Amyloid-independent atrophy patterns predict time to progression to dementia in MCI

M. ten Kate, F. Barkhof, P.J. Visser, C.E. Teunissen, P. Scheltens, W.M. van der Flier, B.M. Tijms

Alzheimer’s Research & Therapy 2017; 9:73
ABSTRACT

Introduction: Amyloid pathology in subjects with mild cognitive impairment (MCI) is an important risk factor for progression to dementia due to Alzheimer’s disease. Predicting the onset of dementia is challenging even in the presence of amyloid, as time to progression varies considerably among patients and depends on the onset of neurodegeneration. Survival analysis can account for variability in time to event, but has not often been applied to MRI measurements beyond singular predefined brain regions such as the hippocampus. Here we used a voxel-wise survival analysis to identify in an unbiased fashion brain regions where decreased grey matter volume is associated with time to dementia, and assessed the effects of amyloid on these associations.

Methods: We included 276 subjects with MCI (mean age 67 ± 8, 41% female, mean MMSE 26.6 ± 2.4), baseline 3D T1-weighted structural MRI, baseline cerebrospinal fluid (CSF) biomarkers and prospective clinical follow-up. We fitted for each voxel a proportional Cox hazards regression model to study whether decreased grey matter volume predicted progression to dementia in the total sample, and stratified for baseline amyloid status.

Results: Dementia at follow-up occurred in 122 (44%) subjects over an average follow-up period of 2.5 ± 1.5 years. Baseline amyloid positivity was associated with progression to dementia (HR 2.4, p < 0.001). Within amyloid positive subjects, decreased grey matter volume in hippocampal, temporal, parietal, and frontal regions was associated with more rapid progression to dementia (median [IQR] HR across significant voxels: 1.35 [1.32 - 1.40]). Repeating the analysis in amyloid negative subjects revealed similar patterns (median [IQR] HR: 1.76 [1.66 - 1.91]).

Conclusions: In subjects with MCI, both abnormal amyloid CSF and decreased grey matter volume were associated with future progression to dementia. The spatial pattern of decreased grey matter volume associated with progression to dementia was consistent for amyloid positive and amyloid negative subjects.
INTRODUCTION

Subjects with mild cognitive impairment (MCI) are at increased risk of dementia with annual conversion rates of 10-15% [1,2]. According to the NIA-AA research criteria, a diagnosis of MCI due to AD requires the presence of amyloid pathology as measured in cerebrospinal fluid (CSF) or on amyloid PET [3]. Since amyloid reaches a plateau relatively early in the disease course [4–6], it has limited prognostic value for the time to onset of dementia. Neuronal injury markers, such as brain atrophy measured with structural MRI, are more closely related to cognitive impairment and could thus be useful for estimating time to clinical progression [7–10]. Previous studies found that hippocampal atrophy can be used to predict time to dementia in MCI patients with positive amyloid markers [11,12]. However, other brain regions may also be valuable for the prediction of progression, as indicated by voxel-based morphometry studies [13–15]. Two previous studies have used hypothesis-free voxel-level survival analyses to show that decreased grey matter in the medial temporal lobe and posterior cingulate cortex can predict time to conversion to AD-type dementia in non-demented subjects [16,17]. However, it is still unclear whether such predictive atrophy patterns are specific for amyloid pathology.

In this study, we performed unbiased voxel-wise survival analyses to detect brain regions where decreased grey matter volume is associated with time to progression to dementia, and examined whether patterns associated with progression to dementia were dependent on amyloid status in a large sample of subjects with MCI.

METHODS

Participants

Subjects with a clinical diagnosis of MCI, a good quality structural MRI and CSF biomarker assessment at baseline, and at least one clinical follow-up were selected from the CODA (COnnectivity in Dementia) study, which includes subjects from the Amsterdam Dementia Cohort [18]. This cohort consists of subjects attending the memory clinic of the VU University Medical Centre Amsterdam since 2000. All subjects in this cohort underwent a routine dementia screening, including physical and neurological examination, neuropsychological testing, brain MRI scanning and usually lumbar puncture (unless contra-indication or patient refusal). The study protocol was approved by the VU University Medical Centre institutional review board. All subjects gave written informed consent for their clinical data to be used for research purposes.
Clinical assessment
Baseline clinical diagnosis of MCI was established during a consensus meeting from a multidisciplinary team according to the Petersen criteria [19]. Subjects were followed annually, and duration of follow-up ranged from 1 to 11 years (mean 2.5 ± 1.5). A follow-up diagnosis was made during a multidisciplinary consensus meeting according to common clinical and research criteria [19–24]. Time-to-dementia was defined as the time between baseline visit and date of dementia diagnosis. The primary analysis included all subjects, regardless of follow-up diagnosis. Analyses were repeated for the subsample of subjects who converted to AD-type dementia.

CSF analysis
CSF was collected at baseline by lumbar puncture using a 25-gauge needle in polypropylene tubes (Sarstedt, Nümbrecht, Germany). CSF was centrifuged at 1800 g for 10 min at 4°C and stored at -20°C until biomarker analysis, within two months after collection. CSF Aβ1–42 was measured using InnoTest sandwich ELISAs (Innogenetics, Fujirebio, Ghent, Belgium) [25]. Subjects were classified as amyloid positive or negative with a cut-off of CSF Aβ1–42 < 640 ng/L [26].

MRI acquisition
Anatomical 3D T1-weighted images were acquired at baseline as part of regular patient care with eight different scanners using a spoiled gradient echo type of sequence (e.g. MPRAGE, FSPGR, TFE). Details of scanners and acquisition parameters can be found in supplementary methods. The MRI protocol also included a 3D Fluid Attenuated Inversion Recovery (FLAIR) sequence, dual-echo T2-weighted sequence, susceptibility weighted imaging (SWI) and diffusion weighted imaging (DWI) to visually assess brain pathology by an experienced neuroradiologist.

MRI analysis
Structural 3D T1 images were segmented using Statistical Parametric Mapping 12 (SPM12) software (Wellcome Trust Centre for Neuroimaging, University College London, UK) running in MATLAB 2011a (MathWorks Inc., Natick, MA, USA). Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) was used to create a custom study-template by non-linearly aligning grey matter segmentations [27]. Subsequently, native space grey and white matter images were spatially normalized to the template using the individual flow fields. The resulting grey matter images (isotropic 1.5 mm³ voxels) were modulated to preserve the total amount of grey matter from the native space image. Images were smoothed with an isotropic Gaussian filter of 6 mm full-width at
Regional atrophy and clinical progression in MCI

half-maximum (FWHM). After processing, the quality of the segmentations was visually checked and none had to be excluded. Total intracranial volume (TIV) was calculated from segmented images in native space (TIV = grey matter + white matter + cerebrospinal fluid).

To limit the analysis to grey matter voxels, a mask was created to include only voxels with a grey matter probability of 0.1 resulting in 311,613 voxels included in the analysis.

**Statistical procedures**

Independent sample t-tests, Mann Whitney U or chi-square tests were used when appropriate to compare the groups on demographic and clinical variables using SPSS (version 22; IBM), with $p < 0.05$ considered statistically significant.

Prior to the imaging statistics, a linear regression was performed at each voxel to correct grey matter volume for the effects of the nuisance variables age, gender, scanner and TIV. Baseline cross-sectional grey matter differences between amyloid positive and amyloid negative subjects were examined using a general linear model. Proportional Cox hazards regressions to predict disease progression were performed at each grey matter voxel using the Coxphfit function implemented in MATLAB 2011a (MathWorks Inc., Natick, MA, USA). The outcome measure was time to dementia onset. The independent variable was residual grey matter at each voxel. At each voxel, the residual grey matter volume was inverted and $Z$-transformed. The hazard ratio (HR) then represents the increased chance of progressing to dementia within the next time point per standard deviation decrease in grey matter volume. Proportional Cox hazards regression was also used to assess the hazard ratio associated with amyloid positivity in the whole sample and for continuous CSF $\text{A}\beta_{1-42}$ values in the amyloid subgroups, while correcting for age and gender. Continuous amyloid measures were inverted so that hazard ratios were directly comparable.

First, the voxel-wise Cox regression analysis was performed on the total sample. Next, analyses were repeated after stratification by amyloid status. Statistical significance was determined with nonparametric permutation tests [28]. The event or group label was randomly reallocated to each subject 10 times. For each of these permutations, the voxel-wise Cox regression was repeated. The results of all permutations at all voxels were pooled to sample the permutation distribution under the null hypothesis ($= 3,427,743$ random tests). The 2.5th and 97.5th percentiles of this null distribution were used as the critical values for statistical significance representing a two-sided test with a probability of type I error of 0.05. Sampling of the null distribution by permutation testing was repeated for all subgroup analyses.
We tested the assumption of proportional hazards for each voxel-level test for the main analysis using Schoenfeld residuals [29] using the cox.zph function in R (R version 3.1.1, http://www.R-project.org) with survival package version 2.37-7. We found no more violations of the proportional hazards assumption than would be expected by chance (3.24% of tests were significant at \( p < 0.05 \)).

**RESULTS**

Of the 276 subjects with MCI, 122 (44%) progressed to dementia. Among those who progressed to dementia, 104 (85%) subjects progressed to AD-type dementia and 18 (15%) subjects to another type of dementia (4 fronto-temporal dementia, 8 vascular dementia, 1 mixed vascular and AD, 3 Lewy body dementia, and 2 dementia unspecified). Clinical characteristics of subjects are summarized in Table 1.

**Table 1: Subject characteristics according to progression and amyloid status.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All subjects (n = 276)</th>
<th>Amyloid negative (n = 116)</th>
<th>Amyloid positive (n = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stable</td>
<td>Progression</td>
<td>Stable</td>
</tr>
<tr>
<td>N</td>
<td>154 (56)</td>
<td>122 (44)</td>
<td>93 (80)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>65.5 ± 7.7</td>
<td>68.3 ± 8.1 *</td>
<td>63.8 ± 7.9</td>
</tr>
<tr>
<td>Male gender</td>
<td>97 (63)</td>
<td>67 (56)</td>
<td>64 (69)</td>
</tr>
<tr>
<td>Education</td>
<td>5.0 ± 1.5</td>
<td>4.9 ± 1.7</td>
<td>4.8 ± 1.7</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.0 ± 2.2</td>
<td>26.1 ± 2.6 *</td>
<td>27.0 ± 2.2</td>
</tr>
<tr>
<td>CSF Aβ1–42</td>
<td>794 ± 307</td>
<td>534 ± 194 *</td>
<td>999 ± 207</td>
</tr>
<tr>
<td>WMH</td>
<td>0.99 ± 0.92</td>
<td>1.03 ± 0.80</td>
<td>0.88 ± 0.93</td>
</tr>
<tr>
<td>NGMV</td>
<td>0.41 ± 0.04</td>
<td>0.39 ± 0.05 *</td>
<td>0.42 ± 0.04</td>
</tr>
<tr>
<td>Follow-up, yrs</td>
<td>2.5 ± 1.5</td>
<td>2.6 ± 1.7</td>
<td>2.3 ± 1.4</td>
</tr>
<tr>
<td>Follow-up diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>-</td>
<td>104 (85)</td>
<td>-</td>
</tr>
<tr>
<td>DLB</td>
<td>-</td>
<td>3 (2)</td>
<td>-</td>
</tr>
<tr>
<td>FTD</td>
<td>-</td>
<td>4 (3)</td>
<td>-</td>
</tr>
<tr>
<td>VaD &amp; mixed</td>
<td>-</td>
<td>9 (7)</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>-</td>
<td>2 (2)</td>
<td>-</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or count (%). AD = Alzheimer’s disease; CSF = cerebrospinal fluid; DLB = Lewy Body dementia; FTD = fronto-temporal dementia; MMSE = Mini-Mental state examination, N = number of subjects; NGMV = normalized grey matter volume; yrs = years; VaD = vascular dementia; WMH = white matter hyperintensities, measured with 4-point Fazekas scale. * \( p < 0.01 \) or † \( p < 0.05 \) different from stable subjects.
Subjects who progressed were on average older, had lower baseline scores on the Mini-Mental State Examination (MMSE), lower baseline CSF Aβ_{1-42} than subjects who remained stable. The groups had similar follow-up times. Subjects who were amyloid positive had a higher risk of progressing to dementia compared to amyloid negative subjects (HR 2.4, \( p < 0.001 \)). When stratifying for amyloid status, 160 subjects were amyloid positive and 99 (62%) of them showed clinical progression. Of those amyloid positive subjects that progressed, most subjects progressed to AD-type dementia (n = 94, 95%). 116 subjects were amyloid negative, of whom 23 (20%) subjects progressed. Amyloid negative subjects more often progressed to non-AD dementias (57%) than AD-type dementia (43%). Within the amyloid positive group, continuous CSF Aβ_{1-42} levels were unrelated to progression to dementia (HR 1.0, \( p = 0.8 \)). Within the amyloid negative group, continuous CSF Aβ_{1-42} levels were associated with an increased risk of progression to dementia (HR 2.2, \( p = 0.01 \)).

### Brain regions predicting time to dementia

The voxel-wise proportional Cox hazards regressions showed that lower grey matter volumes in widespread cortical and subcortical areas were associated with time to progression to dementia (Figure 1). In addition to decreased grey matter volume in well-known AD related areas (i.e., hippocampal and temporal regions), low grey matter volume in parietal and frontal regions was also associated with progression to dementia (Table 2). Repeating the analysis after excluding subjects progressing to non-AD dementia did not substantially change these results (data not shown).

![Brain regions predicting clinical progression in subjects with MCI](image-url)

**Figure 1: Brain regions predicting clinical progression in subjects with MCI.**

The hazard ratio for progression to dementia associated with lower residual grey matter volume is depicted at each voxel. Residual grey matter volumes were standardized prior to the analysis.
Table 2: Regions in which decreased grey matter volume is associated with progression to dementia in subjects with MCI.

<table>
<thead>
<tr>
<th>Cluster size</th>
<th>MNI peak coordinates</th>
<th>Hazard ratio</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>59330</td>
<td>-9</td>
<td>1.78</td>
<td>Left rectal gyrus</td>
</tr>
<tr>
<td></td>
<td>43.5</td>
<td>1.78</td>
<td>Right insula</td>
</tr>
<tr>
<td></td>
<td>-21</td>
<td>1.75</td>
<td>Left hippocampus</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>1.70</td>
<td>Right parahippocampal gyrus</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>1.69</td>
<td>Right middle temporal gyrus</td>
</tr>
<tr>
<td></td>
<td>25.5</td>
<td>1.66</td>
<td>Right middle frontal gyrus</td>
</tr>
<tr>
<td></td>
<td>-39</td>
<td>1.63</td>
<td>Left inferior frontal gyrus</td>
</tr>
<tr>
<td></td>
<td>-54</td>
<td>1.61</td>
<td>Left superior temporal gyrus</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>1.60</td>
<td>Right anterior cingulate</td>
</tr>
<tr>
<td></td>
<td>16.5</td>
<td>1.59</td>
<td>Right medial frontal gyrus</td>
</tr>
<tr>
<td>2571</td>
<td>7.5</td>
<td>1.67</td>
<td>Right cingulate gyrus</td>
</tr>
<tr>
<td></td>
<td>10.5</td>
<td>1.58</td>
<td>Right precuneus</td>
</tr>
<tr>
<td>797</td>
<td>39</td>
<td>1.57</td>
<td>Right inferior parietal lobule</td>
</tr>
<tr>
<td>679</td>
<td>45</td>
<td>1.68</td>
<td>Right inferior temporal gyrus</td>
</tr>
<tr>
<td>540</td>
<td>-55.5</td>
<td>1.42</td>
<td>Left supramarginal gyrus</td>
</tr>
</tbody>
</table>

Presented are the anatomical details of the five largest clusters. For the large clusters, several local maxima spread across the cluster are given.

**Influence of amyloid pathology**

First, we assessed the influence of amyloid status on grey matter volume with standard voxel-based-morphometry. This revealed decreased grey matter volume in amyloid positive subjects when compared to amyloid negative subjects in the hippocampus, temporal, parietal and frontal regions (Supplementary Figure 1). Amyloid negative subjects had lower grey matter volume at baseline in the cerebellum than amyloid positive subjects.

Next, we repeated the survival analysis after stratifying the subjects according to amyloid status. Amyloid positive subjects showed widespread decreases in grey matter volume that were predictive of time to progression to dementia, similar to the analysis in the whole sample (Figure 2). In comparison, the anatomical patterns predicting progression in amyloid negative subjects were qualitatively similar to those observed in amyloid positive subjects, apart from bilateral anterior temporal regions (only significant in amyloid positive subjects) and the right fusiform gyrus (only significant in amyloid negative subjects). To formally assess the difference between amyloid positive and negative subjects, we added an interaction term between voxel grey matter volume and amyloid status to the voxel-level Cox regression on the whole sample. For the majority of voxels (97% of all voxels included in the analyses), this interaction was not significant, supporting that the predictive value
of baseline grey matter volume is largely similar for amyloid positive and amyloid negative subjects (Supplementary Figure 2). Three somewhat larger clusters of voxels showed significant interaction effects of amyloid status: two ventromedial prefrontal regions, which showed a higher hazard ratio in amyloid negative subjects compared to amyloid positive subjects; and one cluster in the right temporal fusiform gyrus that was only significant in amyloid negative subjects.

Since within the amyloid negative group continuous CSF Aβ\textsubscript{1–42} values were associated with progression to dementia, we performed a voxel-wise Cox regression after additionally correcting for continuous CSF Aβ\textsubscript{1–42} values. This analysis resulted in hazard ratios of similar size. When using a voxel-wise threshold of $p < 0.005$ a similar pattern of significant voxels emerged as in the analysis without correction for CSF Aβ\textsubscript{1–42}, but these did not survive correction for multiple testing (Supplementary Figure 3).

![Figure 2: Brain regions predicting clinical progression in amyloid positive and amyloid negative subjects.](image)

Left: significant voxels predicting time to progression to dementia in amyloid positive subjects. Right: significant voxels predicting time to progression to dementia in amyloid negative subjects. Depicted are hazard ratios for progression to dementia, associated with lower residual grey matter volume.
DISCUSSION

The main finding of this paper is that a widespread pattern of decreased grey matter volume, beyond the hippocampal region, is predictive of time to progression to dementia in subjects with MCI. The presence of amyloid pathology was also a predictor of time to progression to dementia. The pattern of decreased grey matter volume that was predictive of progression was mostly similar in amyloid positive and negative subjects.

The cortical pattern of decreased grey matter volume predicting progression to dementia in subjects with MCI included temporal, parietal and frontal regions. Most of the voxels predictive of progression to dementia are located in brain regions that typically show atrophy and hypometabolism as a sign of neurodegeneration in subjects with AD [30,31], and are known to be pathologically involved in AD [32]. Our results are largely in line with previous voxel-based morphometry studies comparing MCI subjects who progress to dementia to those that remain stable over time. These studies have identified the medial and lateral temporal lobe [13–15], and also parietal and frontal areas [15] to be associated with progression. So far, only two studies have also applied voxel-level survival analysis to structural MRI data. Using this method, inter-subject variability in rates of clinical progression and follow-up time can be taken into account. Those studies also reported that atrophy in (mesial) temporal and posterior cingulate structures is predictive of cognitive decline [16,17]. The patterns of low grey matter volume predictive of decline observed in our study were more extensive than in these previous studies and additionally revealed frontal and more widespread parietal regions to be involved. This could partially be explained by our higher power due to larger sample size. Also, Zeifman et al. [17] examined clinical progression from a cognitively normal stage, whereas our sample comprised subjects with MCI at baseline, who have more atrophy and a higher probability to progress to dementia within a follow-up time of a few years.

The regional patterns of decreased grey matter volume predictive of progression to dementia in subjects with evidence of amyloid pathology were largely similar to those found in the whole sample, and located in regions that are known to be associated with AD pathology. This is in line with the notion that subjects with MCI and evidence of amyloid plaques are at an early stage of AD [3]. In addition, we found that decreased grey matter volume in most of these regions was also associated with progression to dementia in MCI subjects with normal amyloid at baseline. This suggests that the regions of decreased grey matter volume we found to be predictive for time to dementia are not specific for amyloid pathology. These findings are in line with MRI studies using a priori defined areas, which have also found that brain regions typically atrophied in AD were predictive of cognitive decline both in MCI...
Regional atrophy and clinical progression in MCI

subjects with and without evidence of amyloid pathology [7,9,11]. We further extend those results by showing that a more widespread anatomical pattern of decreased grey matter volume is related to cognitive decline, independent of the presence of amyloid pathology.

A possible explanation for our results is that the subjects that progressed within the amyloid negative group do have underlying AD-pathology, but are above the cut-off for amyloid positivity. CSF $A\beta_{1-42}$ levels, although well above the threshold, were significantly lower in subjects who progressed than those who remained stable (Table 1). Further characterizing the subjects that progressed within the amyloid negative group revealed that those subjects that progressed to clinical AD type dementia also had lower baseline CSF $A\beta_{1-42}$ levels at the time of dementia diagnosis (not tested), since several studies have shown that higher amyloid burden at baseline, even within the normal range, is associated with future amyloid depositions [10,33,34]. An alternative explanation is that subjects who progressed to clinical dementia in the absence of amyloid pathology are akin to the concept of suspected non-amyloid pathology (SNAP). This concept has been constructed for subjects who present with evidence of AD-like neurodegeneration in the absence of amyloid pathology [35]. We studied subjects with MCI, who suffer from cognitive impairment, suggesting that a neurodegenerative process has already caused neuronal damage, but the underlying cause might not be AD. There are several disorders that show a spatially overlapping atrophy pattern with regions that are typically affected in AD. For example, the medial temporal lobe is involved in hippocampal sclerosis and TDP43 pathology can be associated with widespread cortical atrophy [36–38]. The association between regional amyloid deposition in the brain and cortical atrophy is still unclear [32,39]. Our results support the idea that some brain regions are selectively vulnerable to pathological factors in general, and that amyloid pathology is one possible initiator of a common neurodegenerative pathway [40].

Although the overall anatomical pattern of decreased grey matter volume associated with time to progression was largely similar in amyloid positive and amyloid negative subjects, some subtle differences can be appreciated in Figure 2 and Supplementary Figure 2. In the ventromedial prefrontal cortex, HRs were higher in amyloid negative subjects compared to amyloid positive subjects. Furthermore, the right fusiform gyrus was only significantly associated with time to progression in amyloid negative subjects. This region previously has been included in an AD signature cortical thickness measure [41]. Whether decreased grey matter volume in these regions could be an indication of non-AD pathology in subjects with MCI will need to be examined in larger studies.
A potential limitation of this study is that the data was acquired at a clinical centre over a relatively long period of time, during which the dementia work-up protocols changed, diagnostic criteria evolved and higher field-strength MRI scanners were implemented. Although we have corrected for the potential influences when possible, we cannot exclude the possibility that this variability might have led to an underestimation of our results. Still, this can also be considered to be a strong point of our study, as it supports the robustness of our results. Another limitation is that we defined the follow-up time when the clinical diagnosis changed as outcome parameter for the survival analyses. Since follow-up times were not strictly standardized but rather based on clinical judgment and timing of yearly appointment, this might have biased the results. However, we think this is unlikely since the time of follow-up, with an average of 2.5 ± 1.5 and ranging up to 11 years, was similar for subjects who progressed and those who remained stable.

CONCLUSIONS

Widespread decreases in grey matter volume are useful in the prediction of clinical progression and time to dementia in subjects with MCI. Findings were largely similar in subjects with and without evidence of amyloid pathology. This leads us to consider that although brain atrophy does not seem specific for the underlying pathology, it is a useful marker that reflects incipient dementia and thereby valuable for predicting clinical progression.

Funding
This work has received support from the EU/EFPIA Innovative Medicines Initiative Joint Undertaking (EMIF grant: 115372) (MtK and PJV) and a research grant from Boehringer Ingelheim Pharma GmbH Co KG, Germany (WMvdF).
REFERENCES


based techniques to assess regional atrophy associated with MCI risk of progression to AD. NeuroImage. 2011;54:985–91.


SUPPLEMENTARY DATA

Supplementary methods

MRI acquisition parameters

Subjects were scanned on 8 different scanners: 1T Siemens Magnetom Impact, 1.5T Siemens Vision, 1.5T Siemens Sonata, 1.5T Siemens Avanto, 1.5T GE SignaHDxt, 3T GE SignaHDxt, 3T Toshiba Titan and a 3T Philips Ingenuity PET/MR system.

The following acquisition parameters were used: Impact (MPRAGE): coronal plane, repetition time (TR) 15 ms, echo time (TE) 7 ms, inversion time (TI) 300 ms, flip angle (FA) 15°, voxel size 1 × 1 × 1.5 mm; Vision (MPRAGE): coronal plane, TR 15 ms, TE 7 ms, FA 8°, voxel size 0.98 × 0.98 × 1.5 mm; Sonata (MPRAGE): coronal plane, TR 2700 ms, TE 3.97 ms, TI 950 ms, FA 8°, voxel size 1 × 1 × 1.5 mm; Avanto (MPRAGE) coronal plane, TR 2700 ms, TE 5.2 ms, TI 950 ms, FA 8°, voxel size 1 × 1 × 1.5 mm; 1.5T Signa (FSPGR): sagittal plane, TR 12.4 ms, TE 5.17 ms, TI 450 ms, FA 12°, voxel size 0.98 × 0.98 × 1.5 mm; 3T Signa (FSPGR): sagittal plane, TR 8 ms, TE 3 ms, TI 450, FA 12°, voxel size 0.98 × 0.98 × 1 mm; Titan (FFE): sagittal plane, TR 9.5 ms, TE 3.2 ms, TI 800 ms, FA 7°, voxel size 1 × 1 × 1 mm; PET/MR (TFE): sagittal plane, TR 8 ms, TE 4 ms, FA 12°, voxel size 1 × 1 × 1 mm.
Supplementary Figures

Supplementary Figure 1: Difference in brain atrophy between amyloid positive and negative subjects at baseline.
In yellow-red are depicted voxels where amyloid positive subjects have decreased grey matter compared to amyloid negative subjects. Colour bar represents t-score. R = right; L = left.
Supplementary Figure 2: Difference in predictive value for clinical progression of grey matter volume between amyloid positive and amyloid negative subjects.

Shown are voxels for which the interaction between grey matter volume and amyloid pathology for predicting clinical progression is significant. R = right; L = left.
Supplementary Figure 3: Hazard ratios for clinical progression after correcting for CSF Aβ₁₋₄₂ values in amyloid positive and negative subjects.

Hazard ratios for the voxel-wise Cox analysis with continuous CSF Aβ₁₋₄₂ as covariate. For both groups, the hazard ratios are comparable to the analysis without correction for CSF Aβ₁₋₄₂ (Figure 2 main text). Displayed are voxels significant at a voxel-wise $p < 0.005$. Colour bar represents hazard ratio. R = right; L = left.