¹⁰ This procedure delivers single-subject SPM voxel-based hypometabolism maps corrected for multiple comparisons, which were blindly evaluated by two raters. Depending on whether the SPM-t pattern was suggestive of a neurodegenerative condition, [18F]FDG-

PET images were rated as either *neurodegeneration-negative* (FDG-) or *neurodegeneration-positive* (FDG+).¹⁰ In case of disagreement, each case was reevaluated to reach a consensus.

Statistical analysis for risk progression

Clinical progression was defined according to change in the latest follow-up diagnosis available in ADNI data, including CN to MCI or to AD dementia, and MCI to AD dementia. Statistical analyses were run with R software (www.R-project.org), using the pROC (<https://CRAN.R-project.org/package=pROC>) and survival (<https://CRAN.R-project.org/package=survival>) packages. Survival plots were created with the survminer package (<https://CRAN.R-project.org/package=survminer>). Hazard Ratios (HR) for each variable of interest, including biomarker status, age, sex, Apolipoprotein E $\epsilon 4$ carriage, and Mini-Mental State Examination (MMSE) at baseline, were estimated via Cox proportional hazard models in a univariate approach. Variables that were individually significant ($P < 0.05$, lower limit of 95% HR confidence interval >1 for risk factors, upper limit <1 for protective factors) were then entered in a multivariate model. Significance of the multivariate models was evaluated with log-rank tests.

Results

Standard strategy

Cox proportional hazard models showed that amyloid positivity was strongly associated with a greater risk of clinical progression for both HC and MCI subgroups (multivariate HRs: 2.74 95% c.i. [1.57–4.79] and 3.55 [2.15–5.85], $P = 0.0004$ and $P < 0.0001$, respectively) (see Table 1 and Fig. 1A). Very few amyloid-negative cases progressed clinically, leading to a highly accurate negative prediction for amyloid-PET (negative predictive values – NPV were 0.876 and 0.904, respectively for HC and subjects with MCI).

Still, more than half of the Amy+ subjects (66% HC, 60% subjects with MCI) did not progress during follow-up (average months 44.79 ± 20.5 for HC and 39.0 ± 22.7 for subjects with MCI).

Considering other predictors, Cox regression models showed an additional significant effect of age at amyloid-PET scan time in the HC group (multivariate HR: 1.08 [1.03–1.14], $P = 0.001$), and of APOE status (multivariate HR: 1.66 [1.13–2.46], $P = 0.01$) and MMSE score (multivariate HR: 0.81 [0.75–0.89], $P = <0.001$) in the MCI group. The final multivariate Cox models included age and amyloid-PET status for the HC group and amyloid-PET status, MMSE score and APOE $\epsilon 4$ status for the MCI group (log-rank tests $P = 3e-06$ and $P < 2e-16$,

respectively). The significant predictors in univariate analysis are available in Table S2.

Enriched strategy

$N = 129$ MCI and $N = 31$ HC subjects showed an [18F]FDG-PET pattern suggestive of neurodegenerative conditions. As for MCI, $N = 91/129$ (~70%) subject showed a hypometabolism pattern suggestive of AD, whereas $N = 38/129$ (~30%) showed a pattern suggestive of non-AD conditions, namely $N = 32$ FrontoTemporal Lobar Degeneration (FTLD), $N = 2$ Dementia with Lewy Bodies (DLB), $N = 2$ Multiple System Atrophy (MSA), $N = 2$ possible cerebrovascular disease (CVD). As for HC, $N = 16/31$ (~52%) subjects showed an AD-like hypometabolic pattern, whereas $N = 15$ (~48%) otherwise showed patterns suggestive of non-AD conditions, namely $N = 12$ FTLD and $N = 3$ possible CVD.

Amy+ subjects without evidence of neurodegeneration at [18F]FDG-PET (FDG-) were very likely to remain stable (NPV 0.829 and 0.805 for HC and MCI, respectively) (see Table 1 and Fig. 1B). Conversely, Amy+/FDG+ subjects were more likely to progress clinically during follow-up (multivariate HRs: 3.29 [1.36–7.96] and 5.04 [3.13–8.12] for HC and subjects with MCI, respectively) and at faster rates with respect to Amy+/FDG- subjects, independent of follow-up length (see below and Table S3). As for MCI, the presence of an AD-like versus non AD-like [18F]FDG-PET pattern was not significantly modulating the likelihood of clinical progression ($P = 0.5$), whereas HC subjects with AD-like hypometabolic patterns were more likely to progress during follow-up compared to HC subjects with patterns suggestive of non-AD conditions (HR 3.48, [1.087–11.19], $P = 0.04$). Considering a standard length for clinical trials (i.e., 24 months), about 18% of the Amy+ MCI subjects progressed to dementia during follow-up. Of note, when adding the [18F]FDG-PET status, the observed rate of progression was higher in neurodegeneration-positive subjects, with about 30% of the Amy+/FDG+ MCI subjects progressing, as opposed to only 5% of the Amy+/FDG- MCI subjects. Similarly, 8% of the Amy+ HC subjects progressed to MCI within 24 months. The rate of progression increased in the neurodegeneration-positive subjects, with about 16% of the Amy+/FDG+ HC progressing to MCI within 24 months, as opposed to about 2% of the Amy+/FDG- subjects (see Table S3). For paradigmatic examples of [18F]FDG-PET SPM-t maps, see Figure 2.

Cox models showed an additional significant effect in terms of progression probability for the age at amyloid-PET scan in the HC group (multivariate HR: 1.14 [1.04–1.24], $P = 0.004$) and for the baseline MMSE score in

Table 1. Demographic and biomarker summary split by screening strategy

	Standard strategy			Enriched strategy		
	HC	MCI	<i>P</i>	HC	MCI	<i>P</i>
Sample size (<i>N</i>)	269	518	–	73	259	–
Age (years, mean ± SD)	75.5 ± 6.7	72.7 ± 7.7	<0.001	77.5 ± 5.7	74.1 ± 7.1	<0.001
Sex (female/male)	138/131	230/288	0.08	43/30	113/146	0.03
APOE e4 carrier (pos/neg)	71/198	244/274	<0.001	33/40	169/90	0.003
MMSE (mean ± SD)	29.01 ± 1.25	27.96 ± 1.76	<0.001	28.88 ± 1.30	27.49 ± 1.86	<0.001
Follow-up (months, mean ± SD)	44.79 ± 20.5	39.0 ± 22.7	<0.001	42.76 ± 23.23	34.45 ± 21.98	0.007
Progressors/stable (<i>N</i>)	51/218	138/380	0.02	26/47	105/154	0.53
Amyloid-PET positive (<i>N</i> (%))	84 (31%)	290 (56%)	<0.001	73 (100%)	259 (100%)	–
Stable amyloid-PET positive (<i>N</i> (%))	56 (66%)	174 (60%)	0.33	–	–	–
Amy-PET sensitivity	0.543	0.841	–	–	–	–
Amy-PET specificity	0.743	0.542	–	–	–	–
Amy-PET accuracy	0.706	0.622	–	–	–	–
Amy-PET NPV	0.876	0.904	–	–	–	–
Amy-PET PPV	0.333	0.400	–	–	–	–
Amy-PET hazard ratios	2.74	3.55	–	–	–	–
[18F]FDG-PET positive (<i>N</i> (%))	–	–	–	31 (43%)*	129 (52%)*	0.22
FDG-PET sensitivity	–	–	–	0.731	0.772	–
FDG-PET specificity	–	–	–	0.739	0.651	–
FDG-PET accuracy	–	–	–	0.736	0.700	–
FDG-PET NPV	–	–	–	0.829	0.805	–
FDG-PET PPV	–	–	–	0.613	0.605	–
FDG-PET hazard ratio	–	–	–	3.29	5.04	–
Delay amy-FDG (months, mean ± SD)	–	–	–	0.2 ± 2	0.14 ± 1.9	0.80

Legend: HC, healthy controls; MCI, mild cognitive impairment; *P*, *P*-value; APOE, Apolipoprotein E; MMSE, mini-mental state examination; NPV, negative predictive value; PPV, positive predictive value; Amy, amyloid-PET; FDG, [18F]FDG-PET.

**N* = 1 HC and *N* = 12 MCI [18F]FDG-PET were not evaluated due to technical artifacts.

the MCI group (multivariate HR: 0.87 [0.78–0.96], *P* = 0.007). The final multivariate Cox models included age and [18F]FDG-PET status for the HC group and [18F]FDG-PET status and MMSE score for the MCI group (log-rank tests *P* = 4e-04 and *P* = 7e-15, respectively). The significant predictors in univariate analysis are available in Table S2.

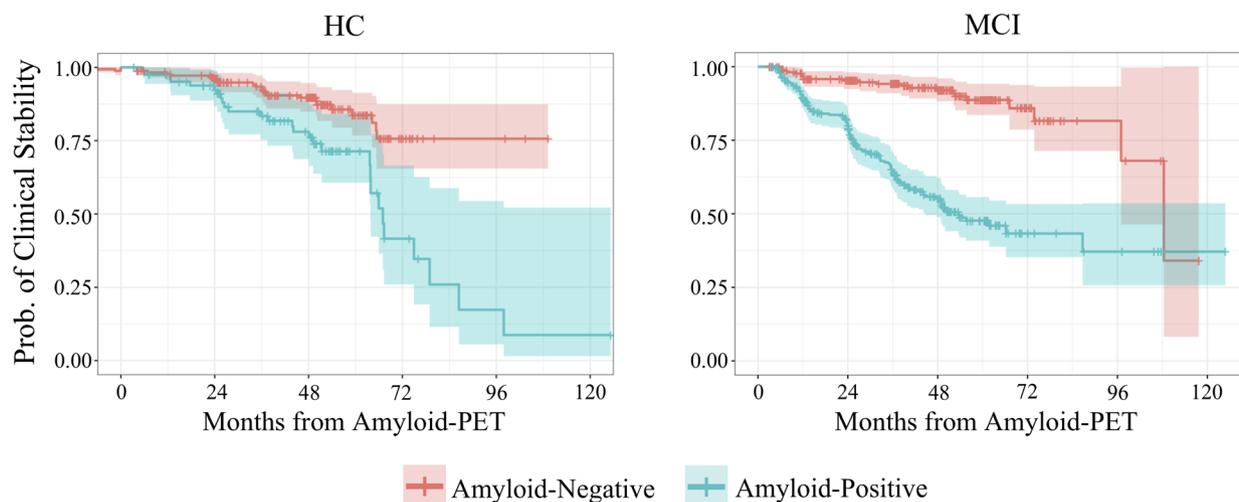
Discussion

Previous studies have evaluated biomarker enrichment strategies,^{13–21} with the aim to provide an ideal biomarker screening paradigm and targeted enrollment of at-risk subjects for clinical trials. Amyloid-PET evidence for significant brain amyloid plaque deposition¹ improves screening accuracy for clinical trials targeting amyloid pathology^{13–15} and is now commonly adopted. Topographical functional or structural measures of ongoing neurodegeneration are included in AD research diagnostic criteria⁸ and could help in the screening of subjects at risk for more rapid cognitive decline and neurodegeneration.²² In this direction, it has been suggested that the inclusion of hippocampal volume,

together with amyloid positivity, could support the identification of subjects more rapidly progressing, with cost reductions and improved statistical power for clinical trials.¹⁵ Another autopsy-based retrospective study modeling the implications for clinical trials on knowing the Braak stage of neurofibrillary tau tangle pathology showed considerable improvement in the statistical power and consistent reduction in the required sample size.¹⁷

Here, we built on and extended the evidence of the role of in vivo biomarkers of neurodegeneration, such as brain hypometabolism, by considering adding [18F]FDG-PET as an enrichment strategy for subject screening in clinical trials. The aim of the present study was to evaluate whether clinical stability (or progression) could be predicted by an advanced marker of neurodegeneration such as brain hypometabolism with [18F]FDG-PET, in cases belonging to the Alzheimer's disease continuum (i.e., amyloid-positive).⁹ Our results support the high predictive value of a [18F]FDG-PET negative scan, in the identification of clinically stable, though amyloid-positive, subjects. The [18F]FDG-PET negative pattern, as evaluated with semiquantitative voxel-wise procedures at

A – Standard Strategy



B – Enriched Strategy

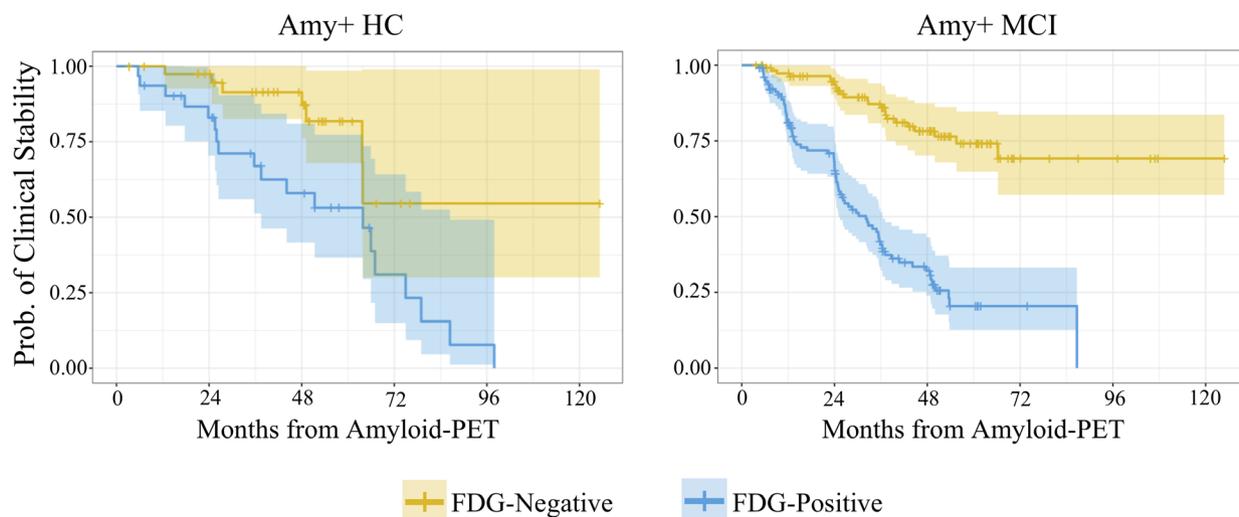


Figure 1. Survival curves split by subgroups and clinical/biomarker combinations. Survival curves split by subgroups (Left, HC; Right, MCI) and strategy (Top, Standard Strategy; Down, Enriched Strategy). Upper panel shows survival curves indicating probability of clinical stability along follow-up in subjects stratified according to Amyloid-PET status. Lower panel shows survival curves in amyloid-positive subjects stratified according to [18F]FDG-PET status (see Results). Legend: HC, healthy controls; MCI, mild cognitive impairment.

single-subject level, was indeed associated with more than 80% chance of remaining clinically stable during follow-up for both HC and subjects with MCI even with amyloid positivity.

The adopted [18F]FDG-PET method¹⁰ additionally allowed to identify brain hypometabolism patterns suggestive of AD and also non-AD neurodegenerative conditions, mostly within the FrontoTemporal Lobar Degeneration spectrum. It is likely that these patterns would be associated with different clinical dementia syndromes at follow-up, as we have previously shown in

MCI.²³ Adding the [18F]FDG-PET status, the observed rate of progression was higher in neurodegeneration-positive MCI subjects, with about 30% of the Amy+/FDG+ MCI subjects progressing to dementia within 24 months of follow-up. There was also some evidence for a more rapid clinical progression in amyloid-positive HC subjects showing an AD-like hypometabolic pattern compared to those with non-AD patterns, which we believe needs further replication in larger cohorts. Overall, our results show that the presence of ongoing downstream neurodegeneration both in HC and MCI subjects

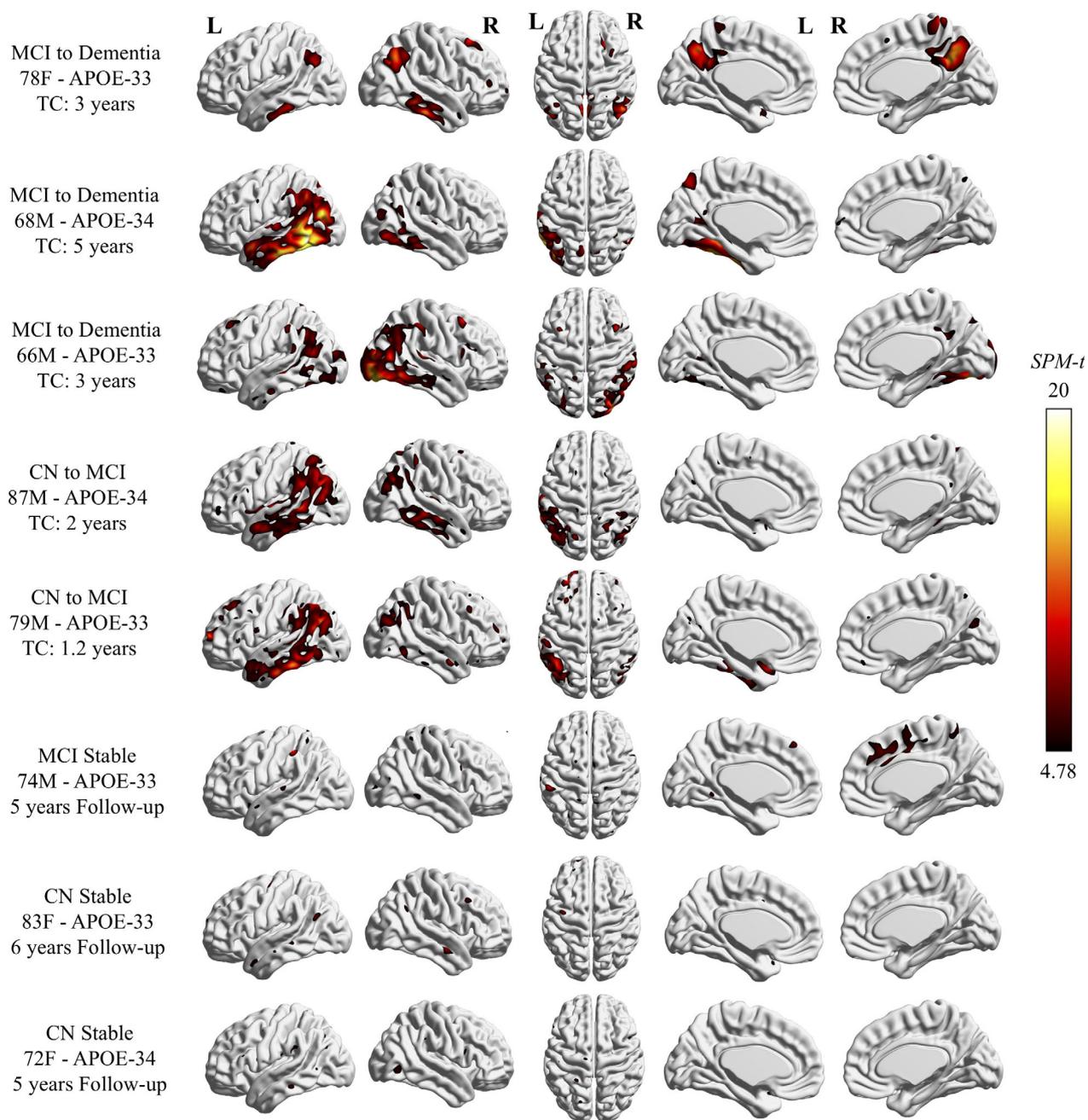


Figure 2. Representative single-subject [18F]FDG-PET hypometabolism patterns. Figure showing paradigmatic single-subject [18F]FDG-PET hypometabolism patterns including clinically stable and progressors for both HC and MCI subgroups. Thresholded SPM-t images ($P < 0.05$ FWE-corrected for multiple comparisons, minimum cluster extent $k = 100$ voxels) are overlaid on a standard ICBM152 surface with BrainNet Viewer.²⁴ Legend: HC, healthy controls; MCI, mild cognitive impairment; TC, Time to conversion; F, Female; M, Male; APOE, Apolipoprotein E

predicts a worse prognostic outcome regardless of the upstream primary pathology.

We suggest that the inclusion of biomarkers of neurodegeneration can reduce the number of recruited subjects who are not on a trajectory to dementia, also avoiding exposure to possible side effects of the tested treatment.

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Author Contributions

Conception of the study: L.I., D.P.; Analysis of data: L.I., A.S.; Drafting of the manuscript: L.I., A.S., D.P.

Conflict of Interest

Nothing to report.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Characteristics of ongoing and starting clinical trials.

Table S2. Significant predictors in univariate analysis, split by groups and samples.

Table S3. Rates of progression along the follow-up split by subgroup.