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Morphometric network differences in ageing versus Alzheimer's disease dementia

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Age being the main risk factor for Alzheimer's disease, it is particularly challenging to disentangle structural changes related to normal brain ageing from those specific to Alzheimer's disease. Most studies aiming to make this distinction focused on older adults only and on *a priori* anatomical regions. Drawing on a large, multi-cohort dataset ranging from young adults ($n = 468$; age range 18–35 years), to older adults with intact cognition ($n = 431$; age range 55–90 years) and with Alzheimer's disease ($n = 50$ with late mild cognitive impairment and 71 with Alzheimer's dementia, age range 56–88 years), we investigated grey matter organization and volume differences in ageing and Alzheimer's disease. Using independent component analysis on all participants' structural MRI, we first derived morphometric networks and extracted grey matter volume in each network. We also derived a measure of whole-brain grey matter pattern organization by correlating grey matter volume in all networks across all participants from the same cohort. We used logistic regressions and receiver operating characteristic analyses to evaluate how well grey matter volume in each network and whole-brain pattern could discriminate between ageing and Alzheimer's disease. Because increased heterogeneity is often reported as one of the main features characterizing brain ageing, we also evaluated interindividual heterogeneity within morphometric networks and across the whole-brain organization in ageing and Alzheimer's disease. Finally, to investigate the clinical validity of the different grey matter features, we evaluated whether grey matter volume or whole-brain pattern was related to clinical progression in cognitively normal older adults. Ageing and Alzheimer's disease contributed additive effects on grey matter volume in nearly all networks, except frontal lobe networks, where differences in grey matter were more specific to ageing. While no networks specifically discriminated Alzheimer's disease from ageing, heterogeneity in grey matter volumes across morphometric networks and in the whole-brain grey matter pattern characterized individuals with cognitive impairments. Preservation of the whole-brain grey matter pattern was also related to lower risk of developing cognitive impairment, more so than grey matter volume. These results suggest both ageing and Alzheimer's disease involve widespread atrophy, but that the clinical expression of Alzheimer's disease is uniquely associated with disruption of morphometric organization.

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Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; AUC = area under the curve; Cam-CAN = Cambridge Centre for Ageing and Neuroscience; HCP = Human Connectome Project; ICA = independent component analysis; MCI = mild cognitive impairment; PREVENT-AD = PRe-symptomatic EValuation of Experimental or Novel Treatments for Alzheimer's Disease; ROC = receiver operating characteristics

Introduction

Alzheimer's disease and normal ageing are both characterized by considerable atrophy. Age is the main risk factor for Alzheimer's disease (Alzheimer's Association, 2017), suggesting these two processes may be closely intertwined. Disentangling brain changes specific to ageing versus Alzheimer's disease has been a challenge (Jagust, 2013; Fjell *et al.*, 2014). For example, whether Alzheimer's disease-related neurodegeneration represents accelerated ageing or a process distinct from ageing has not been fully resolved (Brayne and Calloway, 1988; Buckner, 2004; Ghosh *et al.*, 2011; Toepper, 2017). We sought further insight into this topic by examining grey matter differences across the lifespan and clinical Alzheimer's disease conjointly.

Alzheimer's disease brings neurodegeneration in several regions, especially the hippocampus, the temporal lobe and associative areas (Du *et al.*, 2001; Dickerson *et al.*, 2011; Bakkour *et al.*, 2013; Wirth *et al.*, 2013*b*; Besson *et al.*, 2015; Jack *et al.*, 2015). In ageing, grey matter atrophy in the frontal lobe is consistently reported as a principal contributor to age-related cognitive changes (Resnick *et al.*, 2003; Fjell and Walhovd, 2010), but the temporal lobe seems also particularly vulnerable to advancing age, even in elderly at low risk of Alzheimer's disease (Fjell *et al.*, 2013*b*). While studies investigating large-scale structural networks are less numerous, the pattern of atrophy in Alzheimer's dementia seems to mimic functional and grey matter covariance networks (Seeley *et al.*, 2009). Grey matter covariance networks may also change with advancing age (DuPre and Spreng, 2017; Koini *et al.*, 2018), and possibly more so in clinical Alzheimer's disease relative to ageing (Spreng and Turner, 2013). Together, these findings suggest an additive effect of ageing and disease on volume loss in certain brain regions and/or on the whole-brain structural organization. This raises questions as to which grey matter features, if any, are specific to ageing or Alzheimer's disease (Jagust, 2013). Discerning features specific to Alzheimer's disease beyond those of ageing could suggest novel ways to consider neurodegeneration in research frameworks.

We applied independent component analysis (ICA) to grey matter maps from individual structural MRI of participants from a large, multi-cohort dataset spanning young adults, older adults with intact cognition, and older adults with late mild cognitive impairment and Alzheimer's dementia (here referred to as clinical Alzheimer's disease). Complementary analyses were also conducted on individuals with early mild cognitive impairment (MCI) and cognitively normal individuals with evidence for brain amyloid-β. Through this process, we derived morphometric networks, a term used as an analogy to functional networks created by ICA of functional MRI data. We investigated grey matter volume differences within these morphometric networks, along with changes in their intrinsic organization. Our analyses were framed around a hypothetical model that relegated grey matter differences between groups into three classes, one being disease-specific (Fig. 1A), one being characteristic of ageing alone (Fig. 1B), and one representing an additive effect of both (Fig. 1C).

We first uncovered data-driven morphometric networks that were stable across all individuals using ICA. Age had an impact on all networks, and grey matter volume loss in most networks showed an additive effect of age and Alzheimer's disease. The interindividual variability of grey matter volume across networks was similar in young and cognitively normal older adults, but increased specifically in clinical Alzheimer's disease. Looking at measures of the whole-brain grey matter pattern also revealed a loss of organization specific to clinical Alzheimer's disease, and not to ageing. Furthermore, having a whole-brain grey matter pattern less similar to young adults was associated with increased risk of developing cognitive impairment. Grey matter volume and organization did not differ between groups of early MCI and cognitively normal older adults with or without amyloid-β, leading us to conclude that disruption in whole-brain organization is a late disease phenomenon that precedes the onset of clinical Alzheimer's disease. These findings suggest that whole-brain grey matter organization is important for maintaining good cognition in old age.

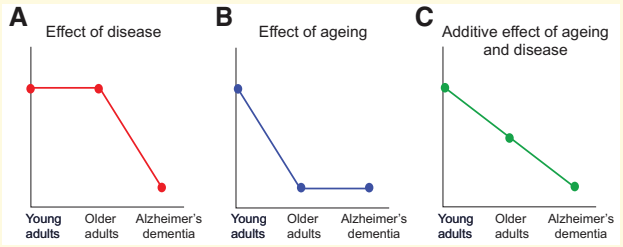

Figure 1 Three proposed trajectories of grey matter changes between groups. (**A**) Effect of disease: a grey matter feature similar between young and older adults, but altered in Alzheimer's dementia. (**B**) Effect of ageing: a grey matter feature similar between older adults with and without Alzheimer's dementia, but different compared to young adults. (**C**) Additive effect of ageing and disease: a grey matter feature changing gradually across lifespan and Alzheimer's dementia continuum. The *y*-axis represents the magnitude of change in morphometric networks and/or intrinsic organization. The *x*-axis represents different conditions.

Material and methods

Participants

We assembled a cross-sectional dataset from four different studies ($n = 1019$) to include cognitively normal young adults (18–35 years old), cognitively normal older adults (55–90 years old), as well as individuals who represented the clearly symptomatic portion of the Alzheimer's disease clinical continuum (late MCI and Alzheimer's dementia, 56–88 years old) to disentangle the effect of age and Alzheimer's disease on grey matter changes. Demographics of this multi-cohort dataset are detailed in Table 1. Written informed consent was obtained from all participants or their legal representatives under protocols approved by the Institutional Review Boards at all participating institutions.

Young adults came from two independent open access databases: the 1000 Functional Connectomes Project (FCP) and the Human Connectome Project (HCP). The FCP is a large-scale initiative combining resting state and structural scans from adult participants from 33 sites worldwide (Biswal *et al.*, 2010). We specifically used data from the 198 subjects between 18 and 30 years of age collected at the Cambridge site (FCP-Cambridge; PI: Buckner, R.L., http://fcon_1000.projects.nitrc.org/). The HCP consortium of several universities provides a large dataset of participants aged 18 to 35 (Van Essen *et al.*, 2013) (http://www.humanconnectome.org/). From these, we used 270 HCP individuals aged between 30 and 35 years old who were gender-matched to the PREVENT-AD cohort (PRe-symptomatic EValuation of Experimental or Novel Treatments for Alzheimer's Disease).

Cognitively normal older individuals were selected from two independent databases: the PREVENT-AD cohort (https://douglas.research.mcgill.ca/prevent-alzheimer-program) and the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). PREVENT-AD enrols older adults with intact cognition who have a parent or two siblings with well-documented histories of Alzheimer's disease-like dementia, and are therefore at increased risk of the disease (Breitner *et al.*, 2016). At enrolment, they must be at least 60 years of age, or between 55 and 59 if <15 years from their relative's age of symptom onset, and must be free of major neurological and psychiatric diseases. Data from the baseline visits of 295 PREVENT-AD participants (Data Release 2.0, November 2015) were used in the present study. All MRI scans were acquired at the Brain Imaging Centre of the Douglas Mental Health University Institute, Montreal, Canada. Cognitive performance was assessed using the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) (Randolph *et al.*, 1998). We selected a memory task of list learning (10 words over four trials) and a test of executive function (coding) to investigate relationships between cognition and grey matter features. These tests have been shown previously to be sensitive to MCI related to Alzheimer's disease (Villeneuve *et al.*, 2009; Peters *et al.*, 2014). Cognitive data were available for 291 participants.

ADNI is a multisite study launched in 2003 as a public-private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early Alzheimer's disease. For up-to-date information, see www.adni-info.org. The ADNI study is divided into different phases, and data for the present analyses came from ADNI2 only. ADNI2 baseline visits for continuing participants or initial visits for newly enrolled participants were selected. One hundred and thirty-five cognitively normal participants (Controls-ADNI) were included in the present study (Clinical Dementia Rating = 0 and no signs of depression, cognitive impairment, or dementia). Additionally, control subjects who converted to MCI during their subsequent follow-up visits (including visits up to ADNI3) ($n = 18$) were identified for exploratory analyses aiming at comparing different grey matter features between Controls-ADNI converters and those who remained cognitively normal. As a measure of cognition, we used the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) (Rosen *et al.*, 1984), where higher scores represent higher degree of cognitive impairment.

Clinically impaired participants were selected from the ADNI2 database. The present study includes 50 participants with late MCI, and 71 with Alzheimer's dementia. Because we sought grey matter changes characteristic of the clinical expression of Alzheimer's disease, we included individuals with severe cognitive impairment only in the primary analysis.

Complementary analyses

Preclinical and early prodromal Alzheimer's disease

Complementary analyses were performed in a restricted set of participants while splitting the group of cognitively normal older adults by their amyloid-β status (Jansen *et al.*, 2015). This procedure was done to test if and how preclinical Alzheimer's disease influenced grey matter features, and more importantly if preclinical Alzheimer's disease influenced our main results.

Table 1 Demographics

	Young adults		Older adults		Alzheimer's dementia	
	FCP-Cambridge	HCP	PREVENT-AD	Controls-ADNI	Late MCI ADNI	AD ADNI
n	198	270	295	135	50	71
Age, mean ± SD (range)	23 ± 5 (18–30)	33 ± 2 (31–35)	64 ± 5 (55–84)	74 ± 6 (56–90)	73 ± 7 (58–85)	74 ± 7 (56–88)
Sex, female, *n* (%)	123 (62)	196 (7)	214 (73)	67 (50)	22 (44)	31 (44)
APOE ε4 carriers, *n* (%)	-	-	104 (35)[a]	36 (27)	24 (48)	52 (73)
Aβ+: Aβ– individuals (% Aβ+)	-	-	20: 130 (13)	43: 90 (32)	24: 17 (50)	62: 8 (89)

Individuals were classified as APOE4 carriers if at least one allele was ε4.
[a]*APOE* status was available for 287 PREVENT-AD participants.

In PREVENT-AD, only half of the participants had a lumbar puncture and/or an amyloid-β-PET scan ($n = 150$) to assess their amyloid status. Amyloid-β-PET scans were done using the tracer ^{18}F-NAV4694, and CSF was analysed with ELISA. More information on the PET processing and CSF analysis is available in the Supplementary material. To determine a threshold of positivity, Gaussian mixture-models were run on the amyloid-β CSF and PET values. The values representing the 90% probability to be in the high distribution for PET and low distribution for CSF were chosen as thresholds, resulting in standardized uptake value ratio (SUVR) = 1.4 for PET and 800 pg/ml for CSF. Forty-four participants had both CSF and PET assessments, and only one participant had a discordant status between CSF and PET; we classified this individual as being amyloid-β+. Overall, there were 20 amyloid-β+ individuals of 150 in PREVENT-AD.

For Controls-ADNI, amyloid-β PET was available for 133 of 136 participants, and thus we did not use the CSF values. The tracer used was ^{18}F-AV45 and global amyloid-β SUVR was available from the ADNI database. PET processing was done at UC Berkeley and the pipeline is similar to the one we applied to the PREVENT-AD group. We used the threshold of 1.11 provided by ADNI to dichotomize participants in amyloid-β+ and amyloid-β– groups (Jagust *et al.*, 2015), which resulted in 43 amyloid-β+ individuals.

Finally, we also repeated the main analyses in a group of early MCI participants ($n = 65$; mean age = 70 ± 7). As per ADNI criteria, early or late MCI status is determined using the Wechsler Memory Scale Logical Memory II. While late MCI are at the boundary of dementia, early MCI are at the boundary of normal cognition.

Lifespan validation cohort

One limitation of the multi-cohort dataset is that participants from different studies were pooled together, bringing effects inherent to different sites, scanners and image acquisitions. To validate our morphometric networks and some of our results, we performed similar analyses using data from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) study. The Cam-CAN study is a large lifespan monocentric cross-sectional population-based study in the UK (Taylor *et al.*, 2015). This cohort is ideal to characterize age-related grey matter changes. We included 647 participants aged between 18 and 88 years old with T_1-weighted structural scans, from the Cam-CAN Stage 2 repository. There were 100 participants or more in each decade, except for the age ranges 18–30 and 80–88, which included 80 and 44 participants, respectively. See Supplementary Table 1 for a breakdown of participants per decade.

MRI acquisition and processing

Image acquisition

T_1-weighted structural images were acquired at 3 T for all individuals. The different MRI sequences from each study are detailed in Supplementary Table 2.

Processing of the grey matter maps

T_1-weighted structural images were segmented into grey matter, white matter, and CSF images using Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), running on MATLAB version 2012a. Grey matter images went through Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra toolbox (DARTEL) (Ashburner, 2007), in which inputs are iteratively aligned to create a group-specific template. Each template underwent non-linear registration with modulation for linear and non-linear deformations to the MNI-ICBM152 template. As a first step, a template was created for each group separately, resulting in six group-specific templates [FCP-Cambridge, HCP, PREVENT-AD, Controls-ADNI, late MCI-ADNI, Alzheimer's disease (AD)-ADNI]. Then the six templates were themselves iteratively aligned using DARTEL to create one common template in MNI space. Importantly, this common template equally weighted each group, as an attempt to reduce the bias towards healthy adults and to have a final template more representative of all subjects. A second registration was done on each participant's grey matter map to warp it with modulation to the final common template. Lastly, grey matter images were smoothed with an 8 mm^3 isotropic Gaussian kernel.

The Cam-CAN dataset was analysed as a separate group, but underwent similar steps. All images were segmented and underwent DARTEL to create a Cam-CAN-specific template.

Every grey matter image was aligned to the Cam-CAN template, warped with modulation to the MNI space and smoothed.

All images underwent visual quality control after segmentation to make sure the grey matter map was well-defined and after non-linear transformation to make sure each participant was properly aligned to the common grey matter template. Two PREVENT-AD and one AD-ADNI participant failed the template registration step and were removed. Six Cam-CAM participants failed the grey matter segmentation step and were removed. The sample size mentioned above already excluded the failed participants.

Independent component analysis

ICA is a computational method to decompose multivariate data into different components by maximizing statistical independence (Beckmann and Smith, 2004). We performed ICA on the grey matter maps of all individuals to derive data-driven regions of grey matter covariance. To apply such a method on structural data, we concatenated the modulated and smoothed grey matter maps to create a 4D file, which became the input for the ICA. To ensure that only grey matter voxels were retained for the ICA, the maps were masked with a maximum probability grey matter mask. This mask was generated from the group-average grey matter, white matter, and CSF images and consists of voxels with highest probability of being grey matter (grey matter > white matter and grey matter > CSF). ICA was performed using the toolbox MELODIC (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC) from the FSL analysis package (Jenkinson *et al.*, 2012) version 5.0.8.

To derive common data-driven components spanning lifespan and the Alzheimer's disease spectrum, the ICA was performed on all subjects ($n = 1019$). There is no clear rule as to how many components to extract from an ICA (Cole *et al.*, 2010) and we set the output at 30 components as done in Zeighami *et al.* (2015), to investigate a more fine-grained structural organization. In supplementary analyses, we also show the results when setting the output at 10 or 20 components (Supplementary Fig. 4). Each component was thresholded at $z = 3.5$ (Beckmann *et al.*, 2009) and binarized to retain the voxels that contributed significantly to the component. These thresholded IC maps are hereafter referred to as 'morphometric networks'. The grey matter volume in each of the morphometric networks was then extracted for each participant for further analysis.

To ensure the morphometric networks we derived were not specific to our multisite, multi-cohort sample and were representative of grey matter organization across the lifespan, we implemented the same ICA technique in the monocentric lifespan Cam-CAN dataset ($n = 647$). We repeated the main analysis in our six groups of interest when extracting grey matter volume from the unbiased morphometric networks derived in the Cam-CAN cohort.

Finally, to investigate whether similar morphometric networks were also present in participants with severe cognitive impairment, two ICAs were fit separately taking only the late MCI- and AD-ADNI groups to derive 30 morphometric networks specific to these groups. Grey matter volume in these morphometric networks was extracted for each participant and the main analyses were repeated in our six groups of interest using these late MCI- and Alzheimer's disease-derived networks.

Statistical analysis

Grey matter volume

To assess group effect on grey matter volume across brain networks, we used repeated measures ANOVA with grey matter volume in the 30 networks as intra-subject measure and the six groups as the inter-subject measure. From grey matter volume in each of the 30 morphometric networks, we aimed to identify which networks were affected most specifically by ageing and by Alzheimer's disease. We grouped the FCP-Cambridge and HCP samples together as 'Young adults' ($n = 468$), the PREVENT-AD and Controls-ADNI as 'Older adults' ($n = 430$), and the late MCI- and AD-ADNI as 'Alzheimer's dementia' ($n = 121$). We used binary logistic regression models with 10-fold cross-validation to classify: (i) Young adults versus Older adults; and (ii) Older adults versus Alzheimer's dementia, with the average grey matter volume in each of the 30 networks as input. We then used receiver operating characteristic (ROC) analyses and measured the area under the curve (AUC) to assess the model performance across the collated test sets. AUC were classified as follows: excellent = 0.90–1, good = 0.80–0.89, fair = 0.70–0.79, poor = 0.60–0.69, or fail = 0.50–0.59 (Safari *et al.*, 2016).

The Cam-CAN dataset was used to validate the effect of age on grey matter volume. Age was entered in a voxelwise regression analysis using SPM12, including sex and total intracranial volume as nuisance variables. Results are reported with a $P < 0.05$ family-wise error (FWE) correction.

Whole-brain grey matter pattern

Next, we assessed how measures of whole-brain grey matter pattern were influenced by ageing and Alzheimer's disease. We derived measures of grey matter pattern similarity by correlating the grey matter volume in the 30 morphometric networks of each individual to the grey matter volume in the 30 brain networks of every other subject. These correlations indicate how one's whole-brain organization is similar to every other individual. This resulted in a 1019×1019 matrix of whole-brain grey matter pattern between all subjects (Fig. 3B).

We evaluated whether there was a coherent grey matter pattern within each group (intrinsic pattern). Within the different groups, we calculated the average and standard deviation of correlation coefficients of grey matter pattern across all individuals. We then compared the difference in correlation coefficients between groups using z-test statistic

$$(z_1 - z_2)/\sqrt{\frac{1}{n_1 - 3} + \frac{1}{n_2 - 3}} \quad (1)$$

to test if the intrinsic grey matter pattern remained organized with ageing and Alzheimer's dementia at the group level. The z-test statistic formally tests if the coefficient of

correlation is greater in a group compared to another given the sample size.

To obtain a measure at the individual level, for each participant, grey matter volume in the 30 networks was correlated to the mean grey matter volume in the 30 networks of their respective group. We then used binary logistic regression and ROC analyses with 10-fold cross-validation to identify whether the grey matter pattern within-group could differentiate young adults from older adults, and older adults from Alzheimer's dementia. This tested if whole-brain pattern homogeneity within the groups characterized ageing or Alzheimer's disease (Fig. 3F). Second, to obtain a measure of whether the pattern itself differed with ageing and dementia, for each participant, grey matter volumes in the 30 networks were correlated to the mean grey matter volume in the 30 networks of the older adults group. This tested if the whole-brain pattern between groups (with older adults as the comparison point) can distinguish young from older adults and older adults from Alzheimer's dementia (Supplementary Fig. 2).

Heterogeneity of grey matter volumes

To assess variability of grey matter volume in ageing and Alzheimer's dementia, we calculated the coefficient of variation (standard deviation/mean of grey matter volume in each network) in the 30 networks. We used the modified signed-likelihood ratio (MSLR) test from the R software package cvequality version 0.1.3 (Marwick and Krishnamoorthy, 2019) to test for significant differences in the coefficients of variation of grey matter volume between groups. A P-value < 0.002 was considered significant, accounting for 30 comparisons.

To assess variability of grey matter volume across lifespan, coefficients of variation in the 30 morphometric networks were also calculated in the Cam-CAN dataset. The 30 networks were registered on the Cam-CAN maps and coefficients of variation in grey matter volume were compared across decades.

Clinical impact of grey matter volume and whole-brain pattern in cognitively normal older adults

In cognitively normal older adults, we also evaluated whether grey matter volume or whole-brain grey matter pattern were related to cognitive performance and clinical progression. We focused on grey matter volume in the network with the best discrimination between young and older adults (age-related network) and between older adults and Alzheimer's dementia (Alzheimer's dementia-related network), and on a metric representing preserved whole-brain grey matter pattern, i.e. pattern similarity to young adults. To test the degree to which older adults had a pattern similar/dissimilar to young adults, we correlated the grey matter volume in the 30 brain networks for each older adult with the mean grey matter volume in the 30 networks of the young adults group. Correlation coefficients were Fisher z-transformed.

We investigated whether the different grey matter features were related to cognitive performance using linear regression models. Memory and executive function performance were the dependent variables in PREVENT-AD. ADAS-Cog was the dependent variable in Controls-ADNI. Models included age, education and total grey matter as covariates. Six tests were performed in PREVENT-AD and three in Controls-ADNI. Analyses were run on SPSS version 20 (IBM Corp., Armonk, NY). A two-sided P-value < 0.05 was considered significant.

We then compared differences in grey matter features between Controls-ADNI stable and converters using Mann-Whitney U-tests. We also performed binary logistic regression with stable or converter status as the dependent variable and grey matter feature as the predictor, followed by ROC analyses to evaluate the discriminative accuracy of the different features. Given the small number of converters, those analyses were conducted with leave-one-out cross-validation. ROC curves were calculated across the collated test sets.

Data availability

The 10, 20 and 30 morphometric networks derived across all participants are available at https://github.com/villeneuvelab/projects. The values of grey matter volume in all those networks along with the total intracranial volume and amyloid status are also provided.

Results

Deriving morphometric networks

Different cohorts of young adults, older adults with intact cognition, and along the Alzheimer's disease clinical continuum ($n = 1019$, Table 1), were processed under a unified pipeline in which each participant's grey matter map was registered to a common template. The resulting 1019 grey matter maps were used as input for an ICA to derive 30 principal components, which explained 62% of variance in the data. The principal components were thresholded and binarized to retain the most significant voxels and are hereafter referred to as morphometric networks. The 30 morphometric networks are shown in Fig. 2A and their anatomical description can be found in Supplementary Table 3. Most morphometric networks were reminiscent of clearly defined anatomical regions, such as the precuneus, basal ganglia, occipital cortex or the thalamus. All networks showed a bilateral distribution, except Networks 23 and 26, which encompassed part of the left occipital lobe and the right temporal lobe, respectively. The average grey matter volume was extracted from each of the 30 morphometric networks, and these values formed the basis of all subsequent analyses.

Additive effect of age and Alzheimer's disease on grey matter volume was found in most morphometric networks

The grey matter volume across morphometric networks differed between cohorts (see repeated measures ANOVA in

Supplementary Fig. 1), showing effects of age and disease. To reduce the potential confound of site effects, we combined the six cohorts into three groups: 'Young adults' (FCP-Cambridge and HCP), 'Older adults' (PREVENT-AD and Controls-ADNI) and 'Alzheimer's dementia' (late MCI- and AD-ADNI), and examined the general differences between these three groups.

We used a 10-fold cross-validated logistic regression procedure to determine if the grey matter volume in each of these morphometric networks could classify young adults versus older adults and older adults versus Alzheimer's dementia in the left-out subjects. The AUCs from the ROC analyses represent the overall performance of each morphometric network to classify participants across the collated test sets (Fig. 2A).

Many of the AUCs showed excellent (AUCs $>$ 90, $n = 11$) or good ($80 <$ AUCs $<$ 90, $n = 10$) performance for classifying young versus older adults (Fig. 2B). Only three networks including the motor cortex (Network 15), the visual cortex (Network 17) and the thalamus/brainstem (Network 22) performed poorly (AUCs $<$ 69). The medial prefrontal cortex (Network 1, Fig. 2C) was the best to discriminate young from older adults (AUC = 0.96) and could not discriminate older adults from Alzheimer's dementia (AUC = 0.58). Grey matter decreased from youth to old age in this network but was stable from older adulthood to dementia, suggesting that this network is more specific to ageing than to Alzheimer's disease (Fig. 2C). The AUCs of the classifiers stratifying older adults versus Alzheimer's dementia were lower, with no AUC being excellent and only two being good discriminators (Fig. 2D). The medial temporal network, including the hippocampus and amygdala (Network 10, Fig. 2E), best discriminated older adults from Alzheimer's dementia (AUC = 0.83). Interestingly, the second best network to discriminate older adults and Alzheimer's dementia (Network 18) included part of the supramarginal and angular gyri, brain regions that have repeatedly been shown to be affected in Alzheimer's disease (Dickerson *et al.*, 2011; Landau *et al.*, 2011). However, grey matter volume in these networks (Fig. 2E showing Network 10), as in most other networks, showed an additive effect of age and disease.

Disruption of intrinsic whole-brain grey matter pattern in Alzheimer's dementia

Grey matter volume signatures across morphometric networks for each participant are shown in Fig. 3A. Based on those values, we derived metrics reflecting whole-brain grey matter pattern similarity by correlating the grey matter volume signatures of the 30 morphometric networks between every other participant (Fig. 3B shows a signature for two participants). This multivariate analysis captured the variability of individuals with their own group as well as with other groups. We averaged the subject-to-subject grey matter signature correlations for each pair-wise group, as a measure of the intrinsic grey matter pattern within-group (diagonal elements of matrix, Fig. 3C), which ranged from 0.64 to 0.82. The intrinsic grey matter patterns within the groups of young and within the groups of older adults were homogeneous, while the pattern was less organized in Alzheimer's dementia, with lower mean correlation values (Fig. 3C and D) and higher standard deviation (Fig. 3E). At the individual level, intrinsic grey matter pattern measure (within-group correlation) discriminated older adults versus Alzheimer's dementia (AUC = 0.72), but not young versus older adults (AUC = 0.57; Fig. 3F).

Young and older adults showed a coherent pattern within their respective groups, but the whole-brain pattern itself differed with ageing and with dementia (off-diagonal elements Fig. 3C). Supplementary Fig. 3 shows that the whole-brain signature correlation values can differentiate between young and older adults (AUC = 0.94) and between older adults and Alzheimer's dementia (AUC = 0.85).

Our results therefore suggest that grey matter volume changes happen in a coherent way across networks in ageing, and that this coherence is lost only with severe cognitive impairment. Thus, higher heterogeneity and a disrupted whole-brain pattern are specific characteristics of clinical Alzheimer's disease, in line with the disease model (Fig. 1A).

Grey matter volume heterogeneity is higher in Alzheimer's disease but not in normal ageing

In line with the loss of grey matter pattern organization with Alzheimer's dementia, there was higher heterogeneity of grey matter volumes across morphometric networks in Alzheimer's dementia, as assessed by comparing coefficients of variation of grey matter volume. There was a main effect of group on coefficients of variation on the 30 networks (all MSLR tests $>$ 33.4, P-values $<$ 0.001). Young and older adults showed lower variation (mean coefficient of variation in the 30 networks of 10.8 and 11.8%, respectively), while Alzheimer's dementia groups showed higher heterogeneity (mean coefficient of variation of 17.8%) (Fig. 3G). The absence of higher heterogeneity over the course of ageing was validated using the Cam-CAN study ($n = 647$; age range 18–88 years old) (Fig. 4A). The coefficients of variation of grey matter volume were similar across decades in 26 of 30 morphometric networks (all P-values $>$ 0.004 from MSLR tests; mean coefficient of variation across decades ranged from 10.5 to 14.1%) (Fig. 4B). Such results challenge the proposition that normal ageing significantly amplifies heterogeneity of grey matter volume. Instead, our results suggest that higher

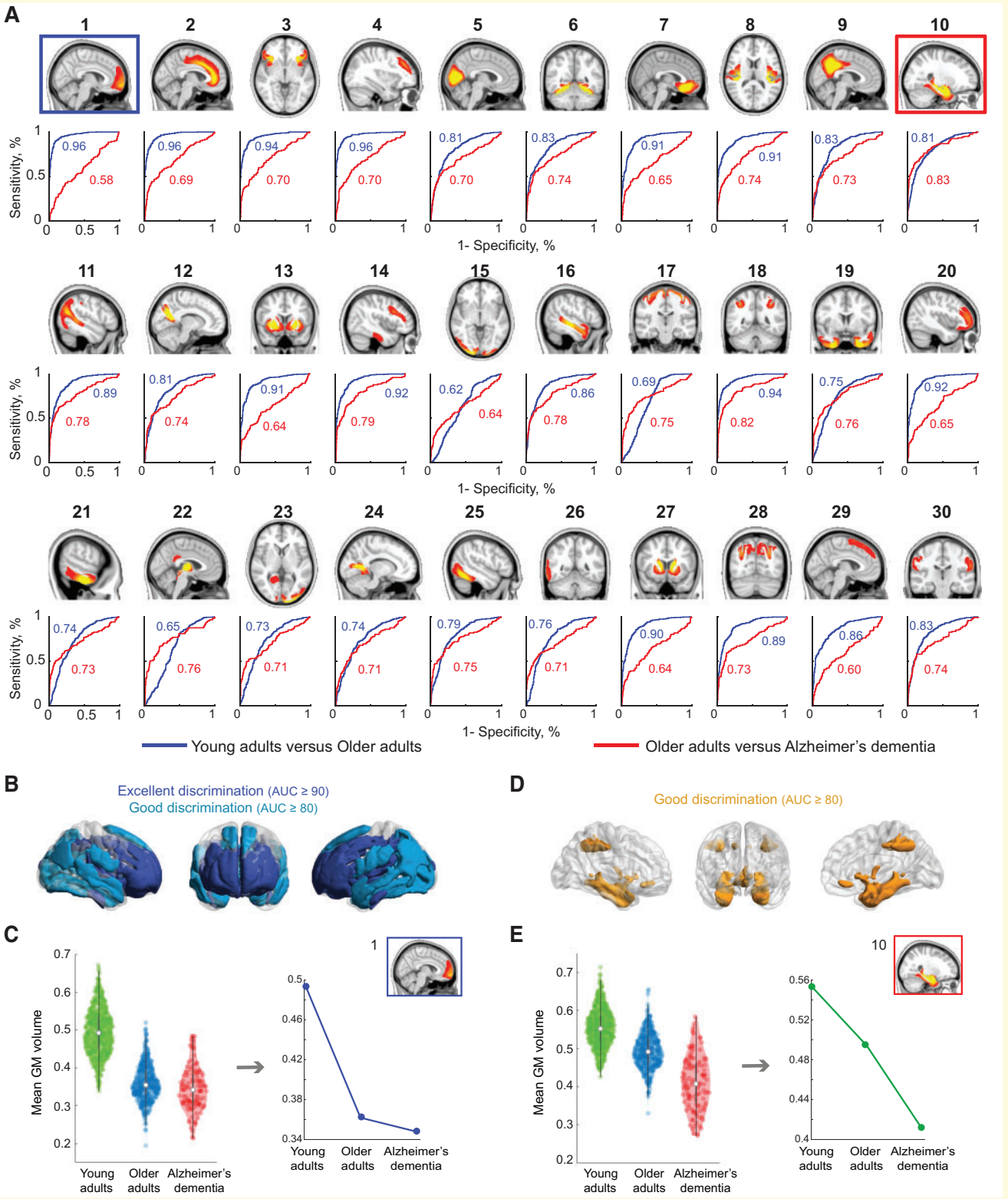

Figure 2 Performance of each morphometric network to discriminate ageing and Alzheimer's dementia. (**A**) The 30 anatomically derived morphometric networks from the ICA thresholded at $Z > 3.5$. Ten-fold cross-validation was used to determine the performance of each network to discriminate between young and older adults (blue ROC curves) and older adults and Alzheimer's dementia (red ROC curves). AUC values are reported on each graph. The blue square highlights the most discriminative network for normal ageing and the red square highlights the most discriminative network for Alzheimer's dementia. Results remained the same when total intracranial volume was added as a covariate in the statistical models. (**B**) Networks with excellent (AUC > 90) and good (AUC > 80) accuracy to discriminate normal ageing. (**C**) Average grey matter volume in the best age-related network. (**D**) Networks with good accuracy to discriminate Alzheimer's dementia. (**E**) Average grey matter volume in the best Alzheimer's dementia-related network. GM = grey matter.

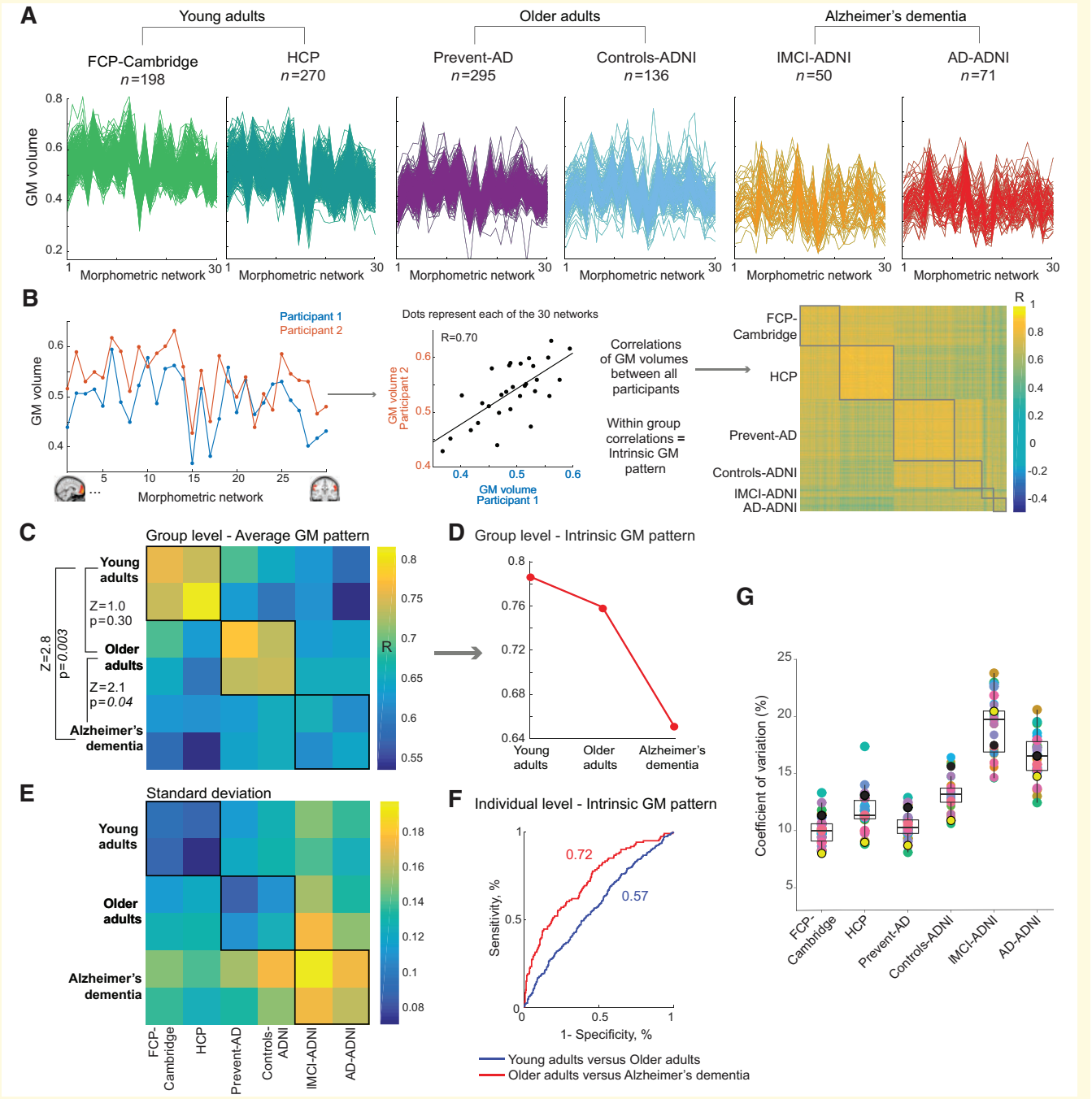

Figure 3 Intrinsic grey matter pattern discriminated between ageing and Alzheimer's disease. (**A**) Grey matter volume (*y*-axis) across the 30 morphometric networks (*x*-axis) for all participants in each of the six groups. All axes are on the same scale. Note that the same pattern emerged when using values of grey matter volume/total intracranial volume for each morphometric network. (**B**) Measures of grey matter pattern were derived by correlating the grey matter volumes across the 30 networks of each participant to every other participant. This resulted in a matrix of 1019 × 1019, comparing the grey matter pattern between all subjects. (**C**) The average correlation of grey matter pattern between and within (diagonal elements) groups. Statistical differences between the intrinsic grey matter pattern (within group correlations) in young adults, older adults, and Alzheimer's dementia are reported on the *left* of the matrix. (**D**) Intrinsic grey matter pattern is preserved in ageing, but not in Alzheimer's dementia, following the disease model. (**E**) Standard deviations of grey matter pattern between and within groups. (**F**) ROC curves showing the discriminative accuracy between young and older adults and between older adults and Alzheimer's dementia based on individual measures of intrinsic grey matter pattern in a 10-fold cross-validation procedure. (**G**) Coefficients of variation (standard deviation/mean) of grey matter volume in the 30 networks across groups. Each dot represents a brain network. Black circles correspond to the age-related network (Network 1) and yellow circles, to the Alzheimer's dementia-related network (Network 10). GM = grey matter; IMCI = late MCI.

interindividual variability in grey matter volume may be a hallmark of Alzheimer's dementia.

Using the Cam-CAN study, a voxel-wise analysis of age confirmed a whole brain reduction of grey matter volume (Fig. 4C). Unsurprisingly, the peaks showing the strongest relationship with advancing ageing were located in the morphometric networks with the highest accuracy to discriminate young from older adults.

Minimal effect of preclinical and prodromal Alzheimer's disease on grey matter metrics

An important aspect to consider in the aforementioned results is the presence of amyloid-β in the brain of cognitively normal older adults (Jansen *et al.*, 2015), which could affect structural changes and bias our results related to cognitively normal older adults. We repeated the main analyses by splitting older adults into amyloid-β+ and amyloid-β– where biomarker status was available (20 of 150 individuals were classified as amyloid-β+ in PREVENT-AD and 43 of 133 individuals in Controls-ADNI). There were no differences in grey matter volume between the amyloid-β+ and amyloid-β– cognitively normal individuals in PREVENT-AD (*P*-values from *t*-tests between 0.28 and 0.91) and no difference in 29 of 30 morphometric networks in ADNI-Controls (morphometric network 22 $P = 0.03$; other networks' *P*-values were between 0.07 and 0.83). The AUCs to discriminate ageing or Alzheimer's disease did not differ between the two groups (Supplementary Fig. 3A). Regarding the whole-brain grey matter pattern, the within-group correlation did not differ between amyloid-β– and amyloid-β+ older adults, but only the former differed from the Alzheimer's dementia group (Supplementary Fig. 3B).

Another aspect to consider is the heterogeneous group formed by the MCI participants. Following the ADNI diagnosis, we used the early and late MCI classification to identify a group of MCI that is closer to normal cognition (early MCI) and a group of MCI that is closer to the onset of dementia (late MCI). *Post hoc* tests from a repeated measure ANOVA using grey matter volume in the 30 morphometric networks revealed that the group of early MCI (46% of participants being amyloid-β+) had grey matter volumes similar to the two groups of cognitively normal older adults, while late MCI and AD-ADNI groups were similar to one another (Supplementary Fig. 5B). Similarly, the discrimination accuracy of grey matter volume of the early MCI group versus young adults and versus older adults was highly similar to the groups of older adults (Supplementary Fig. 3A). As with the amyloid-β+ older adults, the whole-brain organization of the early MCI group was only slightly more heterogeneous than the amyloid-β– older adults, in the sense that only the amyloid-β– older adults were statistically different from the Alzheimer's dementia group (Supplementary Fig. 3B). Overall, amyloid-β status in the asymptomatic phase or the addition of early MCI participants has a minimal effect on the main results, suggesting that while a loss of organization is specific to Alzheimer's disease, this brain feature is not apparent in the asymptomatic or early prodromal phase of the disease.

Results are robust to different sets of morphometric networks

Multiple confirmatory analyses were performed to ensure that the results were robust and not dependent on the way morphometric networks were derived. First, we repeated the same analytical approach when deriving 10 and 20 networks instead of 30 and the main results remained the same (Supplementary Fig. 4). Second, we used the Cam-CAN cohort as an independent monocentric lifespan dataset to derive morphometric networks. These new morphometric networks recapitulated those found in the main analysis and extracting grey matter volume from the six groups of interest within these new networks revealed the main results (Supplementary Fig. 5). Lastly, even when deriving morphometric networks in cognitively impaired individuals, the top ageing and Alzheimer's dementia regions were highly consistent with the networks from the main analysis (Supplementary Fig. 6). However, as we could expect given the high atrophy in those groups, the morphometric networks were smaller and more often unilateral in individuals with advanced disease.

A slower rate of clinical progression is related to a preserved grey matter pattern

Finally, in an effort to relate the descriptive results of grey matter volume and pattern to clinical changes, we evaluated whether different grey matter features were related to cognitive outcomes in older adults. We focused on grey matter volume in the most discriminative morphometric network between young and older adults (age-related network, Network 1) and the most discriminative between older adults and Alzheimer's dementia (Alzheimer's dementia-related network, Network 10), along with a metric of preserved whole-brain pattern (similarity to young adults, i.e. correlation between grey matter volume in the 30 networks to the mean grey matter volumes of young adults in the 30 networks).

In PREVENT-AD, there was no association between cognition and grey matter volume or grey matter pattern (Supplementary Table 5). In Controls-ADNI, participants showing a grey matter pattern more similar to young adults had better cognitive performance. Grey matter volume in the age- or Alzheimer's dementia-related networks was not related to cognition (Supplementary Table 5).

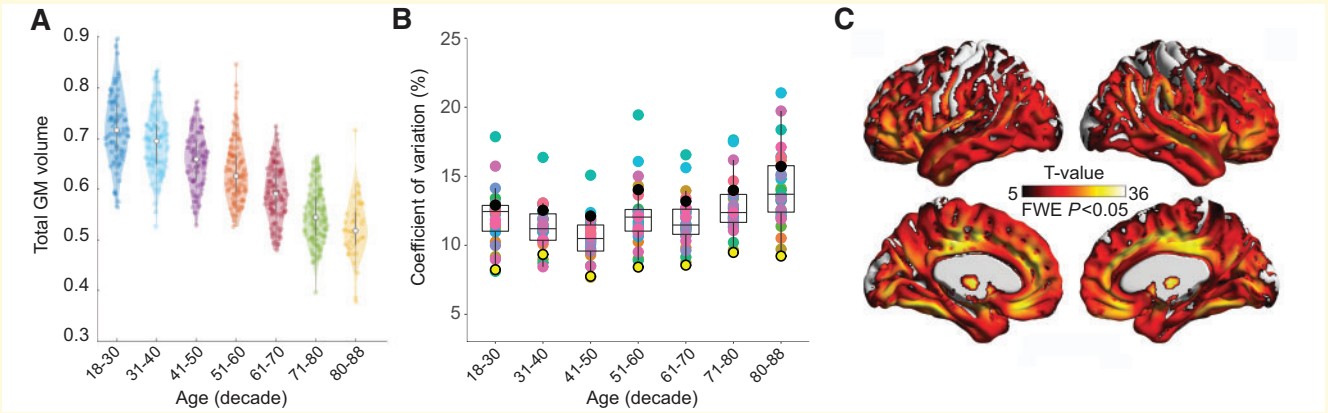

Figure 4 Results related to ageing were validated using the Cam-CAN dataset. (**A**) Reduction in grey matter total volume with advancing age. (**B**) Similar variability of grey matter volume in the 30 morphometric networks across decades. Each dot represents a brain system. Black circles correspond to the age-related network (Network 1) and yellow circles, to the Alzheimer's dementia-related network (Network 10). (**C**) Voxelwise analysis showed that the peaks of grey matter volume reduction associated with age were located in the medial prefrontal cortex, the dorsolateral prefrontal cortex, the cingulate cortex and the medial temporal lobe. Statistical significance is set at $P < 0.05$ FWE-corrected.

In Controls-ADNI, a proportion of cognitively normal participants converted to MCI ($n = 18$), most of them between 2 to 4 years later. When compared to Controls-ADNI who remained cognitively normal ($n = 117$), these converters displayed a grey matter pattern less similar to young adults (Fig. 5A). Trends towards lower grey matter volume in the age- and the Alzheimer's dementia-related networks were found in converters when compared to stable older adults (Fig. 5B and C). Using leave-one-out cross-validation analyses, we showed that whole-brain pattern similarity to young adults differentiated Controls-ADNI converters from stable with a fair accuracy (AUC = 0.71), whereas grey matter volume in the age- and Alzheimer's dementia-related networks yielded poor accuracy (Fig. 5, bottom row). These findings support the previous results suggesting that whole-brain grey matter organization is an important feature of clinical manifestation of cognitive impairment.

Discussion

Using a large, multi-cohort dataset, we identified a set of 30 morphometric networks, and evaluated grey matter volume differences in these networks, individually and in concert, in ageing versus Alzheimer's disease. We used cross-validation procedures to determine how each feature could discriminate young from cognitively normal older adults (effect of age) and cognitively normal older adults from Alzheimer's dementia (effect of the disease). Across the whole brain, we observed an important decrease in grey matter volume in the course of ageing, as almost all morphometric networks could accurately stratify young adults from older adults. Atrophy related to Alzheimer's dementia added to that of ageing in most brain systems, excluding those in the medial frontal cortex. Importantly, Alzheimer's dementia, but not ageing, was associated with increased heterogeneity in grey matter volume across the morphometric networks and in whole-brain grey matter pattern. The robustness of the results was validated in the Cam-CAN monocentric lifespan cohort, where grey matter volume variability was consistent across the decades. Finally, having a grey matter pattern less similar to young adults was related to progression to MCI in Controls-ADNI.

How does the brain age? Is Alzheimer's dementia a form of accelerated ageing? What features distinguish changes of normal ageing from those seen in early Alzheimer's dementia? To disentangle changes of normal ageing versus those leading to neurodegenerative diseases, large longitudinal studies monitoring structural and pathological brain changes across lifespan would be needed. While such studies do not exist, several lifespan and disease cohorts are now available, making it possible to infer longitudinal changes based on large, cross-generational data. Using more than a thousand structural MRI scans from adults aged 18 to 89 years old, among which 12% were diagnosed with late MCI or Alzheimer's dementia, we differentiated grey matter features more specific to Alzheimer's disease from those more specific to ageing, and identified those vulnerable to both phenomena. We were interested in both the magnitude (volume) and the pattern (whole-brain organization) of grey matter features. Also, rather than targeting *a priori* structural brain regions, we used ICA to uncover morphometric networks that were robust and representative of our sample (Bassett *et al.*, 2008; Hafkemeijer *et al.*, 2014; Zeighami *et al.*, 2015).

Frontal systems are preferentially affected by age but not by Alzheimer's dementia, and therefore our results do not support the hypothesis that Alzheimer's disease-related neurodegeneration simply reflects an extension or acceleration of normal ageing processes. Traditionally, the dissociation

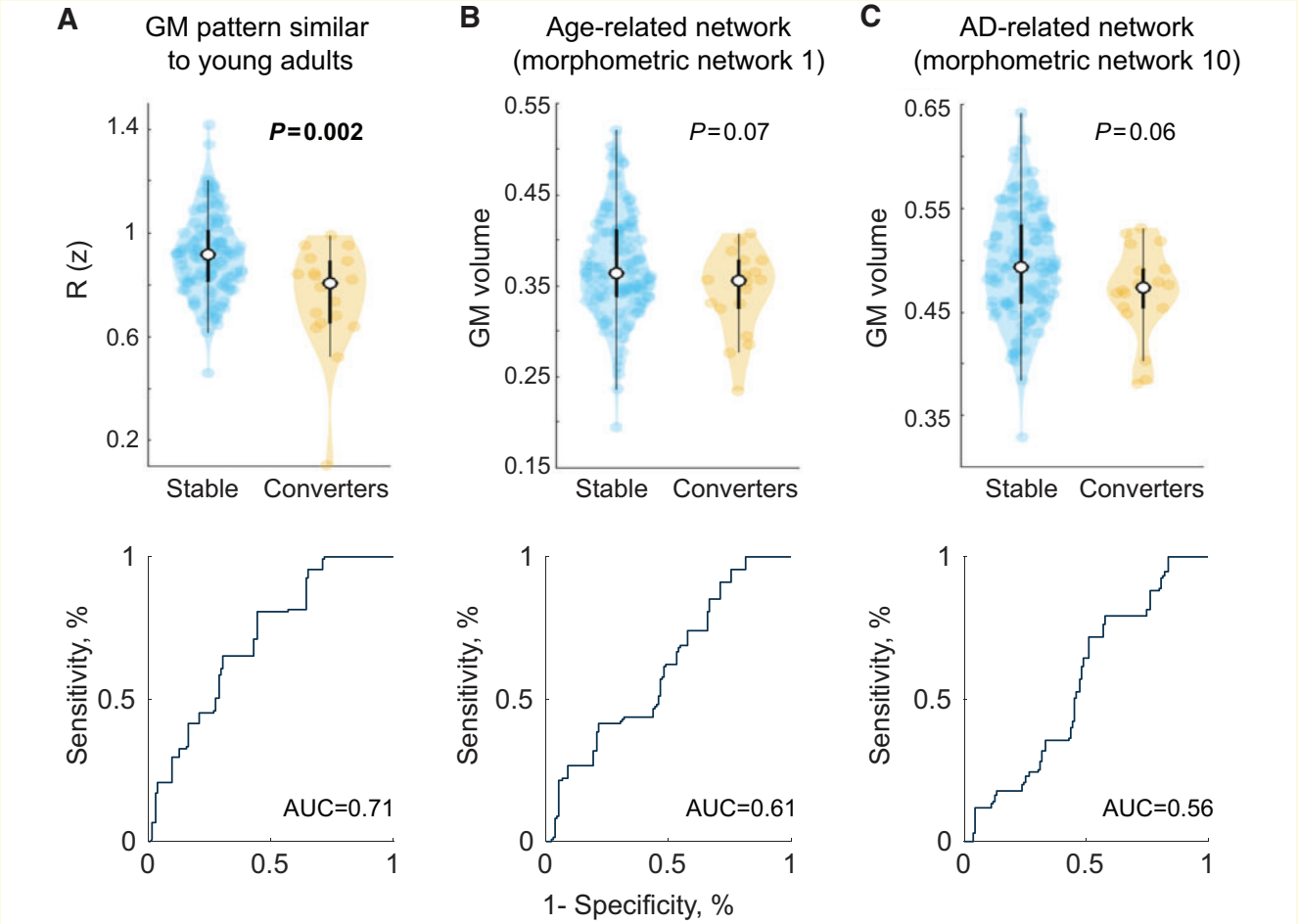

Figure 5 Whole-brain grey matter organization related with cognitive decline. Differences between Controls-ADNI who converted to MCI (Converters, *n* = 18) and those who remained cognitively normal (Stable, *n* = 117) on grey matter pattern similarity to young adults (**A**), grey matter volume in the age-related network (**B**) and the Alzheimer's dementia-related network (**C**). Uncorrected *P*-values from Mann-Whitney U-tests are reported. Bolded value survives Bonferroni corrections for three tests. *Bottom row*: ROC curves discriminate between stable and converter groups. Results remained the same when excluding one extreme case with the lowest grey matter pattern similarity. AD = Alzheimer's dementia; GM = grey matter.

between fronto-striatal and temporal lobe atrophy has been proposed as reflecting different underlying processes in ageing and Alzheimer's dementia (Ohnishi *et al.*, 2001; Buckner, 2004). Many studies also showed that the temporal lobes are preferentially affected by age (Fjell *et al.*, 2009; Raz *et al.*, 2010; Pfefferbaum *et al.*, 2013), even when focusing only on older adults at very low risk of Alzheimer's disease (Fjell *et al.*, 2013*a*). In the current study, we showed that the medial prefrontal networks are relatively specific to ageing, and already show low grey matter volume by the age individuals typically develop Alzheimer's dementia. However, grey matter volume in most of the other morphometric networks decreased almost linearly from young to old adulthood, and was accelerated with Alzheimer's dementia, resulting in an additive effect of both phenomena across most of the cortex. In fact, our results suggest that even the regions most closely related to Alzheimer's disease are probably confounded by a strong influence of ageing. These findings emphasize that by the time an individual develops sporadic dementia, the atrophy due to age, which has spanned over decades, is quantitatively similar, or even greater, to the effect of Alzheimer's disease neurodegeneration.

Grey matter volume in the temporal lobe was the best network to dissociate older adults from Alzheimer's dementia, but it was not specific to the disease. Only increased heterogeneity in the grey matter pattern and grey matter volume across morphometric networks was more specific to Alzheimer's dementia. We showed that the whole-brain pattern was different over the course of ageing and Alzheimer's disease, but while cognitively normal older adults maintained a coherent pattern, this homogeneity was lost in Alzheimer's patients. These results suggest that it is not the 'magnitude' of atrophy in temporal brain systems that is specific to the disease, but rather the 'heterogeneity' that characterizes Alzheimer's disease.

Following this idea, having a grey matter pattern more similar to young adults was related to less progression to MCI, more so than grey matter volume in individual morphometric networks. Such results accord well with the concept of brain maintenance, postulating that maintaining youth-like brain integrity is associated with 'healthier' ageing (Nyberg *et al.*, 2012). It has been suggested that older adults who exhibit more youth-like functional characteristics had higher cognitive performance (Sun *et al.*, 2016; Samu *et al.*, 2017). Adding to this idea of functional maintenance, it is possible that structural maintenance is also an important factor of successful ageing. We hypothesize that preserved grey matter volume in the frontal cortex more specifically might contribute to maintaining a whole-brain pattern more similar to young adults, and, in turn, better cognition. In effect, the prefrontal cortex and anterior cingulate, or networks involving those regions, are often related to preserved cognition in old age or even 'super ageing' (Sun *et al.*, 2016; Arenaza-Urquijo *et al.*, 2019). These alternative ways of exploring age and Alzheimer's disease differences reinforce the importance of looking across the lifespan to untangle underlying processes of normal and pathological ageing.

There are considerable interindividual differences in grey matter volumes (Alexander-Bloch *et al.*, 2013), and it is often assumed that such differences increase with ageing, due in part to early neurodegenerative processes (Jagust, 2013). Looking at changes across the lifespan and dementia allowed us to directly compare heterogeneity in grey matter volume across different age and disease groups. Refuting the popular view that age is associated with increased variability, we found that grey matter volumes across all brain networks were as variable in young adulthood as in old adulthood. Similar findings have previously been shown when only focusing on the hippocampal volume (Lupien *et al.*, 2007), perhaps the brain region most commonly used as a structural proxy of Alzheimer's disease neurodegeneration (Jack *et al.*, 2015). More generally, interindividual differences may influence some cross-sectional differences attributed to age- or disease-related changes. Heterogeneity in grey matter volume in young adults could reflect cortical endophenotypes, being present since childhood (Shaw *et al.*, 2007). Late MCI- and AD-ADNI groups showed higher grey matter variability than young and cognitively normal older adults, suggesting that increased variability is associated with disease stage. While part of this increased heterogeneity might arise from multiple underlying pathologies, the clinical profile of cognitively impaired participants in ADNI is nevertheless quite uniform, i.e. primarily amnestic type. These results also highlight the importance to consider the vast interindividual differences when classifying a biomarker as being normal or abnormal, without refuting that diseases increase interindividual brain variability, at least in advanced stages.

Another important aspect to consider when studying ageing and Alzheimer's disease is the underlying brain pathologies, with amyloid-β being the key pathological measure to define preclinical Alzheimer's disease (Sperling *et al.*, 2011). In the current sample of cognitively normal older adults, 23% of them were amyloid-β+, in line with the expected proportion of ~20% given the age range of our sample (Jack *et al.*, 2017). We found minimal differences between the amyloid-β+ and amyloid-β– groups, which aligns with other studies finding little brain structural differences with amyloid-β load in the presymptomatic stage at a cross-sectional level (Wirth *et al.*, 2013*a*; Dubois *et al.*, 2018). We also assessed the grey matter features of early MCI, a group of individuals with mild memory deficits among which about half have entered the prodromal phase of Alzheimer's disease dementia based on their amyloid status. In line with previous findings, we found that this group had grey matter features more similar to cognitively older adults than demented individuals (Wei *et al.*, 2018; Ofori *et al.*, 2019). Taken together, we believe these findings highlight that Alzheimer's disease grey matter changes happen late in the disease continuum.

There are important methodological confounds to consider in this study, notably the multiple sites and scanners. To minimize the effect of scanner acquisition strength, we included images acquired at 3 T only. Similar to another multi-cohort study on structural covariance (DuPre and Spreng, 2017), we optimized the common grey matter template by averaging the template of each different group so that each group is represented equally. Also, the main findings were consistent across multiple cohorts, both mono- and multi-centric studies. The results were also robust to morphometric networks derived at different resolutions, in an independent lifespan cohort or in individuals with severe cognitive impairments only.

Overall, while atrophy occurred throughout ageing and disease in an additive manner, grey matter volume loss was not specific to clinical Alzheimer's disease in any brain regions. Instead, Alzheimer's disease compounds the effects of normal ageing, but was specifically characterized by higher heterogeneity in both grey matter volume and whole-brain pattern signature. By leveraging structural analyses from a large lifespan dataset, we highlighted the overall brain disorganization that occurs only with severe cognitive impairment. The dissociation between grey matter volume and the intrinsic pattern of morphometric networks could provide new perspectives in our understanding of Alzheimer's disease and might apply to other neurodegenerative diseases. Atrophy of individual brain regions has been studied extensively, and recognizing the importance of whole-brain changes might be as important.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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