MAPPING THREE-YEAR CHANGES IN GRAY MATTER AND METABOLISM IN A β -POSITIVE NONDEMENTED SUBJECTS

Miguel Ángel Araque Caballero, Dr. rer. Nat.¹, Matthias Brendel, MD², Andreas Delker, MSc², Jinyi Ren, MSc¹, Axel Rominger, MD², Peter Bartenstein MD², Martin Dichgans, MD^{1,3}, Michael W. Weiner, MD⁴ and Michael Ewers, PhD¹ for the Alzheimer's Disease Neuroimaging Initiative (ADNI).

¹Institute for Stroke and Dementia Research, Klinikum der Universität München, Ludwig-Maximilian-University, Munich, Germany.

²Department of Nuclear Medicine, Klinikum der Universität München, Ludwig-Maximilian-University, Munich, Germany.

³Munich Cluster for Systems Neurology (SyNergy)

⁴Department of Radiology, University of California, and VA Medical Center, Center for Imaging of Neurodegenerative Diseases San Francisco, CA, USA.

Corresponding author:

Miguel Ángel Araque Caballero.

Address: Institut für Schlaganfall- und Demenzforschung (ISD), Klinikum der Universität München, Feodor-Lynen-Straße 17, 81377 München, Germany.

Telephone: +49-89-4400-46159

Fax: +49-89-7095-8729

Email: miguel.caballero@med.uni-muenchen.de

ABSTRACT

Gray matter atrophy and brain glucose hypometabolism are already detected in the pre-dementia stages of Alzheimer's disease (AD), but the regional and longitudinal associations between the two are not well understood. Here we analyzed the patterns of longitudinal atrophy (MRI) and FDG-PET metabolism decline in forty cognitively healthy (HC) and fifty-two mildly impaired (MCI) subjects over 3 years. Based on CSF and brain amyloid-PET, the subjects were divided into amyloid-beta ($A\beta$)⁻ and $A\beta$ ⁺ subgroups. In voxel-based and ROI analyses, we compared the 3-year rates of change in grey matter and glucose metabolism between $A\beta$ ⁻ subgroups, within each diagnostic group. In joint-ICA analyses we assessed the patterns of covariation between longitudinal change in grey matter volume and glucose metabolism. MCI- $A\beta$ ⁺ showed faster atrophy than MCI- $A\beta$ ⁻ within the temporal, medial-temporal and medial-parietal lobes. HC- $A\beta$ ⁺ showed faster atrophy within the precuneus than HC- $A\beta$ ⁻. For FDG-PET metabolism, MCI- $A\beta$ ⁺ exhibited faster decline than MCI- $A\beta$ ⁻ in temporo-parietal regions, whereas no differences between HC subgroups were observed. Joint-ICA showed that accelerated atrophy and metabolism decline correlated across distant brain regions for MCI- $A\beta$ ⁺. In conclusion, abnormally increased levels of $A\beta$ in non-demented subjects were associated with accelerated decline in both GM and glucose metabolism, where both types of neurodegeneration progress in spatially divergent patterns.

Keywords: Longitudinal; Neurodegeneration; Alzheimer's; Neuroimaging; Multivariate; Multimodal

1. INTRODUCTION

In Alzheimer's disease (AD), pathological brain changes precede the onset of clinical symptoms by many years. Cross-sectional analysis of cerebrospinal fluid (CSF) and amyloid PET based biomarker studies have suggested that abnormal biomarker levels of amyloid- β (A β) can be observed already about 15-20 years before the onset of dementia symptoms in familial AD (Bateman et al., 2012) and sporadic AD (Villemagne et al., 2013). In cognitively healthy subjects (HC), global amyloid PET uptake is abnormally increased in an age-dependent manner ranging from 18% in HC subjects 60-69 years old to over 65% in subjects > 80 years (Rowe et al., 2010). In mild cognitive impairment (MCI), the majority of subjects show abnormally increased global amyloid PET uptake (Klunk, 2011).

Results from a large number of studies including MRI and ^{18}F -Fluorodeoxyglucose-PET (FDG-PET) suggest that increased levels of A β in the brain are associated with increased neurodegeneration in the asymptomatic and prodromal phase of AD: results from cross-sectional studies in preclinical AD (HC with abnormal biomarkers of A β) showed reduced gray matter (GM) volume (atrophy) in the medial temporal lobe and the posterior cingulate (Bourgeat et al., 2010; Oh et al., 2011) suggesting that neurodegeneration has already begun in these asymptomatic healthy controls. Results of longitudinal MRI studies in preclinical AD suggest that over the course of 3 - 4 years, accelerated gray matter atrophy is confined to the medial temporal lobe (Nosheny et al., 2014) and the posterior cingulate (Villemagne et al., 2013).

For FDG-PET, cross-sectional studies showed that A β -associated reductions in brain metabolism are present in the prodromal stage of AD, but have only inconsistently been reported in preclinical AD ((Cohen et al., 2009; Jagust et al., 2012; Oh et al., 2012), reviewed in (Ewers et al., 2011)). Longitudinal studies have shown an acceleration of FDG-PET metabolism decline in subjects with prodromal AD. In preclinical AD, FDG-PET changes over a short follow-up period of 1 – 2 years have been reported to be independent of A β (Ewers et al., 2012; Knopman et al., 2013). It has been proposed that increased levels of A β are not associated with FDG-PET in AD once Apolipoprotein E (ApoE) genotype differences are accounted for (Jagust et al., 2012).

Results from cross-sectional studies in AD dementia patients suggest that the level of FDG-PET hypometabolism exceeds GM atrophy in the posterior parietal cortex, but GM atrophy exceeds FDG-PET hypometabolism within the hippocampal area (La Joie et al., 2012). However, it is currently unclear how the spatial evolution of GM atrophy differs from that of FDG-PET throughout the early amyloid-positive stages of AD. In the present longitudinal 3-year study of combined MRI and FDG-PET, we asked the question whether in non-demented subjects with increased levels of brain A β , the spatial spreading of FDG-PET hypometabolism differs from that of MRI-assessed GM atrophy. The specific aims were 1) to compare the region-dependent

effects of A β on GM change versus FDG-PET metabolism and 2) to assess the regional association between changes in gray matter and changes in FDG-PET in non-demented subjects.

2. MATERIALS AND METHODS

2.1. Subjects

The present study included 40 HC subjects and 52 subjects with MCI from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study ((Mueller et al., 2005) and www.adni-info.org). ADNI I includes 819 subjects, out of which only a subset (see Fig. 1) met the inclusion criteria for the current study: 1) yearly follow-up structural MRI and FDG-PET scans for 3 years after baseline and 2) available CSF A β_{1-42} measurements at baseline, or amyloid-PET (^{11}C -Pittsburgh-Compound-B-PET (PiB-PET) or ^{18}F -AV45 PET) images available at any time point. Due to the study design of the first phase of ADNI, subjects diagnosed with AD dementia at the initial visit were followed up no longer than two years and were thus not included in the current sample.

According to the ADNI diagnostic criteria, subjects were classified as HC at baseline if they showed a clinical dementia rating (CDR) of 0 and Mini-Mental State Exam (MMSE) scores between 24 and 30 (inclusive), and an absence of memory complaints or impaired memory function. Normal memory function was defined with respect to scoring by the delayed Paragraph Recall subscale of the Wechsler Memory Scaled – Revised, corrected for years of education as follows: score ≥ 9 for 16 or more years of education, ≥ 5 for 8-15 years of education and ≥ 3 for 0-7 years of education (Petersen et al., 2010)

MCI was diagnosed according to subjective memory complaints verified by a study partner, CDR = 0.5 and delayed Paragraph Recall scores corrected for years of education as follows: score ≤ 8 for 16 or more years of education, ≤ 4 for 8-15 years of education and ≤ 2 for 0-7 years of education. See the ADNI Procedures Manual for further details on diagnostic criteria and neuropsychological assessments (available at the ADNI study website http://adni.loni.usc.edu/wp-content/uploads/2010/09/ADNI_GeneralProceduresManual.pdf).

The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations as a \$60 million, 5-year public- private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co- investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.

2.2. CSF measurement of A β levels

CSF samples were acquired at the ADNI clinical centers, frozen at -80 °C and shipped for analysis to the ADNI Biomarker Core at the University of Pennsylvania. The concentration of CSF A β was measured at baseline with the multiplex xMAP Luminex platform (Luminex Corp., Austin, TX). For a detailed description of protocols and procedure see (Shaw et al., 2009).

2.3. PiB-PET measurement of A β levels

PiB-PET scans consisted of 4 x 300 second frames measured 50 minutes after injection of 15 ± 1.5 mCi of Pittsburgh compound B. Correction for attenuation was performed with the aid of CT or transmission scans, and the scans were preprocessed to result in standard orientation, voxel size and resolution across subjects. In this study we used global SUVR PiB-PET values obtained as the average of fourteen different representative ROIs throughout the brain: anterior cingulate, frontal cortex, lateral temporal cortex, parietal cortex, precuneus cortex, mesial temporal cortex, occipital cortex, occipital pole, pons, anterior ventral striatum, cerebellum, sensory motor cortex, sub-cortical white matter and thalamus. The cerebellum was taken as reference region. These preprocessing and analysis steps of the PiB-PET scans were performed by the PET Facility of the University of Pittsburgh and the methodology and results of the analyses are available at the ADNI study website (<http://adni.loni.usc.edu/methods/pet-analysis/>).

2.4. AV45-PET measurement of A β levels

AV45-PET scans consisted of 4 x 300 second frames measured 50 minutes after injection of 10 ± 1.0 mCi of Florbetapir (^{18}F). Similar to the PiB-PET case we used SUVR AV45-PET values obtained as the average of

image values within several representative ROIs for images with standard orientation, voxel size and resolution. The cerebellum was taken as the reference region. The pre-processed images a methodology overview and the result analyses are available at the ADNI study website (<http://adni.loni.usc.edu/methods/pet-analysis/>).

2.5. 3D T1-weighted MRI

The MRI scans were obtained from a standardized MRI dataset in ADNI I, which passed image quality criteria established by the ADNI MRI Core. The standard data set has been proposed by Wyman et al. (Wyman et al., 2013) in order to unify selection criteria for MRI scans among researchers working with ADNI data. For the current study, only subjects with yearly follow-up visits for a total of 3 years were included. All of these scans underwent field-gradient correction, B1-calibration correction and N3 correction of residual intensity inhomogeneities by the ADNI MRI core unit (<http://adni.loni.usc.edu/data-samples/mri/>).

2.6. FDG-PET

FDG-PET scans consisted of 6 x 300 second frames measured 30 minutes after injection of 5 ± 0.5 mCi of Fluorodeoxyglucose (^{18}F). All the scans were attenuation-corrected, pre-processed images with standard orientation, voxel size and resolution. (<http://adni.loni.usc.edu/data-samples/pet/>). In order to correct for possible differences in global levels of FDG-PET, each voxel value within the spatially normalized FDG-PET images (see below) were scaled to their average value within the pons and vermis.

2.7. Longitudinal pre-processing of MRI scans

For each subject, the MRI scans of each of the 4 time points (baseline and 3 annual follow-up scans) were rigidly aligned between time points. An intra-subject mean image was obtained by averaging the realigned scans. The rigidly-aligned MRI scans were segmented into three tissue classes: gray matter, white matter (WM) and CSF (Ashburner and Friston, 2005). In order to estimate the spatial normalization parameters, the intra-subject mean image was normalized to the MNI T1-weighted MRI template via nonlinear diffeomorphic transformation (DARTEL tool in SPM8 (Ashburner, 2007)). Subsequently, the estimated spatial normalization parameters were applied to all image segments (GM, WM, CSF) at each time point. The longitudinal pre-processing was performed with the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>) (Luders et al., 2004) of SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>). The quality of the pre-processed scans was assessed visually, resulting in two subjects being excluded due to the presence of artifacts in their GM segmentations. For the statistical analysis (see below) a gray matter mask was generated. All of the spatially normalized gray matter segments

were averaged across subjects and time points and scaled to a maximum value of 1. The average image was binarized, applying a threshold of > 0.3 .

2.8. Longitudinal pre-processing of FDG-PET scans

The FDG-PET scans were coregistered to the MRI intra-subject mean image via affine transformations, for each time point separately. Afterwards, the normalization to MNI-space of the FDG-PET scans was computed by applying the normalization parameters estimated for the average image in the MRI pipeline to the FDG-PET scans at each time point.

We accounted for atrophy effects on FDG-PET SUVR values as explained in the section Statistical Analyses (below). In addition, we performed PVE corrections with two alternative methods for cross-validation purposes: the ROI-based Geometric Transfer Matrix (GTM) method (Rousset et al., 1998) and the voxel-based Müller-Gärtner method (Muller-Gartner et al., 1992).

2.9. ROI value extraction and analysis

We complemented our main voxel-based analysis with an ROI-based assessment of changes in GM volume and FDG-PET metabolism. In particular we focused on two regions commonly investigated in the literature as biomarkers for AD progression: the hippocampus and a composite ROI based on a meta-analysis of regions that show decreased FDG-PET uptake in AD (Landau et al., 2011), such as the posterior cingulate, and the lateral temporo-parietal cortex (we refer to it as the temporo-parietal ROI in the remainder). We extracted GM and FDG-PET values within both ROIs from the MNI-normalized, unsmoothed GM segments and the MNI-normalized, unsmoothed FDG-PET images scaled to the pons/vermis, for each subject and time-point separately. For the hippocampus ROI, the extraction was performed using the Automatic Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002), averaging the values for the left and right hippocampi. The temporo-parietal ROI is available at <http://adni.loni.usc.edu/methods/research-tools/>.

2.10. Dichotomization of diagnostic groups based on A β biomarker measurements

We dichotomized each diagnostic group (HC and MCI) into subgroups of abnormally high A β levels (HC A β + or MCI A β +) and normal A β levels (HC A β - or MCI A β -) based on CSF A β_{1-42} concentration ($N = 65$), and global brain levels of PiB-PET ($N = 12$) or AV45-PET ($N = 15$).

Previous studies have shown good correspondence between the different measures CSF and molecular PET for determining normal vs. abnormal A β levels (Ewers et al., 2012; Fagan et al., 2006). We applied previously

established cut-off values for each measure, i.e. for CSF A β values, subjects with $[A\beta_{CSF}] \leq 192$ pg/mL were classified as A β + (Shaw et al., 2009), and for PiB-PET and AV45-PET imaging, subjects with global SUVR values ≥ 1.5 and ≥ 1.13 respectively were classified as A β + (Jagust et al., 2010; Landau et al., 2013). These cut-off values provided a clear separation of our subjects into normal/abnormal A β levels within each modality as the distribution of CSF A β and amyloid-PET SUVR values has been shown to follow a bimodal distribution within the ADNI cohort (Ewers et al., 2012; Landau et al., 2013).

For subjects without a CSF A β measurement at baseline, the A β status was estimated based on global PiB-PET or AV45-PET binding. In the ADNI I study, amyloid PET scanning was introduced only after the baseline assessment had been done. The PiB-PET scans were obtained between 12 and 48 months after baseline, whereas AV45-PET was obtained between 48 and 72 months after baseline. The change of global levels of amyloid PET binding is relatively slow. For a time span as covered in the current study (maximum of 6 years), a linear extrapolation of the change seems appropriate and has been applied in previous studies (Mattsson et al., 2014a). In order to estimate the A β status (A β + vs. A β -) at baseline, we computed linear regressions with interval duration between visits as the predictor and global brain PiB-PET or AV45-PET SUVR as the dependent variable for each subject lacking CSF A β . The intercepts of the regressions were taken as the PiB-PET and AV45-PET SUVRs at baseline. All subjects with a PiB-PET scan ($N = 12$) had at least one follow-up scan and thus the baseline SUVRs could be estimated from the linear regressions alone. For subjects with only a single AV45-PET (2 out of 15) scan, a subject with $SUVR < 1.13$ (i.e. below cutoff) was considered A β - at baseline, because A β deposition is expected to have increased rather than declined at a post-baseline assessment (Villemagne et al., 2013). For $SUVR \geq 1.13$, we extrapolated the SUVR to baseline based on a regression coefficient (yearly change in AV45-PET SUVR) that was estimated on the basis of a linear regression applied to longitudinal AV45-PET scans in the whole ADNI cohort.

2.11. Statistical analyses

2.11.1. Voxel-wise group comparisons of rates of change in GM and FDG-PET

At the subject level of analysis, the voxel-wise rates of change in GM volume and FDG-PET metabolism were computed in linear regression models for each subject, with time t as the only independent variable:

$$Y(t) = Bt + c \quad (1)$$

where $Y(t)$ represents the voxel value for either GM volume or FDG-PET SUVR, B the corresponding rate of change and c a constant term.

The time point $t = 0$ was defined as baseline, $t = 1$ as the first-year follow-up as and so on until year 3. An intercept at $t = 0$ was included in the regression analysis to control for the baseline differences in GM volume and FDG-PET metabolism between subjects. The first level analysis resulted in one image per subject, B , representing voxel by voxel the slope of the regression, i.e. the rate of change throughout the 3-year span from baseline to the last visit. Finally, the images were smoothed with an isotropic Gaussian kernel of FWHM = 8 mm.

At the group level of analysis, the images containing the slopes B (rates of change) in GM and FDG-PET were subjected to an ANCOVA for group comparison, separately for each imaging modality. The main independent variable was a group factor with four levels: HC A β +, MCI A β +, HC A β - and MCI A β -. The analyses were corrected for age, gender, years of education and ApoE genotype ($\epsilon 4$ carrier vs. noncarrier). Since we were interested in local brain changes, the global mean value of each slope image (computed within the gray-matter mask described above) was included as a covariate to correct for global brain changes. Unless specified otherwise, we applied a family-wise error (FWE) corrected cluster-extent threshold significance level of $\alpha = 0.05$ (with the voxel-level threshold of $\alpha = 0.001$) (Woo et al., 2014). We also computed maps of the effect size (Cohen's d (Cohen, 1992)) of the group comparisons to represent group differences unbiased by sample size. The voxel-based statistical analyses were performed with the Flexible-factorial tool of SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>).

In order to control for the influence of GM changes onto FDG-PET changes, we repeated the voxel-wise regression analysis at the subject level, this time including the voxel-values of GM volume as covariates in the regression model used to estimate the individual rates of change in FDG-PET metabolism:

$$Y_{FDG}(\mathbf{r}) = GM(\mathbf{r}) + \mathbf{B}^T \mathbf{r} + \epsilon \quad (2)$$

where $Y_{FDG}(\mathbf{r})$ represents the voxel value of FDG-PET SUVR, $GM(\mathbf{r})$ the GM voxel-value for each time point and all other terms are as in Eq. (1). In this manner, the individual rates of change in FDG-PET were corrected by both average amount and longitudinal changes of GM volume. The second level analysis was repeated as above, now including the slopes of FDG-PET changes controlled for changes in GM, $\mathbf{B}^T$. The voxel-wise correction for GM volume of the FDG-PET scans as per Eq. (2) was performed with the robust Biological Parametric Mapping toolbox of Matlab (<http://www.nitrc.org/projects/rbpm/>).

2.11.2. ROI statistical analysis

For each ROI, each modality and each time point, we transformed the subject ROI values into z-scores, based on the mean value and the standard deviation of the HC A β - group at baseline (see Supplementary Table 1 for these values). This allowed for cross-sectional and longitudinal comparisons between modalities as well as between groups. We computed the differences between the rates of change in GM volume and FDG-PET metabolism and between A β groups through linear mixed-effects models (Ewers et al., 2012). The random effect term accounted for longitudinal changes at the subject level. The fixed effects were A β -status, time and an interaction term A β -status x time. Similar to our voxel-based analyses, we interpreted significant interaction terms as significant differences in the rate of change in GM volume or FDG-PET metabolism between A β groups. Post-hoc analyses of the main A β effects were used to assess which A β group showed a faster rate of change. Cross-sectional analyses at baseline and year 3 were performed with robust linear regression, with A β -status as main predictor. All longitudinal and cross-sectional analyses included age, gender, years of education and ApoE genotype as covariates and were performed with the packages *nlme* (longitudinal) and *MASS* (cross-sectional) of the statistical software R, version 3.0.2 (<http://www.r-project.org>).

2.11.3. Joint ICA

In order to investigate joint patterns of changes in GM volume and FDG-PET metabolism we performed a joint Independent Component Analysis (jICA) analysis. Briefly, ICA decomposes the signal (i.e. here maps of estimated rates of change in FDG-PET and GM) into stochastically independent spatial components (Calhoun et al., 2009). In jICA, the ICA is applied to the concatenated matrix of maps of rates of change in GM and FDG-PET, thus determining spatial components of joint GM and FDG-PET changes. The first step in the jICA analysis involved an estimation of the number of independent components (IC) to be computed, based on the minimum description length (MDL) algorithm (Calhoun et al., 2009). Ten components were estimated for the HCs and 14 for the MCIs. Group differences in the expression of these joint components were determined by comparing the mixing coefficients of the jICA components between the A β groups (2-sample t-test per component, FDR corrected across components). The jICA analysis was computed with the Fusion ICA Toolbox (FIT, <http://mialab.mrn.org/software/fit/>).

3. RESULTS

3.1. Sample description

Subjects' characteristics for each group are displayed in Table 1. MCI A β + subjects were cognitively more impaired than MCI A β - ($p < 0.05$) as assessed by the cognitive subscale of the ADAS battery (ADAS-Cog). The

difference in ADAS-Cog between HC groups was not significant, although HC A β ⁺ subjects showed slightly worse cognitive performance than HC A β ⁻ ($p = 0.06$). The proportion of ApoE carriers was significantly larger in A β ⁺ subjects both in HC ($p < 0.05$) and MCI when compared with A β ⁻ ($p < 0.001$). The proportion of converters to a diagnosis of either MCI or AD dementia was significantly larger in HC A β ⁺ than in HC A β ⁻ after 3 years of follow-up ($p < 0.05$), and 50% of the HC A β ⁺ subjects had converted after 7 years when compared to only 17% of the HC A β ⁻ ($p < 0.05$). The percentage of converters from MCI to a diagnosis of AD dementia within 3 years was only slightly larger ($p = 0.06$) in MCI A β ⁺ (47%) than in MCI A β ⁻ subjects (18%) but the differences were non-significant after 7 years.

3.2. Effect of high A β levels on the rates of regional GM atrophy

In MCI A β ⁺ subjects, we observed faster rates of GM atrophy when compared to MCI A β ⁻ subjects, with peaks located within medial brain areas (anterior cingulum, hippocampal area), the lateral temporal and ventral prefrontal cortex (Figure 2A, Table 2). Beyond those areas of statistically significant group differences, visual inspection of the map of the voxel-wise effect sizes (unthresholded, Figure 2B) suggested a subtle, yet statistically non-significant, acceleration of GM atrophy rates in wider areas of the prefrontal and temporal lobes in MCI A β ⁺ subjects.

In HCs, the comparison of GM atrophy rates between A β -groups yielded no significant results after correcting for multiple comparisons at the cluster level. Since in HC subjects smaller A β -related effects were expected, we lowered the voxel-level significance threshold to $\alpha = 0.01$ keeping the FWE-corrected cluster-level threshold at $\alpha = 0.05$. At this level, HC A β ⁺ subjects exhibit faster rates of GM atrophy within a single cluster encompassing the precuneus, the cuneus and the posterior cingulum (see Table 2). Group differences in the opposite direction (HC A β ⁻ > HC A β ⁺) were not significant. In Figure 2D the effect size map for the comparison of decline rates between HC groups is shown. Beyond the posterior parietal cortex, where the group effects were statistically significant, the ventral prefrontal cortex, medial temporal lobe and medial-parietal brain regions showed the largest, yet statistically non-significant, effect sizes of group differences between HC A β ⁺ and HC A β ⁻.

3.3. Effect of high A β levels on the rates of regional FDG-PET metabolism decline

In MCI A β ⁺, significantly larger rates of decline in FDG-PET metabolism were observed when compared with MCI A β ⁻ subjects, with peaks located within the temporal and parietal brain regions (Figure 3A, Table 2). The effect sizes for this group comparison are shown in Figure 3B, which confirms that the largest effect-sizes were confined predominantly within the medial and lateral temporal lobe, posterior cingulum region and lateral parietal cortex.

After controlling for decline in GM volume voxel by voxel at the subject level (Eq. (2)), significant faster decline of FDG-PET metabolism for MCI A β ⁺ remained in most brain regions (Figure 3C), although the effect sizes were reduced on average (Figure 3D). The results of the GTM method for PVE correction confirmed significantly increased decline in FDG-PET metabolism within parietal brain regions in MCI A β ⁺ subjects (Supplementary Figure 1). For the Müller-Gärtner method, significantly faster FDG-PET decline in MCI A β ⁺ subjects was not observed. Instead, an increase in FDG-PET within the medial-temporal lobe in the MCI A β ⁺ group was observed (Supplementary Figure 2). However, we did not find any increases in FDG-PET metabolism, neither with the GTM method nor when correcting for GM atrophy at the subject level (Figure 3). There were no significant group differences between HC subgroups, even not at the more lenient significance threshold (0.01 voxel-wise, with cluster-level (FWE-corrected) $\alpha = 0.05$). The unthresholded effect size maps for the HC A β ⁺ vs. HC A β ⁻ group comparison are presented in Supplementary Figure 3.

3.4. ROI-based analysis of longitudinal changes in GM volume and FDG-PET metabolism

In order to test whether A β group differences in the decline were present in a-priori hypothesized brain areas (hippocampus and temporo-parietal lobe) we conducted an ROI analysis.

Within the hippocampus ROI, GM volume declined faster in MCI A β ⁺ (compared to MCI A β ⁻) and in HC A β ⁺ (compared to HC A β ⁻; Figure 4A, Table 3). The decline in FDG-PET metabolism within the hippocampus ROI (Figure 4B) was not significantly different between A β groups, neither for MCI nor for HC.

In the temporo-parietal ROI, GM volume was not significantly different between A β groups, neither for MCI nor for HC (Figure 4C). Decline of FDG-PET metabolism within the temporo-parietal ROI was marginally faster in MCI A β ⁺ compared to MCI A β ⁻, but did not differ between HC groups (Figure 4D).

Cross-sectional analysis at baseline and at year 3 yielded no significant A β group differences. The untransformed GM volume (cm³) and FDG-PET SUVR are provided in Supplementary Figure 4.

3.5. Covariation patterns of the rates of GM atrophy and FDG-PET metabolism decline

In order to assess group differences for the joint changes in GM and FDG-PET, we conducted a joint-ICA analysis in each diagnostic group. MCI A β ⁺ differed from MCI A β ⁻ subjects on one joint-ICA component ($p(\text{FDR}) < 0.01$, Figure 5). The component showed a pattern of GM atrophy within the medial-temporal and parietal lobes covarying with decline in FDG-PET metabolism within the hippocampus and the parietal cortex. This pattern was more strongly expressed in the MCI A β ⁺ subjects compared to the MCI A β ⁻ subjects, suggesting faster joint GM and FDG-PET decline within the medial-temporal and parietal brain areas in the MCI A β ⁺. There were no components with significant differences between HC A β ⁺ and HC A β ⁻.

4. DISCUSSION

Our first major finding was that A β had a differential effect on the rates of GM atrophy and FDG-PET hypometabolism across the preclinical stage and prodromal stages of AD: longitudinal GM changes within the medial temporal and posterior parietal cortices were present at both stages (taking together ROI and voxel-based analyses in HC A β +), while prefrontal GM changes and FDG-PET changes within the temporal, medial and lateral parietal cortices could be detected only in prodromal AD. Secondly, jICA showed joint increased rates of GM atrophy of the medial-temporal lobe and FDG-PET hypometabolism in the parietal cortex, suggesting that GM and metabolic brain changes are associated despite affecting spatially divergent brain regions.

For our first finding, we observed significantly faster rates of GM volume decline in HC A β + subjects in the precuneus and posterior cingulum (voxel-based) and in the hippocampus (ROI-based), which are a subset of the brain regions affected in MCI A β + subjects. Our findings are consistent with previous reports of significantly faster GM atrophy in the precuneus of presymptomatic subjects with autosomal dominantly inherited AD (Benzinger et al., 2013) as well as preclinical sporadic AD (HC A β +) subjects (Chetelat et al., 2012; Mattsson et al., 2014a; Nosheny et al., 2014). Moreover, A β -related longitudinal atrophy of the MTL in HC subjects, has been reported previously (Dickerson et al., 2011; Knopman et al., 2013; Villemagne et al., 2013). Together, these results are consistent with the view that A β -related atrophy starts within the temporal and the medial parietal cortex at the pre-symptomatic (HC A β +), expanding within the temporal, frontal and cingulate cortices at the prodromal stage of AD (MCI A β +) (Benzinger et al., 2013).

Compared to the findings in GM atrophy, the analysis of the rates of decline in FDG-PET metabolism yielded markedly different results. No significant A β -group differences were detected, in HC subjects in either voxel-based or ROI-based analyses. In MCI, A β + subjects showed a faster decline in FDG-PET metabolism within regions centered within the temporo-parietal cortex, consistent with previous studies in MCI (Ewers et al., 2012; Landau et al., 2012). Regions affected by accelerated atrophy, like the medial-frontal and medial-temporal lobes, were largely spared by hypometabolism, but in contrast, the posterior cingulate cortex, showed reductions in both GM and FDG-PET for MCI A β + subjects. FDG-PET hypometabolism was however present even after accounting for GM atrophy, suggesting that hypometabolism was not solely attributable to GM atrophy in our MCI A β + sample.

Previous studies have shown subtle but significant associations between amyloid burden and faster FDG-PET hypometabolism in healthy elderly subjects (Jack et al., 2013), (Lowe et al., 2014), both cross-sectionally and longitudinally. Although we did not find such an associations longitudinally, cross-sectionally HC A β + showed lower temporo-parietal FDG-PET metabolism (Figure 4D) when compared to HC A β - at trend level. However,

other studies have suggested that A β effects on FDG-PET metabolism in HC subjects can be explained by higher ApoE ϵ 4 allele frequency in A β subjects (Jagust et al., 2012; Knopman et al., 2014). Since we controlled for ApoE genotype status as a possible confounding factor in all of our analyses, and since HC ApoE genotype was a significant predictor of FDG-PET hypometabolism in the temporo-parietal ROI for HC cross-sectionally (also reported by (Jagust et al., 2012)), it is possible that ApoE ϵ 4 partially accounts for changes in FDG-PET metabolism. Overall, previous results suggest that FDG-PET decline may start early, possibly earlier than GM atrophy, but that it progresses at a low rate, having accumulated by the preclinical stage of AD. Our results would be consistent with this view, since HC A β ⁺ showed lower cross-sectional FDG-PET uptake (at trend-level, see Figure 4) than HC A β ⁻. If FDG-PET uptake does indeed decline at a slow rate, cross-sectional studies may be more sensitive to cumulative FDG-PET hypometabolism, whereas longitudinal studies may require larger sample sizes to detect such low rates of hypometabolism progression (in contrast to GM atrophy), and to further disentangle the effect of amyloid burden from ApoE-related effects. Finally, it is possible also that the lower spatial resolution of FDG-PET when compared with structural MRI renders FDG-PET simply a less sensitive way to assess brain changes over time, especially in voxel-based analyses.

Our second major finding was the presence of correlated patterns of GM atrophy and FDG-PET metabolism decline in MCI A β ⁺ subjects. Regions with faster GM atrophy in MCI A β ⁺ subjects (medial-temporal lobe, parietal and medial-parietal cortices) were correlated with regions affected by faster FDG-PET metabolism decline (the temporal and parietal cortices). Similar to many previous studies of MCI subjects, these results support the view that prodromal AD is characterized by joint longitudinal atrophy and hypometabolism. Our jICA results expand upon our voxel-based analysis by showing that A β not only influences the rate of decline in GM atrophy and FDG-PET hypometabolism, but also that A β is related to correlations between such changes by the time the first cognitive symptoms appear. This implies that MCI A β ⁺ subjects showing accelerated GM atrophy also show accelerated FDG-PET metabolism even though the patterns of decline do not overlap. The absence of joint patterns of decline of GM atrophy and FDG-PET metabolism in HCs may be due to the absence of significant differences in FDG-PET metabolism decline rates within that group. Results from recent combined cross-sectional MRI & FDG-PET biomarker studies suggest that jICA patterns may improve the clinical prediction of conversion from MCI to AD when compared to either MRI or FDG-PET alone (Shaffer et al., 2013), suggesting the clinical utility of such cross-modal brain differences.

A caveat of the present study is that FDG-PET changes could be driven by the relatively strong GM changes due to Partial Volume Effects (PVE). Thus, the rates of declining FDG-PET metabolism may be overestimated in those brain areas where the rates GM atrophy are large or at the GM/WM boundaries. However, we took several

measures in order to control for this important potential confound. First, we used a GM mask in all our analysis which ensured that most voxels at risk for PVE are excluded, in particular those at the GM/WM boundary. Second, we partialled out GM volume in the estimation of the rates of change in FDG-PET. The observed faster FDG-PET decline in MCI A β ⁺ compared to MCI A β ⁻ was still present after this correction. Third, we performed PVE correction with the GTM method, which yielded results consistent with the correction for GM volume changes as per Eq. (2). The increase in the rates of PVE-corrected FDG-PET metabolism observed in MCI A β ⁺ only with the Müller-Gärtner method may have been a product of overcorrection and thus method-driven. It is thus unlikely that the results reflect compensatory hypermetabolism as suggested by a few other studies in HC (Jack et al., 2013) or MCI (Cohen et al., 2009) subjects.

Another caveat of our study is the definition of preclinical AD, based solely on amyloid burden as recommended by recent consensus group criteria. It should be mentioned that high amyloid burden may be accompanied by increased tau pathology (Braak et al., 2011). In particular, the early pattern of GM atrophy presented in this and other studies resembles the Braak stages of neurofibrillary tangle (NFT) deposition (Braak et al., 2011), which start in the medial-temporal cortex and expand to other medial structures such as the precuneus. In contrast, preclinical A β deposition is relatively lower in the medial-temporal lobe when compared with the rest of the forebrain. It is therefore possible that the observed A β -status effects on GM atrophy are partially due to concomitant tau pathology. Future studies will need to assess jointly the effect of A β and tau pathology on the rates of change in neurodegeneration.

Lastly, it should be mentioned that a substantial proportion of A β -negative HC and MCI subjects may develop signs of neurodegeneration, which has been defined as Suspected Non-Amyloid Pathology subjects (SNAPs) (Caroli et al., 2015; Petersen et al., 2013). Recent studies show that the etiology of those subjects is varied and they can “resemble AD clinically” (hence the presence of HC A β ⁻ and MCI A β ⁻ converters in Table 1), although it remains unclear what the exact underlying pathology is. An investigation of neurodegenerative profiles of SNAPs was however beyond the scope of this study, in particular due to the low number of MCI A β ⁻. In relation to this, it should also be noted that the clinical development of the A β ⁺ subjects in the HC and MCI groups remains uncertain. Half of the HC A β ⁺ subjects within our sample went on to develop MCI or AD over the course of 7 years after baseline, suggesting that the patterns of ongoing GM atrophy reported in this study may herald the development of later cognitive symptoms. However, owing to the low total number of converters and non-converters in our sample, we could not directly assess whether such patterns are predictors of cognitive decline, which remains to be determined in future studies.

5. CONCLUSION

Our results demonstrate that, in cognitively healthy individuals, the patterns of subtle, A β -related changes in the pace of GM atrophy resemble those of mildly impaired subjects. Atrophy progressed at a faster pace than FDG-PET hypometabolism throughout the early stages of AD and both kinds of neurodegeneration became associated across distant brain regions by the time the first cognitive symptoms started to arise.

Acknowledgements: Dr. Ewers received support for this work from LMUexcellent, European Commission and the Alzheimer's Forschung Initiative (AFI). Dr. Weiner received funding from the grants 2U01AG024904, W81XWH-13-1-0259, W81XWH-12-2-0012, R01 AG10897, 1P41 EB015904, P01 AG19724, R01 AG032306, R01A G03879, ADNI 2-12-233036, 20110506, R01 MH098062-01 from the following sources; NIH/NIA/National Institute of Mental Health, DOD, Alzheimer's Association, Alzheimer's Drug Discovery Foundation.

References

- Ashburner J. (2007): A fast diffeomorphic image registration algorithm. *Neuroimage* 38(1):95-113.
- Ashburner J, Friston KJ. (2005): Unified segmentation. *Neuroimage* 26(3):839-51.
- Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM and others. (2012): Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med* 367(9):795-804.
- Benzinger TL, Blazey T, Jack CR, Jr., Koeppe RA, Su Y, Xiong C, Raichle ME, Snyder AZ, Ances BM, Bateman RJ and others. (2013): Regional variability of imaging biomarkers in autosomal dominant Alzheimer's disease. *Proc Natl Acad Sci U S A* 110(47):E4502-9.
- Bourgeat P, Chetelat G, Villemagne VL, Fripp J, Raniga P, Pike K, Acosta O, Szeke C, Ourselin S, Ames D and others. (2010): Beta-amyloid burden in the temporal neocortex is related to hippocampal atrophy in elderly subjects without dementia. *Neurology* 74(2):121-7.
- Braak H, Thal DR, Ghebremedhin E, Del Tredici K. (2011): Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol* 70(11):960-9.
- Calhoun VD, Liu J, Adali T. (2009): A review of group ICA for fMRI data and ICA for joint inference of imaging, genetic, and ERP data. *Neuroimage* 45(1):S163-S172.
- Caroli A, Prestia A, Galluzzi S, Ferrari C, van der Flier WM, Ossenkoppele R, Van Berckel B, Barkhof F, Teunissen C, Wall AE and others. (2015): Mild cognitive impairment with suspected nonamyloid pathology (SNAP): Prediction of progression. *Neurology* 84(5):508-15.
- Chetelat G, Villemagne VL, Villain N, Jones G, Ellis KA, Ames D, Martins RN, Masters CL, Rowe CC, Grp AR. (2012): Accelerated cortical atrophy in cognitively normal elderly with high beta-amyloid deposition. *Neurology* 78(7):477-484.
- Cohen AD, Price JC, Weissfeld LA, James J, Rosario BL, Bi W, Nebes RD, Saxton JA, Snitz BE, Aizenstein HA and others. (2009): Basal Cerebral Metabolism May Modulate the Cognitive Effects of A{beta} in Mild Cognitive Impairment: An Example of Brain Reserve. *J Neurosci* 29(47):14770-14778.
- Cohen J. (1992): A Power Primer. *Psychological Bulletin* 112(1):155-159.
- Dickerson BC, Stoub TR, Shah RC, Sperling RA, Killiany RJ, Albert MS, Hyman BT, Blacker D, Detolledo-Morrell L. (2011): Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. *Neurology* 76(16):1395-402.

- Ewers M, Insel P, Jagust WJ, Shaw L, Trojanowski JJ, Aisen P, Petersen RC, Schuff N, Weiner MW. (2012): CSF Biomarker and PIB-PET-Derived Beta-Amyloid Signature Predicts Metabolic, Gray Matter, and Cognitive Changes in Nondemented Subjects. *Cereb Cortex* 22(9):1993-2004.
- Ewers M, Sperling RA, Klunk WE, Weiner MW, Hampel H. (2011): Neuroimaging markers for the prediction and early diagnosis of Alzheimer's disease dementia. *Trends Neurosci* 34(8):430-42.
- Fagan AM, Mintun MA, Mach RH, Lee SY, Dence CS, Shah AR, LaRossa GN, Spinner ML, Klunk WE, Mathis CA and others. (2006): Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. *Ann Neurol* 59(3):512-9.
- Jack CR, Jr., Wiste HJ, Weigand SD, Knopman DS, Lowe V, Vemuri P, Mielke MM, Jones DT, Senjem ML, Gunter JL and others. (2013): Amyloid-first and neurodegeneration-first profiles characterize incident amyloid PET positivity. *Neurology* 81(20):1732-40.
- Jagust WJ, Bandy D, Chen K, Foster NL, Landau SM, Mathis CA, Price JC, Reiman EM, Skovronsky D, Koeppe RA. (2010): The Alzheimer's Disease Neuroimaging Initiative positron emission tomography core. *Alzheimer's & Dementia* 6(3):221-229.
- Jagust WJ, Landau SM, Alzheimer's Disease Neuroimaging I. (2012): Apolipoprotein E, not fibrillar beta-amyloid, reduces cerebral glucose metabolism in normal aging. *J Neurosci* 32(50):18227-33.
- Klunk WE. (2011): Amyloid imaging as a biomarker for cerebral beta-amyloidosis and risk prediction for Alzheimer dementia. *Neurobiol Aging* 32 Suppl 1:S20-36.
- Knopman DS, Jack CR, Jr, Wiste HJ, et al. (2013): Selective worsening of brain injury biomarker abnormalities in cognitively normal elderly persons with β -amyloidosis. *JAMA Neurology* 70(8):1030-1038.
- Knopman DS, Jack CR, Jr., Wiste HJ, Lundt ES, Weigand SD, Vemuri P, Lowe VJ, Kantarci K, Gunter JL, Senjem ML and others. (2014): 18F-fluorodeoxyglucose positron emission tomography, aging, and apolipoprotein E genotype in cognitively normal persons. *Neurobiol Aging* 35(9):2096-106.
- La Joie R, Perrotin A, Barre L, Hommet C, Mezenge F, Ibáñez M, Camus V, Abbas A, Landeau B, Guilloteau D and others. (2012): Region-specific hierarchy between atrophy, hypometabolism, and beta-amyloid (A β) load in Alzheimer's disease dementia. *J Neurosci* 32(46):16265-73.
- Landau SM, Breault C, Joshi AD, Pontecorvo M, Mathis CA, Jagust WJ, Mintun MA, Alzheimer's Disease Neuroimaging I. (2013): Amyloid-beta imaging with Pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods. *J Nucl Med* 54(1):70-7.

- Landau SM, Harvey D, Madison CM, Koeppe RA, Reiman EM, Foster NL, Weiner MW, Jagust WJ, Alzheimer's Disease Neuroimaging I. (2011): Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiol Aging* 32(7):1207-18.
- Landau SM, Mintun MA, Joshi AD, Koeppe RA, Petersen RC, Aisen PS, Weiner MW, Jagust WJ, Initi AsDN. (2012): Amyloid deposition, hypometabolism, and longitudinal cognitive decline. *Annals of Neurology* 72(4):578-586.
- Lowe VJ, Weigand SD, Senjem ML, Vemuri P, Jordan L, Kantarci K, Boeve B, Jack CR, Jr., Knopman D, Petersen RC. (2014): Association of hypometabolism and amyloid levels in aging, normal subjects. *Neurology* 82(22):1959-67.
- Luders E, Gaser C, Jancke L, Schlaug G. (2004): A voxel-based approach to gray matter asymmetries. *Neuroimage* 22(2):656-64.
- Mattsson N, Insel PS, Nosheny R, Tosun D, Trojanowski JQ, Shaw LM, Jack CR, Jr., Donohue MC, Weiner MW. (2014a): Emerging beta-amyloid pathology and accelerated cortical atrophy. *JAMA Neurol* 71(6):725-34.
- Mattsson N, Insel PS, Nosheny R, Tosun D, Trojanowski JQ, Shaw LM, Jack CR, Jr., Donohue MC, Weiner MW, Alzheimer's Disease Neuroimaging I. (2014b): Emerging beta-amyloid pathology and accelerated cortical atrophy. *JAMA Neurol* 71(6):725-34.
- Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack C, Jagust W, Trojanowski JQ, Toga AW, Beckett L. (2005): The Alzheimer's disease neuroimaging initiative. *Neuroimaging Clin N Am* 15(4):869-77, xi-xii.
- Muller-Gartner HW, Links JM, Prince JL, Bryan RN, McVeigh E, Leal JP, Davatzikos C, Frost JJ. (1992): Measurement of radiotracer concentration in brain gray matter using positron emission tomography: MRI-based correction for partial volume effects. *J Cereb Blood Flow Metab* 12(4):571-83.
- Nosheny RL, Insel PS, Truran D, Schuff N, Jack CR, Jr., Aisen PS, Shaw LM, Trojanowski JQ, Weiner MW. (2014): Variables associated with hippocampal atrophy rate in normal aging and mild cognitive impairment. *Neurobiol Aging*.
- Oh H, Habeck C, Madison C, Jagust W. (2012): Covarying alterations in A β deposition, glucose metabolism, and gray matter volume in cognitively normal elderly. *Hum Brain Mapp*.
- Oh H, Mormino EC, Madison C, Hayenga A, Smiljic A, Jagust WJ. (2011): beta-Amyloid affects frontal and posterior brain networks in normal aging. *Neuroimage* 54(3):1887-95.

- Petersen RC, Aisen P, Boeve BF, Geda YE, Ivnik RJ, Knopman DS, Mielke M, Pankratz VS, Roberts R, Rocca WA and others. (2013): Mild cognitive impairment due to Alzheimer disease in the community. *Ann Neurol* 74(2):199-208.
- Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, Jack CR, Jr., Jagust WJ, Shaw LM, Toga AW and others. (2010): Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology* 74(3):201-9.
- Rousset OG, Ma Y, Evans AC. (1998): Correction for partial volume effects in PET: principle and validation. *J Nucl Med* 39(5):904-11.
- Rowe CC, Ellis KA, Rimajova M, Bourgeat P, Pike KE, Jones G, Fripp J, Tochon-Danguy H, Morandau L, O'Keefe G and others. (2010): Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging* 31(8):1275-83.
- Shaffer JL, Petrella JR, Sheldon FC, Choudhury KR, Calhoun VD, Coleman RE, Doraiswamy PM. (2013): Predicting cognitive decline in subjects at risk for Alzheimer disease by using combined cerebrospinal fluid, MR imaging, and PET biomarkers. *Radiology* 266(2):583-91.
- Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P and others. (2009): Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann Neurol* 65(4):403-13.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. (2002): Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15(1):273-89.
- Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, Szeke C, Macaulay SL, Martins R, Maruff P and others. (2013): Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *The Lancet Neurology* 12(4):357-367.
- Woo CW, Krishnan A, Wager TD. (2014): Cluster-extent based thresholding in fMRI analyses: pitfalls and recommendations. *Neuroimage* 91:412-9.
- Wyman BT, Harvey DJ, Crawford K, Bernstein MA, Carmichael O, Cole PE, Crane PK, DeCarli C, Fox NC, Gunter JL and others. (2013): Standardization of analysis sets for reporting results from ADNI MRI data. *Alzheimers Dement* 9(3):332-7.

TABLES

Table 1: Subject characteristics at baseline

Group	HC A β +	HC A β -	MCI A β +	MCI A β -
N	14	26	36	16
Gender (f/m)	3/11	13/13	12/24	2/14
Age ^a	74.5 (5.3)	75.5 (4.3)	74.0 (7.0)	75.6 (7.6)
Years of education ^a	15.7 (3.2)	15.9 (3.0)	16.2 (2.6)	16.6 (2.9)
ADAS-Cog ^a	8.8 (3.2)	6.6 (2.9)	11.2 (4.0)*	8.9 (3.9)
ApoE (ϵ 4+/ ϵ 4-)	8/6*	5/21	26/10**	1/15
Converters after 3/after 7 years ^b	4*/7*	1/3	17/23	3/6

Abbreviations: HC = healthy control, MCI = mild cognitive impairment, ADAS-Cog = Alzheimer's Disease Assessment Scale, Cognitive subscale.

^a Values are mean (SD)

^b Number of subjects who converted from HC to MCI or AD, or from MCI to AD within 3/within 7 years after the initial visit.

* $p < 0.05$

** $p < 0.001$

The comparisons were done between A β groups within each diagnostic group.

Table 2: Results for voxel-wise group comparison of rates of decline in GM and FDG-PET

Modality	Comparison	Label (AAL atlas)	Size (voxels)	Size (mm ³)	p (FWE)	p (unc.)	T	(x, y, z) (mm)
GM atrophy rates	MCI Aβ ⁺ > MCI Aβ ⁻	Middle Temporal Gyrus	49019	$1.7 \cdot 10^5$	<0.001	<0.001	7.9	(-63, -4, -15)
	HC Aβ ⁺ > HC Aβ ⁻	Middle Cingulate Gyrus	3082	$1.0 \cdot 10^4$	0.033	0.001	4.1	(4, -54, 31)
FDG-PET decline rates	MCI Aβ ⁺ > MCI Aβ ⁻	Precuneus	16826	$5.7 \cdot 10^4$	<0.001	0.001	5.1	(-3, -75, 49)
		Inferior Temporal Gyrus	4333	$1.5 \cdot 10^4$	0.013	<0.001	5.0	(68, -40, -15)
		Angular Gyrus	6908	$2.0 \cdot 10^4$	0.002	<0.001	6.0	(-46, -66, 33)
Atrophy-corrected FDG-PET decline rates	MCI Aβ ⁺ > MCI Aβ ⁻	Angular Gyrus	13491	$4.6 \cdot 10^4$	<0.001	<0.001	6.0	(-46, -66, 33)
		Posterior Cingulum	3187	$5.2 \cdot 10^4$	0.003	<0.001	4.5	(-3, -39, 22)
		Angular Gyrus	1534	$1.1 \cdot 10^4$	0.043	<0.001	3.9	(48, -66, 36)

Abbreviations: MCI = mild cognitive impairment, FWE = Family-wise Error corrected, unc. = uncorrected,.

Table 3: Results for ROI group comparison of rates of change in GM and FDG-PET

ROI	Modality	Group	Rate of change	Group difference in rates of change
Hippocampus	MRI	HC A β +	-0.28 (0.06)**	-0.13 (0.05)*
		HC A β -	-0.15 (0.02)**	
		MCI A β +	-0.38 (0.03)**	-0.19 (0.06)**
		MCI A β -	-0.19 (0.07)*	
	FDG-PET	HC A β +	n.s.	n.s.
		HC A β -	n.s.	
		MCI A β +	-0.15 (0.02)**	n.s.
		MCI A β -	-0.18 (0.05)*	
Temporo-Parietal	MRI	HC A β +	-0.09 (0.03)*	n.s.
		HC A β -	n.s.	
		MCI A β +	-0.11 (0.02)**	n.s.
		MCI A β -	n.s.	
	FDG-PET	HC A β +	0.08 (0.05)+	n.s.
		HC A β -	n.s.	
		MCI A β +	-0.15 (0.03)**	0.11 (0.06)+
		MCI A β -	n.s.	

Abbreviations: HC = healthy control, MCI = mild cognitive impairment

+ $p \sim 0.1$ (trend-level association)

* $p < 0.05$

** $p < 0.001$

Average rates of change (standard error) are shown. The p-values refer to the difference of the rates of change compared to zero within each group (column “rates of change”) or to the difference in the rates of changes between two groups (column “Group difference in rates of change”)

FIGURE LEGENDS

Figure 1: Flowchart for subject inclusion.

Figure 2: For the rates of GM atrophy, the t-map of the group difference between MCI A β + vs. MCI A β - (A) and HC A β + vs. HC A β - (C) are superimposed onto axial brain slices. The t-map of the group differences within the MCI subjects (A) is thresholded at $\alpha = 0.001$ at the voxel-level and $\alpha = 0.05$ (FWE-corrected) at the cluster-level. The t-map of the group differences within the HC subjects (B) is thresholded at $\alpha = 0.01$ at the voxel-level and $\alpha = 0.05$ (FWE corrected) at the cluster-level. The unthresholded maps of the effect size d of the group differences between MCI A β + vs. MCI A β - (B) and HC A β + vs. HC A β - (D) are shown. Red represents faster decline in MCI A β + (B) and HC A β + (D) compared to the corresponding A β - groups, whereas blue represent A β -group differences in the opposite direction.

Figure 3: For the rates of decline in FDG-PET metabolism, the t-map of the group difference between MCI A β + vs. MCI A β - is superimposed onto axial brain slices in (A) for FDG-PET changes uncorrected for atrophy and in (C) for corrected FDG-PET. The t-maps are thresholded at $\alpha = 0.001$ at the voxel-level and $\alpha = 0.05$ (FWE corrected) at the cluster-level. The unthresholded maps of the effect size d of the group differences between MCI A β + vs. MCI A β - are shown in (B) and (D) for uncorrected and corrected FDG-PET respectively. Red represents faster decline for MCI A β + whereas blue represent differences in the opposite direction.

Figure 4: The GM volume and FDG-PET metabolism within the hippocampus and the temporo-parietal ROIs are displayed as z-scores for each time point (in years) and group. The error bars represent the standard error around the mean z-score. A linear regression line is shown for each group separately.

Figure 5: Joint-ICA component maps of joint group differences in GM atrophy rates (left panel) and FDG-PET rates of decline (right panel) of MCI subjects. The pattern of joint GM and FDG-PET changes was stronger expressed in MCI A β + than MCI A β - subjects ($p(\text{FDR}) < 0.01$) The z-score-transformed maps of the component were thresholded at $|z| > 2.4$.

Figure(s)

Figure(s)

Figure(s)

Figure(s)

Figure(s)