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Age differentiation within grey matter, white matter and between memory and white matter in an adult lifespan cohort

Susanne M.M. de Mooij[*,1], Richard N.A. Henson[2], Lourens J. Waldorp[1], Cam-CAN[3] & Rogier A. Kievit[2]

Abstract

It is well-established that brain structures and cognitive functions change across the lifespan. A longstanding hypothesis called *age differentiation* additionally posits that the relations between cognitive functions also change with age. To date however, evidence for age-related differentiation is mixed, and no study has examined differentiation of the relationship between brain and cognition. Here we use multi-group Structural Equation Modeling to study differences *within* and *between* brain and cognition across the adult lifespan (18-88 years) in a large (*N*>646), population-derived sample of healthy adults from the Cambridge Centre for Ageing and Neuroscience (www.cam-can.org). After factor analyses of grey-matter volume (from T1- and T2-weighted MRI) and white-matter organisation (fractional anisotropy from Diffusion-weighted MRI), we found evidence for differentiation for grey and white matter, such that the covariance between brain factors decreased with age. However, we found no evidence for age differentiation between fluid intelligence, language and memory, suggesting a relatively stable covariance pattern between cognitive factors. This pattern is compatible with adaptive reorganization of cognitive functions in the face of neural decline, and/or with the emergence of specific subpopulations in old age. Finally, we observed a specific pattern of age differentiation between brain and cognitive factors, such that a white matter factor, which loaded most strongly on the hippocampal cingulum, became less correlated with memory performance in later life.

Key words: Ageing, Differentiation, Grey Matter, White Matter, Structural Equation Modeling

Significance statement

The theory of age differentiation posits age-related changes in the relationships between brain structures and between cognitive domains, either weakening (differentiation) or strengthening (de-differentiation), but evidence for this hypothesis is mixed. Using multigroup models in a large cross-sectional adult lifespan sample we found age-related reductions in the covariance among both brain measures (neural differentiation), but no significant changes in the covariance between cognitive factors of fluid intelligence, language and memory. We also observed evidence of uncoupling (differentiation) between white matter factor and memory in older age. Together our findings support age-related differentiation as a complex, multifaceted pattern that differs for brain and cognition, and discuss several mechanisms that might explain the changing relationship between brain and cognition across the lifespan.

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1. Introduction

Ageing involves changes along many dimensions, from brain structure to cognitive function, and much is known about changes in individual measurements such as brain volume or memory performance. Determining the factors that affect these changes is important for understanding healthy ageing. However, comparatively little is known about age-related changes in the interrelations *between* various neural and cognitive measurements.

Within the cognitive domain, the age differentiation hypothesis states that the interrelations between cognitive abilities decrease during childhood development (Spearman, 1927; Deary & Pagliari, 1990). In contrast, some researchers have claimed that the opposite happens in old age, where cognitive abilities become more correlated, or de-differentiated (Garrett, 1946, de Frias et al., 2007). For instance, Ghisletta & Lindenberger (2003) used bivariate dual change score models in a large longitudinal sample to observe dedifferentiation between speed and knowledge domains in older age with declining ability. However, the evidence for this age differentiation-dedifferentiation hypothesis is mixed: Some studies also observe a pattern of differentiation followed by de-differentiation (Li et al., 2004) and still others observe no change (Tucker-Drob, 2009; Juan-Espinosa et al., 2002; Deary et al., 1996). These differences may partly reflect differences in analytical methods and sample sizes (Molenaar et al., 2010).

Fewer studies have examined age differentiation of brain organisation. An important feature of brain organisation is *structural covariance*, defined by the extent to which inter-individual differences in the structure of a brain region covary with inter-individual differences in other brain regions (Mechelli et al., 2005; Alexander-Bloch, Giedd, & Bullmore, 2013). Previous studies have demonstrated that measures of structural connectivity show similarities with resting-state functional connectivity (Damoiseux & Greicius, 2009; Seeley et al., 2009; Honey et al., 2009, but see Di et al., 2017; Tsang et al., 2017), developmental changes (Zielinski, et al., 2010; Alexander-Bloch et al., 2013) and anatomical (white matter) connectivity (Alexander-Bloch, Giedd, & Bullmore, 2013. Recently, Cox et al. (2016) examined white matter across the adult lifespan, and found that a single factor capturing covariance among white matter tracts increased in prominence with increasing age, suggesting de-differentiation. Various mechanisms have been posited to explain this de-differentiation, including selective vulnerability (Gianaros et al., 2006), scaffolding (Cabeza et al., 2002; Park & Reuter-Lorenz, 2009) or increased age-related aggregation of systemic adverse effects on brain structure (Cox et al., 2016).

An open question is whether age (de)differentiation occurs not just *within* neural or cognitive dimensions, but also between brain and cognition, such that psychological factors become more or less related to brain structure and function across the lifespan. Theories such as cognitive reserve seek to explain how "inter-individual differences in task processing allow some people to cope better than others with brain pathology" (Stern 2002, 2009). This notion of cognitive reserve explains the association of higher levels of education and occupation with slower rates of cognitive decline in healthy ageing. Accordingly, the covariance between brain structure and cognitive function would be lowest in

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individuals who display greatest cognitive reserve (Whalley et al., 2004). Conversely, theories such as brain maintenance, where preserved cognitive functioning is directly related to maintained brain capacity (e.g. Nyberg et al., 2012), would not predict age-related changes in brain-cognition covariance.

Here we examine age differentiation within and between cognitive and brain factors in a relatively large, healthy, population-based sample (18-88 years; Cam-CAN, Shafto et al., 2014), containing a range of brain measures (from T1/T2/Diffusion-weighted MRI) and cognitive measures. We tested (de)differentiation formally by testing age-related differences in covariance using multigroup, equality-constrained structural equation modeling (SEM). We examined both grey-matter volume and white-matter integrity, given prior evidence for their complementary roles in healthy cognitive aging (Kievit et al, 2014; Henson et al, 2016). To the best of our knowledge, this is the first study to simultaneously examine age (de)differentiation of grey matter, white matter and cognitive factors; and in particular age differentiation between cognitive and brain domains.

2. Methods

2.1 Participants

As part of Phase 2 of the Cambridge Centre for Ageing and Neuroscience (Cam-CAN), data on a wide range of lifestyle, cognitive and neural tests was collected from a healthy, population-based sample, described in more detail in (Shafto et al., 2014). Exclusion criteria include low Mini Mental State Exam (MMSE) (24 or lower), poor hearing (failing to hear 35dB at 1000 Hz in either ear), poor vision (below 20/50 on Snellen test), poor English knowledge (non-native or non-bilingual English speakers), self-reported substance abuse, and serious health conditions that affect participation (e.g. self-reported major psychiatric conditions, current chemo/radiotherapy, or a history of stroke). We also excluded people with MRI contraindications including disallowed implants, pacemakers, recent surgery or any previous brain surgery, current pregnancy, facial- or very recent tattoos, or a history of multiple seizures or fits) as well as comfort-related contraindications (e.g. claustrophobia or self-reported inability to lie still for an hour). A total of 707 people were recruited for the cognitive assessment (359 women) including approximately 100 individuals from each decile (age range 18-88, M=54.63, SD=18.62); usable grey matter was collected from 651 people and white matter from 646 people; sample sizes that are sufficient for moderately complex structural equation models (Wolf et al., 2013). Ethical approval for the study was obtained from the Cambridgeshire 2 (now East of England-Cambridge Central) Research Ethics Committee. Participants gave full informed consent. The raw data and code to reproduce all analyses can be acquired through the Cam-CAN data portal (https://camcan-archive.mrc-cbu.cam.ac.uk/dataaccess/index.php).

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2.2 Grey Matter (GM)

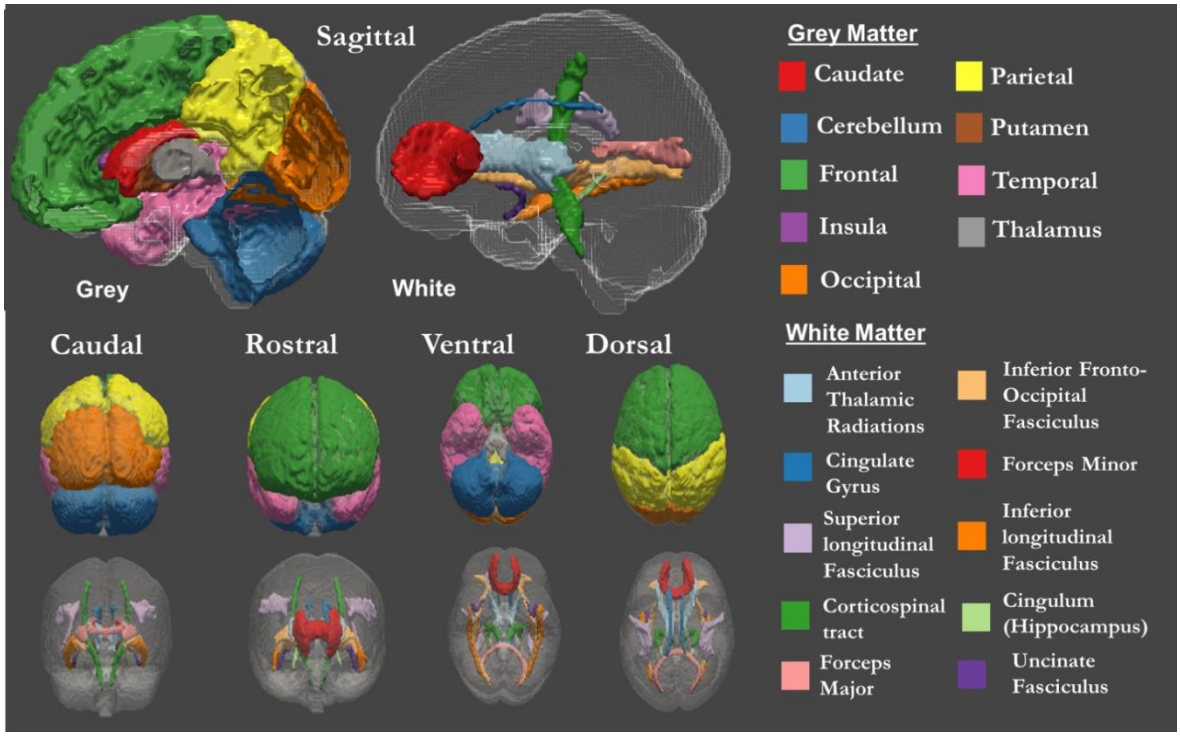

Figure 1. Nine grey and ten white matter tracts as defined by Montreal Neurological Institute (Mazziotta et al., 2001) and Johns Hopkins University white-matter tractography atlas (Hua et al., 2008).

To examine grey matter structure, we estimated grey matter volume (GMV) based on the combined segmentation and normalization of 1mm^3, T1- and T2-weighted MR images. For more detail on the preprocessing pipeline, see Taylor et al. (2015). We here use GMV for nine ROIs as defined by the Montreal Neurological Institute (Mazziotta et al., 2001). This atlas captures a set of canonical grey matter structures and has a similar number of ROI's (nine versus ten) as our white matter measure (see below), allowing us to compare evidence for (de)differentiation across grey and white matter using models of comparable complexity. The nine ROIs in the MNI atlas are Caudate, Cerebellum, Frontal Lobe, Insula, Occipital Lobe, Parietal Lobe, Putamen, Temporal Lobe and Thalamus (Figure 1).

2.3 White Matter (WM)

To investigate covariance in white matter structure, we estimated Fractional Anisotropy (FA) values in a set of white-matter ROIs. FA is a measure of the diffusivity of water molecules that is thought to reflect fiber density, axonal diameter and myelination. It is also sensitive to age-related changes in cerebral myelin (Kochunov et al., 2012), although there is discussion on the challenges and limitations of FA (Jones & Cercignani, 2010; Jones, Knösche, & Turner, 2013; Wandell, 2016). We computed the mean FA for ten ROIs as defined by Johns Hopkins University white-matter tractography atlas (Figure 1; Hua et al., 2008): Anterior Thalamic Radiations (ATR), Cerebrospinal Tract (CST), Dorsal Cingulate Gyrus (CING), Ventral Cingulate Gyrus (CINGHipp), Forceps Major (FMaj), Forceps Minor (FMin), Inferior Fronto-Occipital Fasciculus (IFOF), Inferior Longitudinal Fasciculus (ILF), Superior Longitudinal Fasciculus

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(SLF) and the Uncinate Fasciculus (UNC). For further details on the white matter pipeline, see Kievit et al. (2016).

2.4 Cognitive tasks

Five cognitive tasks were used to assess cognitive processing across three broad cognitive domains: language, memory and fluid intelligence. *Language* was measured using two tasks: 1) the Spot-the-Word test (Baddeley, Emslie, & Nimmo-Smith, 1993), in which word-nonword pairs (e.g. daffodil, gombie) are presented and the participant has to decide which is the real word, and 2) a proverb comprehension test, in which participants were asked to provide the meaning of three common proverbs in English (e.g. "Still waters run deep") yielding a score between 0 and 6. Our measure of *fluid intelligence* was the standard form of the Cattell Culture Fair, Scale 2 Form A (Cattell, 1971). This pen-and-paper test contains four subsets with different types of abstract reasoning tasks, namely matrices, series completion, classification and conditions. Finally, the third domain *memory* was assessed using measures of immediate and delayed (after 30-minutes) story recall, as well as recognition, from the logical memory sub-test of the Wechsler Memory Scale Third UK edition (Wechsler, 1997).

2.5 SEM Analyses

To improve convergence, prior to the SEM analyses, the neural and cognitive measures were scaled to a standard normal distribution. We used full information maximum likelihood estimation (FIML) and Robust Maximum Likelihood estimator with a Yuan-Bentler scaled test statistic (MLR) to account for violations of multivariate normality. To ensure possible outliers did not affect the results, we fit the models with both the raw data, as well as treating univariate outliers (z-scores greater than 4 or -4) as missing. Doing so did not affect any model comparison meaningfully, so we report the results for the full (raw) dataset. We used SEM to test for evidence for neural and cognitive age (de)differentiation in the following three steps: 1) establish an appropriate measurement model, 2) examine adult lifespan patterns of the factor scores, and 3) formally test for age (de)differentiation using Multigroup confirmatory factor analysis (MGCFA).

All models were fit using the package Lavaan (Rosseel, 2012) in the statistical software R (R Core Team, 2016). We assessed overall model fit using the χ^2 test, RMSEA and its associated confidence interval, CFI and SRMR (Schermelleh-Engel, Moosbrugger, & Müller, 2003). We considered good fits as follows: RMSEA < 0.05 (0.05-0.08 is acceptable), CFI > 0.97 (0.95-0.97 is acceptable) and SRMR < 0.05 (0.05-0.10 is acceptable). For the MGCFA, we compared models directly with the likelihood ratio test, the AIC (and Akaike Weights, Wagenmakers & Farrell, 2004) and the sample size adjusted BIC (saBIC, with associated Schwarz weights). For all age comparisons, we defined three discrete, equally sized subgroups: Young, Middle and Old (see Table 1). For each lifespan multigroup comparison, we compared a model where factor covariances were equality-constrained across the three age groups to a model where they were freely estimated. In the constrained model, all parameters were constrained between the groups,

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except for the means of the factors (to allow for age-related declines). By comparing these nested models, we could determine whether there is evidence for changing factor covariance structure across the lifespan.

Table 1 Demographics of age groups (young, middle and old) for neural and cognitive measures

	Age group	Sample size (*N*)	Mean age (*M*)	Standard deviation age (*SD*)
Grey Matter	Young	217	32.82	6.92
	Middle	217	54.56	6.25
	Old	217	75.56	5.91
White Matter	Young	215	32.87	6.89
	Middle	216	54.69	6.32
	Old	215	75.66	5.85
Cognition	Young	235	33.10	7.19
	Middle	236	54.86	6.37
	Old	236	75.84	5.87

In cases where the likelihood ratio test yielded evidence for age differentiation, we visualised the differences by using a technique inspired by *Local Structural Equation Models* (LSEMs). This technique allows us to visualize age gradients in model parameters of the covariance structure in a more continuous matter, rather than creating age groups. To do so, we estimated the covariance between factors using a series of age-weighted SEMs for the CFA models with subsets of the sample (N = 260 for WM; N=300 for GM, due to estimation variability) in one year steps from 18 to 88 years. Next, a kernel function was used to weigh and smooth the observations according to the age gradients (Hildebrandt, Wilhelm, & Robitzsch, 2009). The following bandwidth (bw) of the kernel function was used to smooth the age-weighted samples:

$$bw = 2 \times N^{(-1/5)} \times SD_{age} \quad (1)$$

Visualising factor covariances allowed for the identification of lifespan patterns including differentiation and de-differentiation. If the data are in line with age differentiation, we expect to find that the nested multigroup model with the freely estimated covariance structure is preferred, in such a way that the older subgroup has lower covariance between factors. Evidence for age de-differentiation would suggest a preference for the freely estimated model, but with higher covariance between the factors in the older subgroup. We first examine differentiation within each domain (grey matter, white matter and cognition), and finally examine brain-cognition covariance differences.

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3. Results

3.1 Grey and white matter covariance

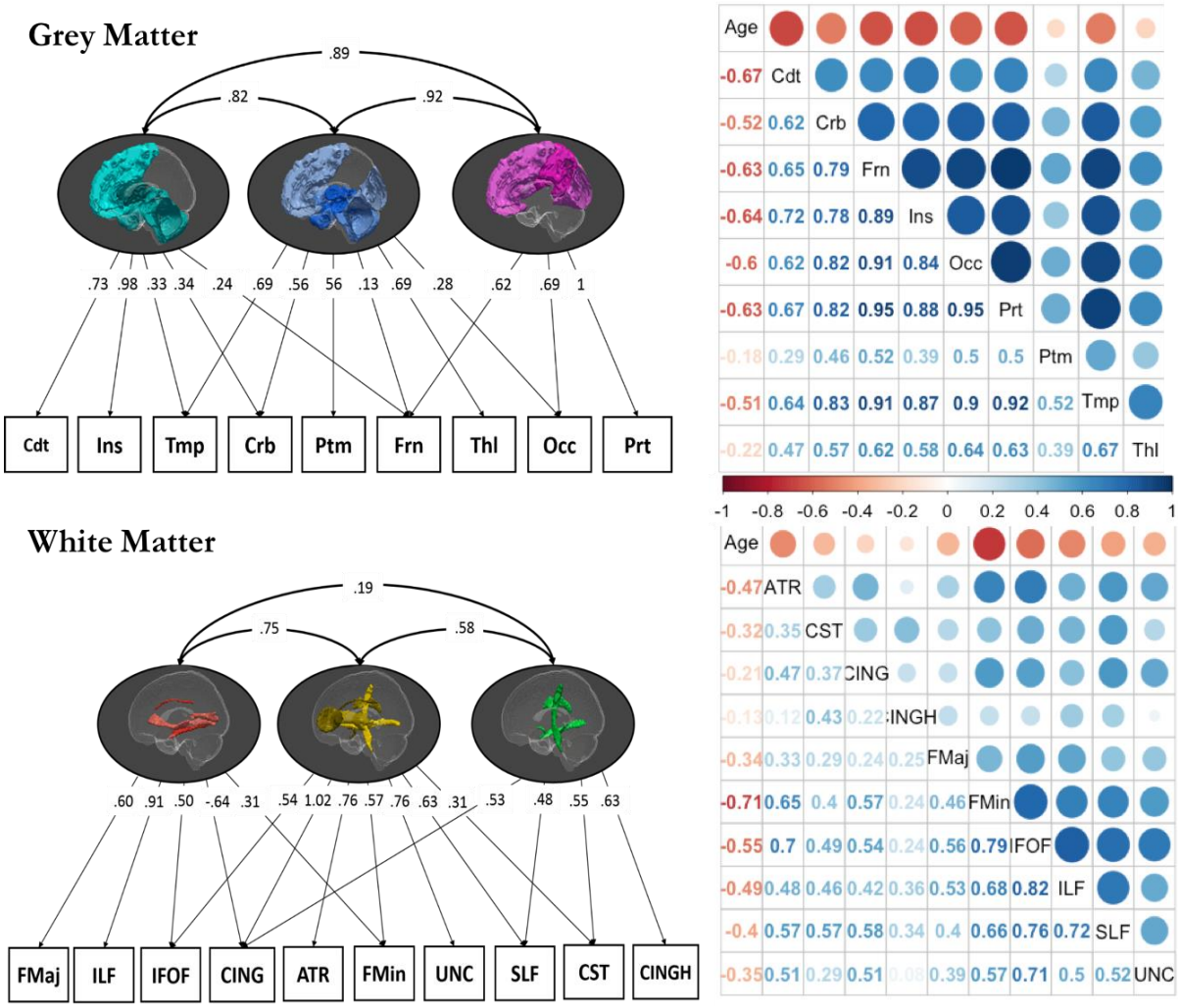

Figure 2. The three factor model for grey-matter (top left) underlies nine ROIs: Caudate (Cdt), Insula (Ins), Temporal (Tmp), Cerebellum (Crb), Putamen (Ptm), Frontal (Frn), Thalamus (Thl), Occipital (Occ), Parietal (Prt). The three-factor model for white-matter (bottom left) with ten ROIs: Forceps Major (FMaj), Cingulate Gyrus (CING), Inferior Fronto-Occipital Fasciculus (IFOF), Inferior Longitudinal Fasciculus (ILF), Anterior Thalamic Radiations (ATR), Forceps Minor (FMin), Uncinate Fasciculus (UNC), Superior Longitudinal Fasciculus (SLF), Corticospinal Tract (CST), Hippocampal Cingulum (CINGH). The darker colours in the lateral brain views represent the regions with the highest factor loadings. Path coefficients are fully standardized. The correlation matrices are shown for grey matter (top right) and white matter (bottom right), along with age.

In order to specify a measurement model amenable to Multigroup Confirmatory Factor Analysis, we first examined a plausible candidate model using an Exploratory Factor Analysis (EFA). For grey matter, we established a three-factor solution was preferred. This three factor model showed adequate fit in the following CFA analysis: $\chi 2$ (19) = 82.384, $p < .001$, RMSEA = .072 [.057 .087], CFI = .990, SRMR = .016. For white matter, a three-factor model showed marginally acceptable fit: $\chi 2$ (26) = 133.897, $p < .001$, RMSEA = .080 [.068 .093], CFI = .966, SRMR = .025. The measurement models are shown in Figure 2,

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along with their correlation matrices. The effects of age on the factor scores are shown in Figure 3, revealing different effect sizes, as well as different functional forms (linear and non-linear).

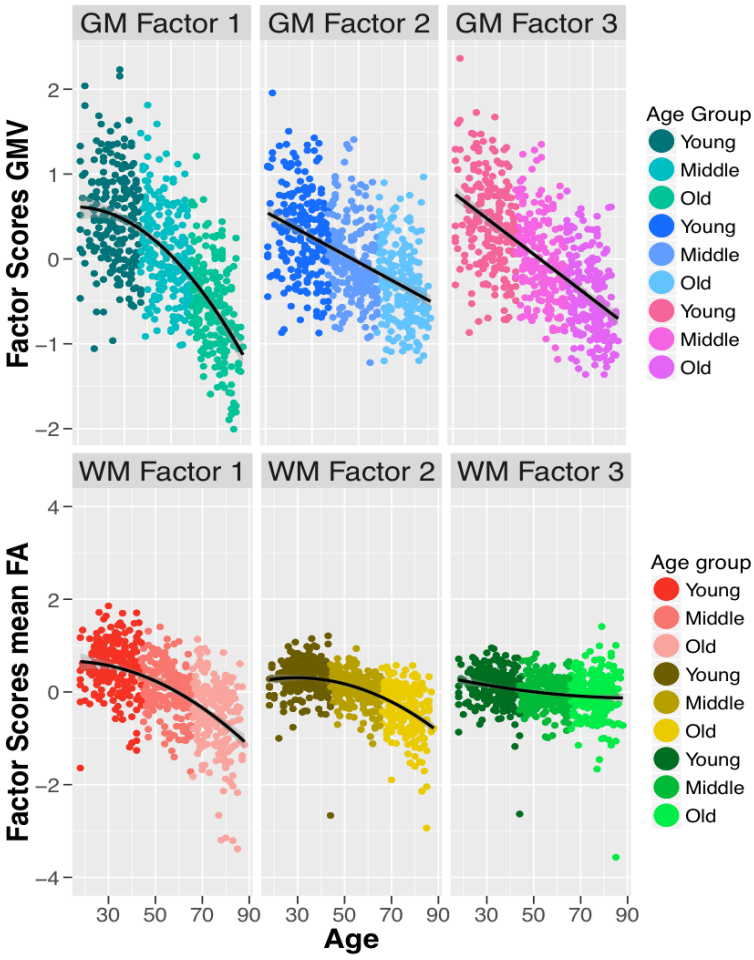

Figure 3. Age-related decline in grey matter (upper three plots) and white matter (lower plots) factor scores, according to the age groups (Young, Middle & Old) with best functional form shown (linear or non-linear). William's test for dependent correlations showed that the effects of age were significantly different across the grey matter ROIs, t_{cor1_2} (651) = -9.46, $p < .001$; t_{cor1_3} (651) = -2.14, $p = .033$; t_{cor2_3} (651) = 12.79, $p < .001$, and across white matter ROIs, t_{cor1_2} (646) = -12.07, $p < .001$, t_{cor1_3} (646) = -12.07, $p < .001$, t_{cor2_3} (646) = -8.28, $p < .001$.

To investigate age differentiation, we fit the same measurement model in three age groups: young, middle & old (Table 1), using Multigroup Confirmatory Factor Analysis (MGCFA). This group-level comparison tests for age-related differences in specific parameters, while constraining the rest of the model (Δdf=6, as either three or nine factor covariances were estimated). Although constraints will generally lead to poorer model fit overall, we were interested in the specific comparison between the two nested models that represent age (de)differentiation versus no differentiation. Fitting these two models, we found that for the grey matter factors, a model where covariances were estimated freely showed better fit: $\Delta\chi2$ (6) = 19.591, $p = .003$ (Table 2). Akaike weights showed that the freely-estimated model (with

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age-varying factor covariance) was 696 times more likely to be the best model given the data (Wagenmakers & Farrell, 2004). Using the same procedure for white matter, we found that the model with the freely estimated covariance also showed better fit: $\Delta\chi2$ (6) = 25.430, p = .001, Akaike weights= 6297 in favor of the freely-estimated model.

	Model	*df*	*AIC*	$w_i(AIC)$	*saBIC*	$w_i(saBIC)$	$\chi2$	$\Delta\chi2$	Δdf	p
Grey Matter	Freely estimated	115	8834.1	.999	8905	.998	579.79			
	Constrained	121	8847.2	.001	8911	.002	604.88	19.59	6	.003
White Matter	Freely estimated	144	14229	.999	14295	.996	769.83			
	Constrained	150	14246	.001	14305	.004	799.32	25.43	6	.001

Table 2. Model fit indices within white and grey matter, where the model with freely estimated covariance structure was preferred for both.

Next, we visualized the changing covariance within grey and white matter to assess evidence for age differentiation, de-differentiation, or some other pattern. The upper three plots in Figure 4 illustrate the difference in covariance between each pair (GM1-GM2, GM1-GM3 and GM2-GM3) of grey matter factors. The strongest pattern is that factor GM1 displays considerable age differentiation: GM1 becomes more *dissimilar* to the two other grey matter factors with increasing age. For the white matter factors, the dominant pattern in the lower three plots of Figure 4 is the differentiation between factors WM1 and WM3, while the covariance between factors WM1 and WM2, and between factors WM2 and WM3, remains relatively stable.

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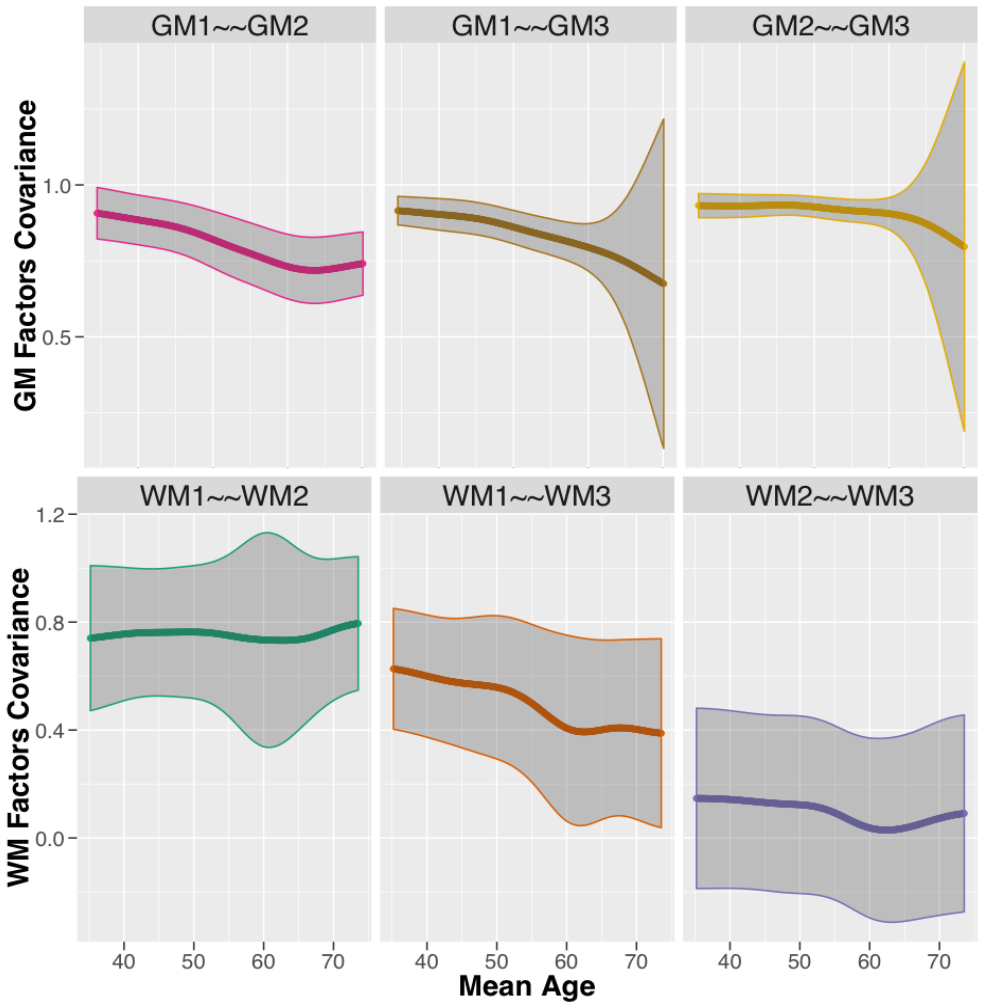

Figure 4. Differences in covariance between grey matter factors (top) and white matter factors (bottom) with age. 95% confidence intervals are displayed as the shaded area around the mean.

A recent paper by Cox et al. (2016) employed a different analytic strategy than ours: Instead of focusing on factor covariances, they imposed a single factor model and examined factor loadings as they changed across the lifespan. To examine the robustness of our findings to such alternative approaches, we likewise imposed a single factor model across all brain regions, and tested whether factor loadings, rather than covariance, differ across three age groups (Young, Middle & Old). For grey matter, even though the one factor model did not fit well ($\chi 2$ (27) = 320.516, p < .001, RMSEA = .129 [.117 .141], CFI = .955, SRMR = .026), and a likelihood ratio test showed that it was a worse description of the data than the three-factor model ($\Delta\chi 2$ (8) = 227.66, p <.001), the model with freely-estimated factor loadings is again the better than the constrained model ($\Delta\chi 2$ (16) = 109.27, p <.001, Akaike weights= $6.13 * 10^{22}$), supporting differences in grey matter factor loadings across the adult lifespan. A visual inspection of the smoothed LOSEM shows that all factor loadings decline with age, again in line with age *differentiation* (Figure 5). Together, this represents strong evidence for age differentiation for grey matter factors; a pattern that does not depend on the precise analytical method.

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For the white matter, we again found that the one factor model for white matter did not fit well ($\chi 2$ (35) = 418.652, p < .001, RMSEA = .130 [.120 .140], CFI = .879, SRMR = .062), with the three-factor model showing better fit ($\Delta\chi 2$ (9) = 259.23, p <.001; Table 2). This is in contrast to some previous studies (Ritchie et al., 2015; Cox et al., 2016; Penke et al., 2010; Wahl et al., 2010), but in line with others (Lövden et al., 2013; Kievit et al., 2016). Nonetheless, within the single factor conceptualization, we again observe that the freely-estimated factor loadings were preferred over the constrained version (Akaike weights = 7.90 * 10^{28}). The LOSEM plot in Figure 5 shows a complex pattern, with several factor loadings increasing (e.g. Forceps Minor and Superior Longitudinal Fasciculus), while others remain stable (e.g. Inferior Fronto-Occipital Fasciculus, Anterior Thalamic Radiations) or decline (e.g. Hippocampal Cingulum). The subset of increasing factor loadings is partly in line with Cox et al. (2016), who suggested age de-differentiation of white matter tracts as the role of the general factor increases with age. However, the poor fit of the one-factor model, and the fact that factor loadings in our sample show both evidence for age differentiation as well as de-differentiation, suggest a cautious interpretation is warranted, with further, ideally longitudinal, investigation being crucial to understand the complex age-related differences in white matter covariance.

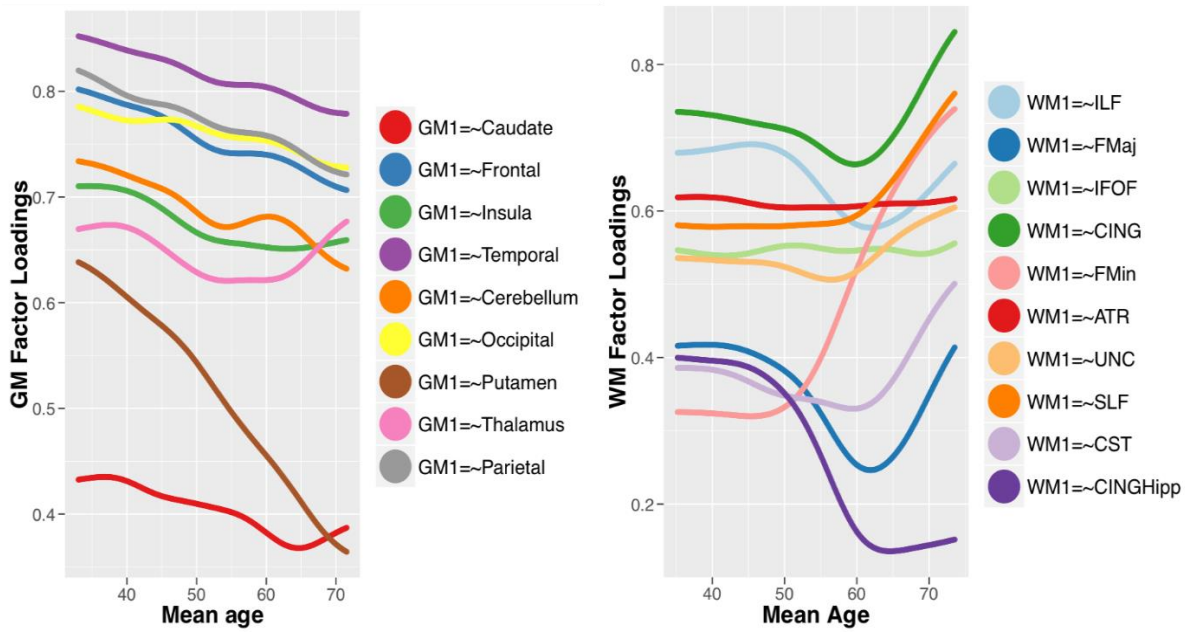

Figure 5. Factor loadings in one factor model of grey matter (left) and white matter (right) across the lifespan

Finally, we implemented MGCFA on the combination of white and grey matter, with the same measurement models imposed, to see if the covariance between white and grey matter factors changes across the lifespan. We did not find evidence for age-related difference in the covariance between WM and GM: The more parsimonious constrained model of the covariance structure was more likely ($\Delta\chi 2$ (18) = 24.10, p = 0.152). These tests establish that the covariance within neural factors for both grey and white matter is different across the three age groups, but the covariance between the two neural measures does not differ across age groups

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3.2 Cognitive factors

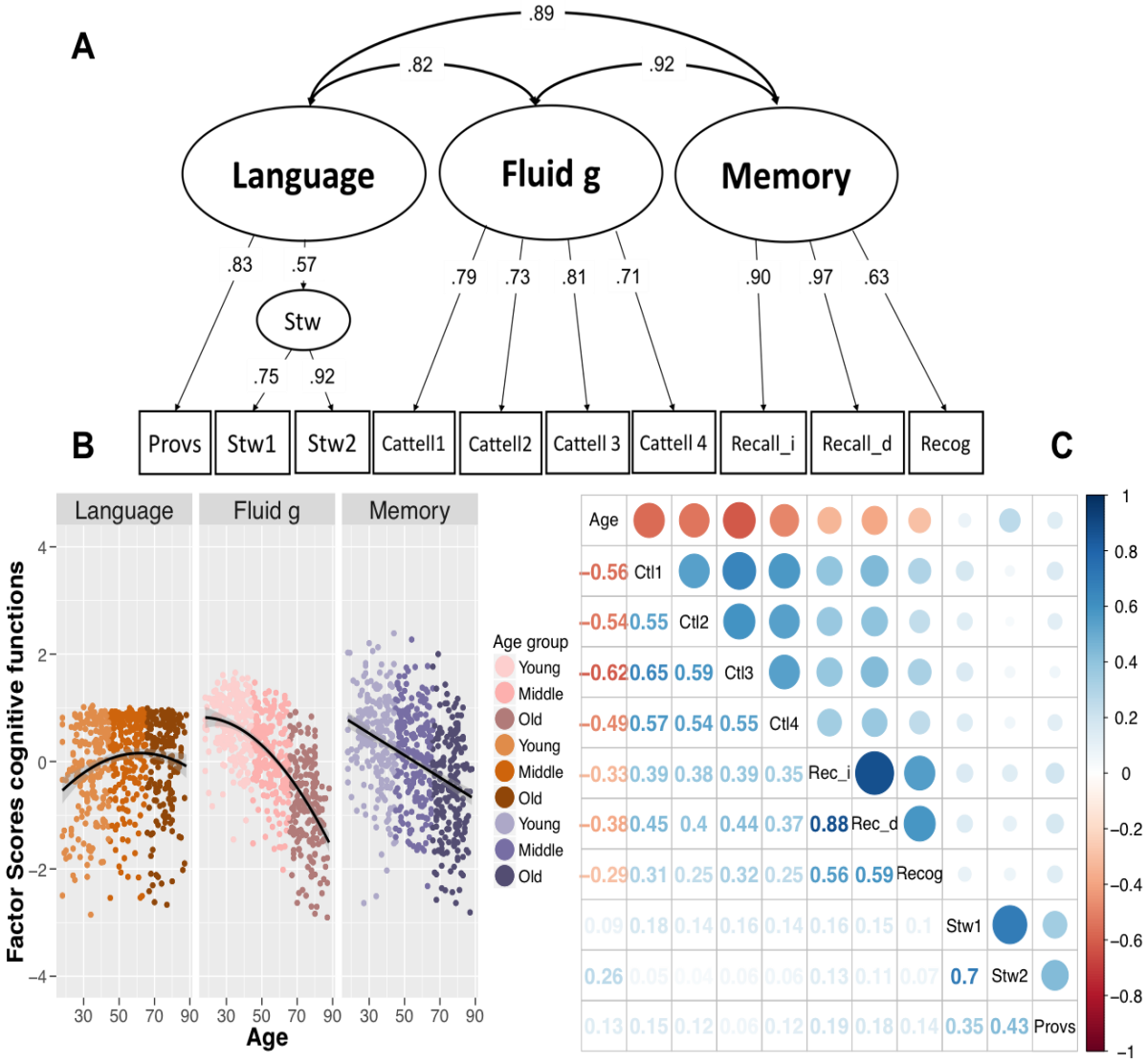

Figure 6. (**A**) Confirmatory factor model for cognitive processing based on Proverb Comprehension (Provs), two spot-the-word tasks (Stw1 and Stw2), four Catell subtests (Catell 1-4) relating fluid intelligence (Fluid g), immediate and delayed recall (Recall_i, Recall_d) and delayed recognition (Recog). (**B**) Age-related difference according to the age groups of the three cognitive factors: Language, Fluid intelligence and Memory, with best functional form shown (linear or nonlinear). William's test for dependent correlations showed that the effects of age were significantly different between language and fluid g: $t(707) = 24.21$, $p < .001$; between fluid g and memory $t\ (707) = -11.07$, $p < .001$; and between language and memory: : $t(707) = 12.9$, $p < .001$. **(C)** correlation matrices between all cognitive tasks and age.

We next examined age-related differences in covariance across cognitive factors. We defined three latent factors for the measurement model (see Figure 6A), based on a priori defined cognitive domains: (1) *language,* modelled by two Spot-the-Words tasks as a first order factor and single proverb comprehension task, (2) *fluid intelligence,* fit to the four scores on Cattell subtests and (3) *memory,* fit to immediate recall, delayed recall and delayed recognition scores. The three-cognitive-factor model, shown in Figure 6A, fit the data well: $\chi 2\ (31) = 59.030$, $p = .002$, RMSEA = .036 [.022 .049], CFI = .988, SRMR = .030. The three factor model fit considerably better than a one-factor solution ($\Delta\chi 2\ (4) = 336.43$, $p <$

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0.001; Akaike weights: 3.31 * 10^{273}). Figure 6B shows the lifespan differences in the three cognitive factor scores. Next, we tested for age differentiation among the cognitive factors across the three age groups, and found that the constrained covariance model was more likely: $\Delta\chi2$ (6) = 4.984, p = 0.546, in line with an absence of either age-related cognitive differentiation or dedifferentiation. The lack of evidence for (de)differentiation suggests a relative static covariance structure of cognitive abilities across the lifespan, contrary to studies of e.g. De Frias et al. (2007), but in line with Tucker-Drob (2009), Deary et al. (1996) and Juan-Espinosa et al. (2002).

3.3 Interaction cognitive and neural measures

Finally, having examined brain and cognitive differentiation separately, we investigated their interaction to explore differences in brain-cognition covariance across the lifespan. To do so, we imposed the same measurement models as used above, first for grey matter and cognition, then for white matter and cognition. Our goal was to see if there is evidence for neurocognitive age (de)differentiation, indicated by differing covariance between brain structure and cognitive function across the lifespan.

For grey matter, we did not find evidence for age-related difference in the covariance with cognition: The more parsimonious constrained model of the covariance structure was preferred ($\Delta\chi2$ (18) = 21.53, p = 0.253), suggesting a relative stable relationship between the grey matter and cognitive factors across the lifespan. However, for white matter, the freely estimated covariance structure was preferred: $\Delta\chi2$ (18) = 37.27, p = .005, suggesting age-related differences in the relationship between white matter and cognitive factors.

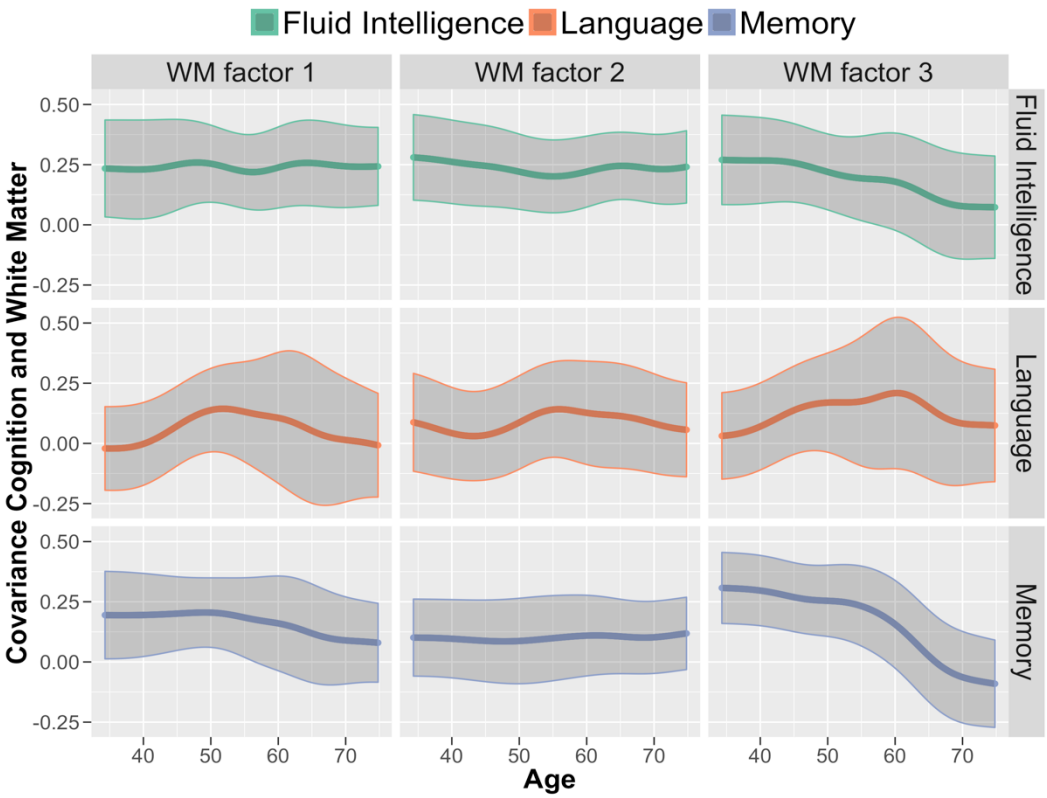

Figure 7. Differences in the covariance between the cognitive and white matter factors across the lifespan. The bottom right shows the one pathway that displays evidence for neurocognitive age differentiation.

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To examine the source of this neurocognitive age (de)differentiation, we plotted smoothed LOSEM age-weighted measurement models of the nine covariances between the three cognitive and three white matter factors (Figure 7). Visual inspection suggested that this age-related difference in the relationship between cognition and white matter was driven by a specific pathway, namely the covariance between WM3 and memory. This visual inspection was confirmed by a post-hoc test, where a model with a freely-estimated covariance between WM3 and memory was preferred over the constrained model: $\Delta\chi 2$ (2) = 27.34, p = <.001. The covariance between this white matter factor and memory performance declined steadily, especially in old age, suggesting a form of neurocognitive differentiation. Further post-hoc comparisons for the other factors were not significant, suggesting that they remained relatively stable across the lifespan. It is noteworthy that the third white-matter factor was the (only) factor characterized by the ventral cingulum (CINGHipp), the part of the cingulum that is directly interconnected with the hippocampal formation (Hua et al. 2008, Fig. 2). This suggests a decoupling of memory performance from the white matter networks associated with the hippocampus; an intriguing pattern that we return to below.

4. Discussion

In this study, we examined the notion of age (de)differentiation within and between cognitive and neural factors across the adult lifespan. We found evidence for age differentiation within both GM and WM, such that the covariance between (a subset of) GM factors and the covariance between (a subset of) WM factors is lower in older adults. In contrast, cognitive factors displayed a stable covariance structure, providing no evidence for (de)differentiation. Finally, we observed a specific pattern of age differentiation between WM and cognition, apparently driven exclusively by a decoupling between a WM factor highly loading on the hippocampal cingulum and the cognitive factor associated with memory.

For GM, exploratory factor analysis revealed that a three-factor model was preferred. The main effect of age was to reduce the covariance between the first factor (which loaded most on caudate and insula) and the other two factors. Notably, this conclusion was largely unchanged by instead imposing a single-factor model, as we still find evidence for a decline in the factor loadings across the lifespan, supporting neural differentiation. Note that the precise number and nature of factors is likely to depend on the dimensionality of the data. Here we chose a mask characterized by a small number of ROIs (nine in total), in order to keep the GM model comparable in dimensionality to the white-matter tracts and cognitive variables. Moreover, a limited number of ROIs was necessary to achieve tractable SEM complexity given the sample size and subgroup analyses. Nonetheless, our ROIs had sufficient resolution to suggest that distinct networks of those regions differentiate in unique ways, resulting in structural networks that become more dissimilar across individuals in old age.

For WM, a three-factor model of the ten major WM tracts was also preferred. With this model, we again found evidence for differentiation, with the most noticeable effect being age-related reductions in

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the covariance between the first factor (which loaded most highly on the inferior fronto-occipital fasciculus and inferior longitudinal fasciculus) and the third factor (which loaded most highly on the ventral cingulum and projection fibers of corticospinal tract). The results from fitting an alternative single-factor model (e.g. Cox et al., 2016) were less clear, with both deceases and increases in various factor loadings with age, with the increases suggesting some *de*-differentiation. A promising future avenue to better understand this complex pattern of white matter covariance differences is to examine longitudinal changes in white matter covariance, although at present there are few such datasets available.

Several mechanisms might contribute to our findings of differentiation within GM and within WM. First, the differentiation may reflect the declines in structural connectivity during healthy ageing (Spreng & Turner, 2013). For example, reductions in grey matter covariance may follow reductions in white matter covariance (e.g. myelination) that cause less efficient communication and co-activation between brain regions, over time leading to decreased structural similarity. This is consistent with the present lack of evidence for differentiation *between* GM and WM. Another possibility is that the differentiation reflects distinct subpopulations of people that diverge across the lifespan. For instance, if subsets of the older population suffer from medical conditions that differentially affect specific brain regions (e.g. higher blood pressure, Gianaros et al., 2006), this will also lead to a more complex covariance pattern for the older population. Note that it is also possible that systemic age-related effects lead to age-related *increases* in covariance, or dominance of a single factor (Cox et al., 2016), which may be disguised by the causes of differentiation described above. Future studies should combine longitudinal imaging approaches with repeated health data to test the plausibility of these explanations in explaining the patterns observed here.

In line with most previous findings (e.g. Deary et al., 1996; Juan-Espinosa, 2002; Tucker-Drob, 2009), we did not observe evidence for cognitive age differentiation or dedifferentiation, instead finding a stable covariance structure across the lifespan. More importantly, we examined, for the first time, age differentiation between neural and cognitive factors. Specifically, we observed decreased covariance between a WM factor associated with hippocampal connectivity and a factor associated with memory. This decreased dependency of memory performance on WM integrity may relate to recent functional MRI work in healthy aging. For instance, Salami, Pudas and Nyberg (2014) observed greater connectivity within a hippocampal network during rest in older relative to younger people, but *decreased* connectivity between the hippocampal network and other cortical networks during mnemonic tasks. Notably, this pattern of 'aberrant hippocampal decoupling' (p. 17654) was stronger in individuals with lower white matter integrity near the hippocampus, and was associated with poorer memory performance. Westlye et al. (2011) also found aberrant hippocampal connectivity associated with poorer performance, and suggested that failures of task-related hippocampal decoupling may elevate the risk of cognitive decline by increasing the metabolic burden on the hippocampus. To tease apart these multiple interacting patterns, future studies should simultaneously investigate cognitive changes (memory performance), structural changes (e.g. white matter connectivity) and functional changes (compensatory and/or maladaptive changes in connectivity during task and rest) using longitudinal designs.

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An alternative explanation of the decreased covariance between WM and memory observed here is the notion of *cognitive reserve* (Stern 2002, 2009; Whalley et al., 2004), which posits that the degree of brain pathology in certain individuals does not directly correspond to the manifestation of cognitive impairment. Certain lifespan exposures (e.g. high levels of education) are considered protective against cognitive decline. This implies that in older age, as the compensatory mechanisms of cognitive reserve become more prominent, memory performance should depend less on the brain structure, leading to the type of neurocognitive differentiation (i.e. decreased covariance) observed here. However, the precise consequences of cognitive reserve on covariance patterns likely depend on the idiosyncrasies of the sample under investigation. Moreover, it is unclear why we observe a specific age-related differentiation (between WM and memory), rather than a more general neurocognitive differentiation.

A limitation of this study is that the sample is cross-sectional. The consequence is that, although we can examine age differentiation between individuals, we cannot generalize our findings to intra-individual changes over the lifespan (Salthouse, 2011). Acquiring longitudinal imaging and cognitive data would allow more detailed investigation of age-related changes in covariance among cognitive and neural factors. Furthermore, we here focus on a relatively limited range of cognitive and neural variables, in order to enable SEMs with a tractable set of parameters, which also leads to poorer model fits. Larger samples, possibly depending on integration across cohorts, may allow fitting of higher dimensional measurement models (with possibly an overall better fit) and simultaneously explore generalizability. A second limitation of our study concerns potential differences in data quality across the lifespan. For instance, if older adults move more, and the effects of this motion of the imaging data cannot be fully accommodated (Geerligs et al., in press), this may induce a decrease in covariance simply due to less reliable measurement. However, age-related decreases in data quality cannot fully explain our findings, given that the pattern of age differentiation was limited to some, but not all, neural factors: increased measurement error in older adults would produce consistent decreases in covariance between all pairs of factors.

Taken together, we were able to show a complex pattern of age-related differentiation in grey and white matter, but not in cognition, together with a specific differentiation in the relationship between white-matter tracts and memory. Our findings show how Multigroup Confirmatory Factor Analysis can be a powerful framework for investigating theories of neurocognitive aging, such as age differentiation, allowing researchers to investigate mechanisms of healthy and pathological ageing in a flexible yet principled manner.

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Acknowledgements

The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) research was supported by the Biotechnology and Biological Sciences Research Council (grant number BB/H008217/1). R.N.A.H. was supported by MRC Programme Grant MC-A060-5PR10. RAK is supported by the Sir Henry Wellcome Trust (grant number 107392/Z/15/Z) and MRC Programme Grant MC-A060-5PR60. We are grateful to the Cam-CAN respondents and their primary care team in Cambridge for their participation in this study. We also thank colleagues at the MRC Cognition and Brain Sciences Unit MEG and MRI facilities for their assistance.

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