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Reduced functional segregation between the default mode network and the executive control network in healthy older adults: A longitudinal study

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ABSTRACT

The effects of age on functional connectivity (FC) of intrinsic connectivity networks (ICNs) have largely been derived from cross-sectional studies. Far less is known about longitudinal changes in FC and how they relate to ageing-related cognitive decline. We evaluated intra- and inter-network FC in 78 healthy older adults two or three times over a period of 4 years. Using linear mixed modeling we found progressive loss of functional specialization with ageing, evidenced by a decline in intra-network FC within the executive control (ECN) and default mode networks (DMN). In contrast, longitudinal inter-network FC between ECN and DMN showed a u-shaped trajectory whereby functional segregation between these two networks initially increased over time and later decreased as participants aged. The rate of loss in functional segregation between ECN and DMN was associated with ageing-related decline in processing speed. The observed longitudinal FC changes and their associations with processing speed remained after correcting for longitudinal reduction in gray matter volume. These findings help connect ageing-related changes in FC with ageing-related decline in cognitive performance and underscore the value of collecting concurrent longitudinal imaging and behavioral data.

Introduction

Neuroimaging has proven informative about the structural and functional changes in the ageing brain and how these relate to accompanying cognitive changes (Grady, 2012). Degradation of processing speed, perception, memory, and executive function (Cabeza et al., 2005; Craik and Salthouse, 2008; Lindenberger and Baltes, 1994; Park and Reuter-Lorenz, 2009) erode the benefits of increased longevity and motivate the search for the underlying mechanisms of these functional losses. Task-free fMRI provides information about the integrity of several highly reproducible intrinsic connectivity networks (ICNs) and is well suited for characterizing age and ageing related changes in brain function, as it requires minimal participant input.

Of the multiple ICNs that exist, three are particularly relevant to the study of loss of cognitive function in older adults because their age-related changes and associated cognitive alterations have been replicated in multiple studies (Damoiseaux et al., 2008; Fjell et al., 2015a, 2015b; Shaw et al., 2015). The three ICNS are: the default mode network (DMN), the executive control network (ECN), and the salience network (SN) (Menon, 2011; Voss et al., 2013). The DMN is associated with internally oriented mentation and autobiographical memory (Buckner et al., 2008), while the ECN is associated with demanding externally oriented processes that have a high cognitive load or require cognitive control (Seeley et al., 2007; Turner and Spreng, 2015). The SN serves as the 'dynamic switch', biasing activation of one or the other network when a salient external event is detected (Menon and Uddin, 2010; Seeley et al., 2007). The integrity of these three networks and their interactions appear fundamental to higher-level cognition and are therefore relevant to our understanding of the ageing brain (Greicius and Kimmel, 2012).

Indicative of their functional specialization, each ICN typically demonstrates high intra-network functional connectivity (Honey et al., 2010; Sporns, 2013; Zhang and Raichle, 2010). High signal coherence within a network renders its sub-components more functionally coupled, possibly resulting in greater distinctiveness of functional specialization (Dennis and Thompson, 2014; Sternberg, 2011; Wig et al., 2011). Cross-sectional studies of older adults have highlighted the loss of functional specialization evidenced by decreased intra-network FC in the ECN (Allen et al., 2011; Geerligs et al., 2015) or DMN (Andrews-Hanna et al., 2007; Ferreira and Busatto, 2013; Sambataro et al., 2010). Loss of DMN and/or ECN connectivity has been associated with poorer executive function, memory, and processing speed (Andrews-Hanna et al., 2007; Mevel et al., 2013). Less commonly,

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intra-network FC can also increase with age, for example within the SN (Voss et al., 2013), where increased connectivity has been linked to superior emotional regulation in old adults (Mather, 2012; Sze et al., 2012).

Complementing changes in intra-network connectivity are those involving inter-network FC, which denote functional segregation between ICNs, for example, between task-positive ICNs (ECN and SN) and task-negative ICN (DMN). The negative correlation of spontaneous oscillations (labeled as 'anti-correlation' in seminal studies) between these networks suggests that they normally have opposing functional roles, such that when one network is engaged, the other has to be suppressed (Chen et al., 2013; Fox et al., 2005; see Fig. 6 in Yeo et al., 2015 for an illustration).

Specifically negatively correlated fluctuations in BOLD signal between 'segregated' networks are thought to mediate transitions between internal and externally oriented cognition (Uddin et al., 2009). Reduced segregation between DMN and task-positive networks is characteristic of reduced functioning in many psychiatric conditions (Mattfeld et al., 2014; Whitfield-Gabrieli and Ford, 2012) as well as states associated with reduced cognitive performance like sleep-deprivation (De Havas et al., 2012; Yeo et al., 2015).

Age-related alteration in between-ICN connectivity manifests in the form of either reduced negative correlation or increased positive correlation among various ICNs (Biswal et al., 2010; Ferreira et al., 2015). A higher degree of network segregation at rest may be associated with better episodic (Chan et al., 2014) and working memory (Keller et al., 2015). During task performance, increased coupling (reduced negative correlation) between the DMN and task-positive ICNs was also associated with poorer cognitive performance (Spreng and Schacter, 2011).

While cross-sectional studies are pertinent to the construction of new hypotheses, longitudinal studies are equally or maybe even more important because it may not be appropriate to extrapolate cross-sectional findings to predict the effects of ageing (Kraemer et al., 2000; Mungas et al., 2010; Salthouse, 2009). Longitudinal studies are necessary to demonstrate with-subject ageing trajectories and the possible interactions between ageing with other factors (Li et al., 2014; Raz and Lindenberger, 2011; Voss et al., 2010). Relative to the wealth of cross-sectional data amassed to date, there is relatively little longitudinal data on changes in FC with ageing (Bernard et al., 2015). For instance, Bernard et al. (2015) reported greater decline in the functional connectivity of the posterior cingulate cortex and the DMN in memory decliners; Fjell et al. (2015a) found that recall change was related to change in functional connectivity over time and such positive relationship differed between young and older adults.

Here, we examined the longitudinal intra- and inter-network FC changes in a cohort of relatively healthy older adults. We focused on task-free FC within and between three ICNs (DMN, ECN, and SN) and their relationships with cognitive performance across five domains. We expected intra-network FC in the three ICNs, i.e. functional specialization, to decrease as participants age (Ferreira and Busatto, 2013; Onoda et al., 2012), although that in the SN may increase or remain unchanged given previous mixing results (Geerligs et al., 2015; Voss et al., 2013). Secondly, we anticipated reduced segregation of inter-network FC between task-positive networks (ECN and SN) and default mode network with ageing, commensurate with expectations of reduced regulation (Menon and Uddin, 2010) and functional segregation (Chan et al., 2014; Geerligs et al., 2015) of brain networks. Lastly, we sought to determine whether the rate of change in intra- and inter-network FC would be associated with longitudinal cognitive decline.

Methods

Participants

We studied 78 relatively healthy Chinese older adults (38 females; 4 left-handed; mean age = 68.03 years, SD = 5.73 years at the baseline; mean education = 12.48 years, SD = 3.15 years) from the Singapore-Longitudinal Ageing Brain Study (S-LABS) (Chee et al., 2009). Participants who met study criteria underwent brain imaging at approximately 2-year intervals between 2009 and 2014. Eligible participants had to have participated in at least two time points of the longitudinal study and to have completed both neuropsychological assessment and brain imaging (with satisfactory data quality[1]). Second, they had a Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score of 26 or greater (mean = 28.15, SD = 1.40) and a modified-Geriatric Depression Screening Scale (GDS) (Yesavage and Sheikh, 1986) score of less than 9 (mean = 0.98, SD = 1.10) at the baseline. Third, they did not have any of the following at any time point: (1) a history of significant vascular events (i.e., myocardial infarction, stroke, or peripheral vascular disease); (2) a history of malignant neoplasia of any form; (3) a history of cardiac, lung, liver, or kidney failure; (4) active or inadequately treated thyroid disease; (5) active neurological or psychiatric conditions; or (6) a history of head trauma with loss of consciousness. The study was approved by the Institutional Review Board of the National University of Singapore. All participants provided written informed consent prior to participation.

Neuropsychological assessments

Within 3 months of undergoing magnetic resonance imaging (MRI), all participants underwent neuropsychological assessment by trained researchers (Chee et al., 2009; Lo et al., 2014). Five cognitive domains were evaluated: processing speed, attention, verbal memory, visuospatial memory, and executive functioning. Processing speed was assessed with the Symbol Digit Modalities Test (Smith, 1991), the Symbol Search Task in the Wechsler Memory Scale-Third Edition (WMS-III) (Wechsler, 1997), and the Trail Making Test A (Reitan and Wolfson, 1985). Attention was assessed with the Digit Span Test and the Spatial Span Test in WMS-III. Verbal memory was assessed with the Rey Auditory Verbal Learning Test (Lezak et al., 2004). Visuospatial memory was assessed with a Visual Paired Associates Test. Executive functioning was assessed with the Categorical Verbal Fluency Test (Lezak et al., 2004), the Design Fluency Test in the Delis-Kaplan Executive Function System (Delis Kaplan et al., 2001), and the Trail Making Test B (Reitan and Wolfson, 1985). The scores of each test at each time point were standardized to *T* scores (mean = 50, SD = 10) with respect to the baseline. For domains evaluated with multiple tests, the domain-average composite scores per participant per time point were computed by taking the mean of the summated *T* scores from the relevant tests.

Image acquisition

MRI scans were conducted on a 3 T Siemens Magnetom Tim Trio System (Siemens, Erlangen, Germany). All participants performed an 8-min task-free fMRI scan when they fixated on a cross at the center of a projector screen (36 continuous axial slices, TR/TE = 2000/30 ms, flip angle = 90°, FOV = 192 × 192, matrix size = 64 × 64, isotropic voxel size = 3.0 × 3.0 × 3.0 mm^3, bandwidth = 2112 Hz/pixel). High-resolution T1-weighted structural MRI was acquired using magnetization-prepared rapid gradient echo sequence (MPRAGE; 192 continuous sagittal slices, TR/TE/TI = 2300/2.98/900 ms, flip angle = 9°, FOV = 256 × 240 mm^2, matrix = 256 × 240, isotropic voxel size = 1.0 × 1.0 × 1.0 mm^3, bandwidth = 240 Hz/pixel).

Image processing

Both functional and structural images were preprocessed using a standard pipeline (Susanto et al., 2015; Zhou et al., 2012) based on FSL (Jenkinson et al., 2012) and AFNI (Cox, 1996). For the structural

[1] Thirty-eight participants provided data from all three phases, 37 provided data from two consecutive phases, and 3 provided data from the first and third phases.

image, steps included 1) image noise reduction (SUSAN), 2) skull stripping using the Brain Extraction Tool (BET), 3) linear (FLIRT) and nonlinear (FNIRT) registration to the Montreal Neurological Institute (MNI) 152 standard space, and 4) segmentation of the brain into gray matter, white matter and cerebrospinal fluid (CSF) compartments. For the functional data, we 1) excluded the first five volumes, before performing 2) slice-time correction, 3) motion correction, 4) despiking and grand-mean scaling, 5) spatial smoothing with a 6-mm FWHM Gaussian kernel, temporal band-pass filtering (0.009–0.1 Hz) and detrending (first and second order), 6) structural MRI coregistration using Boundary-Based Registration (BBR), and nonlinear (FNIRT) registration to the MNI space, and 7) nuisance signals reduction by regressing out signals estimated from CSF, white matter, whole-brain global signal, and six motion parameters. Motion quality control was performed (maximum absolute motion ≤ 3 mm) and coregistration quality was visual inspected for each session of all participants.

Similar to recent functional connectivity work in healthy ageing (Andrews-Hanna et al., 2007; Betzel et al., 2014; Chan et al., 2014; Geerligs et al., 2014), global signal regression was performed to reduce nuisance signals and positive bias in correlations (Chen et al., 2012; Hayasaka, 2013). The global negative index (Chen et al., 2012) was computed to check the percentage of voxels showing negative correlation with the global signal in each participant and study time point (Shu et al., 2014). Most percentages fell below 3% (max. 6%), suggesting that the global signal was representative of nuisance signals and should be removed. For completeness, we also analyzed the data without global signal regression (Supplementary Materials S2).

Functional connectivity derivation

We focused on three ICNs: the default mode network (DMN), the executive control network (ECN), and the salience network (SN) spatially defined by an FC-based brain parcellation scheme (Yeo et al., 2011) (Fig. 1, step 1). Each of the three ICNs was classified into smaller sub-networks comprising multiple regions of interest (e.g., the DMN comprises six sub-networks, three on each hemisphere). At subject-level, FC between two cortical regions of interest (ROIs) was computed as the Pearson's correlation coefficient between the mean fMRI time series of the two ROIs. Each correlation coefficient was then Fisher's *r*-to-*z* transformed. A subject-level FC *z*-score matrix involving 74 ROIs from the three ICNs was then constructed for each study time point. Average *z*-scores of intra-network (DMN, ECN, and SN) and inter-network FC (ECN–DMN, ECN–SN, DMN–SN) were then calculated for each participant at each time point for further statistical analyses.

Gray matter volume derivation

To take age and ageing-related gray matter volume (GMV) changes into account (Chee et al., 2009), we applied an optimized voxel-based morphometry (VBM) protocol (Good et al., 2001) using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8/) in Statistical Parametric Mapping (SPM12) (http://www.fil.ion.ucl.ac.uk/spm/). We derived subject-level GMV probability maps at each time point from T1 structural images using the longitudinal preprocessing pipeline, including (1) realigned the intra-subject images across time points; (2) created a mean reference image for every subject; (3) corrected for intra-subjects signal inhomogeneities using the reference image; (4) segmented the bias-corrected and reference images into GM, WM and cerebrospinal fluid (CSF) using an adaptive Maximum A Posterior (MAP) technique that does not require a priori tissue probabilities (Rajapakse et al., 1997); (5) created a study-specific template using nonlinear DARTEL registration (Ashburner, 2007) using the segmented images after an initial affine registration; (6) normalized the segmented reference GM/WM probability maps to the customized template in MNI

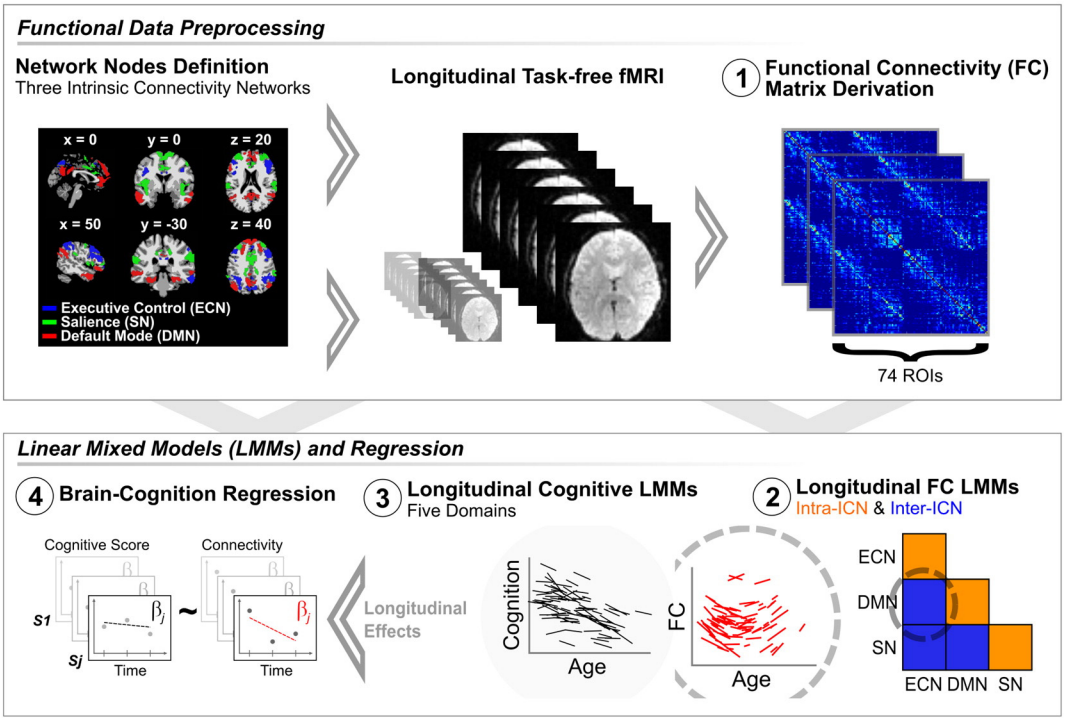

Fig. 1. Longitudinal study design schematic. Participants underwent 2 or 3 task-free fMRI and neuropsychological assessments over a period of approximately 4 years. Step 1: the functional connectivity (FC) matrix among 74 regions of interest (ROIs) covering the three intrinsic connectivity networks (ICN) of interest was derived for each participant and at each time point. Step 2: the intra- (orange cells) and inter-network FCs (blue cells) of the three ICNs: default mode network (DMN), executive control network (ECN), and salience network (SN) were obtained by averaging the corresponding cells in the matrices and submitted to linear mixed modeling (LMM) to examine the effects of ageing and age on FC in each pair of ICNS. Step 3: the same LMM were also applied to performance in each of the five cognitive domains. Step 4: brain–cognition associations were examined by correlating the estimated longitudinal changes in cognitive test scores with changes in functional connectivity.

space; (7) applied the same spatial normalization to the individual's segmented GM/WM probability maps; (8) performed modulation by multiplying voxel values by only the nonlinear components of the Jacobian determinants derived from the spatial normalization step, to account for individual brain sizes. From the subject-level GMV probability maps, we applied binarized masks of the 3 ICNs (registered to the study-specific template) to extract network average GMVs per subject at each time point for further statistical analysis.

Statistical analysis on longitudinal changes

We modeled the longitudinal changes in FC, GMV, and cognitive performance using linear mixed models (Fig. 1, step 2 & 3), that modeled fixed and random effects simultaneously, accounting for unequal sampling intervals, and missing data (Cnaan et al., 1997; Long, 2012; Singer and Willett, 2003).

For each participant j, the dependent variable Y (FC or cognitive score) was measured at each Time i, the longitudinal variable representing time interval since the first available session. The first available session of each participant was defined as the earliest session with quality task-free fMRI data or neuropsychological assessment. Time always started from zero. The longitudinal *ageing* effect was expressed as a simple regression between Time and Y, plus a residual r.

$$Y_{ij} = \beta_{0j} + \beta_{1j}(Time_{ij}) + r_{ij} \quad (1)$$

Individual differences in intercepts (β_{0j}) and slopes (β_{1j}) were then modeled separately with a similar regression approach, estimated in relation to Age, defined as participant's age at the first available session. Education and Gender were included as covariates in the intercept.

$$\beta_{0j} = \gamma_{00} + \gamma_{01}(Gender_j) + \gamma_{02}(Education_j) + \gamma_{03}\left(Age_j\right) + \mu_{0j} \quad (2a)$$

$$\beta_{1j} = \gamma_{10} + \gamma_{11}\left(Age_j\right) + \mu_{1j} \quad (2b)$$

Gender was a binary dummy variable, while Age and Education were the grand-mean-centered versions of the respective variables. Replacing the corresponding terms in Eq. (1) with Eqs. (2a) and (2b) resulted in Eq. (3). While equivalent to Eqs. (1) and (2a) and (2b), it highlights the cross-level interaction effects (Morrell et al., 2009): the intercepts (β_{0j}) and the longitudinal changes (slopes β_{1j}) were different for each participant (random effect μs) and this difference might be explained by individual differences (fixed effects γs). Specifically, ageing (Time) may proceed at different rates depending on cohort (Age), i.e., $\gamma_{11}(Age_j{}^{*}Time_{ij})$.

$$Y_{ij} = \gamma_{00} + \gamma_{01}(Gender_j) + \gamma_{02}(Education_j) + \gamma_{03}\left(Age_j\right) + \gamma_{10}(Time_{ij}) + \gamma_{11}\left(Age_j * Time_{ij}\right) + \mu_{0j} + \mu_{1j}(Time_{ij}) + r_{ij} \quad (3)$$

Using the proposed linear mixed model, we first examined the longitudinal ageing effects on ICN (Fig. 1, step 2). Each of the intra-network and inter-network FC was modeled separately. This was followed by modeling of each of the five cognitive domains (Fig. 1, step 3) as well as the GMV of each of the three ICN in the same fashion. To focus on ageing effects, we primarily reported longitudinal effects related to Time (β_{1j}), i.e., γ_{10} and γ_{11} (Eqs. (2b) and (3)), followed by statistically significant cross-sectional age effects related to Age, i.e., γ_{03} (Eqs. (2a) and (3)), if any, in the same models (see also Supplementary Materials S5).

Since the brain measurement models were constructed based on our prior network hypotheses, we interpreted effects that were statistically significant at the conventional threshold of $p < 0.05$ (Ruxton and Beauchamp, 2008). Any models passing multiple comparison correction (FC: corrected for 6 models; GMV: corrected for 3 models) were also reported. For cognitive models, we reported ageing effects with $p < 0.05$ corrected for multiple comparisons (5 domains).

To determine if motion scrubbing and GMV changes with age would alter the FC results, we ran the same linear mixed models after motion scrubbing (Supplementary Materials S1) and including GMV as a covariate (Supplementary Materials S3).

Statistical analyses on brain–cognition associations

To investigate the brain–cognition associations in their longitudinal trends (Fig. 1, step 4) (Goh et al., 2013), we focused on network FC and cognitive domains that showed significant effects of ageing (i.e. time or its relevant interactions). We identified three sets of slopes reflecting longitudinal changes in FC ($\beta_{1j.Connectivity}$), GMV ($\beta_{1j.GMV}$) and cognitive performance ($\beta_{1j.Cognition}$). We computed 1) the predicted values of each variable based on their respective linear mixed models (i.e., Eq. (3)) at each Time i and for each participant j; 2) the subject-specific slopes of the regression line between Time and the predicted FCs, and cognitive scores. This gave rise to $\beta_{1j.Connectivity}$, $\beta_{1j.GMV}$, and $\beta_{1j.Cognition}$, respectively; and finally, 3) these slopes were then evaluated using multiple regression models associating cognition and FC as follows:

$$\beta_{1j.Cognition} = b_0 + b_1\left(Age_j\right) + b_2(\beta_{1j.Connectivity}) + b_3\left(\beta_{1j.Connectivity} * Age_j\right) \quad (4)$$

where b_2 and b_3 are the estimated FC–cognition coefficient parameters.

To determine whether the observed FC–cognition correlations were influenced by the ageing-related gray matter volume loss, we re-analyzed the FC–cognition multiple regression by including the GMV slope $\beta_{1j.GMV}$ as additional covariate.

All statistical analyses and visualization were performed in R 3.0.3 (R Core Team, 2014) with RStudio (RStudio Team, 2012) using linear mixed model packages lme4 (Bates et al., 2014), lmerTest (Kuznetsova et al., 2014), and effects (Fox, 2003), and the graphical package ggplot2 (Wickham, 2009).

Results

Longitudinal changes in intra-network and inter-network FC

We found significant longitudinal decreases in intra-network FC within DMN ($p = 0.007$) and ECN ($p = 0.044$) (Fig. 2), and a marginal effect in SN ($p = 0.054$). Additionally, there was a significant effect of age on DMN connectivity, with older participants showing lower FC ($p = 0.017$). These indicate reduced functional specialization of the DMN with ageing and also in older participants (Table 1; Supplementary Table S5.1 for a full summary).

Modeling inter-network FC between each of the three ICNs (ECN–DMN, ECN–SN, DMN–SN), we found a significant Ageing × Age interaction involving ECN–DMN functional connectivity ($p = 0.032$). The aggregate of individual trajectories of ECN–DMN coupled activity was u-shaped with respect to age, with a turning point at around the age of 65–70 years (Fig. 3 and Table 1). Longitudinal effects in the remaining two inter-network FC were not statistically significant ($p > 0.20$). There was a significant effect of age on the functional coupling between DMN and SN with the oldest participants showing stronger coupling than their younger counterparts ($p = 0.013$; Supplementary Table S5.1 for a full summary).

Of all changes reported for functional connectivity, only intra-DMN decline survived multiple comparison correction ($p < 0.05$ corrected for 6 models). Motion scrubbing did not alter the results (Supplementary Tables S1.1 and S1.2; Supplementary Figs. S1.1 and S1.2). This suggests that the longitudinal changes in FC were unlikely to be due to motion. As global signal regression is one of the more contentious issues

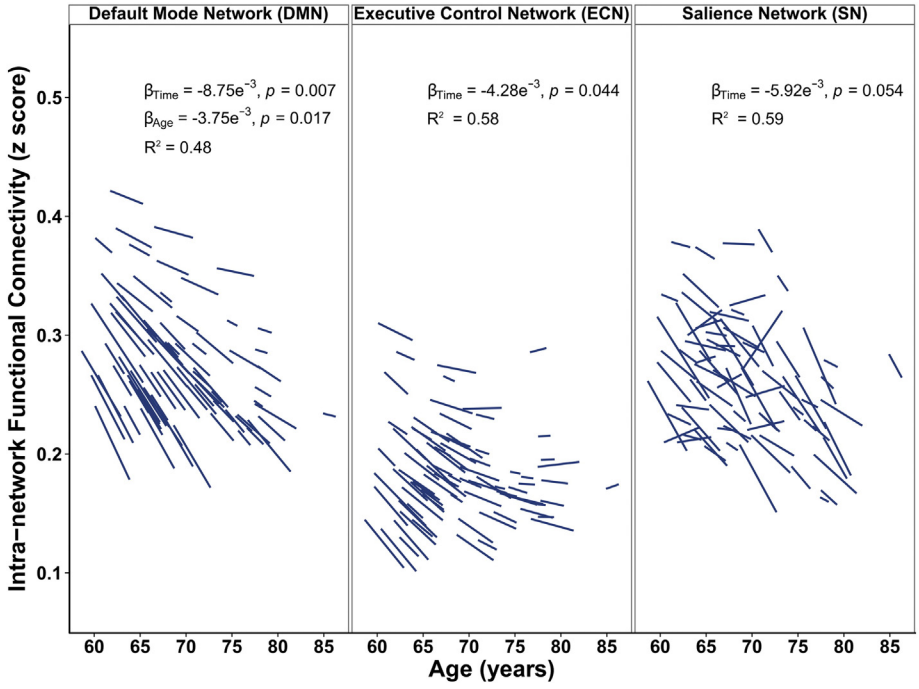

Fig. 2. Intra-network functional connectivity decreased with ageing. Spaghetti plots of the model-fitted longitudinal FC changes for each individual. Both DMN and ECN evidenced longitudinal decline (β_{Time}) in functional connectivity (FC) with ageing. Such decline was marginally significant in SN. Additionally, FC within DMN showed a significant effect of age (β_{Age}).

in intrinsic functional connectivity derivation (see recent review in Power et al., 2015), we repeated our analyses omitting global signal regression. Of note, the longitudinal changes were not statistically significant (Supplementary Table S2.1), suggesting that global signal regression is an important factor in revealing the ageing effects in our data, consistent with recent studies (Chan et al., 2014; Fox et al., 2009).

Table 1
Longitudinal ageing (Time) and cross-sectional age (Age) effects in the linear mixed models of intra-network (DMN, ECN, SN) and inter-network (ECN–DMN) functional connectivity (FC). Statistically significant effects ($p < 0.05$) appear in bold.

Network FC	Predictor	Coefficient	Standard error	*t*	*p*[a]
DMN	Gender	0.012	0.016	0.75	0.46
	Education	$-2.99e^{-3}$	$2.67e^{-3}$	−1.12	0.27
	Age	$\mathbf{-3.75e^{-3}}$	$\mathbf{1.53e^{-3}}$	**−2.45**	**0.017**
	Time	$\mathbf{-8.75e^{-3}}$	$\mathbf{3.19e^{-3}}$	**−2.74**	**7.20e^{-3}**[b]
	Age × Time	$3.41e^{-4}$	$5.98e^{-4}$	0.57	0.57
ECN	Gender	0.015	0.009	1.26	0.21
	Education	$3.48e^{-4}$	$2.03e^{-3}$	0.17	0.86
	Age	$-1.14e^{-3}$	$1.14e^{-3}$	−1.00	0.32
	Time	$\mathbf{-4.28e^{-3}}$	$\mathbf{2.06e^{-3}}$	**−2.08**	**0.044**[b]
	Age × Time	$4.11e^{-4}$	$3.87e^{-4}$	1.06	0.29
SN	Gender	$-2.83e^{-3}$	0.015	−0.19	0.85
	Education	$6.90e^{-4}$	$2.53e^{-3}$	0.27	0.79
	Age	$-2.59e^{-3}$	$1.50e^{-3}$	−1.73	0.088
	Time	$-5.92e^{-3}$	$3.00e^{-3}$	−1.97	0.054
	Age × Time	$2.97e^{-4}$	$5.62e^{-4}$	0.53	0.60
ECN–DMN	Gender	$8.67e^{-3}$	0.01	0.86	0.39
	Education	$-2.19e^{-3}$	$1.68e^{-3}$	−1.31	0.20
	Age	$-9.19e^{-4}$	$9.82e^{-4}$	−0.94	0.35
	Time	$-4.96e^{-4}$	$1.79e^{-3}$	−0.28	0.78
	Age × Time	$\mathbf{7.34e^{-4}}$	$\mathbf{3.36e^{-4}}$	**2.19**	**0.032**

Abbreviations: DMN = default mode network, ECN = executive control network, SN = salience network.

[a] *P*-values based on Satterthwaite approximation for denominator degrees of freedom, as implemented in the lmerTest package.

[b] The ageing effects in DMN and ECN intra-network FC were also statistically significant in the reduced model without Age × Time interaction, confirming the longitudinal decline independent of Age.

Longitudinal changes in gray matter volume

We found robust longitudinal GMV reduction in DMN, ECN, and SN ($p < 0.001$, $p < 0.05$ corrected for 3 models) (Fig. 4 and Table 2). Additionally, there was also an effect of age on GMV in DMN ($p = 0.022$) and SN ($p = 0.0014$), while the effect of age was marginal in ECN ($p = 0.055$) (Table 2).

Adding GMV as covariate(s) to the intra- and inter-network FC models produced qualitatively similar results (Supplementary Figs. S3.1 and S3.2; Supplementary Tables S3.1 and S3.2), although the longitudinal decline of the ECN became non-significant ($p = 0.07$). As

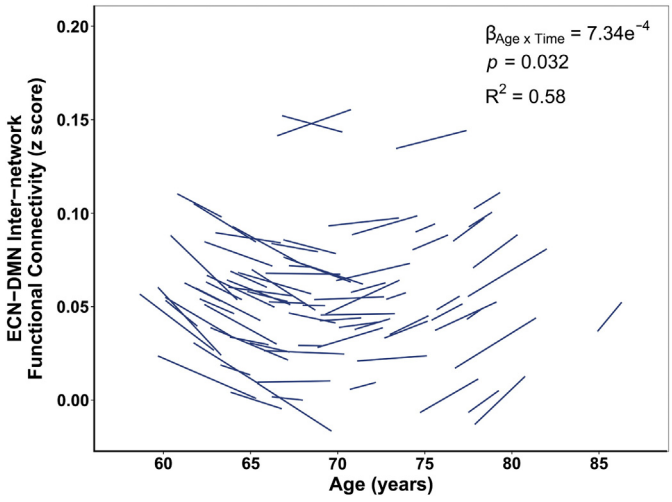

Fig. 3. Age-dependent changes in inter-network functional connectivity between default mode network (DMN) and executive control network (ECN) with ageing. Spaghetti plot of the model-fitted longitudinal FC changes for each individual. Between-network FC involving the ECN–DMN showed a u-shaped trajectory whereby functional coupling between these networks initially decreased over time and later increased as with older participants.

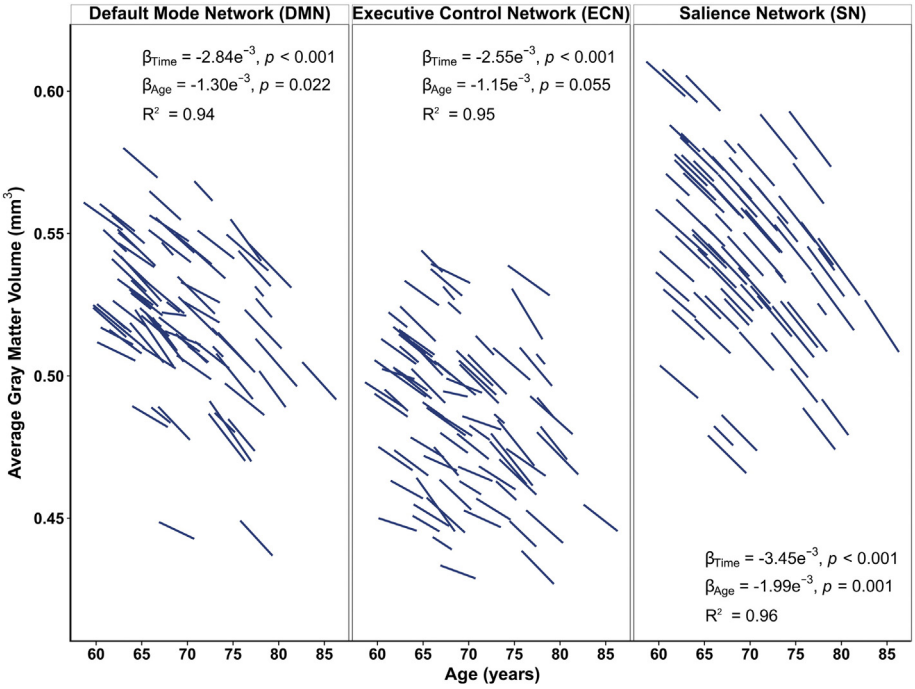

Fig. 4. Average gray matter volume (GMV) of all three intrinsic connectivity networks (ICNs) decreased with ageing. Spaghetti plots of the model-fitted longitudinal GMV changes for each individual. All networks evidenced longitudinal decline (β_{Time}) in GMV with ageing. Additionally, DMN and SN showed a significant effect of age (β_{Age}).

such, the longitudinal changes in FC observed here are unlikely to be solely a result of gray matter atrophy.

Longitudinal changes in cognitive performance

The same linear mixed model was applied to scores in each of the five cognitive domains. Processing speed showed unequivocal decline with ageing (Time, $p = 0.002$) at different ages (Age, $p < 0.001$) (Fig. 5 and Table 3). There was an *increase* in verbal memory with ageing ($p < 0.001$), likely due to practice effect (Rönnlund et al., 2005; Salthouse, 2009). All statistically significant ageing effects survived multiple comparison corrections ($p < 0.05$ corrected for 5 domains).

Table 2
Longitudinal ageing (Time) and cross-sectional age (Age) effects in the linear mixed models of grey matter volume (GMV). Statistically significant effects ($p < 0.05$) appear in bold.

Network FC	Predictor	Coefficient	Standard error	*t*	*p*[a]
DMN	Gender	$-5.90e^{-3}$	$5.90e^{-3}$	−1.00	0.32
	Education	$-8.78e^{-4}$	$9.84e^{-4}$	0.89	0.36
	Age	$\mathbf{-1.30e^{-3}}$	$\mathbf{5.56e^{-4}}$	**−2.34**	**0.022**
	Time	$\mathbf{-2.84^{-3}}$	$\mathbf{3.68e^{-4}}$	**−7.72**	**<0.001**
	Age × Time	$-6.12e^{-5}$	$6.63e^{-5}$	−0.92	0.36
ECN	**Gender**	**−0.015**	$\mathbf{6.19e^{-3}}$	**−2.34**	**0.022**[b]
	Education	$2.78e^{-4}$	$1.03e^{-3}$	0.27	0.79
	Age	$-1.15e^{-3}$	$5.87e^{-4}$	−1.95	0.055
	Time	$\mathbf{-2.55e^{-3}}$	$\mathbf{3.33e^{-4}}$	**−7.65**	**<0.001**
	Age × Time	$-5.99e^{-5}$	$6.00e^{-5}$	−1.00	0.32
SN	**Gender**	**−0.021**	$\mathbf{6.42e^{-3}}$	**−3.19**	**0.0021**
	Education	$-6.49e^{-4}$	$1.07e^{-3}$	0.61	0.55
	Age	$\mathbf{-1.99e^{-3}}$	$\mathbf{5.99e^{-4}}$	**−3.32**	**0.0014**
	Time	$\mathbf{-3.45e^{-3}}$	$\mathbf{2.77e^{-4}}$	**−12.46**	**<0.001**
	Age × Time	$-9.15e^{-5}$	$4.95e^{-5}$	−1.85	0.67

Abbreviations: DMN = default mode network, ECN = executive control network, SN = salience network.

[a] *P*-values based on Satterthwaite approximation for denominator degrees of freedom, as implemented in the lmerTest package.

[b] Male had lower GMV than female.

No other cognitive domains showed significant effects of ageing ($p > 0.40$), although executive function showed a statistically significant decline with age, ($p = 0.005$; also see Supplementary Table S5.2 and S5.3 for a full documentation of all cognitive domains). More work is needed to verify if the absence of longitudinal changes in these domains can be attributed to stable trajectory, differences in sample characteristics and tests, or repeated exposure to tests (Goh et al., 2012; Lamar et al., 2003; Salthouse, 2010, 2014).

Association between changes in FC and cognitive performance

Based on the presence of longitudinal ageing effects, three brain–cognition regressions were conducted, associating the longitudinal

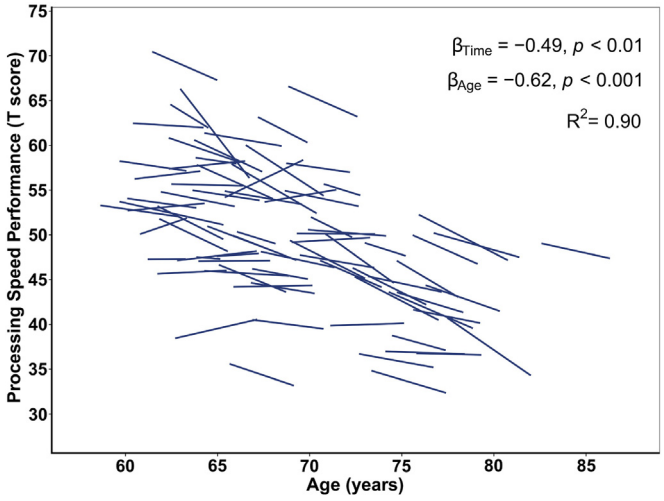

Fig. 5. Processing speed decreased with ageing in healthy older adults. Spaghetti plot of model-fitted longitudinal changes in processing speed with ageing for each individual. Processing speed evidenced a longitudinal decline (β_{Time}) with ageing as well as a significant effect of age (β_{Age}).

Table 3
Longitudinal ageing (Time) and cross-sectional age (Age) effects in the linear mixed model of speed of processing performance. Statistically significant effects ($p < 0.05$) appear in bold.

Model	Predictor	Coefficient	Standard error	t	p[a]
Processing speed	Gender	1.71	1.48	1.16	0.25
	Education	**0.65**	**0.25**	**2.62**	**0.011**
	Age	**−0.62**	**0.15**	**−4.01**	**$1.44e^{-4}$**
	Time	**−0.49**	**0.15**	**−3.26**	**$1.77e^{-3}$**[b]
	Age × Time	−0.026	0.028	−0.94	0.35

[a] *P*-values based on Satterthwaite approximation for denominator degrees of freedom, as implemented in the lmerTest package.
[b] The ageing effect in processing speed was also statistically significant in the reduced model without Age × Time interaction, confirming the longitudinal decline independent of Age.

change in processing speed with three FC measures in 3 ICNs- intra-DMN, intra-ECN, and inter-network (ECN–DMN), separately. There was a significant association between longitudinal change in processing speed and inter-network connectivity between the ECN and DMN ($p = 0.03$) such that faster decline in inter-network segregation (ECN–DMN) was associated with more rapid decline in processing speed (Fig. 6 and Table 4). This relationship remained after the longitudinal decline of the GMV of the DMN and ECN was incorporated as covariates in the brain–cognition regression. The coefficient of FC almost unchanged (coefficient = −83.90, $p = 0.038$; Supplementary Table S3.2), suggesting that the FC–cognition association cannot be solely attributed to reduced gray matter with age/ageing.

Analyses using motion scrubbed data revealed qualitatively similar negative correlation between longitudinal change in processing speed and ECN–DMN FC, with slightly reduced significance level (see details in Supplementary Materials S4).

Reductions in intra-DMN and intra-ECN FC with ageing had no significant association with decline in processing speed ($p > 0.24$).

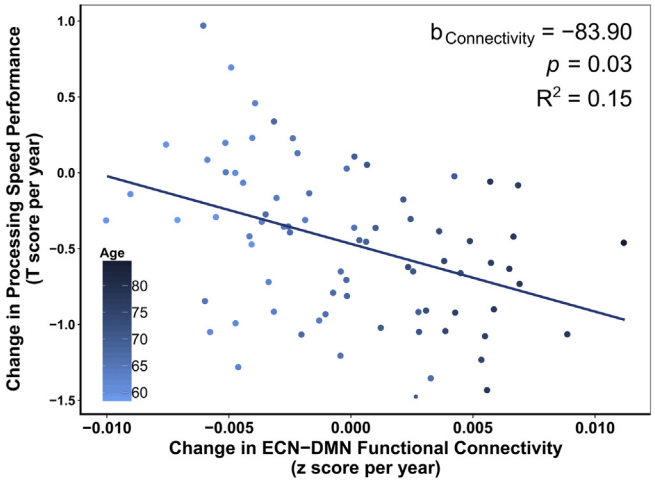

Fig. 6. Greater increase in inter-network functional coupling between executive control (ECN) and default mode (DMN) networks was associated with faster decline in processing speed. Each point represents the subject-level longitudinal change in brain inter-network FC between ECN and DMN (*x*-axis, higher values indicate greater loss of functional segregation) and corresponding longitudinal change in processing speed (*y*-axis, lower values indicate more rapid decline in processing speed). The color of the points indicates the participant's age at baseline. Greater ageing-related loss in functional segregation between ECN and DMN evidenced by the increase in network coupling between these networks was associated with faster decline in processing speed ($b_{connectivity}$, estimated coefficient b_2 in Eq. (4)).

Table 4
Association between speed of processing and inter-network functional connectivity (ECN–DMN FC) in the multiple regression model. Statistically significant effects ($p < 0.05$) appear in bold.

Model	Predictor	Coefficient	Standard error	t	p
Processing speed	Age	0.031	0.031	1	0.32
	ECN–DMN FC	**−83.90**	**37.80**	**−2.22**	**0.030**[a]
	Age × FC	1.17	2.01	0.58	0.56

Abbreviations: ECN–DMN FC = inter-network functional connectivity between executive control network and default mode network.
[a] The association with DMN–ECN FC was also statistically significant in the reduced model without Age × FC interaction, confirming the brain–cognition correlation independent of Age.

Discussion

In observing functional connectivity and cognitive performance among relatively healthy older adults over a period of 4 years, we found evidence for both within-network and between-network changes in functional connectivity. Ageing related decreases in intra-network FC within the ECN and DMN, likely signify loss of functional specialization. The u-shaped trajectory of ageing-related functional segregation between ECN and DMN suggests initial compensatory efforts and that ends with declining functional segregation of networks in older age. Greater decline in this ECN–DMN segregation, evidenced by increased coupling between the networks, was associated with faster decline in processing speed.

Ageing was associated with linear decline in intra-network functional connectivity

Our longitudinal data affirm prior cross-sectional reports on age-related lowering of FC within higher-order ICNs such as DMN and ECN (Andrews-Hanna et al., 2007; Geerligs et al., 2014, 2015). We found only marginal decline in SN connectivity with ageing, but this is consistent with the mixed findings of both reduced (Geerligs et al., 2015) and increased SN connectivity (Voss et al., 2013) in existing cross-sectional studies. This might be due to the more heterogeneous age-related functional changes of SN (Song et al., 2012), making statistical characterization of its longitudinal trajectory more difficult. Overall, our findings support the notion that ageing is accompanied by progressive loss of functional specialization within brain networks related to higher cognitive functions.

Ageing was associated with a u-shaped trajectory of change in between-network functional connectivity with increasing age

Previous cross-sectional studies on old adults have shown reduced anti-correlation or increased coupling between ECN and DMN compared to young adults (Biswal et al., 2010; Chan et al., 2014; Ferreira et al., 2015; Geerligs et al., 2015). For instance, Ferreira et al. (2015) recently reported both increased positive correlation and reduced anti-correlation in a cross-sectional study of old and young adults. Increased synchrony between networks observed with greater age is thought to reflect loss of segregation between functionally distinct neural modules (Chai et al., 2013; Ferreira et al., 2015; Yeo et al., 2015). Here, our longitudinal analysis revealed an ageing by age interaction of ECN–DMN functional connectivity. Specifically, we found a u-shaped evolution of FC with *ageing* (cf. age). Nonlinear age-related FC change has been documented in both longitudinal and cross-sectional studies (Fernández et al., 2012; Fjell et al., 2015a, 2015b; Raz et al., 2005). Chan et al. (2014) found an inverted u-shaped trend in the *cross-sectional* lifespan trajectory of the functional segregation among task-positive networks and DMN.

We attributed this nonlinear change in inter-network coupling to a compensation mechanism that might depend on the intricate balance

between intra-network integrity and inter-network coupling (Antonenko and Flöel, 2014). In the face of ageing related decline of functional specialization *within* DMN and ECN, younger elderly might still be able to maintain cognitive function by recruiting additional brain areas (Daselaar et al., 2015; Reuter-Lorenz and Cappell, 2008) or by maintaining the segregation between ECN and DMN during task performance (Fornito et al., 2012; Liang et al., 2015; Turner and Spreng, 2015). These compensatory efforts can be accompanied by reorganization of intrinsic connectivity networks until the age of 60s (Fernández et al., 2012; Song et al., 2014). With further ageing, adaptive mechanisms appear to eventually fail (Walhovd et al., 2014), as evidenced by increased DMN–ECN coupling.

Interestingly, structural connectivity may also show nonlinear age-related changes (Zhao et al., 2015). An age-varying association between white matter integrity and processing speed has also been demonstrated (Hong et al., 2015). Future investigations could find out whether and how functional connectivity is related to white matter microstructure and/or structural connectivity in the process of ageing.

Reduced functional segregation and decline in processing speed

Decline in processing speed was observed with ageing and processing speed was lowest in the oldest adults. Younger elderly who evidenced *increasing* DMN–ECN coupling in the short observation period, showed slower decline in processing speed. In contrast, the oldest participants showed ageing related increase in network coupling and evidenced a faster decline in processing speed. These crucial findings remained after taking into account age-related reduction in gray matter volume within the two relevant ICNs.

As argued, increased coupling between ECN and DMN may indicate poorer modularity of the ageing brain (Geerligs et al., 2015; Meunier et al., 2010), which can compromise the balance between DMN suppression and ECN activation during task performance (Grady et al., 2006; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Park, 2014; Sporns, 2013; Turner and Spreng, 2015). From a cognitive perspective, this imbalance could mean poorer ability to differentiate goal-related and goal-irrelevant information (Braver and West, 2008; Grady et al., 2010; Logan et al., 2002) that ultimately contributes to a decline in processing speed.

We did not observe any association between lower functional integration within ECN and DMN and decline in processing speed. This is in contrast with earlier cross-sectional studies that have linked age-related decrease in DMN functional connectivity with processing speed (Andrews-Hanna et al., 2007) as well as decline in ECN functional connectivity with diminished executive function (Shaw et al., 2015).

However, congruent with the present findings, in several psychiatric conditions such as schizophrenia and depression, loss of functional segregation rather than functional specialization appears to be better correlated with degraded cognitive performance (Whitfield-Gabrieli and Ford, 2012).

Limitations

Several limitations in our study should be noted. First, our sample size is comparable with previous cross-sectional FC studies (Andrews-Hanna et al., 2007; Keller et al., 2015) and longitudinal multimodal neuroimaging studies in ageing (Bernard et al., 2015; Goh et al., 2013; Persson et al., 2014; Vik et al., 2015) and it doubles the suggested sample size for task-based fMRI studies (Thirion et al., 2007). However, it provides power to detect only moderate to large effect sizes ($r > .3$). Larger samples may be required to detect the more subtle relationships involving age, connectivity, and cognition suggested by the cross-sectional literature (Biswal et al., 2010; Shaw et al., 2015). Second, although we did not explicitly evaluate the reliability of our task-free functional connectivity measures, a number of studies have demonstrated satisfactory reliability using healthy older adults and multiple-seed functional connectivity methods (Blautzik et al., 2013; Guo et al., 2012; Jovicich et al., 2016; Song et al., 2012). Third, the selection of parcellation schema could potentially influence experimental outcomes in task-free studies (Zalesky et al., 2010). However, the brain parcellation and labeling used here (Yeo et al., 2011) has been widely used in ageing and life span studies (Betzel et al., 2014; Chan et al., 2014; Ferreira et al., 2015; Fjell et al., 2015a). Use of surface-based registration methods and native space analysis might further account for individual differences in network topography and provide important finer-grained insights on age-related connectivity changes (Razlighi et al., 2014). More work is needed to investigate the possible nonlinear brain–cognition relationships in middle-aged persons in terms of both inter-individual differences and intra-individual changes (Walhovd et al., 2014).

Conclusion

In sum, we found that ageing is accompanied by linear reductions in functional connectivity within integrated networks, as well as a u-shaped evolution of segregation of the DMN and ECN networks. The rate of change of functional segregation correlated with the rate of processing speed decline. This association was maintained when gray matter volume reduction was taken into account. These findings reiterate the value of longitudinal studies when investigating the effect of ageing on brain and cognition.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2016.03.029.

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