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The impact of aging on gray matter structural covariance networks

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ABSTRACT

Previous anatomical volumetric studies have shown that healthy aging is associated with gray matter tissue loss in specific cerebral regions. However, these studies may have potentially missed critical elements of age-related brain changes, which largely exist within interrelationships among brain regions. This magnetic resonance imaging research aims to assess the effects of aging on the organization of gray matter structural covariance networks. Here, we used voxel-based morphometry on high-definition brain scans to compare the patterns of gray matter structural covariance networks that sustain different sensorimotor and high-order cognitive functions among young ($n = 88$, mean age $= 23.5 \pm 3.1$ years, female/male $= 55/33$) and older ($n = 88$, mean age $= 67.3 \pm 5.9$ years, female/male $= 55/33$) participants. This approach relies on the assumption that functionally correlated brain regions show correlations in gray matter volume as a result of mutually trophic influences or common experience-related plasticity. We found reduced structural association in older adults compared with younger adults, specifically in high-order cognitive networks. Major differences were observed in the structural covariance networks that subserve the following: a) the language-related semantic network, b) the executive control network, and c) the default-mode network. Moreover, these cognitive functions are typically altered in the older population. Our results indicate that healthy aging alters the structural organization of cognitive networks, shifting from a more distributed (in young adulthood) to a more localized topological organization in older individuals.

Introduction

It has been well established that healthy aging is associated with anatomical changes in the brain. Although the majority of magnetic resonance imaging (MRI) studies have shown that significant anatomical variability exists within the senior population (Raz and Rodrigue, 2006; Walhovd et al., 2005), a common pattern of atrophy in the prefrontal cortex (Lemaitre et al., 2012; Raz et al., 1997, 2005; Tisserand et al., 2002, 2004) and the medial temporal lobe (Bigler et al., 2002; Du et al., 2006; Tisserand et al., 2004) has been consistently reported when comparing older and younger adults. In particular, these anatomical changes have been associated with an age-related decline in executive functions (Cardenas et al., 2011; Du et al., 2006) and episodic memory (Pardo et al., 2007; Petersen et al., 2000; Rusinek et al., 2003), respectively.

However, these anatomical volumetric studies may have potentially missed critical elements of age-related brain changes that exist largely within networks. It has been proposed that the aging brain may not simply be characterized by regional atrophy, but rather by a "cortical disconnection" within different neurocognitive networks (Charlton et al., 2006; Gunning-Dixon et al., 2009; Madden et al., 2009; O'Sullivan et al., 2001; Schmahmann et al., 2008). It has been hypothesized that this disconnection may be determined by an alteration of white matter integrity in an older population. The recent development of anatomical neuroimaging techniques aimed at characterizing anatomical brain connectivity has provided substantial support for this hypothesis. In particular, the use of diffusion tensor MRI techniques has consistently shown a diffuse loss of axonal integrity in older populations (Benedetti et al., 2006; Pagani et al., 2008; Pfefferbaum et al., 2000; Salat et al., 2005). Consistent with these findings, a quantitative analysis of complex networks applied to the study of the topological organization of the brain revealed less dense connections and a more localized network organization in older individuals (Wu et al., 2011).

A novel valuable tool used to investigate structural brain networks that sustain different sensorimotor or high-order cognitive functions

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is the study of structural covariance networks (SCNs) using voxel-based morphometry (VBM) (Ashburner and Friston, 2000). This method has been previously used to examine the pattern of covariance between the gray matter (GM) volume of an *a priori* selected "seed" brain region (i.e., a critical region of the network itself) and the GM volume throughout the entire brain (Mechelli et al., 2005; Modinos et al., 2009; Nosarti et al., 2010; Seeley et al., 2009; Zielinski et al., 2010). This approach relies on the assumption that related regions covary in volume as a result of mutually trophic influences (Ferrer et al., 1995) or from common experience-related plasticity (Draganski et al., 2004; Mechelli et al., 2004). For example, this hypothesis is supported by the observation that related components of the visual system (i.e., the optic tract, the lateral geniculate nucleus, and the primary visual cortex) covary in volume across individuals (Andrews et al., 1997). According to several studies, the topological organization of SCNs reflects the pattern of functional organization of different networks. Therefore, regions that are positively associated in GM volume may also be a part of the same functional network. Supporting evidence for this hypothesis derives from a study conducted by Seeley and colleagues, which demonstrated a direct link between the pattern of structural covariance and the architecture of the intrinsic functional networks as measured by resting-state functional magnetic resonance imaging (fMRI) (Seeley et al., 2009).

The study of SCNs using VBM has proven to be a powerful tool to characterize age-related changes in GM structural relationships between cortical nodes that contribute to large-scale functional networks during development (Zielinski et al., 2010) and the understanding of human brain maturation. In particular, Zielinski and colleagues compared the pattern of structural covariance among four age categories (early childhood, 5–8 years; late childhood, 8.5–11 years; early adolescence, 12–14 years; late adolescence, 16–18 years) in the SCNs that subserves the following functions: a) the visual system; b) the auditory system; c) the motor system; d) speech; e) language-related semantics; f) the ability to identify novel or relevant stimuli to guide behavior (salience network); g) executive functions and working memory (executive control network); and h) visual imagery and mentalization (default-mode network). These studies reported that SCNs derived from the use of primary sensory and motor cortical seeds (a, b, and c) were already well developed in early childhood and had expanded in early adolescence prior to pruning into a more restricted topology by late adolescence. In contrast, the language, social–emotional, and other cognitive networks are relatively underdeveloped in younger age groups and showed an increasingly distributed topology in older children. To date, there has been a lack of studies focused on examining how these SCNs evolve from early adulthood to older age.

In this MRI study, we investigated the effects of aging on the GM structural covariance in 176 healthy subjects that were divided into two age groups, i.e., young adults (18–35 years) and older adult groups (60–84 years). To compare our findings with previous results of age-related SCN changes during development, the same three sensorimotor (a–c) and five high-order cognitive (d–h) SCNs investigated by Zielinski and colleagues were included in this study (Zielinski et al., 2010). A reduced structural covariance in the older adults compared to the young adults would provide critical support to the hypothesis that the age-related decline in different sensorimotor and cognitive functions is associated with a disconnection within their scaffolding networks.

Methods

Subjects

De-identified T1 magnetic resonance imaging (MRI) brain scans were obtained from the database of anatomical images of the Unité de Neuroimagerie Fonctionnelle (UNF) of the Institut Universitaire de Gériatrie de Montréal (IUGM), according to the rules of the Comité mixte d'éthique de la recherche du Regroupement Neuroimagerie/Québec (CMER-RNQ) of the Centre de Recherche IUGM (CRIUGM). These anatomical images were obtained in the framework of previous functional or anatomical neuroimaging studies directed by different investigators of the CRIUGM. In addition, only the scans of participants who were younger than 35 years (the young adults group) and older than 60 years (the older adults group) were considered for this study. From a pool of 188 scans (young adults: $n=97$, F/M = 55/42; older adults: $n=91$, F/M = 58/33), we constructed two sex-matched groups. To match the two groups by the number of subjects and by gender, nine younger males (the oldest of the group) and three older females (the youngest of the group) were excluded from the analysis, resulting in 88 young (age range 18–35 years, mean age = 23.5 ± 3.1 years, females/males = 55/33) and 88 older adults ($n=88$, age range 60–84 years, mean age = 67.3 ± 5.9 years, females/males = 55/33) being included in the study. All of the participants were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), and had a negative history of neurological disease and mental illness.

All of the older adults underwent an extensive neuropsychological battery evaluating different cognitive domains, such as the general cognitive status (as measured by the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) or the Mini-Mental State Evaluation (MMSE) (Folstein et al., 1975)), memory, executive functions, language and visuo-spatial abilities, to exclude participants with significant cognitive impairments. However, because the subjects included in this study had already participated in different research protocols, not all of the subjects performed the same battery of tests.

Image acquisition

MRI images were obtained on a 3 T Siemens Trio MRI (Siemens, Erlangen, Germany) at the UNF of the IUGM. For each subject, a volumetric magnetization-prepared rapid gradient echo (MPRAGE) sequence was used to acquire a high-resolution T1-weighted 3D anatomical image, using the following parameters: TR = 2.3 s, TE = 2.91 ms, TI = 900 ms, flip angle = 9°, FOV = 240 × 256, voxel size = 1 × 1 × 1 mm^3. The scans of thirteen young adults and eight older adults (χ^2 (1, 176) = .14, $p=.25$) were acquired with a voxel size dimension of 1 × 1 × 1.2 mm^3. In addition, a 12-channel head coil was used.

Data analysis

Image preprocessing

The structural images were preprocessed using voxel-based morphometry (VBM) implemented in SPM8 using MATLAB 7.10.0 (Mathworks, Natick, MA). First, the T1-weighted volumetric images were manually re-oriented to be approximately aligned with the ICBM152-space (i.e., MNI-space) average template distributed with SPM8. This was performed to ensure reasonable starting estimates for the segmentation routine. The re-oriented T1 scans were then segmented into gray and white matter using the 'new segment' toolbox. The images obtained in the segmentation routine were used to create a custom template using the DARTEL (diffeomorphic anatomical registration using exponentiated lie algebra) approach (Ashburner, 2007). For each participant, the flow fields were calculated during a template creation, which described the transformation from each native GM image to the template. These were then applied to each participant's GM image. The VBM analysis was based on modulated GM images, whereby the GM value for each voxel was multiplied by the Jacobian determinant derived from spatial normalization to preserve the total amount of GM from the original images (Ashburner and Friston, 2000). The resulting modulated and normalized images were then smoothed with a Gaussian kernel of 8 mm FWHM.

Statistical analysis

A statistical analysis was performed on modulated gray matter (GM) images using the general linear model (GLM) as implemented in SPM8. To investigate the network structural covariance, regional GM volumes of eight regions of interest (ROIs) were extracted from the 176 preprocessed images.

The same ROIs included in a previous study investigating structural covariance in the developing brain (Zielinski et al., 2010) were adopted in this study. The ROIs were selected within the right calcarine sulcus (9, −81, 7), right Heschl's gyrus (46, −18, 10), right precentral gyrus (28, −16, 66), pars opercularis in the left inferior frontal gyrus (Broca's area) (−50, 18, 7), left temporal pole (−38, 10, −28), right frontoinsular cortex (38, 26, −10), right dorsolateral prefrontal cortex (44, 36, 20), and right angular gyrus (46, −59, 23). These regions anchor the visual, auditory, motor, speech, language-related semantic, salience, executive control, and default-mode networks, respectively (Zielinski et al., 2010). The GM volume was then calculated and extracted from a 4 mm radius sphere around those coordinates from the modified gray matter images.

Eight separate correlation analyses were performed by entering the extracted GM volumes from each ROI as a covariate of interest. To characterize the age-specific effects, both the young and older adults were separately modeled in all of the analyses (i.e., we modeled age-group by regional-GM interactions). Because the scans of the thirteen young adults and eight older adults were acquired with a different voxel size dimension of $1\times1\times1.2$ mm^3 (see the Image acquisition section), a binary covariate indicating each subject's scanning sequence was included in the statistical model. The global nuisance effects were then accounted for by scaling the images so that they all had the same global value (proportional scaling).

These statistical analyses were aimed at identifying, for each region of interest, voxels that expressed differences in the regression slopes between the young and older adults. For this study, we will refer to these differences in slopes as the differences in 'structural association.'

Specific T contrasts were established to map the voxels that expressed a stronger structural association in the young compared to the older adults, and vice versa. The threshold for the resulting statistical parametric maps was established at a voxel-wise $p<0.001$ (uncorrected) and then FWE corrected for multiple comparisons at $p<0.05$, based on the cluster extent and Gaussian Random Field (GRF) theory. A correction for non-stationary smoothness was then applied (Hayasaka et al., 2004) using the implementation of this method in the VBM5 toolbox (vbm5_v1.19, http://dbm.neuro.uni-jena.de/vbm) because this is necessary to avoid false positives with VBM (Ashburner and Friston, 2000).

Additional analyses were performed to test 1) the common patterns of positive correlations across the groups using a conjunction analysis, 2) the significant differences between young and older adults using contralateral seeds by changing the sign on each seed's *x* coordinate, as in Zielinski et al. (2010).

Results

The common pattern of structural association of the young and older adults identified by means of conjunction analyses is reported in Supplemental Table 1.

Decreased structural association was only observed in the older compared to the young adults, but not in the young compared to the older adults (Tables 1 and 2, and Fig. 1).

Primary sensory and motor networks (visual, auditory and motor structural covariance networks)

Within the visual, auditory and motor networks, there were no differences observed in the structural association between the younger and older adults.

Language-related speech and semantic networks

Within the speech network, the patterns of structural association derived from the pars opercularis in the left inferior frontal gyrus (including Broca's area) (language-related speech network) showed no differences between the young and older groups. Moreover, no differences were observed in the analysis with the contralateral seed region (right inferior frontal gyrus).

Conversely, age-related differences were observed within the language-related semantic SCN, which is anchored to the temporal poles. Decreased structural association in the older adults was mainly observed between the left temporal pole and the occipital visual regions, including the bilateral lingual gyri and bilateral calcarine sulcus. Areas of significant differences were also observed in the right precuneus and in the left inferior parietal lobule. Decreased structural association of the left inferior parietal lobule was also observed in the analysis of the contralateral seed region, i.e., the right temporal pole.

Salience, executive control and default-mode network

There were no differences observed between the young and older adults in the SCN anchored in the bilateral frontoinsular cortex and associated with the salience network.

Table 1
The age differences in the SCN topology based on the comparison young > older adults. Max *T* is the maximum *T* statistic of each local maximum. $p<0.05$ based on non-stationary cluster-extent correction.

		MNI coordinates			Extent (mm^3)	Max *T*
		x	*y*	*z*		
Language-related semantic network (L TP)						
Lingual gyrus (17)	L	−6	−80	−1	1579	4.65
	R	6	−81	−1		4.08
Calcarine sulcus (17)	L	−6	−63	18	879	4.24
	R	12	−60	17		3.70
Precuneus (23)	R	17	−54	26		4.00
Inferior parietal lobule (40)	L	−51	−50	47	1098	4.01
Executive control (R DLPFC)						
Inferior parietal lobule (40)	L	−48	−50	39	1082	5.04
Default-mode network (R ANG)						
Inferior frontal gyrus, pars orbitalis (46)	R	54	45	−9	1066	4.40
Middle frontal gyrus (46)	R	49	54	2		4.14
	R	51	49	12		3.62

Table 2
The age differences in the SCN topology based on the comparison young > older adults in the contralateral seeds. Max *T* is the maximum *T* statistic of each local maximum. $p<0.05$ based on non-stationary cluster-extent correction.

		MNI coordinates			Extent (mm^3)	Max *T*
		x	*y*	*z*		
Language-related semantic network (R TP)						
Inferior Parietal Lobule (40)	L	−51	−47	62	1509	4.74
		−53	−54	39		3.35
Executive control (L DLPFC)						
Inferior Parietal Lobule (40)	L	−57	−57	48	1050	4.43
		−48	−50	45		4.11

Within the SCN related to executive control functions and working memory, decreased structural association in the older group was observed between the left inferior parietal lobule, and both the right and left dorsolateral prefrontal cortex.

Decreased structural association was also observed in the SCN anchored to the right angular gyrus and related to the default-mode network. The right angular gyrus showed a decreased structural association with the right middle frontal gyrus and the right inferior frontal gyrus (pars orbitalis). Surprisingly, no differences were observed when the contralateral seed was investigated. However, reduced structural association was observed between the left angular gyrus and the anterior inferior temporal gyrus when a less conservative threshold of significance ($p<0.001$ uncorrected) was adapted.

Discussion

In this study, we used voxel-based morphometry (VBM) to identify age-related changes in the pattern of gray matter (GM) structural covariance in different sensorimotor and high-order cognitive networks in younger (age range 18–35 years) and older (60–84 years) adults. Our results showed reduced structural association in high-order cognitive networks in the older adults compared with young adults, while no differences were observed in the sensorimotor networks. In addition, no reduced association was observed in the young adults compared with the older adults.

The development of modern cognitive neuroscience and of functional neuroimaging techniques has revealed that brain functions are organized into large, interacting complex networks with defined topological organization (Mesulam, 2009). Recent evidence has associated the pattern of functional organization of different sensorimotor and cognitive networks with the topological structural organization of the brain. In particular, it has been reported that in healthy individuals, functionally correlated brain regions feature not only defined axonal connections (Greicius et al., 2009; Seeley et al., 2007), but also a cortical thickness covariance (Gong et al., 2012; Lerch et al., 2006). The causes of the relationship between GM function and volume are still unclear. One potential explanation is that structural covariance networks (SCNs) may emerge during development in response to an inherited projection map and that they may continue to be reshaped during the lifespan as a result of mutual trophic influences (Ferrer et al., 1995) or common experience-related plasticity (Draganski et al., 2004; Mechelli et al., 2004).

The emergence of SCNs during normal development from early childhood to young adulthood has been the subject of previous investigations (Lerch et al., 2006; Shaw et al., 2008; Zielinski et al., 2010). Converging evidence from these studies indicate the presence of different levels of complexity of neurodevelopmental trajectories in the human cerebral cortex which would depend on the function sustained by the network. In particular, Zielinski and colleagues have shown that rudimentary intrinsic connectivity networks (sensorimotor networks) are already well developed at early stages, expand into early adolescence, and are then pruned to a more restricted topology (Zielinski et al., 2010). In contrast, high-level cognitive networks show increasingly distributed topology in older children. In this study, we investigated the effects of healthy aging on the topographical organization of the same SCNs investigated by Zielinski and colleagues. Consistent with what was observed during development, our results revealed that healthy aging does not indiscriminately alter the organization of all of the brain networks, but rather targets some SCNs based on their functional specialization. In particular, while sensorimotor SCN topography tends to remain stable over time, the brain goes from a distributed to a more local covariance topology in high-order cognitive SCNs.

Major differences in the high-order cognitive SCNs between older and younger adults were observed in the SCNs that subserve language-related semantics, executive functions and working memory (executive control network), as well as visual imagery and mentalization (default-mode network).

Within the language-related semantic SCN, main differences were observed in the structural association between the left temporal pole and the visual occipital regions. These findings are consistent with a previous investigation that reported a reduced white matter fiber connection between these areas, i.e., in the inferior longitudinal fasciculus (Kantarci et al., 2011; Voineskos et al., 2012). This age-related reduced structural association between the semantic and visual areas could represent an anatomical counterpart of some language-related semantic difficulties that have been previously reported in senior populations. Although the semantic store of conceptual knowledge does not seem to be affected with healthy aging, effortful aspects of language-related semantics, such as naming, decline with age (Langlois et al., 2009; McDowd et al., 2011; Zec et al., 2005).

A reduced structural association in older adults was also observed in the executive-control network. The executive-control network specializes in control processes, by directing the attention on relevant stimuli to guide behavior. Based on this role, it is not surprising that this network includes known sites for sustained attention and working memory, such as the DLPFC and lateral parietal cortex (Curtis and D'Esposito, 2003). The reduced structural covariance between the DLPFC and the inferior parietal regions observed in the older adult group may explain the difficulties in cognitively demanding tasks observed in the older population. Finally, age-related differences were also demonstrated in the SCN underlying the default-mode network (DMN). In particular, differences in structural association were observed between the seed region (i.e. the right AG) and the right middle and inferior frontal areas that are typically thought to be part of the DMN. These findings are consistent with previous functional studies. In fact, recent work investigating resting-state brain activity during normal aging has reported reduced activity in the older population in the DMN (Koch et al., 2010).

From a theoretical standpoint, the decreased structural association observed in the older adult group in different high-cognitive SCNs is coherent with the "cortical disconnection" theory. According to this theory, healthy aging would not only determine cortical regional changes, but also impact the integration of regional brain activities (Charlton et al., 2006; Gunning-Dixon et al., 2009; Madden et al., 2009; O'Sullivan et al., 2001; Schmahmann et al., 2008). These changes are also consistent with previous findings (Wu et al., 2011), which showed that the topological organization of the brain revealed less dense connections and more localized organization in the older compared to younger individuals,. In the present study, the more localized topological organization in the older adults group can be observed by the fact that some regions that were distant from the seed regions were more strongly connected in the SCNs of the young adult group than in those of the older adults (e.g., the occipital regions in the language-related semantic SCN). The fact that in the older adults, those distant regions exhibited significantly less structural association with the seed regions supports the results of Tomasi and Volkow (2011) suggesting that

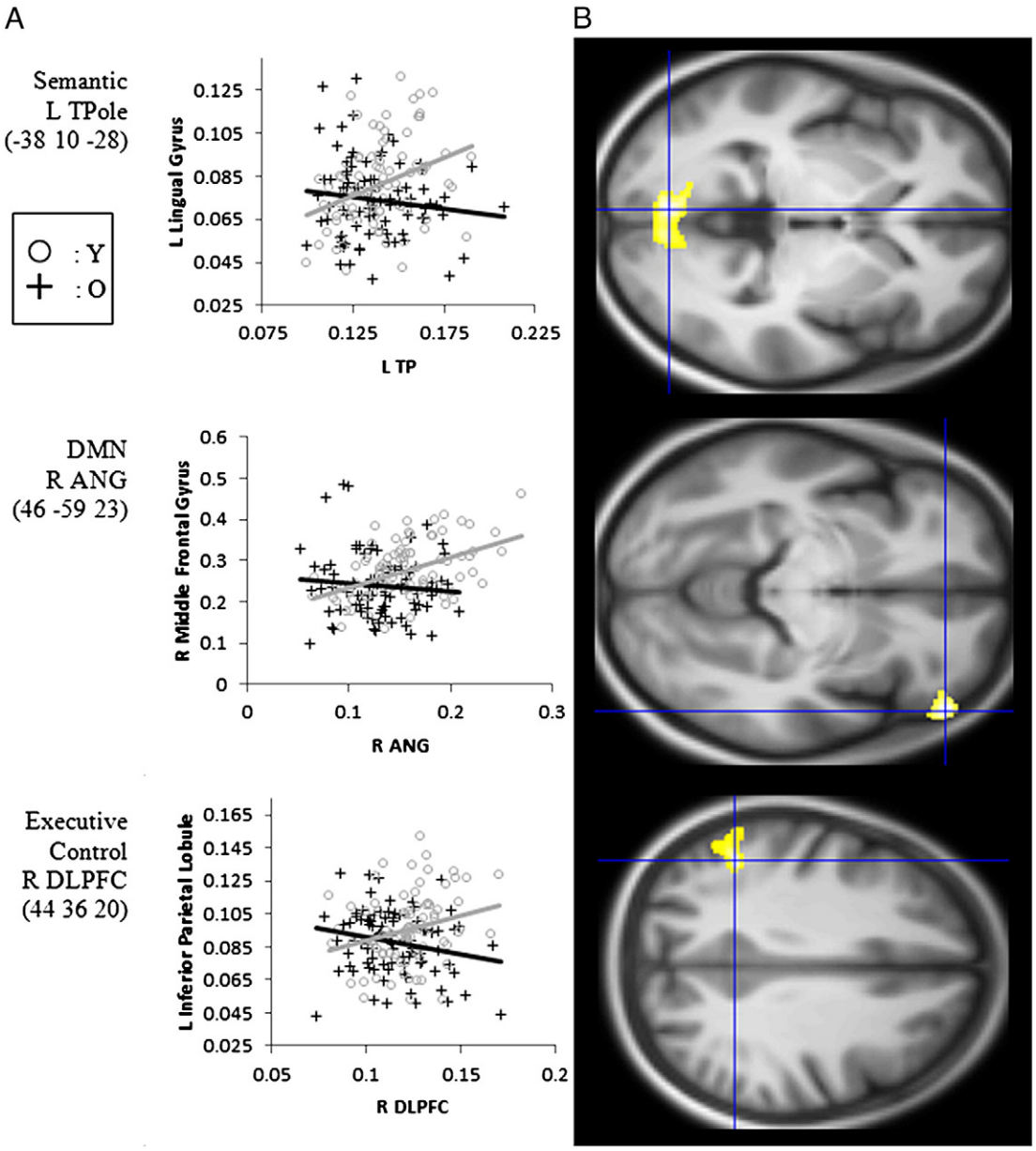

Fig. 1. A) The GM correlations between the selected ROIs and a 4-mm radius sphere centered on the peak voxel expressing decreased **structural association** in the older compared to the young adults. B) The voxels that expressed decreased **structural association** in the older adults compared to the young adults. The crosshairs are centered on the global peak. *Abbreviations Y = Young adults, O = Older adults.*

long-range connections may be more vulnerable to aging effects than short-range connections.

It must be mentioned that some factors related to the quality of the images may have partially affected the decreased long-distance correlations observed in the older population. Recent resting-state functional MRI studies have revealed that many long-distance correlations are decreased by subject motion (Power et al., 2012; Van Dijk et al., 2012). An additional factor that may partially influence the results is the reduction in the tissue contrast in the scans of older participants (Salat et al., 2009). Although we acknowledge that subject motion and tissue contrast may potentially represent a bias in the correlation analysis, it is unlikely that these factors alone would determine the differences observed in the results of this study.

In summary, this work demonstrates that the study of SCNs using VBM is an effective method to comprehensively investigate different networks that are of interest in the aging brain. Our data also provide preliminary evidence for the hypothesis that the aging brain is characterized by reduced structural association. In conclusion, we suggest that the study of structural covariance represents a valuable complementary tool to better characterize the aging brain. Future studies that combine different techniques, such as SCNs, intrinsic functional networks and diffusion imaging, as well as neuropsychological data may also help to clarify the effects of aging on brain structural networks and function.

Disclosure statement

The authors have nothing to disclose.

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