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When functional blurring becomes deleterious: Reduced system segregation is associated with less white matter integrity and cognitive decline in aging

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ABSTRACT

Healthy aging is accompanied by progressive decline in cognitive performance and concomitant changes in brain structure and functional architecture. Age-accompanied alterations in brain function have been characterized on a network level as weaker functional connections within brain networks along with stronger interactions between networks. This phenomenon has been described as age-related differences in functional network segregation. It has been suggested that functional networks related to associative processes are particularly sensitive to age-related deterioration in segregation, possibly related to cognitive decline in aging. However, there have been only a few longitudinal studies with inconclusive results. Here, we used a large longitudinal sample of 284 participants between 25 to 80 years of age at baseline, with cognitive and neuroimaging data collected at up to three time points over a 10-year period. We investigated age-related changes in functional segregation among two large-scale systems comprising associative and sensorimotor-related resting-state networks. We found that functional segregation of associative systems declines in aging with exacerbated deterioration from the late fifties. Changes in associative segregation were positively associated with changes in global cognitive ability, suggesting that decreased segregation has negative consequences for domain-general cognitive functions. Age-related changes in system segregation were partly accounted for by changes in white matter integrity, but white matter integrity only weakly influenced the association between segregation and cognition. Together, these novel findings suggest a cascade where reduced white-matter integrity leads to less distinctive functional systems which in turn contributes to cognitive decline in aging.

1. Introduction

Healthy aging is accompanied by progressive decline of cognitive performance (Nyberg et al., 2003a; Nilsson et al., 2004; Gorbach et al., 2017; Tucker-Drob et al., 2019) and concomitant changes in brain structure (Fjell and Walhovd, 2010; Raz et al., 2005; Salami et al., 2012a), dopaminergic neurotransmission (Bäckman et al. 2010; Rieckmann et al., 2011), and metabolism (Kalpouzos et al., 2009; Camandola and Mattson, 2017). Common observations also include age-related alterations in brain activation across several cognitive domains, such as working memory and executive function (Reuter-Lorenz and Cappell, 2008; Schneider-Garces et al., 2010; Nyberg et al., 2003b, 2014), episodic memory (Cabeza et al., 2002; Cabeza, 2004; Nyberg et al., 2019; Salami et al., 2012b), and perceptual processing (Grady et al., 1994; Goh et al., 2010; Burianová et al., 2013). These changes are accompanied by a pronounced reduction in functional specialization in the brains of elderly individuals compared to younger adults, i.e., reduced specificity of activation in distinct neural structures related to particular processing roles, often referred to as neural dedifferentiation (e.g., Park et al., 2004; Dennis and Cabeza, 2011; Goh, 2011).

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In line with observations of less specific brain activation in older age, resting-state fMRI studies have provided support for reduced synchronicity of activation on a network level. In healthy younger adults, functional brain networks exhibit a modular organization characterized by greater functional connectivity, i.e. synchronicity of brain activation, among regions belonging to the same network, and sparser connections between regions of different networks (Bullmore and Sporns, 2009, 2012; He and Evans, 2010; Meunier et al., 2010; Bullmore and Bassett, 2011; Van den Heuvel and Sporns, 2013). However, elderly individuals typically show less segregated networks compared to their younger counterparts, with relatively weaker connections within networks, along with stronger interactions between networks (Chan et al., 2014; Cao et al., 2014, Geerligs et al., 2012, 2014; Wig, 2017; for a review see Damoiseaux, 2017; Liem et al., 2019). These observations suggest that aging is accompanied by progressive degeneration of functional network architecture, disrupting the brain's functional organization even in the absence of disease. Importantly, age-related disruptions in functional brain architecture may have detrimental consequences for cognitive function, as maintenance of segregated systems is particularly important for optimal brain function and metabolic efficiency (Van den Heuvel and Sporns, 2011; Bullmore and Sporns, 2012; Wig, 2017). Along these lines, previous studies have reported a positive association between particular cognitive processes and the degree of system segregation at different levels of organization (Chan et al., 2014; Gu et al., 2015; Cohen and D'Esposito, 2016; Grady et al., 2016; Yue et al., 2017; Nashiro et al., 2017). Notably, a cross-sectional study by Chan et al. (2014) found episodic memory performance to be positively associated with the degree of segregation among associative systems, but not segregation among sensorimotor systems. Importantly, the same study found associative system segregation to decline quadratically in relation to age, whereas segregation of sensorimotor systems followed a linear age-trajectory. This finding suggests that higher-order networks related to associative processes are particularly sensitive to age-related deterioration. However, cross-sectional estimates of age-related changes may deviate from their longitudinal counterparts (e.g., Nyberg et al., 2010), calling for further examination of changes in functional segregation in relation to cognitive decline in a longitudinal setting.

To date, only a few longitudinal studies have investigated age-related changes in functional system segregation, corroborating findings of age-related decline among particular resting-state networks (Ng et al., 2016, Chong et al., 2019, Malagurski et al., 2020). Results from one study suggest that greater maintenance of fronto-parietal system segregation is beneficial for maintaining efficient processing speed in aging (Malagurski et al., 2020). However, a similar longitudinal study found no such change-change association between functional segregation and processing speed (Chong et al., 2019). It is therefore still unclear whether age-related changes in functional segregation have implications for cognitive functioning.

A notable difference between longitudinal and cross-sectional work to date, is that the former has been relatively limited in the scope of investigation, with a focus on age-related changes in a particular resting-state network in relation to a specific cognitive domain (Ng et al., 2016; Chong et al., 2019; Malagurski et al., 2020). In contrast, previous cross-sectional studies have investigated individual differences in cognitive function in relation to segregation across multiple scales, from distinct resting-state networks (e.g., Stevens et al., 2012; Geerligs et al., 2014; Grady et al., 2016; Nashiro et al., 2017) to large-scale associative and sensorimotor systems (e.g. Chan et al., 2014; Gallen et al, 2016; Manza et al., 2020). The absence of longitudinal investigation of age-related changes in large-scale systems, incorporating multiple higher-order networks, is a critical omission in the literature, knowing that age-sensitive fluid-type cognitive functions likely depend on interactions between multiple brain systems (Baltes and Lindenberger, 1997; Corbetta and Shulman, 2002; Cohen and D'Esposito, 2016; Posner and Petersen, 1990). Longitudinal investigation of changes in a large-scale associative system (c.f. Chan et al., 2014) may therefore reveal greater correspondence between functional segregation and general fluid-type cognition than previously observed for individual networks. In addition, previous longitudinal studies have been limited to age-related changes in older age, due to the absence of lifespan data (Ng et al., 2016, Chong et al., 2019, Malagurski et al., 2020). It therefore remains unclear when decline in functional segregation sets in, and whether there are differences in the trajectory of changes between large-scale associative and sensorimotor systems.

While the underlying mechanisms of age-related changes in functional architecture are still largely unknown, individual differences in functional connectivity are at least in part related to differences in structural connectivity (Damoiseaux and Greicius, 2009; Van den Heuvel et al., 2009; Honey et al., 2009, 2010; Bettinardi et al., 2017; Suárez et al., 2020; Avelar-Pereira et al., 2020), with some variation across associative and sensory regions (Vázquez-Rodríguez et al., 2019; Baum et al., 2019). Cross-sectional and longitudinal studies have shown that aging is accompanied by deterioration in white matter microstructure (Madden et al., 2009, 2012; Nyberg and Salami, 2014; Sexton et al., 2014), contributing to disconnection among distributed neural systems. The relation between age-related differences in structural and functional connectivity is, however, less clear. Whereas some studies have reported that age-related alterations in functional connectivity are related to differences in structural connectivity (Andrews-Hanna et al., 2007; Chen et al., 2009; Avelar-Pereira et al., 2020), others showed that changes in structural and functional connectivity are mostly independent and only weakly interrelated (Fjell et al., 2016; Tsang et al., 2017; Madden et al., 2020). On the other hand, it is possible that age-related disconnection in the brain's structural wiring may result in aberrant balance of within- and between-network connectivity, and in turn lead to alterations in functional segregation (Wig, 2017). However, no longitudinal study has explored associations between changes in white matter integrity and functional segregation, and their consequences for cognitive decline.

In the current work, we used a large longitudinal brain imaging sample, comprising 284 participants between 25 and 80 years of age at baseline, with up to three measurements over 10 years to investigate changes in global functional segregation, and segregation of two large scale systems related to associative and sensorimotor operations (c.f. Chan et al, 2014). First, we predicted that functional segregation decreases over 10 years, and secondly, that associative functional systems decline at a relatively greater rate in aging compared to sensorimotor-related systems. Secondly, we set out to explore when age-related decline in functional segregation begins throughout the lifespan. Thirdly, we assumed that age-related reductions in segregation are associated with a domain-general decline of cognitive abilities, given that functional segregation reflects between-network interactions that generalizes across all functional brain systems (see e.g., Wig, 2017). This assumption is supported by previous studies suggesting that measures of global cognitive abilities display age-related changes above and beyond specific cognitive domains (Wilson et al., 2002; Lindenberger and Ghisletta, 2009; but see (Salthouse, 2010) and correlate to a greater degree with certain brain derived measures such as white-matter integrity (Power et al., 2019). Fourth and finally, we set out to explore change-change associations between white matter integrity and functional segregation. Given the assumption that white matter disruptions in aging may underlie alterations in functional architecture, we expected changes in white matter integrity to, at least in part, contribute to changes in functional segregation.

2. Methods

2.1. Participants

Participants in the current study were part of the Swedish Betula prospective cohort study on memory, health, and aging (Nilsson et al., 1997). The Betula study was approved by the local Regional Ethical

Table 1
Sample size and attrition per data collection wave.

	W5	W6	W7
MRI sample, n	376	231	103
Sample attrition			
Dropouts w.r.t. previous wave, n (%)	-	145 (38.6)	49 (32.9)
rs-fMRI missing/corrupt/incomplete, n (%)	14 (3.7)	4 (1.73)	3 (2.9)
dwMRI missing/corrupt/incomplete, n (%)	10 (2.7)	6 (2.6)	1 (0.9)
Cog. eval. missing/corrupt/incomplete, n (%)	1 (0.3)	2 (0.9)	0 (0.0)
Dementia/misc. pathology, n (%)	44 (11.7)	26 (11.3)	7 (6.8)
Excessive head movement, n (%)	47 (12.5)	33 (14.3)	24 (23.3)
Analytical sample			
rs-fMRI/cog. sample, n	270	166	69
dw-MRI subsample, n	260	160	68
Sample characteristics (rs-fMRI/cog. sample)			
Age range, y	25–80	30–85	65–85
Age at baseline, mean y (SD)	59.6 (13.9)	58.4 (13.3)	63.1 (5.9)
Sex, female, n (%)	137 (50.7)	77 (46.4)	30 (44.1)

Note. Table of data availability stratified by data collection wave. Sample sizes reflect wave-wise complete cases. The analytical sample comprised data from 284 participants with up to three time points: n = 123 (1 time point), n = 101 (2 time points), and n = 60 (3 time points). Abbreviations: rs-fMRI = resting-state fMRI, dw-MRI = diffusion-weighted MRI.

Vetting Board at Umeå University, and all participants provided written informed consent in accordance with the guidelines of the Swedish Council for Research in the Humanities and Social Sciences. The Betula project has acquired a comprehensive set of health and cognitive data in six major data collection waves (W1–W6) between 1988-2014, with each follow-up approximately five years apart. A neuroimaging (MRI/fMRI) sample was recruited for waves five and six, including a total of 376 subjects aged 25-80 years at W5. A subsample of participants, aged 65 years and older, with imaging data from W5 and W6 were invited back for a third MRI/fMRI follow-up in 2017 (W7) including limited health and cognitive assessments. For a comprehensive summary of the Betula project, see Nyberg et al. (2020).

The current work was based on MRI/fMRI and cognitive data acquired at W5, W6, and W7. Following rigorous quality control and data cleaning procedures (see methods 2.3 and 2.6), the main analytical sample comprised a total of 284 healthy participants (50.7% females) aged 25–80 years at baseline. Based on the initial Betula imaging sample, only participants with both resting-state fMRI (rs-fMRI) and cognitive data were considered from each data collection wave following quality control and data cleaning procedures. This resulted in a longitudinal sample of 102 participants with data from two time points, and 60 participants with data from three time points, approximately five years apart. A wave-by-wave breakdown of data availability and attrition is summarized in Table 1. In brief, 44 participants were excluded due to pathology, predominately dementia disorder diagnosed at follow-up evaluations (see Nyberg et al., 2020). Careful attention was given to control for the effect of in-scanner head movement, which has been shown to correlate with increasing age (Savalia et al., 2016) and systematically affect resting-state correlations (Power et al., 2012; Gorbach et al., 2020). We therefore excluded rs-fMRI scans from 47 participants at W5, 33 participants at W6, and 24 participants at W7 due to excessive head movement (see details in Methods 2.3). The white-matter integrity analyses included a slightly smaller subsample due to missing/corrupt/incomplete diffusion-weighted MRI (dw-MRI) data. Consequently, the dw-MRI subsample contained 10 fewer participants at W5, six at W6, and one less at W7, compared to the rs-fMRI sample.

The dropout rate, prior to exclusion, was 38.6% (n = 145) from W5 to W6, and 32.9% (n = 49) from W6 to W7, only accounting eligible participants at least 60 years old at W6. The average age of dropouts was significantly greater than returnees for each follow-up (mean age difference ± SD between waves = 5.37 ± 0.14; W5-W6: $t = 4.63$, $p < 0.001$; W6-W7: $t = 2.42$, $p = 0.016$; two-sample t-tests between mean age of dropouts and returnees for each wave). However, dropouts and returnees did not differ in the primary measures of segregation, global cognition, or white matter integrity at baseline (all $ps > 0.05$), suggesting that our measures of interest were not biased due to attrition. See Supplementary Material S.1. for additional details about attrition analyses.

2.2. Image acquisition

All brain imaging data were collected using a 3T Discovery MR750 (General Electric) scanner equipped with a 32-channel head coil. Resting-state fMRI images were acquired with a six-minute gradient-echo EPI sequence using the following parameters: 37 trans-axial slices, 3.4 mm thickness, 0.5 mm gap, repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, flip angle = 80°, 96 × 96 matrix (zero-filled to 128 × 128), field of view (FOV) = 250 × 250 mm. Ten dummy scans were collected and discarded prior to experimental image acquisition to allow for progressive saturation of the signal. Participants were instructed to keep their eyes open, let their mind wander, and focus on a fixation cross presented on a computer screen visible through a tilted mirror attached to the head coil. High-resolution T1-weighted structural images were collected with a 3D fast spoiled gradient-echo sequence using the following parameters: 176 slices, 1-mm thickness, flip angle = 12°, FOV = 250 × 250 mm. Diffusion-weighted images were acquired with a spin-echo-planar T2-weighted sequence as follows: 64 slices, TR = 8,000 ms, TE = 84.4 ms, flip angle = 90°, FOV = 250 × 250 mm, b = 1000 s/mm^2, 32 independent directions, and six $b = 0$ images. Three sequence repetitions were acquired at W5 and W6, whereas W7 only included one repetition. To allow for consistency between waves, only the first repetition at each wave was used. Head movement was minimized using cushions inside the head coil for all imaging sequences. Each imaging occasion followed identical experimental designs and procedures, i.e., the same scanner, acquisition times, and head coil were used at each data collection wave.

2.3. Resting-state fMRI preprocessing

Resting-state fMRI data from each imaging session were preprocessed using the Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, University College London, London, United Kingdom). All images were first corrected for head motion using the realign and unwarp function in SPM12, which realigns all volumes with reference to the first volume in the series and unwarps the images to account for non-linear effects of head movement. Within-

subject rigid body registration was then carried out for functional-to-structural image alignment at each time point. Due to movement artifacts in eight participants' structural images, their functional images were instead co-registered to structural images collected at a previous or subsequent time point. The anatomical images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) likelihood maps, and subject-specific longitudinal templates were created with diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL; Ashburner, 2007) by a six-step iterative procedure. Next, a group-specific DARTEL template was created from all subject-specific templates. Flow-field mappings acquired from the template generation procedure were used in a two-step process to normalize individual rs-fMRI images to the group-specific template, followed by affine transformation to MNI-space. The images were then spatially smoothed using an 8-mm FWHM Gaussian filter. Finally, subject-induced B_0-inhomogeneities were corrected for using a median B_0-inhomogenity map.

Additional preprocessing steps were applied for the functional connectivity graphs to regress out linear and quadratic effects of average cerebrospinal fluid and white matter time courses, in addition to global signal using tissue probability maps (threshold of 0.5). Global signal regression (GSR) was employed to minimize vascular and motion-related artifacts (Power et al., 2017; Murphy and Fox, 2017). To correct for motion, a 24-parameter model was used: six motion parameters, six temporal derivatives, and their squares (Friston et al., 1996; Yan et al., 2013). In addition to the 24-parameter motion model and global signal regression, which has shown to be an efficient denoising strategy (Yan et al., 2013; Ciric et al., 2017), participants with resting-state scans exceeding an average absolute frame-wise displacement (FD; Power et al., 2012) of 0.28 mm between volumes were excluded from the analyses. This threshold was found to sufficiently negate association ($p > 0.05$) between in-scanner head-motion (FD) and segregation estimates for the two systems of interest (associative and sensorimotor) using Linear Mixed Effects models (LME; Fitzmaurice et al., 2012; see Eq. 2). Further, we applied a temporal high-pass filter with a cut-off at 0.01 Hz to control for low-frequency signal drift. While a more restrictive bandpass filter is commonly used, several studies have demonstrated that higher frequencies contain important signals for functional connectivity (Boubela et al., 2013; Kalcher et al., 2014; Chen and Glover, 2015), contributing to more robust connectivity estimates (Davey et al., 2013; Shirer et al., 2015) and produce stronger and more-reliable age effects (Geerligs et al., 2017). In line with previous studies, we observed that a high-pass filter yielded greater within-participant reliability, stronger age-effects, and better model fit (Table S2). It also reduced effects of head motion on connectivity (High-pass: $b = 0.059$, $t_{218} = 1.94$, $p = 0.054$; Bandpass: $b = 0.101$, $t_{218} = 3.09$, $p = 0.002$). We therefore considered high-pass filtering in the main pre-processing pipeline, although, results from the bandpass pipeline and additional comparisons are reported in the Supplementary Material S.2.

2.4. Graph construction

For each participant and time point, average resting-state time series were extracted from 264 cortical and subcortical brain regions (3-mm radius spheres) based on a commonly used functional connectivity parcellation by Power et al. (2011). Each brain region, or node, was labeled according to 13 resting-state networks defined by a consensus partition across several thresholds (see Power et al. 2011 for details about network assignments). To reduce the probability of deriving time series from non-gray matter voxels, we eroded each node by a liberal gray matter mask (voxels < 0.1% GM threshold were eroded). Time series from each node were subsequently correlated using Pearson's correlation followed by Fisher's r-to-z transformation to create a 264 × 264 connectivity matrix for each participant and data collection wave. Correlation coefficient along the main diagonals were replaced with NaNs. To avoid spurious negative associations introduced by GSR, negative coefficients were set to zero in accordance with previous work (Chan et al., 2014; Malagurski et al., 2020; for a discussion about the effects of GSR, see e.g., Murphy and Fox, 2017). Moreover, removal of negative correlations may ease the interpretability of segregation metrics (Chan et al., 2014; Malagurski et al., 2020).

Additional segregation estimates were computed for a set of robustness analyses to investigate the sensitivity of parcellation selection. Specifically, an alternative parcellation by Schaefer et al. (2017), based on 400 nodes assigned to seven resting-state networks (Yeo et al., 2011), was used to compute segregation estimates following the same method outlined above. Results from the robustness analyses and further details are reported in Supplementary Material S.2. In short, the robustness analyses yielded largely similar results to the main analyses, suggesting that the reported findings are robust to differences in nodal placement and network assignment.

2.5. System segregation

System segregation is a summary metric of the relative strength of functional connections within a network (i.e., "within-network connectivity") in relation to connections to other networks (i.e., "between-network connectivity"). Here, we quantified system segregation using a common metric formally defined as the difference between the mean within-network connectivity and the mean between-network connectivity, divided by the mean within-network connectivity (Chan et al., 2014; Malagurski et al., 2020). Accordingly, system segregation was computed for each resting-state network as follows:

$$Segregation_{nti} = \frac{\bar{Z}_{w,nti} - \bar{Z}_{b,nti}}{\bar{Z}_{w,nti}} \quad (1)$$

where $\bar{Z}_{w,nti}$ is the mean Fisher z-transformed correlation between regions *within* network n at data collection timepoint t for participant i, and $\bar{Z}_{b,nti}$ is the mean Fisher z-transformed correlation *between* regions in network n and all other networks at timepoint t for participant i. This procedure resulted in a segregation index for each network, participant, and time point, respectively. A whole-brain "global" average was subsequently computed by averaging functional segregation values across all networks. In addition, we averaged segregation values across networks that are functionally related to either associative or sensorimotor functions according to the system assignments reported by Chan et al. (2014). Accordingly, associative system segregation was defined by averaging segregation scores for the Cingulo-Opercular Network (CON), Default Mode Network (DMN), Dorsal and Ventral Attention Networks (DAN and VAN), the Fronto-Parietal Network (FPN), and the Salience network for each participant and timepoint. Sensorimotor system segregation was similarly computed by averaging segregation scores for the Sensorimotor hand and mouth network, as well as Visual and Auditory networks. The remaining networks defined by Power et al. (2011); i.e., cerebellar, memory, subcortical, and unknown network nodes; were kept to account for between-network connectivity across the entire brain.

The segregation measures used here effectively reflect the average distinctiveness of networks within a greater system, such that a high degree of segregation relates to relatively greater within-network connectivity than between-network connectivity. However, the method outlined above differs slightly from the method proposed by Chan et al. (2014), which averages the within and between network connections across systems before estimating segregation. While our method results in an equal contribution of each functional network to the segregation metric, the method by Chan et al. (2014) results in an equal contribution of each node. We found both methods to yield highly similar scores (associative system, $r = 0.95$; sensorimotor system, $r = 0.89$) but the method presented here proved to be less sensitive to in-scanner head-motion (FD; Table S5).

2.6. General cognitive ability

To compute a proxy for general fluid-type cognitive ability, we used principal component analysis (PCA) to decompose summary scores from a battery of cognitive tests completed at W5, W6, and W7. The cognitive test battery included measures selected to broadly represent cognitive abilities of episodic memory, fluid intelligence, processing speed, and word fluency. However, cognitive assessments at W7 were based on a reduced version of the test battery with fewer tests per cognitive domain. Methods of application and key references have been described in detail elsewhere (Nilsson et al., 1997; Salami et al., 2012a; Gorbach et al., 2017; Nyberg et al., 2020).

In brief, episodic memory (EM) was assessed as the sum of unstandardized scores from five tests at W5 and W6, and two tests in the reduced version of the test battery at W7. The five-item score included the following tests: (1) immediate free recall of 16 sentences with enactment (i.e. verb-noun phrases including an action [e.g., "lift the book"]); (2) delayed cued recall of verb-nouns from the previously presented sentences with enactment; (3) immediate free recall of 16 sentences without enactment; (4) delayed cued recall of sentences without enactment; and (5) immediate free recall of unrelated nouns (e.g., "watch; peace"). The two-item summary score at W7 included test (3) and (5). Fluid intelligence (henceforth called 'BD') was assessed as raw scores from a visuospatial Block Design task performed at each test wave, where participants were instructed to recreate spatial patterns shown on cards using colored blocks. Processing speed (PS) was assessed as the sum of correct responses in three timed tests at W5 and W6: letter-digit substitution, letter comparison, and a figure comparison test, whereas W7 only included the letter-digit substitution task. Word fluency (FL) was computed as the sum of unstandardized scores from three tests at W5 and W6, where participants were required to generate as many words as possible, starting with the letter 'A' in the first test, five-letter words starting with the letter 'M' in the second test, and profession names with the initial letter 'B' in the third test. The first and the third tests were included at W7.

Using a similar method as in previous work from the Betula project (Johansson et al., 2019), summary scores from the reduced test battery completed at W7 were transformed to be on the same scale as scores acquired at W5 and W6. This was achieved by multiplying each score at W7 by a scaling factor, defined as a group-averaged ratio of scores acquired at W5 and W6 (mean of W5 and W6) in relation to scores acquired at W7. First, individual scaling factors were computed for each participant and cognitive measure. An average factor was used for participants whose individual scaling factors deviated more than 1.5 SD from the mean (n = 8). Finally, individual scaling factors were averaged across all participants to reflect the mean difference between the full-scale measure completed at W5 and W6 and the reduced test performed at W7, for each cognitive domain respectively. This method yielded highly similar results as the ratio between full-scale measures and reduced versions at W5 and W6 (c.f. Johansson et al., 2019). Participants' missing cognitive data from three or more tests were excluded from the analysis (n = 3), while missing scores from up to two tests (n = 16) were replaced by age-matched averages acquired at the same data collection wave. Pearson correlations between the four summary measures (EM, FL, PS, and BD) ranged between $r = 0.26 - 0.58$ (n = 270; mean = 0.41) at W5, $r = 0.39 - 0.66$ (n = 166; mean = 0.48) at W6, and $r = 0.23 - 0.42$ (n = 69; mean = 0.30) at W7.

A general fluid-type cognitive measure was computed using PCA on standardized baseline scores from the entire sample, prior to fMRI data exclusion due to in-scanner head movement, using singular value decomposition as implemented in the *prcomp*-function in R (version 3.6.2; R Core Team, 2019). Follow-up scores were omitted in the PC estimation to avoid bias of within-subject variance unrelated to trait-specific variation. This resulted in four components, of which only the first unrotated principal component (FUPC) had an eigenvalue greater than one (eigenvalue = 2.29) and accounted for 57% of the total test variance. The remaining components were therefore omitted from further analyses. The component loadings were relatively similar for each of the four summary measures (EM = 0.51, FL = 0.41, PS = 0.55, BD = 0.51), suggesting that each measure contributed to the FUPC to a similar extent. Finally, a general cognitive ability score was computed by applying the rotation matrix (scaled by the component's standard deviation) to the original summary scores from each participant and time point.

2.7. White matter integrity

Individual differences in white matter (WM) microstructural integrity were assessed using fractional anisotropy (FA). FA is a widely used measure of WM fiber integrity, reflecting the degree of relative directionality of water molecules in white matter fiber bundles (Pierpaoli and Basser, 1996; Beaulieu, 2014). Individual measures of FA were computed using tract-based spatial statistics (TBSS; Smith et al., 2006) as implemented in the University of Oxford's Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl).

Diffusion-weighted images (DWI) from the three time points (W5, W6, and W7) were first corrected for head motion and eddy-current-induced distortions. Each participant's *B*-matrix was subsequently reoriented based on the transformation matrix (Leemans and Jones, 2009), followed by brain masking by thresholding the first ($b = 0$) gradient map. DTIfit (Jenkinson and Smith, 2001) was used to fit diffusion tensors to each voxel in the brain mask, yielding voxel-wise maps of fractional anisotropy (FA) for each participant and time point. Next, the FA maps were aligned to a common space using the Nonlinear Image Registration Tool (FNIRT) in FSL, followed by affine-aligning images into MNI152 standard space. This approach yields a highly similar result to alternative longitudinal pipelines (e.g., as suggested by Engvig et al., 2011; for a comparison see Avelar-Pereira et al., 2020).

Individual WM tracts were labeled according to the ICBM DTI-81 atlas, developed at Johns Hopkins University and distributed with the FSL package (Wakana et al., 2004). As a proxy measure of whole-brain WM integrity, global FA was computed for each participant and time point by averaging the mean FA across all atlas-labeled tracts: the genu, splenium, and body of the corpus callosum, fornix, the right and left corticospinal tracts, cingulum cingulate gyrus and parahippocampal bundles, the corona radiata and posterior thalamic radiation, the internal and external capsule, superior longitudinal and fronto-occipital fasciculus, sagittal stratum, and tapetum.

2.8. Statistical analyses

Longitudinal changes in functional segregation (global, associative, and sensorimotor systems), general cognitive ability, and WM integrity, were assessed using linear mixed effects (LME) models implemented in the *lme4*-package (v. 1.1-23; Bates et al., 2012) in R (version 3.6.2; R Core Team, 2019). Using LME, we were able to account for different number of observations across participants. For each segregation measure, we modelled fixed and random effects simultaneously as follows:

$$Y_{ij} = \gamma_{00} + \gamma_{01} Age_j + \gamma_{02} Sex_j + \gamma_{10} Time_{ij} + \gamma_{20} FD_{ij} + \gamma_{11} Age_j \times Time_{ij} + \mu_{0j} + \mu_{1j} Time_{ij} + \varepsilon_{ij} \quad (2)$$

where Y_{ij} denotes either global, associative, or sensorimotor system segregation for each participant j at time point i. Random intercepts μ_{0j} and slopes μ_{1j} for the effect of time were modeled for each subject, in addition to a population-level fixed effect of longitudinal change γ_{10}. $Time_{ij}$ was defined as 0 at W5 for participant j, increasing in increments of five for wave W6 and W7 respectively, reflecting the 5-year interval between each data collection wave. A fixed effect of participants' age at baseline γ_{01} was included in the model. Age_j denoted the mean-centered age of participant j at T5, approximated by participants' age-cohort in five-year intervals, i.e., 25, 30, 35, …, 80; largely reflecting

each participant's actual age (see Nyberg et al., 2020). A binary dummy variable of participants' sex, Sex_j, was added as a nuisance variable (1 for females, 0 for males), along with individual and session-specific average frame-wise displacement, FD_{ij}, to control for confounding effects of motion. We also included the interaction term $Age_j \times Time_{ij}$ to account for differences in longitudinal changes between participants of different ages. We used the same LME model defined in Eq. 2 to assess cross-sectional age-differences and longitudinal changes in WM integrity and global cognition, with the exception that the fixed effect for FD, γ_{20}, was omitted. In addition, previous studies have suggested that education may have an impact on brain integrity and segregation (Ng et al., 2016; Malagurski et al., 2020). A set of supplementary analyses revealed that both longitudinal changes in segregation and associations with cognition remained after controlling for education (Table S4).

To investigate associations of age-related changes between measures, we considered models with a significant fixed effect of γ_{10}Time. We applied a similar method used in previous studies investigating longitudinal associations between brain-cognition measures (e.g., Ng et al., 2016; Malagurski et al., 2020) by using individual slopes derived from the main LME models. Here, we defined change by combining both the fixed effects estimate and random predictors for each participant and time point at follows:

$$\beta_{1j} = \gamma_{10} + \mu_{1j} \quad (3)$$

yielding a change coefficient β_{1j} for each participant j. Using both population level fixed effects and random deviations (random slopes), the change coefficient reflects individual participants' magnitude of change, whereas zero indicate no change across time points. Change coefficients were computed for each measure and participant, respectively. Upon initial inspection, one participant's segregation slope was deemed as a statistical outlier (deviating >4.64 SD from the mean) due to a disproportionally low score at the first follow-up (less than half with respect to baseline and second follow-up). Thus, only baseline and second follow-up scores were used for this individual for slope estimation. Supplementary tests without outlier removal revealed an inflated association with global cognition (Fig. S2).

We used a similar approach as described above to test cross-sectional associations between measures. Here, we replaced slopes (eq. 3) with population level intercepts γ_{00} and random intercepts μ_{0j}. The individually estimated intercept coefficients effectively yielded a proxy of baseline scores based on multiple measurements, orthogonal in regard to participants' age and sex. Next, we discarded slopes, but not intercept, estimated for participants with a single observation. Finally, pairwise association tests were performed for intercepts and slopes between measures using partial correlations, while controlling for confounding age-effects.

To investigate the age for onset of accelerated decline in system segregation, we explored the first derivative of age-fitted trajectories using Generalized Additive Mixed Models (GAMM; Wood, 2017), implemented in the gamm4 R-package (Wood et al., 2017). Accordingly, system segregation was fitted as a smooth function S of time-varying age, grouped by each participant's unique ID. This can be expressed as follows:

$$Y_{ij} = \beta_0 + S(Age_{ij}) + b_i + \varepsilon_{ij} \quad (4)$$

where Age_{ij} denotes the age of participant j at time point i. The first derivative of the fitted spline was subsequently estimated using finite difference approximation. The onset of accelerated decline was estimated at the inflection point of the first significant negative derivative, with significance indicated by confidence intervals given by $\pm 2 \times$ standard errors (c.f., Salami et al., 2016).

The reported results include cross-sectional age-effects and longitudinal effects of time, and their interactions. Non-significant effects, or effects of nuisance variables, are reported in the main results when relevant. Complete models and results, along with complete results from the sensitivity analyses are reported in the supplementary material. Effects were otherwise considered statistically significant at the conventional 5% significance level. Bonferroni correction was applied for intercept-intercept correlations due to multiple testing (three tests: $\alpha = 0.05/3$). Associations which did not survive family-wise error correction are mentioned for each case respectively.

3. Results

3.1. Age-related changes in system segregation

Regarding our primary question (see Table 2), we found significant longitudinal decline in average whole-brain segregation ($b = -1.92 \times 10^{-3}$, $t_{218} = -4.58$, $p < 0.001$). Similar to previous studies, we also observed a negative association between global segregation and baseline age ($b = -1.13 \times 10^{-3}$, $t_{281} = -7.89$, $p < 0.001$), indicating that older individuals typically show less segregated systems compared to their younger counterparts. No interaction was observed between time and age ($b = -6.35 \times 10^{-5}, t_{218} = -1.63, p = 0.105$), suggesting that the global level of network segregation roughly declines at the same rate throughout the lifespan. However, visualizing a smoothed age-trajectory using generalized additive mixed models (GAMM) (Fig. 1) suggest a slight curvilinear age-trend for global segregation, with steeper decline at greater age. Although, the visualized GAMM-fits are not an exact representation of the fitted LME models (c.f. Fig. S3). The non-significant Time × Age interaction may therefore be a consequence of the fewer longitudinal observations in the younger cohorts < 55 years.

To explore the question whether associative and sensorimotor systems are differentially sensitive to age-related changes, we subsequently examined relative differences between the two systems by extending the LME model outlined in Eq. 2. Here, using system segregation as a dependent variable, we added a binary term of System (associative = 1, sensorimotor = 0) as a fixed effect, along with interaction terms of System × Time, and System × Age, and a three-way interaction of System × Age × Time. We found segregation among associative systems to decline at a greater rate over a 10-year period compared to sensorimotor systems (System × Time; $b = -3.31 \times 10^{-3}$, $t_{719} = -4.66$, $p < 0.001$), with exacerbated differences between the two systems at older age (System × Age × Time; $b = -1.51 \times 10^{-4}$, $t_{719} = -2.17$, $p = 0.03$). Moreover, associative systems were found to be less segregated at baseline (main effect of System; $b = -0.1176$, $t_{719} = -28.33$, $p < 0.001$) and trendline differences in average age-association between the two systems (System × Age; $b = -4.43 \times 10^{-4}, t_{719} = -1.83$, $p = 0.067$). We take these results to suggest that functional systems related to associative processes are comparatively more susceptible to age-related disruptions in functional architecture compared with sensorimotor-related systems.

In view of the observed differences in age-related changes between associative and sensorimotor segregation, we subsequently fitted independent LME models (according to Eq. 2) for each system respectively (see Table 2). We found significant negative associations of baseline age for both associative and sensorimotor systems ($ps < 0.001$). However, only the associative system showed significant longitudinal decline ($b = -4.15 \times 10^{-3}$, $t_{218} = -7.87$, $p < 0.001$), and a significant Age × Time interaction ($b = -1.20 \times 10^{-4}$, $t_{218} = -2.46$, $p = 0.015$), indicating accelerated decline with older age.

The non-linear age-related trajectory of associative system segregation suggest an inflection point of accelerated decline. To assess the onset of acceleration, we explored the age-trajectory using a generalized additive mixed model (GAMM; Wood, 2017). A population-level age-trajectory of system segregation was fitted as a smooth function of time-varying age (fitted splines depicted in Fig. 1). Accordingly, the onset of acceleration was determined by the first significant derivative following the inflection point of the fitted spline. We found a significant acceleration of decline in associative system segregation at the age of 58, whereas no inflection point could be determined for the relatively linear trajectory observed in global and sensorimotor system segregation.

Table 2
Linear mixed effects model of longitudinal aging (Time) and cross-sectional age (Age)-effects of Global, Associative, and Sensorimotor system segregation across ten years. Statistically significant effects ($p < 0.05$) appear in bold.

System	Predictors	Coefficient	Std. Error	*t*	*p*
Global average	**Age**	**-1.13×10^{-3}**	**1.43×10^{-4}**	**-7.89**	**<0.001**
	Time	**-1.92×10^{-3}**	**4.18×10^{-4}**	**-4.58**	**<0.001**
	Age × Time	-6.35×10^{-5}	3.90×10^{-5}	-1.63	0.105
Associative System	**Age**	**-1.38×10^{-3}**	**2.14×10^{-4}**	**-6.48**	**<0.001**
	Time	**-4.15×10^{-3}**	**5.27×10^{-4}**	**-7.87**	**<0.001**
	Age × Time	**-1.20×10^{-4}**	**4.86×10^{-5}**	**-2.46**	**0.015**
Sensorimotor System	**Age**	**-1.03×10^{-3}**	**1.99×10^{-4}**	**-5.18**	**<0.001**
	Time	-7.34×10^{-4}	5.73×10^{-4}	-1.28	0.2
	Age × Time	-2.06×10^{-5}	5.40×10^{-5}	-0.38	0.7

Note: P-values based on Satterthwaite approximation for denominator degrees of freedom, as implemented in the lmerTest package.

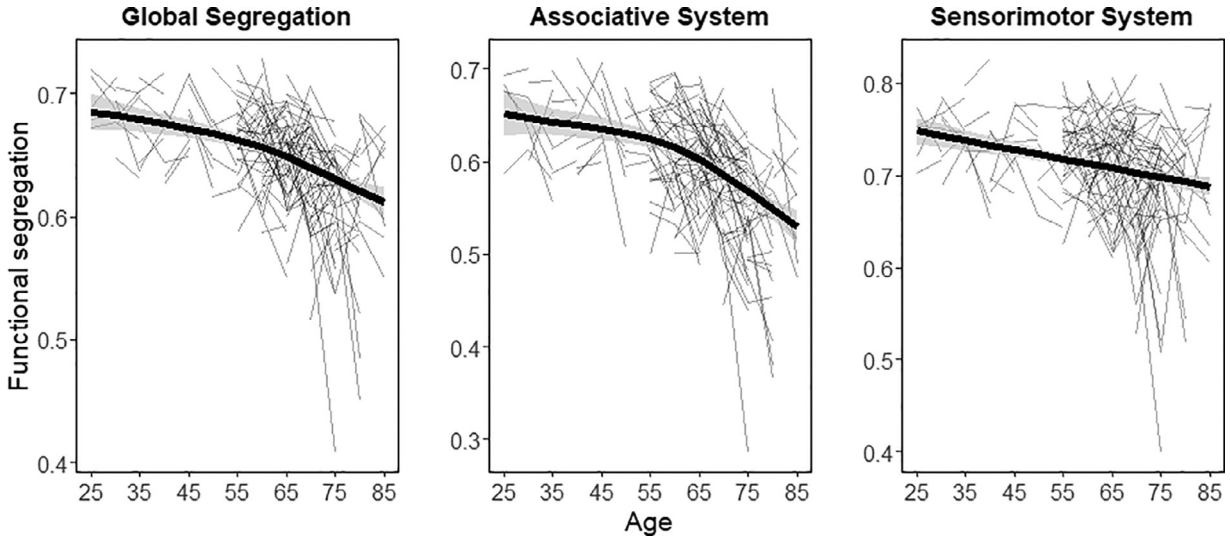

Fig. 1. Whole-brain global segregation, associative system, and sensorimotor system segregation differed in trajectory across the adult life span, with differences in intercept and rate of decline. For visualization, generalized additive mixed models were used to fit a smoothed spline (bold line) of segregation in relation to age. Confidence intervals (shaded area) given by 2 × Std. Error.

In summary, these results suggest divergent changes in segregation across discrete functional systems, with relatively greater age-sensitivity among associative systems. Both the sensorimotor and associative systems showed negative cross-sectional associations with age, however, only the associative system showed longitudinal decline of segregation, in addition to showing an accelerated rate of decline from approximately 58 years of age.

3.2. Age-related changes in system segregation in relation to cognitive decline

Next, we set out to investigate associations between changes in functional segregation and cognition. First, similar to the age-related decline in associative system segregation, we observed significant longitudinal decline in global cognition ($b = -0.24$, $t_{219} = -4.21$, $p < 0.001$). Moreover, longitudinal changes were found to be exacerbated at older age (Age × Time; $b = -2.41 \times 10^{-2}$, $t_{219} = -4.53$, $p < 0.001$), suggesting a non-linear trajectory of change in aging (Fig. 2A).

Associations between segregation and global cognition were explored cross-sectionally using partial correlations of individually fitted intercepts based on the main LME models, controlling for participants' age as a covariate of no interest. In line with previous cross-sectional studies, we found a positive association between the average level of associative system segregation and domain-general cognitive performance ($n = 284$, $r = 0.18$, $t_{280} = 2.48$, $p = 0.009$), but no association was observed for sensorimotor system segregation ($n = 284$, $r = -0.04$, $t_{280} = 0.49$, $p = 0.624$) or the global average ($n = 284$, $r = 0.08$, $t_{280} = 1.04$, $p = 0.289$). To test the hypothesis that the rate of age-related change in associative system segregation is associated with changes in cognitive function, we similarly used partial correlations of change coefficients based on individually fitted random slopes (Eq.3). We found that the rate of change in associative system segregation was positively associated with the rate of change in general cognitive function ($n = 161$, $r = 0.18$, $t_{158} = 2.21$, $p = 0.028$; Fig. 2B), such that greater decline in segregation was associated with worsened cognitive performance over time, independent of participants' age. While the strength of this association was relatively weak, we could replicate this finding in a set of robustness analyses ($r = 0.17$, $t_{158} = 2.10$, $p = 0.037$), using an alternative parcellation by Schaefer et al. (2017). Importantly, additional exploratory analyses revealed that the association between associative system segregation and domain general cognition was more robust than each cognitive summary score individually (i.e., episodic memory, fluid intelligence, processing speed, and word fluency; Table S6). Here, only changes in episodic memory was found to be significantly associated with changes in associative system segregation. However, this association was only observed in the main parcellation and could not be replicated in additional robustness analyses. Moreover, in contrast to observations by Malagurski et al. (2020), we observed significantly weaker associations between segregation and cognition in the bandpass pipeline, independent of network parcellation. This suggests that age-related associations between segregation and domain general cognitive function are robust to nodal placement and network assignment, but contingent on segregation estimates from a wider BOLD-frequency spectrum (Supplementary Material S.2).

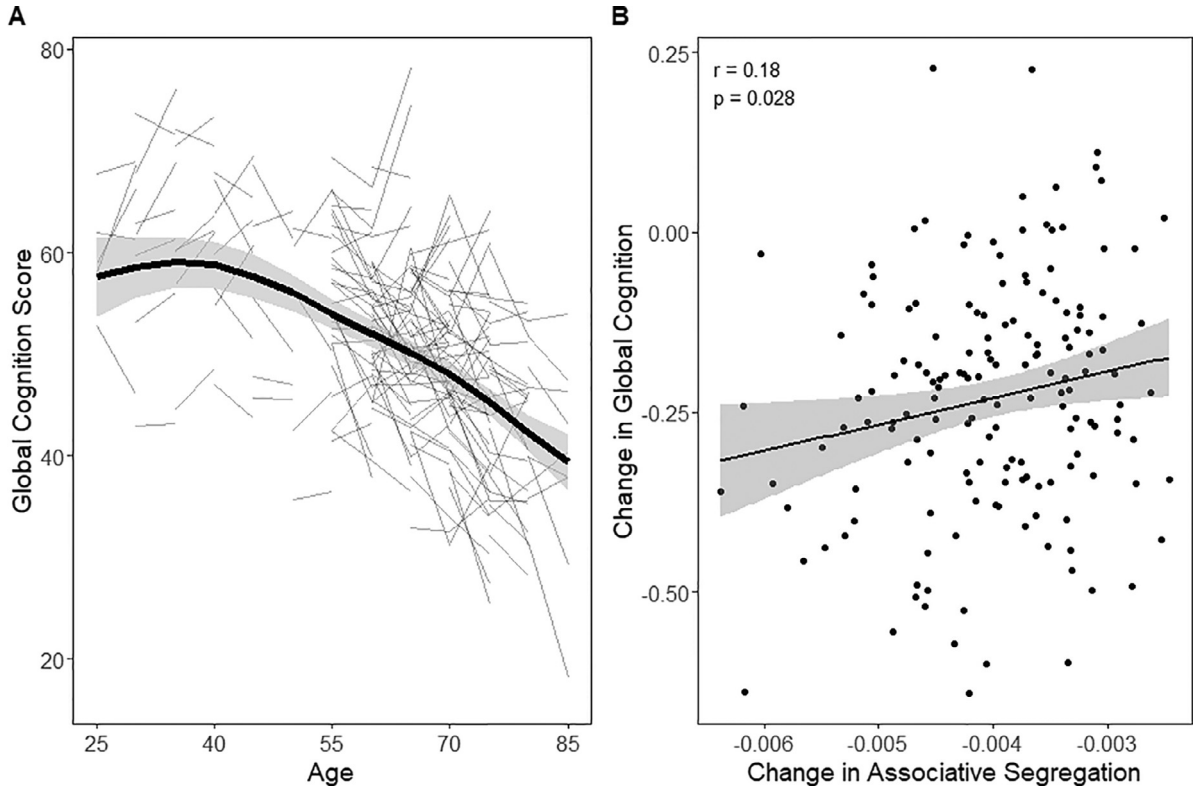

Fig. 2. (A) We observed significant longitudinal decline in global cognitive function, with exacerbated decline at older age. For visualization, a generalized additive mixed model was used to fit a smoothed spline (bold line) of global cognitive function in relation to age. Confidence intervals (shaded area) given by 2 × Std. Error. **(B)** We found changes in associative system segregation to be associated with changes in global cognitive function over a 10-year period.

3.3. Age-related decline in functional segregation in relation to changes in white matter integrity

In the view of age-related decline in functional segregation, we explored the hypothesis that declining system segregation is associated with changes in global white matter integrity (average FA). Similar to our previous work (e.g. Avelar-Pereira et al., 2020; Gorbach et al., 2017; Salami et al., 2012a), we observed longitudinal decline in FA (Time; $b = -5.99 \times 10^{-4}$, $t_{209} = -5.68$, $p < 0.001$). Greater age was found to be accompanied by exacerbated decline (Age × Time, $b = -5.83 \times 10^{-5}$, $t_{209} = -6.44$, $p < 0.001$; Fig. 3A) along with lower WM integrity at baseline (Age, $b = -1.12 \times 10^{-3}$, $t_{274} = -12.44$, $p < 0.001$). In addition to the global measure of white matter integrity, longitudinal decline in association fibers were considered in supplementary analyses. However, average white matter integrity for association fibers declined comparatively less than the global average (see Supplementary Material S.4).

Next, we set out to investigate whether age-related changes in white matter integrity may explain changes in associative system segregation, using partial correlations between individually fitted slopes as described previously (see Eq. 3). We found that the rate of change in associative system segregation was associated with changes in WM integrity ($n = 159$, $r = 0.20, t_{156} = 2.61$, $p = 0.009$), independent of participants' age. This suggests that the degree of deterioration in white matter integrity partly correspond to the degree of decline in segregation over time.

Given an association between longitudinal changes in white matter and segregation, we set out to explore whether changes in white matter integrity mediate the observed association between global cognition and associative system segregation. Thus, a multiple regression model was fitted with change coefficients for global cognition as a dependent variable, and change coefficients for average white matter integrity and associative system segregation as independent variables, while controlling for participants' baseline age. The results showed that the inclusion of white matter integrity partially mediated the effect of segregation ($b = 0.15, t_{155} = 1.87$, $p = 0.064$), while no association was observed between white matter integrity and global cognition ($b = 0.10$, $t_{155} = 1.29$, $p = 0.199$). However, a trend-level association was observed between changes in white matter integrity and cognition when segregation was dropped from the model ($b = 0.15$, $t_{156} = 1.85$, $p = 0.066$). We take these results to suggest that the association between associative system segregation and global cognition is largely independent of white matter integrity changes. Although, changes in segregation may mediate a link between white matter integrity and cognition.

4. Discussion

In the present study we investigated longitudinal trajectories and onset of change in functional segregation, along with associations with white matter integrity and cognitive function. In line with our first hypothesis, we found that global segregation declined over a 10-year period across the adult lifespan. Moreover, we observed divergent trajectories of change in segregation between associative and sensorimotor-related systems, such that only the associative system exhibited reduced segregation in aging. Critically, segregation of the associative system declined non-linearly in relation to age, characterized by a relatively stable age-trajectory until the late fifties, followed by steeper decline at older age. The onset of accelerated decline was estimated to be 58 years. However, it is possible that the onset of acceleration occurs at an earlier age than estimated here due to a greater number of longitudinal observations among older participants in the current study. Overall, our results extend previous cross-sectional findings implying that aging is accompanied by decreases in segregation of functional brain networks (Chan et al., 2014, Geerligs et al., 2014, Grady et al., 2016), with divergent trajectories between associative and sensorimotor sys-

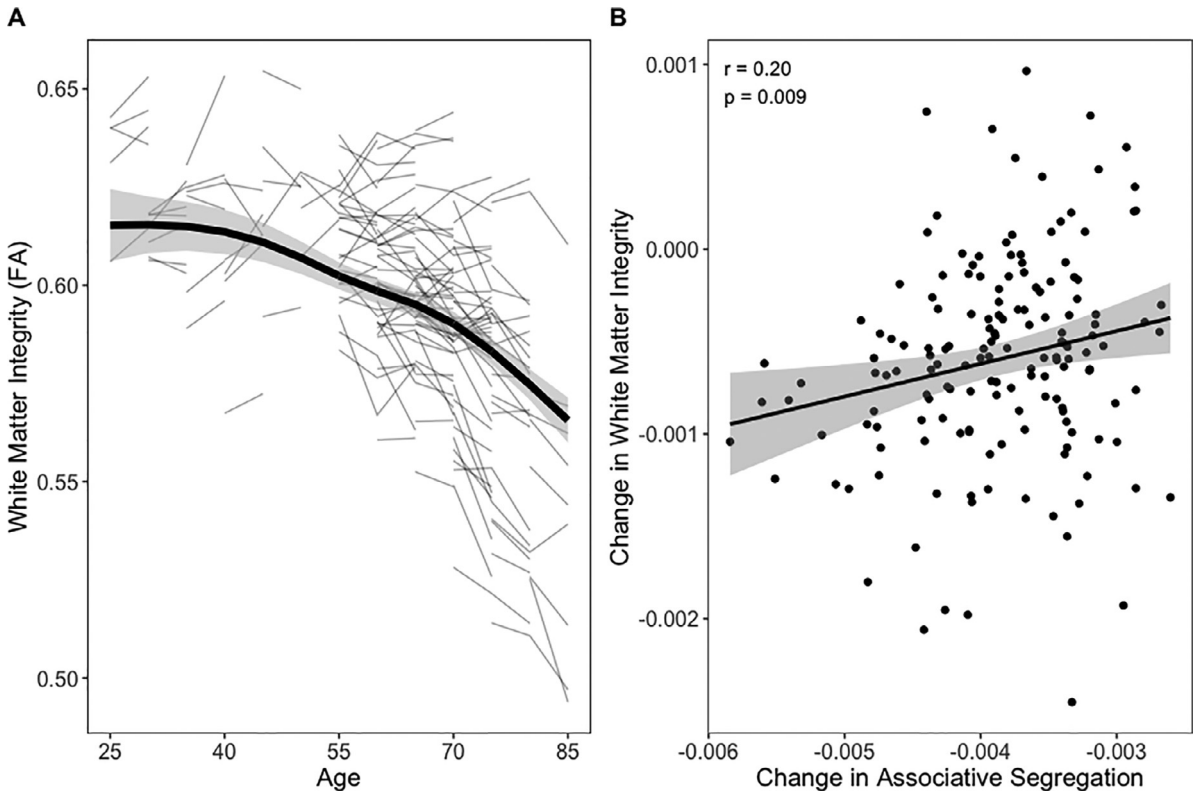

Fig. 3. (A) Average white matter integrity (FA) declined over time, with exacerbated decline at older age. For visualization, a generalized additive mixed model was used to fit a smoothed spline (bold line) of mean global FA in relation age. Confidence intervals (shaded area) given by 2 × Std. Error. **(B)** We found changes in white matter integrity to be associated with changes in associative system segregation over a 10-year period.

tems (Chan et al., 2014). Our findings also corroborate previous longitudinal studies of changes in functional segregation in older age (c.f. Chong et al., 2019; Ng et al., 2016, Malagurski et al., 2020). In contrast to the current work, previous longitudinal reports have mostly focused on individual networks, reporting relatively greater decline in segregation among higher-order resting-state networks (e.g., the fronto-parietal network or the default-mode network), concordant with the idea that phylogenetically late-developed brain structures are relatively more vulnerability to the effects of aging (Ribot, 1881; Raz, 2000, 2001; but see Douaud et al., 2014). Our findings compliment and expand upon previous reports by observing relatively greater reduction in segregation within in large-scale associative systems in comparison to sensorimotor systems. Moreover, assessing longitudinal decline over 10 years across a wide age-range (i.e., 25 to 80 years) is a unique feature of the present study, which allowed us to estimate onset of longitudinal decline among associative networks. Together, our results suggest that segregation of a phylogenetically late-developed system, encompassing associative regions, is particularly vulnerable to age-related decline.

Past studies suggest that severe cognitive impairment due to injury is typically a consequence of insult to a large-scale brain network (Seeley et al., 2009; Sharp et al., 2014). On this view, it is perceivable that cognitive decline in old age might be related to decreased functional segregation of age-sensitive systems. Given the age-sensitive nature of the associative system, along with its role for cognitive operations, such as allocation of attention, executive control, and mnemonic retrieval, we set out to explore whether age-related changes in system segregation related to domain-general cognitive decline. We found a positive association between changes in cognitive performance and segregation of the associative system. Given that both associative system segregation and cognitive performance declined in a majority of individuals, a positive change-change association suggest that greater maintenance of system segregation (i.e., less decline), in the associative system in particular, is beneficial for maintaining cognitive function in aging (c.f. Nyberg et al., 2012; Zuo et al., 2020). These results are in line with findings from several previous studies (e.g., Gu et al., 2015; King et al., 2017; Yue et al., 2017; Chong et al., 2019; but see Wig, 2017) which have reported associations between segregation and cognition. However, these studies have been restricted to specific networks and cognitive abilities. Our novel findings expand upon previous reports by linking changes in associative system segregation with domain-general cognitive decline, suggesting that network segregation may be of general importance for cognition function. While the effect size of the observed association was low in absolute terms, the relative effect is similar to previous reports of brain-cognition associations in general, and change-change associations between segregation and cognition in particular (c.f. Malagurski et al., 2020). However, there are only a few longitudinal studies to date that have investigated change-change associations between segregation and cognition (Chong et al., 2019; Malagurski et al., 2020), of which only one study by Malagurski et al. (2020) reported a significant association, specifically between fronto-parietal system segregation and processing speed. However, another longitudinal study by Chong et al. (2019) did not find any such change-change association between segregation and cognition. While we could not observe an association between associative system segregation and processing speed in the current study, we observed an association between segregation and episodic memory in a set of supplementary analyses (Table S5). Episodic memory has been found to be associated with system segregation before in a previous cross-sectional study (Chan et al., 2014). Although, we found the association with episodic memory to be parcellation-specific and could not be replicated using an alternative parcellation. Overall, the findings in the current study therefore corroborate and expands upon previous reports by observing an association between a global composite measure

of cognition and age-related changes in functional system segregation, and that these associations mainly are expressed in in segregation in a wider frequency range than previously used.

The mechanisms behind the observed association between segregation and cognition are still unclear, although, evidence suggests that fluid-type cognitive functions likely depend on interactions between multiple brain systems (Baltes and Lindenberger, 1997; Cohen and D'Esposito, 2016; Corbetta and Shulman, 2002; Posner and Petersen, 1990; Zuo et al., 2020). Changes in large-scale network topography, as reflected in age-related decreases in segregation of the associative system, may disrupt distributed network interactions that are critical for general cognitive function. On this view, our finding concords with previous studies suggesting that cognitive decline in aging is accompanied by reduced specificity in cognitive measures, as previously reported in work based on the Betula project (de Frias et al., 2007), which might be a consequence of dedifferentiation in brain function (Park et al., 2004; Lindenberger and Ghisletta, 2009; Dennis and Cabeza, 2011). Reduced distinctiveness of brain systems might therefore be a central mechanism of reduced specificity of task-related brain activation, as commonly have been observed in elderly individuals (e.g., Park et al., 2004; Dennis and Cabeza, 2011; Goh, 2011). Results by Chan et al., (2017) support this idea, showing that age-related reductions in network distinctiveness was accompanied by age-related reduction in task-related activation, in particular among association and sensorimotor systems. Taken together, reduced distinctiveness (i.e., decreased segregation) might reflect a fundamental age-related mechanism that contributes to age-related decline in older age.

In addition to age-related change in functional architecture, we found longitudinal decline in white matter integrity. Similar to changes in associative system segregation, we found a non-linear age-trajectory of global white matter integrity, with exacerbated decline in older age. These findings are in line with previous longitudinal studies of white matter microstructural decline in aging (e.g., Barrick et al., 2010; Sexton et al., 2014; De Groot et al., 2016; Gorbach et al., 2017). Previous cross-sectional studies have indicated that individual differences in functional connectivity among particular networks are, at least in part, related to differences in structural connectivity (Damoiseaux and Greicius, 2009; van den Heuvel et al., 2009; Honey et al., 2009; 2010; Bettinardi et al., 2017; Suárez et al., 2020). In addition, a recent longitudinal study showed that age-related decline in the genu of corpus callosum was related to longitudinal changes in prefrontal resting-state connectivity (Avelar-Pereira et al., 2020). In line with these reports, we found age-related decline in global white matter integrity to partly explain reductions in associative system segregation. Based on previous hypothetical models of structural and functional connectivity (Wig, 2017), it is reasonable to speculate that age-related disconnection in the brain's structural wiring may disrupt the balance of within- and between-network connectivity, leading to aberrant changes in functional segregation, consequently resulting in cognitive decline. That said, it is important to acknowledge that the observed association between changes in white matter integrity and associative system segregation was relatively weak, corroborating a recent report indicating limited correspondence between functional segregation and structural connectivity in aging (Madden et al., 2020). However, previous studies have reported regional discrepancies, with relatively weaker structural-functional correspondence among associative systems compared to sensory systems (Vázquez-Rodríguez et al., 2019; Baum et al., 2019), suggesting that associations between functional and structural properties may be constrained to specific networks and tracts (e.g., Fjell et al., 2016). In the current study, we found the association between changes in associative system segregation and global cognition to be relatively independent of white matter decline. No association was observed between changes in white matter integrity and cognitive performance while accounting for segregation, leaving the association between cognition and functional segregation mostly unchanged. This finding is in line with a recent study (Madden et al., 2020), reporting that functional system segregation mediates age-related decline in executive function to a greater degree than white matter integrity. Still, a cross-sectional study suggest that white matter integrity may account for greater variance in cognitive aging than functional connectivity within higher-order networks (Hedden et al., 2014). While differences between cross-sectional and longitudinal evaluations may differ, this may suggest that the segregation metric, which accounts for both within- and between-network connectivity, is a more sensitive biomarker for cognitive aging than within-network connectivity of a particular network. This notion is supported by previous reports corroborating the importance of between-network connectivity in relation to cognitive aging (e.g., Cohen and D'Esposito, 2016; Ng et al., 2016).

It is noteworthy that we used mean FA across the white-matter fibers defined by the ICBM DTI-81 atlas as a proxy for white matter integrity (Jones, Knösche, and Turner, 2013). However, it is not possible to rule out that other graph measures of structural connectivity might be more sensitive in relation to changes in functional segregation (but see Madden et al., 2020). Although our results showed partial contributions of white matter integrity to changes in functional segregation, it is important to note that neurochemical factors, such as glucose energy utilization, dopamine, and noradrenaline and their alterations in aging may contribute to age-related changes in functional segregation (c.f. Shine and Poldrack, 2018, Shine et al 2019, Manza et al., 2020). Future studies should further explore biological origins of the system segregation to better understand whether preserving factors such as neurotransmitter signaling may serve as a key factor to maintain system segregation and in turn cognitive function in older age.

5. Concluding remarks

The results in the current study indicate that functional segregation declines over a period up to 10 years, with divergent trajectories of change between associative and sensorimotor-related systems. We observed that age-related reduction in associative system segregation was exacerbated at greater age, with an accelerated rate of decline from the late fifties. Moreover, changes in associative system segregation mediated age-related decline in a domain-general measure of cognition, suggesting that greater decline in system segregation is detrimental to cognitive function independent of age. Finally, age-related decline in functional segregation was party accounted for by white matter integrity changes, suggesting a cascade of structural and functional changes resulting in cognitive decline in aging.

Credit author statement

AS, LN, and **LG** contributed to the conceptualization and design of the study. **RP** performed data analysis and wrote the first draft of the manuscript. **MA** contributed to data processing and software resources. **TG** contributed to formal analysis. **BAP** contributed to data processing and resources. **AW** and **AR** contributed to analysis and interpretation. **LN** is principal investigator for the Betula project and **AS** supervised the current study. **All authors** contributed to writing, reviewing and editing the manuscript.

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Disclosure statement

The authors have no current or potential conflicts of interest.

Data availability statement

The data that support the findings of this study are not publicly available due to privacy or ethical restrictions but are available upon reasonable request. Access to data by qualified investigators is a subject to scientific and ethical review and must comply with the European Union General Data Protection Regulations (GDPR) and all relevant guidelines. The completion of a data transfer agreement signed by an institutional official will be required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118449.

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