Structural covariance networks and their association with age, features of cerebral small-vessel disease, and cognitive functioning in older persons

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Short title: Structural covariance networks and cognition in the elderly

Keywords: elderly; grey matter; magnetic resonance imaging; brain imaging; structural covariance brain networks; cognition; cerebral small vessel disease

Abbreviations

DANTE	Discontinuation of Antihypertensive Treatment in the Elderly
FA	flip angle
FLAIR	fluid attenuated inversion recovery
FMRIB	Oxford Centre for Functional MRI of the Brain
IQR	interquartile range
LDST	Letter-Digit Substitution Test
MMSE	Mini-Mental State Examination
MNI152	montreal neurological institute 152
WMH	white matter hyperintensities
SCNs	structural covariance networks
SD	standard deviation
SVD	small vessel disease
TE	echo time
TMT	Trail Making Test
TR	repetition time
VAT	Visual Association Test
15-WVLT	15-Word Verbal Learning Test

Abstract

Recently, cerebral structural covariance networks (SCNs) have been shown to partially overlap with functional networks. However, although for some of these SCNs a strong association with age is reported, less is known about the association of individual SCNs with separate cognition domains and the potential mediation effect in this of cerebral small vessel disease (SVD).

In 219 participants (aged 75-96 years) with mild cognitive deficits, eight SCNs were defined based on structural covariance of grey matter intensity with independent component analysis on 3DT1-weighted MRI. Features of SVD included: volume of white matter hyperintensities (WMH), lacunar infarcts and microbleeds. Associations with SCNs were examined with multiple linear regression analyses, adjusted for age and/or gender.

In addition to higher age, which was associated with decreased expression of: subcortical, pre-motor, temporal, and occipital-precuneus networks, the presence of SVD and especially higher WMH volume, was associated with a decreased expression in the occipital, cerebellar, subcortical, and anterior cingulate network. The temporal network was associated with memory (P=0.005), whereas the cerebellar-occipital and occipital-precuneus networks were associated with psychomotor speed (P=0.002 and P<0.001).

Our data show that a decreased expression of specific networks, including the temporal, occipital lobe and cerebellum, was related to decreased cognitive functioning, independently of age and SVD. This indicates the potential of SCNs in substantiating cognitive functioning in older persons.

Introduction

It has recently been shown that structural networks based on covariance of grey matter in the brain partially overlap with functional connectivity networks (Alexander-Bloch et al, 2013; Seeley et al, 2009; Segall et al, 2012). Structural covariance networks (SCNs) have been studied using a region of interest approach (Li et al, 2013; Montembeault et al, 2012), for this approach inferable hypotheses are essential. An alternative method is to define SCNs by an exploratory data-driven multivariate approach, such as a voxel-based morphometry independent component analysis (ICA) approach (Douaud et al, 2014; Douaud et al, 2007; Xu et al, 2009), this way information of multiple brain regions can be combined and patterns of structural covariance in grey matter density can be detected. Brain regions containing similar information (grey matter volume, thickness and surface area) are clustered and can be defined as a specific network. SCNs may offer implications as to how functional brain networks originate from their structural underpinnings (He et al, 2007) and it has been suggested that SCNs reflect synchronized maturational change, possibly mediated by subcortical-cortical connections (Mechelli et al, 2005).

The expression of some SCNs is strongly associated with age, whereas the expression of other SCNs seem unaffected by age (Bergfield et al, 2010; Hafkemeijer et al, 2014; Li et al, 2013; Montembeault et al, 2012; Segall et al, 2012). With increasing age, features of cerebral small vessel disease (SVD) common MRI findings are more frequently observed (Wardlaw et al, 2013). These SVD features have been associated with grey matter reductions (Lambert et al, 2015; Wen et al, 2006) and play a role in the pathogenesis of brain atrophy and therefore with a decrease in cognitive abilities (Light, 1991; Raz, et al., 1998). The association between aging and SCNs (Bergfield et al, 2010; Hafkemeijer et al, 2014; Li et al, 2013; Montembeault et al, 2012; Segall et al, 2012) and the relation between the covariation of grey matter volume and cognitive decline in healthy aging (Oh et al, 2011; Tijms et al, 2016) and in persons with

different stage of dementia is well described (Hafkemeijer et al, 2016; Spreng et al, 2013; Yao et al, 2010). However, the mediating effects of other common features that come along with ageing such as an increased level of manifest vascular changes on the association between SCNs and cognition are unknown.

The working hypothesis of the present study is that in older persons the presence of manifest SVD has an independent effect on SCN expression. Since both atrophy and SVD are related to worse cognitive functioning, we expect that, in a population of older persons with mild cognitive deficits, the association between SCN expression and cognitive domains (memory function, executive function, and psychomotor speed) is influenced by both age and the presence of manifest SVD.

Methods

Participants

Data for this study were obtained from the MRI sub-study of the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE) trial; a randomized trial evaluating the effect of discontinuation of antihypertensive therapy in older persons with mild cognitive deficits on neuropsychological functioning (Moonen et al, 2015). A detailed description of the design of the DANTE Study Leiden is described elsewhere (Foster-Dingley et al, 2015b; Moonen et al, 2015).

In short, participants were included when they were aged 75 years and over, using antihypertensive medication, and with a Mini-Mental State Examination (MMSE) score of 21-27. In total, 220 of the DANTE participants underwent MRI scans. One participant was excluded due to movement artefacts, leaving a total of 219 participants for the current study.

The Medical Ethics committee of the Leiden University Medical Center approved the DANTE Study Leiden and all participants gave written informed consent.

Brain imaging

Whole brain, 3D T1-weighted (repetition time [TR]/echo time [TE]=9.7/4.6, flip angle [FA]=8°, voxel size=1.17×1.17×1.40 mm) images were acquired on a 3 T MRI scanner (Philips Medical Systems, Best, the Netherlands). With increasing age concomitant signs of beginning or more overt forms of SVD are frequently observed on brain MRI (Wardlaw et al, 2013). These signs include cerebral white matter hyperintensities (Debette et al, 2010), and lacunar infarcts (Vermeer et al, 2007), cerebral microbleeds (Cordonnier et al, 2007). For the

evaluation of SVD-related pathologies, fluid attenuated inversion recovery (FLAIR) images (TR/TE=11 000/125 ms, FA=90°, FOV=220×176×137 mm, matrix size=320×240, 25 transverse slices, 5 mm thick), T2*-weighted images (TR/TE=45/31 ms, FA=13 °, field of view=250×175×112 mm) and T2-weighted images (TR/TE=4200/80 ms, FA= 90°) were acquired.

Cerebral small vessel disease

To assess the presence of SVD, the volume of white matter hyperintensities (WMH) was quantified, and the presence of lacunar infarcts and cerebral microbleeds were assessed. FMRIB Software Version 5.0.1. Library (FSL; http://www.fmrib.ox.ac.uk/fsl) (Woolrich et al, 2009) was used to quantify WMH volume in an automated manner. WMH are defined as hyperintense regions on FLAIR. First, the 3DT1-weighted images were skull stripped (Smith SM, 2002), and then FLAIR and 3DT1 images were linearly co-registered (Jenkinson et al, 2002; Jenkinson et al, 2001). The brain extracted FLAIR image was affine-registered to MNI152 standard space. A conservative MNI152 white matter mask was used to extract the white matter from FLAIR image. Subsequently, we set a threshold to identify which white matter voxels were hyperintense, followed by manually checking and editing for quality control.

Lacunar infarcts, assessed on FLAIR, T2 and 3DT1-weighted images, were defined as parenchymal defects (signal intensity identical to cerebrospinal fluid on all sequences) of at least 3 mm in diameter, surrounded by a zone of parenchyma with increased signal intensity on T2-weighted and FLAIR images. Cerebral microbleeds were defined as focal areas of signal void (on T2 images), which increased in size on T2*-weighted images (blooming

effect) (Greenberg et al, 2009). Symmetric hypointensities in the basal ganglia, likely to represent calcifications or non-hemorrhagic iron deposits, were disregarded. Lacunar infracts and cerebral microbleeds were scored by a single rater (JFD) who was blinded to clinical data, and who was supervised by a second rater (JG), having more than 15 years neuroradiological experience.

Structural covariance networks

SCNs were assessed with FMRIB Software Version 5.0.1. Library (FSL; http://www.fmrib.ox.ac.uk/fsl) (Woolrich, et al., 2009) as reported previously (Hafkemeijer et al, 2014). The 3DT1 images were pre-processed using the pre-processing steps used for voxel-based morphometric analysis (Ashburner et al, 2000). In short, non-brain tissue was removed from the T1-weighted images using the brain extraction tool (Smith SM et al, 2001). A control check was performed after each pre-processing step to ensure appropriate brain extraction and tissue-type segmentation. In order to correct for the partial volume effect (i.e., voxels "containing" more than one tissue type), tissue-type segmentation was carried out with partial volume estimation (Zhang et al, 2001). The resulting grey matter partial volume images were affine registered to MNI152 (Jenkinson et al, 2002) and then nonlinearly registrated (Andersson et al, 2007). The resulting images were averaged to create a study-specific grey-matter template, to which the native grey matter images were nonlinearly registered (Ashburner et al, 2000; Good et al, 2001). To correct for local expansion or contraction, the registered partial volume images were modulated by multiplying by the Jacobian of the warp field, and smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.

The modulated and smoothed individual grey matter images in MNI152 space were used as four-dimensional dataset on which independent component analysis was performed (Beckmann C.F. et al, 2005). Independent component analysis was applied using the multivariate exploratory linear optimised decomposition into independent components tool (Beckmann C.F. et al, 2005), this statistical technique decomposes a set of signals into spatial component maps of maximal statistical independence (Beckmann C. F. et al, 2004). When applied on grey matter images of different participants, this method defines spatial components based on the inter-correlation or structural covariance of grey matter density among participants (i.e., SCNs) (Hafkemeijer et al, 2014), without a priori selected regions of interest.

SCN's and functional resting state networks are generally studied using eight to ten components (Beckmann C.F. et al, 2005; Damoiseaux et al, 2006; Li et al, 2013; Segall et al, 2012). Therefore, we restricted the independent component analysis output to eight components.

Individual SCN expression was calculated using the four-dimensional data set of grey matter images in a spatial regression against the eight SCN probability maps (general linear model approach integrated in FSL) (Filippini et al, 2009). This procedure provides for the 219 participants an index reflecting the degree to which each participant expresses the identified network pattern (i.e., SCN expression, the beta weights of the regression analysis). A higher score indicates a stronger the expression of the identified SCN. With the use of a mixture model significance was assigned to different voxels within the spatial map, a standard threshold level of 0.5 was used (Beckmann C. F. et al, 2004). Within each SCN the topographical structures and MNI coordinates of these were defined with FSL cluster and using the Harvard-Oxford cortical and subcortical structures atlas integrated in FSL.

Cognitive functioning

Trained research staff administered a battery of six cognitive tests. In detail, global cognitive functioning was assessed with the MMSE (Folstein et al, 1975). To measure memory function the immediate (3 trials) and delayed recall on the 15-Word Verbal Learning Test (15-WVLT), and the Visual Association Test (VAT) were used (Lezak et al, 2004). Executive function was assessed with the interference score of the abbreviated Stroop Colour Word Test (Houx et al, 1993), and the difference between the time to complete the Trail Making Test part A and B (TMT delta) (Arbuthnott et al, 2000). Psychomotor speed was evaluated with the Letter-Digit Substitution Test (LDST) (Van der Elst et al, 2006). For analysis, first the individual test scores (of the Stroop interference score and the TMT delta score) were inversed; consequently, higher scores indicate better performance on all tests. The psychomotor speed score and compound cognitive scores for memory and executive function were computed by converting the crude scores of each test to standardized z scores [(test score – mean)/SD] and calculating the mean *z* score across the tests in each compound.

Demographic and clinical characteristics

Demographic and clinical characteristics were obtained by research staff using a standardized interview. Information about medication and medical history were obtained from the general practitioners of the participants with the aid of structured questionnaires.

Statistical analyses

Characteristics of participants are presented as mean (standard deviation; SD), median (interquartile range; IQR) or as number (percentage) where appropriate. WMH volume was log transformed to ensure normal distribution.

All variables including age, WMH volume, lacunar infarcts, cerebral microbleeds and the eight SCNs were standardized. Standardization of variables allowed effect sizes to be comparable throughout. Using a multivariate linear regression model we assessed whether age and the presence of SVD including: WMH volume, the presence of lacunar infarcts, and cerebral microbleeds (independent variables), were associated with expression of SCNs (dependent variable). The analyses for the association between age and expression of SCNs were adjusted for gender. It has been suggested that the relationship between grey matter networks and age might be non-linear (Fjell et al, 2013; Sowell et al, 2003; Tijms et al, 2016). Therefore, we assessed whether the associations found between age and SNCs were non-linear by separately adding quadratic and log terms of age to the model. For the analyses of the association between WMH volume, the presence of lacunar infarcts and cerebral microbleeds and expression of SCN we adjusted for age and gender.

The associations between expression of SCNs and cognitive functioning were also analysed using multivariate linear regression analyses. In these analyses expression of SCNs were the independent variables and standardized cognition scores (memory and executive function, and psychomotor speed) the dependent variables. We adjusted for age, gender and SVD (including WMH volume, the presence of lacunar infarcts, and cerebral microbleeds). As MMSE is a global and readily available cognitive assessment tool, we additionally assessed the association between expression of SCNs and MMSE.

In order to correct for multiple testing the statistical threshold was set at (0.05/8; based on eight networks) $P \leq 0.006$.

Results

The characteristics of the study population are shown in Table 1. Included were 219 participants with a mean age of 80.7 years and of whom 42.9% male. Participants had mild cognitive deficits as reflected by the median MMSE score of 26 (IQR 25-27) points. Median WMH volume was 22.0 (IQR 9.0-56.1) ml. Lacunar infarcts and cerebral microbleeds were present in 26.9% and 24.7% of the participants, respectively.

Figure 1 shows eight SCNs, these networks included: a cerebellar-occipital network (SCN a), lateral occipital network (SCN b), cerebellar network (SCN c), subcortical network (SCN d), a pre-motor network (SCN e), temporal network (SCN f), occipital-precuneus network (SCN g) and an anterior cingulate network (SCN h). Details of the topographical brain regions within each of the SCNs were identified with the Harvard Oxford atlas (Table 2).

Table 3 shows that a higher age was significantly associated with a lower expression of four SCNs: subcortical (SCN d), the pre-motor (SCN e), temporal (SCN f), and occipital-precuneus (SCN g) networks independent of gender (B = -0.18, P =0.006; B = -0.25, P <0.001; B = -0.26, P <0.001 and B = -0.34, P <0.001, respectively). To test whether associations were non-linear, quadratic and log age terms were added. These analyses did not yield any significant results.

As shown in table 3a higher WMH volume was associated with lower structural connectivity of four of eight networks independent of age and gender, including the lateral occipital (SCN b), cerebellar (SCN c), subcortical (SCN d), and the anterior cingulate network (SCN h), (all $P \leq 0.002$). The presence of lacunar infarcts was associated with a lower expression of the subcortical network (B = -0.21, P = 0.001), and cerebral microbleeds with lower expression of the anterior cingulate network (B = -0.20, P = 0.003).

When combining these data: i) age was predominantly associated with the pre-motor and temporal network (SCN e and f; both $P < 0.001$), ii) age and the presence of SVD were both associated with the subcortical network (SCN d; all $P \leq 0.006$), whereas iii) independently of age, WMH volume was predominantly associated with the lateral occipital and the anterior cingulate network (SCN b and h; $B = -0.30$, $P < 0.001$ and $B = -0.21$, $P = 0.002$, respectively).

Table 4 shows the association between SCNs and cognitive functioning. After adjusting for the presence of SVD (i.e. WMH volume and the presence of lacunar infarcts and microbleeds), a lower expression of three SCNs was associated with worse memory or psychomotor speed. The temporal network (SCN f) was associated with memory function ($B = 0.20$, $P = 0.005$), whereas the cerebellar-occipital network (SCN a) and occipital-precuneus network (SCN-g) were associated with psychomotor speed ($B = 0.22$, $P = 0.002$ and $B = 0.27$, $P < 0.001$, respectively). Furthermore, the additional analyses for the association between the eight SCNs and MMSE score, showed no significant associations.

Discussion

In this population of older persons with mild cognitive deficits, a higher age and features of small vessel disease are associated with a decrease in expression of several structural covariance networks. Of the SVD features, predominantly a higher WMH volume was associated with a lower expression of four SCNs. A lower expression of SCNs is related to worse cognitive functioning in particular cognitive domains (memory function or psychomotor speed) independently of SVD.

Independent component analysis identified SCNs that were similar to functionally correlated brain regions described previously (Beckmann C.F. et al, 2005; Damoiseaux et al, 2006; Smith SM et al, 2009). In populations with younger persons who were cognitively healthy, studies show that when dividing the participants into groups according to age, the 'older' age group had a lower expression of SCNs (Bergfield et al, 2010; Hafkemeijer et al, 2014; Li et al, 2013; Montembeault et al, 2012; Oh et al, 2011; Segall et al, 2012; Tijms et al, 2016). Similar to studies in younger healthy populations our results showed that increased age was associated with lower expression of the temporal networks (Bergfield et al, 2010; Li et al, 2013) Overall, in line with findings of previous studies, we found that in our sample of older persons with mild cognitive deficits higher age was associated with reduced structural covariance network expression.

In the present study population of older persons with a mean age of 80.7 years, the prevalence of SVD was relatively high compared with other populations of older persons, as discussed previously (Foster-Dingley et al, 2015a). Our data show that signs of SVD, predominantly WMH volume, were associated with reduced network expression of four SCNs independent of gender and age. As a reduced SCN expression reflects specific grey matter patterns (grey matter volume, thickness and surface area), our results enhances previous volumetric studies

showing that WMH load (Du et al, 2005; Kloppenborg et al, 2012; Lambert et al, 2015; Seo et al, 2012; Smith EE et al, 2008; Taki et al, 2011; Wen et al, 2006), the presence of lacunar infarcts (Appelman et al, 2010; Grau-Olivares et al, 2010), and cerebral microbleeds (Lee et al, 2004) are associated with a reduction in total grey matter. Moreover, it has been shown that WMH is associated with volumetric grey matter loss around the supramarginal gyrus and occipital-parietal junction (Lambert et al, 2015). This is in line with our results which showed that WMH volume was associated with reduced expression of the lateral occipital network which contained these structures.

Our data show that, independent of SVD, a lower expression of the temporal network that included the parahippocampal gyrus was associated with worse memory function. This is in line with MRI studies showing an association of hippocampal (Apostolova et al, 2010; Kramer et al, 2007; Mungas et al, 2002; Risacher et al, 2010; Van Petten et al, 2004) and (temporal lobe) parahippocampal atrophy (Kohler et al, 1998; Ward et al, 2014) with memory function. Furthermore, as psychomotor speed tests include a visual component, it is of interest that a lower expression of a network including the occipital lobe (cerebellar-occipital network and occipital-precuneus network) was associated with lower psychomotor speed scores. A study assessed whether SCNs were associated with processing speed (Eckert et al, 2010). In contrast to our results, this study in healthy persons (aged 19-79 years) showed that slower processing speed corresponded to changes in a grey matter network composed of anterior cingulate cortex and dorsolateral prefrontal cortex (Eckert et al, 2010). However, whereas we included older persons with mild cognitive deficits, the latter population had an MMSE score of ≥ 27 and with no history of neurologic or psychiatric events. Therefore, these contrasting results may be attributable to differences in the health and age of the study populations. In addition, our results showed that expression of none of the SCNs was

associated with the global measure of cognition. A reason for this might be that MMSE is a global and therefore less sensitive tool than the compound scores for memory function, executive function and psychomotor speed.

The association between SVD, specifically WMH, and SCNs may be attributable to deafferentiation of the connections between cortical cells and their subcortical targets. Compared with WMH, lacunar infarcts and cerebral microbleeds are less likely to interrupt the cortical-subcortical connections in the subcortical white matter, as these are frequently located in the subcortical grey matter structures. Although strong associations were found between SVD and SCNs, and SVD has been associated with cognitive impairment (Light, 1991; Raz et al, 1998), the associations between SCNs and cognitive functioning remained even after adjusting for SVD. This may indicate that SCNs play a role in cognitive functioning. The expression of SCNs could be a reflection of specific grey matter patterns, as a result of disrupted subcortical-cortical connections, that affect cognitive functioning.

Some limitations of the present study need to be addressed. First, our results suggest that SVD and cognitive functioning are related to reduced network expression in old age; however, due to the cross-sectional design it is not possible to determine a temporal or causal relationship. Also, because we used an exploratory approach, no correction was made for multiple testing. Our population was a selection of older persons who had mild cognitive deficits but no history of serious cardiovascular disease. Due to the exclusion of persons with serious cardiovascular disease, brain MRIs were useful for the current study; however, the current findings cannot be extrapolated to the general population. Furthermore, for the present study whole-brain grey matter networks were based on structural covariance of grey matter density, using a voxel-based morphometry ICA (Beckmann C. F. et al, 2004) approach to identify naturally clustering, maximally independent SCNs. However, other methods can

be used for defining SCNs (Alexander-Bloch et al, 2013; Bassett et al, 2008; Lerch et al, 2006). As the voxel-based morphometry ICA method was used in the current study, expression of SCNs relies on a group average and consequently we can only speculate on the value of individual diagnostic evaluation. Moreover, future research should delineate whether SCNs defined at participant level, which have been related to cognition (Tijms et al, 2012; Tijms et al, 2014; van Duinkerken et al, 2016), are spatially comparable with SCNs defined with the voxel-based morphometry ICA method.

Conclusion

This study shows that in older persons, in addition to age, of the SVD features (predominantly a higher white matter hyperintensity volume) are associated with a decreased expression of SCNs. A lower temporal network expression is associated with worse memory function, and a decreased cerebellar-occipital and occipital-precuneus network expression with lower psychomotor speed independently of age and SVD . This indicates the determination of SCNs may be important in substantiating cognitive functioning in older persons.

Acknowledgments

The authors thank all the co-investigators of the DANTE Study Leiden. This study was supported by a grant from the Netherlands Organization for Health Research and Development (ZonMW), Program Priority Medicines for the Elderly (No. 40-41600-98-9014). Rombouts is supported by VICI grant no. 016.130.677 of the Netherlands Organisation for Scientific Research (NWO).

Author Disclosure Statement

No competing financial interests exist.

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Table 1. Characteristics of the study population

Characteristic	(n=219)
Demographic and clinical	
Age (years)	80.7 (4.1)
Male	94 (42.9%)
Cardiovascular disease[^]	20 (9.1%)
Systolic blood pressure (mmHg)	146 (21.2)
Diastolic blood pressure (mmHg)	81 (10.8)
Cognition	
MMSE score (points)	26 (25-27)
Memory	
15-WVLT immediate recall score (words remembered)	16.6 (5.7)
15 WVLT delayed recall score (words remembered)	4.4 (2.7)
Visual Association Test (pictures remembered)	12 (10-12)
Executive function[*]	
Trail Making Test delta (seconds)	131.8 (67.3)
Stroop interference score (seconds)	39.2 (33.1)
Psychomotor speed [*]	
Letter-Digit Substitution Test (digits coded)	31.2 (9.4)
Cerebral	
White matter hyperintensity volume, ml[**]	22.0 (9.0-56.1)
Lacunar infarcts present[^^]	59 (26.9%)
Cerebral microbleeds present†	54 (24.7%)
Brain volume total, ml	1003 (92.3)
Grey matter volume, ml	499 (47.9)
White matter volume, ml	505 (52.0)

Data are presented as mean (standard deviation), median (interquartile range) or as number (percentage) where appropriate. [^] Includes myocardial infarction or coronary intervention procedure ≥3 years ago, or peripheral arterial disease. [*] Higher scores indicate worse functioning. [**] missing for n=3 participants. [^^] missing for n=1 participant. †missing for n=6 participants. MMSE=mini-mental state examination; 15-WVLT= 15-Word Verbal Learning Test; TMT=Trail Making Test. TMT delta denotes difference between TMT-B and TMT-A.

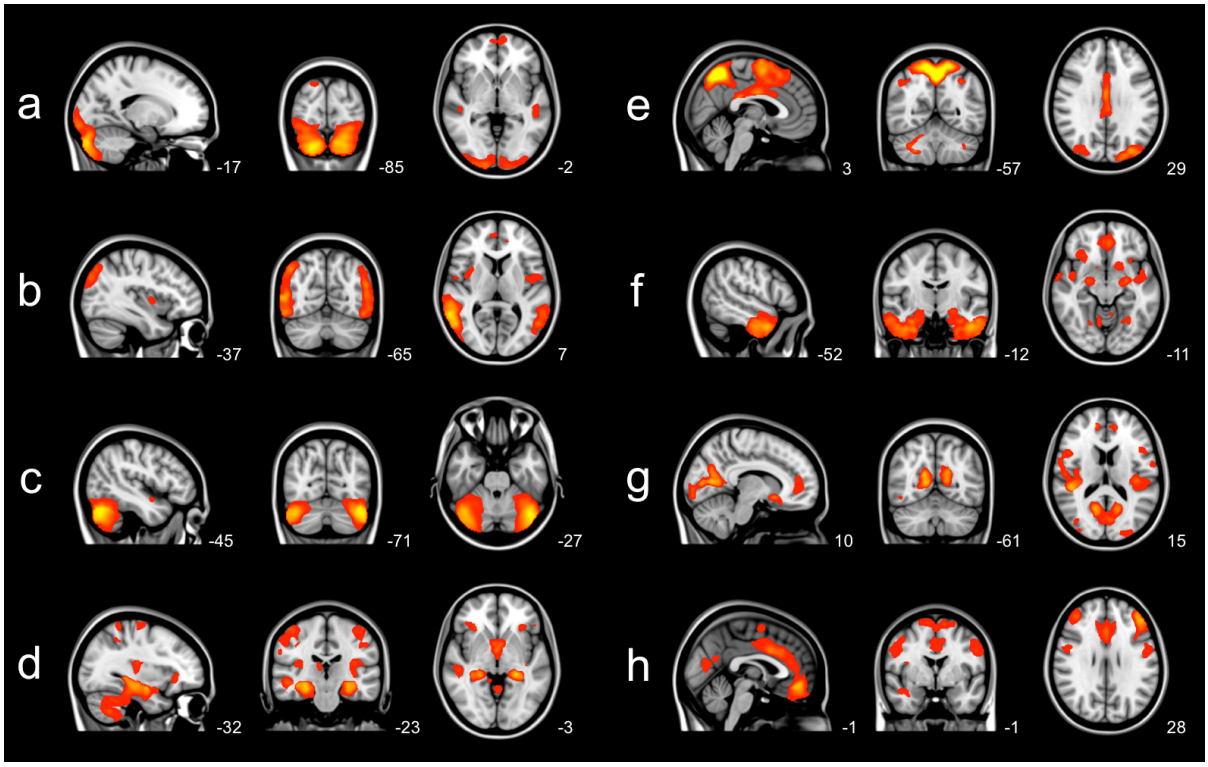

Figure 1. Eight structural covariance networks overlaid on the three most informative orthogonal slices of the Montreal Neurological Institute 152 standard space template image. Networks a-h: a, cerebellar-occipital network; b lateral occipital network; c, cerebellar network; d, subcortical network; e, pre-motor network; f, temporal network; g, occipital-precuneus network; h, anterior cingulate gyrus network. A detailed description and MNI x, y and z-coordinates of each cluster per structural covariance network is given in the appendix Table 2.

Table 2. Brain clusters of the structural covariance networks

	Brain cluster[a]	MNI coordinates		
		x	y	z
Network a	Cerebellum	20	-86	-40
	cluster also contains occipital pole			
	Frontal pole	-8	62	-4
	Middle temporal gyrus	46	-18	-12
	Superior temporal gyrus	-48	-26	-2
	(Lateral occipital cortex)	18	-64	64
Network b	Lateral occipital cortex	-52	-68	24
	cluster also contains supramarginal gyrus, angular gyrus, (middle temporal gyrus)			
	Planum polare	48	0	-12
	Superior frontal gyrus	-6	38	50
	Insular cortex	36	4	4
	(Posterior cingulate gyrus)	6	-34	50
Network c	Cerebellum	-45	-71	-27
	cluster also contains occipital fusiform gyrus			
	Planum polare	-46	-2	-12
Network d	Hippocampus	28	-12	-16
	cluster also contains parahippocampal gyrus, amygdala, thalamus, accumbens, cerebellum			
	Middle temporal gyrus	51	-23	-9
	Postcentral gyrus	26	-26	64
	Insular cortex	39	-15	18
Network e	Precuneus cortex	4	-60	56
	Juxtapositional lobule cortex			
	cluster also contains anterior cingulate gyrus, superior frontal gyrus	3	-4	67
	(Middle temporal gyrus)	54	-10	-22
	Cerebellum	26	-62	-42
	(Precentral gyrus)	-24	-24	66
	Occipital pole	-32	-98	-8
Network f	Temporal pole	30	0	-30
	cluster also contains parahippocampal gyrus, inferior temporal gyrus, planum polare			
	Frontal medial cortex	-4	40	-14
	Frontal orbital cortex	31	25	-11
	Amygdala	-26	-9	-11
Network g	Intracalcarine cortex	34	-74	-22
	cluster also contains precuneus cortex			
	Planum temporale and inferior frontal gyrus	46	-34	16
	Subcallosal cortex	-2	24	-12
	Occipital pole	34	-92	0
	Paracingulate gyrus	10	46	5
Network h	Frontal medial cortex	-44	40	16
	cluster also anterior cingulate gyrus, frontal pole, superior frontal gyrus			
	Middle frontal gyrus	38	20	48
	(Cerebellum)	-20	-72	-42
	(Lateral occipital cortex)	42	-66	48
	(Superior temporal gyrus)	44	-8	-18
	Supracalcarine cortex	0	-74	16

[a]Each structural covariance network is divided in brain clusters using the cluster tool integrated in FSL. MNI x-, y-, and z-coordinates of each cluster are given. Brain structures are anatomically identified using the Harvard-Oxford atlas integrated in FSL. Figure 1 shows the most informative sagittal, coronal, and transverse slices. Structures in parentheses in the table are not visible in Figure 1. MNI= Montreal Neurological Institute 152 standard space image.

Table 3. Associations between age, white matter hyperintensity volume, presence of lacunar infarcts and microbleeds, and the expression of structural covariance networks (n=219)

	SCN a cerebellar-occipital	SCN b lateral occipital	SCN c Cerebellar	SCN d subcortical	SCN e pre-motor	SCN f temporal	SCN g occipital-precuneus	SCN h anterior cingulate
	B (95% CI)	*B* (95% CI)	*B* (95% CI)	*B* (95% CI)	*B* (95% CI)	*B* (95% CI)	*B* (95% CI)	*B* (95% CI)
	P-value	*P*-value	*P*-value	*P*-value	*P*-value	*P*-value	*P*-value	*P*-value
Age^								
	-.16 (-.29, .02)	.03 (-.10, .17)	-.18 (-.31, -.05)	-.18 (-.31, -.05)	-.25 (-.38, -.12)	-.26 (-.40, -.14)	-.34 (-.47, -.21)	-.14 (-.26, -.01)
	.022	.635	.008	.006*	<.001*	<.001*	<.001*	.037
White matter hyperintensity volume								
	.02 (-.11, .16)	-.30 (-.43, -.17)	-.21 (-.34, -.08)	-.36 (-.49, -.24)	-.14 (-.27, -.003)	-.15 (-.28, -.02)	-.15 (-.27, -.02)	-.21 (-.33, -.08)
	.726	<.001*	.002*	<.001*	.044	.021	.021	.002*
Lacunar infarcts								
	-.11 (-.24, .02)	-.03 (-.17, .10)	-.13 (-.26, .01)	-.21 (-.34, -.09)	-.13 (-.25, .004)	.06 (-.07, .19)	-.13 (-.25, .001)	-.06 (-.19, .07)
	.100	.649	.062	.001*	.057	.397	.052	.376
Cerebral microbleeds								
	-.06 (-.20, .07)	-.10 (-.24, .04)	-.14 (-.28, -.01)	-.16 (-.29, -.03)	-.13 (-.26, .004)	-.09 (-.22, .04)	-.16 (-.28, -.03)	-.20 (-.33, -.07)
	.356	.162	.038	.018	.057	.171	.013	.003*

B (95% CI) represents mean change in SCN expression per standard deviation increase in WMH volume, lacunar infarcts or microbleeds

*indicates statistical significance after correction for multiple testing *P*≤.006

^ analyses were adjusted gender

Unless depicted otherwise all analyses were adjusted for gender and age

SCN= Structural covariance network.

Table 4. Associations between structural covariance networks and cognitive functioning (n=219)

	Memory function		Executive function		Psychomotor speed	
	***B* (95% CI)**	***P*-value**	***B* (95% CI)**	***P*-value**	***B* (95% CI)**	***P*-value**
SCN a – cerebellar-occipital						
	.13 (-.004, .26)	.057	.17 (.03, .31)	.016	.22 (.08, .34)	.002*
SCN b – lateral occipital						
	-.08 (-.22, .06)	.258	-.12(-.26, .02)	.097	-.14 (-.28, -.003)	.045
SCN c – cerebellar						
	-.02 (-.15, .12)	.786	.17 (.03, .31)	.018	-.01 (-.13, .14)	.942
SCN d – subcortical						
	.11 (-.04, .26)	.155	-.06 (-.22, .09)	.422	-.004 (-.15, .15)	.959
SCN e – pre-motor						
	.04 (-.10, .17)	.623	.06 (-.08, .20)	.389	.04 (-.10, .18)	.555
SCN f – temporal						
	.20 (.06, .34)	.005*	.12 (-.03, .27)	.105	.0.12 (-.03, .26)	.107
SCN g – occipital-precuneus						
	.12 (-.02, .27)	.093	.12 (-.04, .27)	.134	.27 (.12, .41)	<.001*
SCN h – anterior cingulate						
	-.002 (-.14, .14)	.974	.01 (-.08, .21)	.380	.08 (-.07, .22)	.284

B (95% CI) represent mean change in cognitive z-scores per standard deviation increase in SCN expression. For memory, executive function, psychomotor speed and overall cognitive function a lower score indicates worse performance

*indicates statistical significance after correction for multiple testing *P*≤.006

All analyses were adjusted for gender, age, white matter hyperintensity volume, the presence of lacunar infarcts, and microbleeds

SCN= Structural covariance network.