Supplementary Material

Pure WM density analyses

White matter atrophy as measured with modulated voxel based morphometry is sensitive to boundary changes between brain partitions. Therefore white matter atrophy patterns observed in this study, and particularly the longitudinal assessment of white matter change in aMCI, could be the consequence of the enlargement of the frontal horn of lateral ventricles across the 18-month follow-up, inducing white matter-CSF boundary changes. To rule out this artefact, the white matter analyses were re-run using 'pure density' voxel-based morphometry approach, which consisted in a segmentation purely dependent upon MRI intensity values and a precise boundary matching across examinations and subjects without modulation in order to avoid any white matter-CSF boundary change. The segmentation of softmean MRI was performed using VBM5.1 without priors nor Markov field application for probabilities calculation, so that white matter probabilities would only be influenced by MRI intensity values. These 'pure density' white matter maps were then masked by the maximum *a posteriori* white matter map segmented with priors and Markov fields (to remove non white matter probabilities inherent to this segmentation) and warped without modulation using the previously estimated DARTEL parameters. These parameters were estimated from almost binary maps (VBM5.1 segmented maps with application of priors and Markov fields), and therefore consisted in very precise boundary matching between partitions regarding the high degree of freedom of DARTEL registration (~6.4 million; Ashburner, 2007). Finally these maps were smoothed at 9 mm FWHM and masked. The resulting white matter pattern of alterations in aMCI compared to controls (Figure S1) was highly similar to that highlighted with the standard pre-processing (Figure 2 of the manuscript). These findings strongly argue

that white matter-CSF boundary shift was not responsible for our findings regarding white matter atrophy.

Testing the unidirectionality of intermodality distant relationships with alternative ROI definitions

The sequential analysis approach used in this study could be biased because the ROI definition for data extraction between the imaging modalities was not symmetric and therefore not independent. Indeed, baseline white matter values for instance were extracted from ROI based on the results of the correlation between baseline grey matter values and white matter percent change maps while grey matter ROI (hippocampus and posterior cingulate cortex) were defined according to baseline differences between aMCI patients and healthy aged controls. We decided to use this sequential approach because it could be applied to most ROI and because there was no other unique method allowing to individualize all the ROI we were interested in (see below). We have however re-performed the statistical analyses of partial correlation coefficients comparisons using alternative ROI definitions:

i) The uncinate fasciculus white matter cluster was individualized from the comparison between aMCI patients and healthy aged controls. It was well superimposed to the uncinate fasciculus cluster found within the correlation between hippocampal baseline grey matter values and white matter percent change maps (see Figures 2 and 4). When we used this new cluster for correlation coefficients comparisons with hippocampal grey matter, the results were strictly similar to that highlighted in the manuscript (see Table S1).

ii) The anterior cingulate and subgenual clusters could not be individualized from the baseline comparison between aMCI patients and healthy aged controls because there was no significant atrophy in MCI at baseline in these regions. These two regions could only be isolated using the analysis described in Fouquet et al. (2009), i.e. a two-way ANOVA with

"conversion status" and "follow-up" as factors. Extracting ^{18}FDG-PET percent change and baseline values in the anterior cingulate and subgenual cortex using this approach for the comparisons of correlation coefficients led to the same findings as those reported in the manuscript (see Table S2).

iii) The cingulum white matter region found to be significantly atrophied at baseline in aMCI subjects compared to healthy aged controls was included in a very extended cluster, encompassing the cingulum bundle but also other white matter tracts such as the perforant path, the corpus callosum, etc (see Figure 2). By contrast to the hippocampus that could be isolated within a cluster using AAL, this was not possible for the cingulum bundle as there is no corresponding automatic atlas for the white matter. Using this very large and unspecific cluster to assess the correlation with ^{18}FDG-PET percent change maps, we failed to identify any significant finding, which we thought results from the diversity of white matter tracts gathered here within a single value.

Supplementary Figure Legend

Figure S1: Illustrations of white matter alterations using the 'pure density' approach.

Areas of significant progression of white matter atrophy in aMCI over the 18-month follow-up period using the 'pure density' approach (red; $p < .001$ uncorrected with $k > 50$ mm^3). Results are projected onto sagittal sections of the mean aMCI MRI group template.

Supplementary Tables

Table S1: Multiple regressions between Baseline-to-Percent Change, Percent Change-to-Baseline, and Baseline-to-Baseline values of the uncinate fasciculus region of interest (ROI) (with TIV as a covariate), and statistical comparisons among the partial correlation coefficients highlighted in the regressions. Results are presented using the sequential approach as reported in the manuscript and using the alternative ROI definitions detailed in the Supplementary Material.

	Alteration A	Alteration B	Partial Correlations Coefficients (*p* value)		
			Baseline A-B Percent Change	A Percent Change-Baseline B	Baseline A-Baseline B
Sequential ROI definition (Manuscript Results)	Hippocampus Grey Matter	Uncinate Fasciculus White Matter (extracted from correlation between Hippocampal baseline Grey Matter values and White Matter Percent Change maps)	0.75 (7.10^{-4})	-0.05 (0.84)**	0.51 (0.04)
Alternative ROI definitions	Hippocampus Grey Matter	Uncinate Fasciculus White Matter (extracted from the comparison of baseline White Matter maps between aMCI	0.71 (2.10^{-3})	-0.09 (0.74)**	0.46 (0.07)

		patients and healthy aged controls)			

Stars indicate that the *r* value is significantly lower than the corresponding partial correlation coefficient for Baseline A - B Percent Change (*: $p < .05$; **: $p < .01$).

Table S2: Multiple regressions between Baseline-to-Percent Change, Percent Change-to-Baseline, and Baseline-to-Baseline values of the anterior cingulate and subgenual regions of interest (with TIV as a covariate), and statistical comparisons among the partial correlation coefficients highlighted in the regressions. Results are presented using the sequential approach as reported in the manuscript and using the alternative ROI definitions detailed in the Supplementary Material.

	Alteration A	Alteration B	Partial Correlations Coefficients (*p* value)		
			Baseline A-B Percent Change	A Percent Change-Baseline B	Baseline A-Baseline B
Sequential ROI definition (Manuscript Results)	Cingulum Bundle White Matter	Anterior Cingulate Cortex ^{18}FDG-PET (extracted from correlation between Cingulum baseline White Matter values and PET Percent Change maps)	0.74 (1.10^{-3})	0.24 (0.37)*	0.11 (0.69)**
	Uncinate Fasciculus White Matter	Subgenual Area ^{18}FDG-PET PET (extracted from	0.65 (6.10^{-3})	-0.08 (0.77)**	-0.09 (0.73)**

		correlation between Uncinate baseline White Matter values and PET Percent Change maps)			
Alternative ROI definitions	Cingulum Bundle White Matter	Anterior Cingulate Cortex ^{18}FDG-PET (extracted from the two-way ANOVA in MCI patients with "conversion status" and "follow-up" as factors)	0.72 (1.10^{-3})	0.21 (0.42)*	0.05 (0.85)**
	Uncinate Fasciculus White Matter	Subgenual Area ^{18}FDG-PET (extracted from the two-way ANOVA in MCI patients with "conversion status" and "follow-up" as factors)	0.66 (4.10^{-3})	-0.04 (0.86)**	-0.14 (0.60)**

Stars indicate that the *r* value is significantly lower than the corresponding partial correlation coefficient for Baseline A - B Percent Change (*: $p < .05$; **: $p < .01$).