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Age-related changes in topological patterns of large-scale brain functional networks during memory encoding and recognition

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ABSTRACT

In this study we used functional magnetic resonance imaging to investigate age-related changes in large-scale brain functional networks during memory encoding and recognition in 12 younger and 16 older adults. For each participant, functional brain networks were constructed by computing temporal correlation matrices of 90 brain regions and analyzed using graph theoretical approaches. We found the age-related changes mainly in the long-range connections with widespread reductions associated with aging in the fronto-temporal and temporo-parietal regions, and a few age-related increases in the posterior parietal regions. Graph theoretical analysis revealed that the older adults had longer path lengths linking different regions in the functional brain networks as compared to the younger adults. Further analysis indicated that the increases in shortest path length in the networks were combined with the loss of long-range connections. Finally, we showed that for older adults, frontal areas played reduced roles in the network (reduced regional centrality), whereas several default-mode regions played increased roles relative to younger subjects (increased regional centrality). Together, our results suggest that normal aging is associated with disruption of large-scale brain systems during the performance of memory tasks, which provides novel insights into the understanding of age-related decline in multiple cognitive functions.

Introduction

The decline of memory and other cognitive functions has commonly been observed in normal aging (Park et al., 1996; Salthouse and Ferrer-Caja, 2003). A large body of evidence from functional neuroimaging studies has suggested that this decline is accompanied by focal changes in neuronal activity in many brain areas, such as the prefrontal cortex (Grady et al., 1995; Cabeza et al., 1997b; Logan et al., 2002; Madden et al., 2004; Mitchell et al., 2006; Nielson et al., 2006; Kukolja et al., 2009), medial temporal lobe (Grady et al., 1995; Cabeza et al., 2004; Gutchess et al., 2005; Nielson et al., 2006), parietal (Madden et al., 2004; Townsend et al., 2006; Persson et al., 2007; Miller et al., 2008) and occipital regions (Cabeza et al., 2004; Davis et al., 2008). There is also accumulating evidence that this decline is associated with alterations in the relationship among different brain regions (Grady et al., 1995; Cabeza et al., 1997a; Della-Maggiore et al., 2000; Grady et al., 2003; Daselaar et al., 2006; Andrews-Hanna et al., 2007; Taniwaki et al., 2007; Damoiseaux et al., 2008) in terms of functional or effective connectivity (Friston, 1994), possibly due to subtle anatomical disconnections between brain regions that ordinarily function in a coordinated fashion (O'Sullivan et al., 2001; Davis et al., 2009). It has been suggested that the performance of complex cognitive tasks, such as memory tasks, require highly segregated and integrated processing in these functionally linked, large-scale brain networks (Bressler and Kelso, 2001). However, it remains unclear to what extent the age-related abnormalities of both regional brain activation and functional connectivity affect these large-scale functional networks. To address this issue, in this study we sought to investigate changes in topological patterns of large-scale functional brain networks in normal aging during the performance of memory tasks.

Brain networks can be conceived of as neurocognitive entities that incorporate both local and global processes (Sporns and Tononi, 2002). Recently, there has been increasing interest in assessing cognitive brain networks using multivariate identification of whole-brain patterns of activity (Della-Maggiore et al., 2000; Grady et al., 2003, 2006). In recent years, the development of graph theoretical approaches has brought a fresh perspective to the investigation of complex brain networks (for reviews, see Boccaletti et al., 2006; Bullmore and Sporns, 2009). Many studies have consistently demonstrated that the normal brain is organized according to a highly efficient neuronal architecture,

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generally referred to as a small-world structure (Stam, 2004; Achard et al., 2006; He et al., 2007; Hagmann et al., 2008), which is characterized by high local specification and high global integration between brain regions. Moreover, this organization pattern is known to be disrupted in brain diseases (for recent reviews, see Bassett and Bullmore, 2009; He et al., 2009a). Recent findings indicate that development and normal aging are also accompanied by alterations in topology of functional brain networks (Achard and Bullmore, 2007; Fair et al., 2009; Meunier et al., 2009; Supekar et al., 2009). For instance, Achard and Bullmore (2007) showed that, compared with younger adults, older adults had decreased topological efficiency in spontaneous functional brain networks derived from resting-state functional magnetic resonance imaging (fMRI). Furthermore, they found that the age-related changes were mainly located at the connections between different functional clusters, such as fronto-parietal clusters (Meunier et al., 2009). As a whole, these studies have mainly investigated abnormal cognitive aging networks based on the spontaneous activity in the resting human brain. However, it has been found that specific cognitive tasks can provide novel information about brain activity (Morcom and Fletcher, 2007) compared to that obtained from resting-state data, and thus task-related functional connectivity is a useful tool for investigating interdependence among brain regions. In addition, previous studies on cognitive changes in aging have indicated that a single underlying mechanism may lead to age-related changes across multiple cognitive domains (Grady et al., 2006). In the current study we sought to investigate whether the effects of age on functional brain networks were task specific, or whether they reflected the influence of a common factor.

In this study, participants were scanned during the encoding and recognition portions of a memory task. Based on previous studies reporting age-related changes in brain activity and functional connectivity, we hypothesized that compared with younger adults, older adults would demonstrate altered topological patterns in large-scale functional brain networks during task performance. Additionally, based on converging evidence for a common factor underlying age-related changes (Grady et al., 2006) and for encoding–retrieval overlap in brain activation patterns (Nyberg, 2002), we hypothesized that each group would show a similar topological configuration in both the encoding and the recognition tasks. To address these hypotheses, we first measured functional connectivity among brain regions during the tasks in a group of younger and older adults, and then performed a weighted graph theoretical analysis to investigate both global and local network properties.

Materials and methods

Participants

Data from 12 younger adults (5 males, 7 females; mean age: 23.2 years, range: 20–27) and 16 older adults (8 males, 8 females; mean age: 74.4 years, range: 75–87) were obtained from the fMRI Data Center (http://www.fmridc.org). All subjects were right-handed and screened for neurological and psychiatric illnesses. These subjects represented a subset of individuals whose data were previously analyzed (Grady et al., 2006) using partial least squares (McIntosh et al., 1996). The previous study also examined a group of middle aged adults (4 males, 8 females; mean age: 41.3 years, range: 41–58) whose data were not included in the present study because their imaging parameters differed from those of the younger and older adults. For detailed demographic data, see Grady et al. (2006).

Experimental tasks

Each participant completed functional scanning sessions comprising four encoding runs of 3.2 min each and two recognition runs of 6.4 min each. The stimuli were presented using E-prime software (Psychology Software Tools, Pittsburgh, PA) and projected from a computer located outside of the scanner room onto a mirror inside the head coil or, for participants needing correctional lenses, through Silent Vision Goggles (Avotec, Stuart, FL) placed over the participants' eyes. The encoding tasks involved the presentation of pictures or words in either perceptual or semantic conditions. In the perceptual condition, participants were asked to determine whether the pictures presented were large or small, or whether the words were displayed in capital or lower case letters. In the semantic condition, participants judged whether the pictures or words corresponded to living or nonliving entities. The participants pressed one of two buttons with either the right middle or right index finger to indicate their response. The stimulus lists for each encoding condition were divided into blocks of six words or pictures; each presented for 3 s with 1 s between stimuli presentations. Following each 24 s stimulus block was a baseline block of equal duration. After completion of the encoding tasks, all subjects performed two recognition tasks. Each recognition list contained 48 trials (32 old and 16 new) and was divided into blocks of six words or pictures (4 old and 2 new); each probe item was presented for 3 s with 1 s between stimuli. In each recognition condition, participants similarly indicated via button press whether each stimulus was old or new. For additional details regarding the experimental design, see Grady et al. (2006).

Data acquisition and preprocessing

All MRI scans were performed using a 1.5-T MRI scanner with a standard head coil (CV/i hardware, LX8.3 software; General Electric Medical Systems, Waukesha, WI). Structural images were obtained by using a 3-D T1-weighted pulse sequence [124 axial slices, thickness = 1.4 mm, repetition time (TR) = 12.4 ms, echo time (TE) = 5.4 ms, flip angle (FA) = 35°, field of view (FOV) = 220 × 165 mm]. Functional images were obtained by using a single shot T2*-weighted pulse sequence with spiral readout [26 axial slices, thickness = 5 mm, TR = 2500 ms, TE = 5.4 ms, FA = 80°]. For the fMRI data, a total of 77 and 154 volumes were acquired in each of four encoding runs and each of two recognition runs, respectively.

Image preprocessing was carried out using SPM2 (http://www.fil.ion.ucl.ac.uk/spm). All datasets were initially corrected for temporal offsets using sinc interpolation and head movement-related effects using a six-parameter (rigid body) spatial transformation (Friston et al., 1995). To minimize movement artifacts, individuals with an estimated maximum displacement in any direction of larger than 1 mm or head rotation of larger than 1° were discarded from the study. No data were excluded under this criterion. The datasets were further spatially normalized to the Montreal Neurological Institute (MNI) stereotaxic space using an optimum 12-parameter affine transformation and nonlinear deformations (Ashburner and Friston, 1999), and resampled to 3-mm isotropic voxels. The fMRI time series data was subsequently filtered using a high-pass filter with a cut-off of (1/100) Hz.

Construction of brain functional networks

The filtered fMRI data from each subject was further parcellated into 90 cortical and subcortical regions (Table 1) by using an automated anatomical labeling brain atlas (Tzourio-Mazoyer et al., 2002). For each region, a representative time series of 77 (or 154) data points was extracted by averaging the time series over all voxels in each run of the encoding (or recognition) task. Subsequently, interregional connectivity was measured by computing Pearson's correlation coefficients (see supplementary materials for methods and results for partial correlation analysis of the same dataset) between all possible pairs of the representative time series without using regression to remove the global signal (Bokde et al., 2006). Then

Table 1
Regions of interest.

Region	Abbreviation	Region	Abbreviation
Precentral gyrus	PreCG	Lingual gyrus	LING
Superior frontal gyrus (dorsal)	SFGdor	Superior occipital gyrus	SOG
Orbitofrontal cortex (superior)	ORBsup	Middle occipital gyrus	MOG
Middle frontal gyrus	MFG	Inferior occipital gyrus	IOG
Orbitofrontal cortex (middle)	ORBmid	Fusiform gyrus	FFG
Inferior frontal gyrus (opercular)	IFGoperc	Postcentral gyrus	PoCG
Inferior frontal gyrus (triangular)	IFGtriang	Superior parietal gyrus	SPG
Orbitofrontal cortex (inferior)	ORBinf	Inferior parietal lobule	IPL
Rolandic operculum	ROL	Supramarginal gyrus	SMG
Supplementary motor area	SMA	Angular gyrus	ANG
Olfactory	OLF	Precuneus	PCUN
Superior frontal gyrus (medial)	SFGmed	Paracentral lobule	PCL
Orbitofrontal cortex (medial)	ORBmed	Caudate	CAU
Rectus gyrus	REC	Putamen	PUT
Insula	INS	Pallidum	PAL
Anterior cingulate gyrus	ACG	Thalamus	THA
Middler cingulate gyrus	MCG	Heschl gyrus	HES
Posterior cingulate gyrus	PCG	Superior temporal gyrus	STG
Hippocampus	HIP	Temporal pole (superior)	TPOsup
Parahippocampal gyrus	PHG	Middle temporal gyrus	MTG
Amygdala	AMYG	Temporal pole (middle)	TPOmid
Calcarine cortex	CAL	Inferior temporal gyrus	ITG
Cuneus	CUN		

Cortical and subcortical regions (45 in each cerebral hemisphere) are defined by a standard brain atlas (Tzourio-Mazoyer et al., 2002).

task-specific correlation matrices were obtained by averaging the connectivity matrices over all four runs of the encoding task, and over both runs of the recognition task.

Graph theoretical approaches

Threshold selection

To date, many brain network studies have investigated the brain's topological properties by way of binarized graphs in which every "edge" (i.e., correlation that passes a threshold) has an equal weight of 1 (Bullmore and Sporns, 2009), thereby neglecting the weights of edges. In this study, we used weighted brain networks to characterize the age-related changes in coordinated patterns of activity during memory tasks. A same sparsity threshold (defined as the existing number of edges divided by the all possible number of edges in a graph) was employed to convert connectivity matrices into a graph, ensuring that the graphs of both groups in each condition have identical numbers of edges (Achard and Bullmore, 2007; Wang et al., 2009). The absolute value of the correlation coefficients surviving the sparsity threshold was preserved as the weights of the edges. As expected, any single threshold may influence the topological properties in the resulting graphs. However, since there is currently no definitive way to select a single threshold, we thresholded each correlation matrix repeatedly over a wide range of possible sparsity values from 0.06 to 0.4 using increments of 0.02 and then estimated the network properties at each threshold value. This enabled us to compare the small-world parameters between the two groups in each condition as a function of sparsity, independently of the precise selection of threshold. The range of sparsity was chosen to allow small-world network properties to be properly estimated and the number of spurious edges in each network minimized (Achard and Bullmore, 2007; He et al., 2008; Wang et al., 2009). The network parameters used in this study were defined as follows.

Weighted clustering coefficient

For a weighted graph, the weighted clustering coefficient, C_i^w, of a node i is defined as (Barrat et al., 2004)

$$C_i^w = \frac{1}{s_i(k_i-1)}\sum_{(j,m)}\frac{w_{ij}+w_{im}}{2}a_{ij}a_{im}a_{jm}$$

where the normalizing factor $s_i(k_i-1)$ [s_i is the strength of the vertex defined as the sum of the weights w_{ij} (absolute value of correlation coefficient) of the connected edges: $s_i=\sum_j w_{ij}$] assures that $0\le C_i^w\le 1$; k_i is the number of the edges connected to the node i; a_{ij} is an element of the adjacency matrix, which is equal to 1 if there is an edge connecting the node i and node j, otherwise it is equal to 0. The manipulation was applicable to both a_{im} and a_{jm} ($j\neq m$). Thus, the weighted clustering coefficient of a weighted network with N nodes, which quantifies the extent of local cliquishness of a network, is defined as:

$$C^w = \frac{1}{N}\sum_i C_i^w$$

Weighted shortest path length

For an unweighted graph, the shortest path length L_p is the average length of the shortest path between any two nodes of a network (Watts and Strogatz, 1998). However, this original definition is uninformative in graphs that include more than one component (i.e., a subgraph in which all nodes are reachable from every other) because the path length between disconnected nodes will be infinite (Latora and Marchiori, 2001). To avoid this situation, L_p was measured here by using an inverse of the harmonic mean of the minimum path length as proposed by Newman (2003). L_p quantifies the ability of parallel information propagation over a network. For a weighted graph, the weighted shortest path length is defined as:

$$L^w = \frac{1}{\frac{1}{N(N-1)}\sum_{i\neq j}\frac{1}{l_{ij}^w}}$$

where $l_{ij}^w = \min_{i\leadsto j}(\mathrm{sum}(d_{ij}))$ and $d_{ij}=1/w_{ij}$. Here, the shortest weighted path length l_{ij}^w between any pair of nodes i and j in the graph indicates the minimum value of the sum of transformed weights d_{ij} (i.e. functional distance) over all possible paths.

In this study, to correct for potential differences in mean connection weights across subjects, we also computed the normalized $C^w(C^w/C^w_{\mathrm{rand}})$ and $L^w(L^w/L^w_{\mathrm{rand}})$ by comparing real C^w and L^w values with the corresponding index obtained by averaging over 50 degree-matched surrogate networks (Maslov and Sneppen, 2002), where

each edge was randomly rewired to up to two times the number of edges in a graph.

Betweenness centrality

In this study, we also analyzed nodal (regional) characteristics of the brain network, which were measured by using betweenness centrality (Freeman, 1977)

$$B_i = \sum_{s \neq i \neq t} \frac{P_{st}(i)}{P_{st}}$$

where B_i is the betweenness of a node i in the network; $P_{st}(i)$ indicates the number of shortest paths between any two nodes (s and t) that pass through node i; P_{st} denotes the total number of shortest paths between the two nodes (s and t). Further, we calculated the normalized betweenness centrality $BC_i = B_i / \langle B \rangle$ (He et al., 2008), where $\langle B \rangle$ was the averaged betweenness across all the nodes. In general, network hubs exhibit high betweenness centrality. In this study a hub of the task-specific functional networks was the region with averaged nodal centrality greater than 1 standard deviation away from the averaged BC per group.

Statistical analysis

Correlation coefficients were first converted into z values using Fisher's r-to-z transformation to correct for non-normality. To test

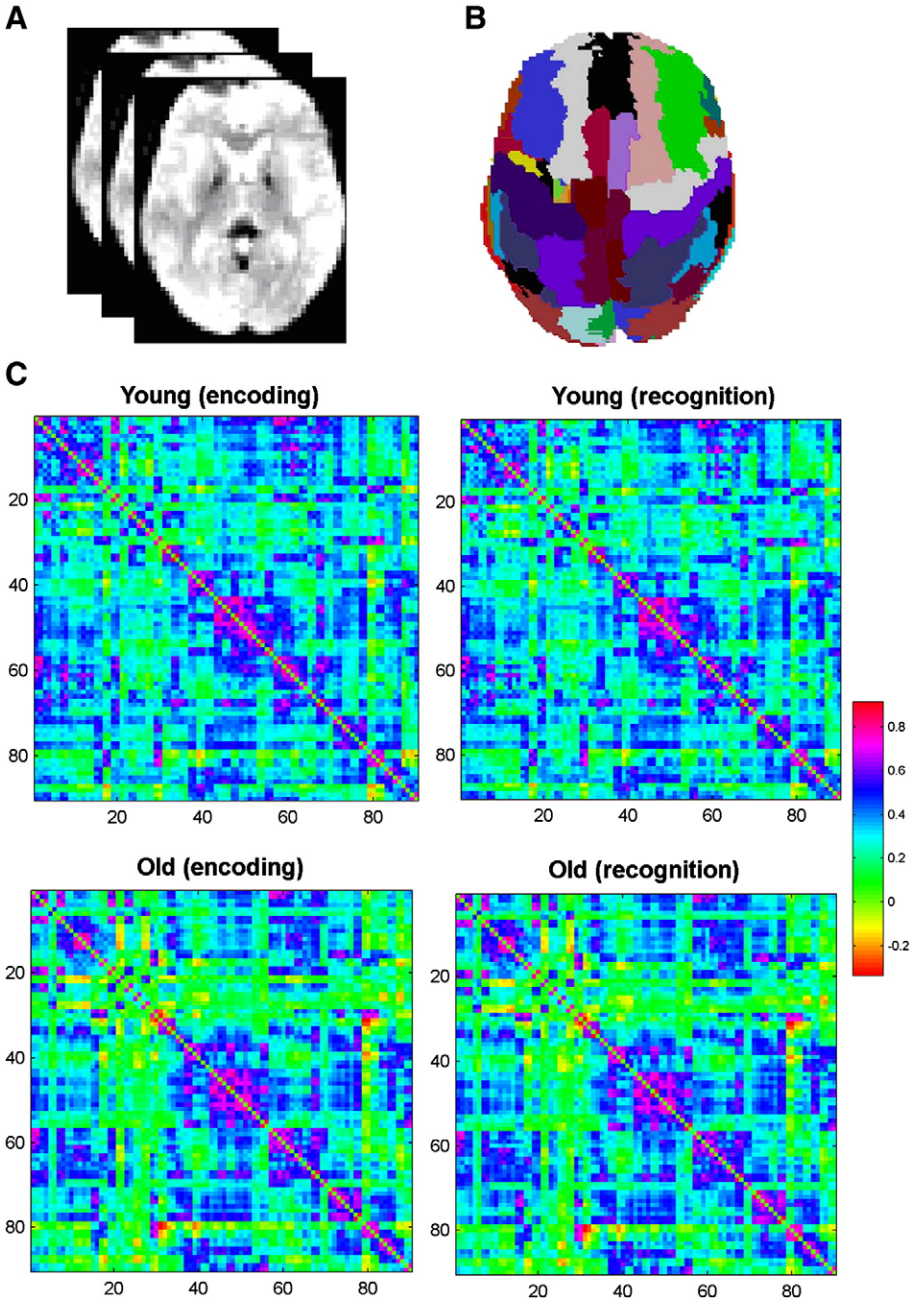

Fig. 1. Schematic of the procedure used to construct large-scale brain functional networks. Raw functional MR images are preprocessed to produce normalized data (A) that are further parcellated by a prior brain atlas (B) into 90 brain regions. Then the regional representative time course was extracted by averaging the time series over all voxels in each subject for each session of the experimental task. The correlations between all possible pairs of 90 time courses for each specific task is computed and averaged for the same task session for each subject. An averaged correlation matrix over all subjects is shown for each task (C). The axial three-dimensional image of the template is shown using MRIcroN software (http://www.sph.sc.edu/comd/rorden/mricron/).

for the significance of the effect of interest (the main effect of both group and condition as well as the interaction of group × condition), a two-way repeated-measures analysis of variance (ANOVA) was carried out on each transformed z value; group (young, old) as a between-subject factor and condition (encoding, recognition) as a repeated measure factor. A false discovery rate (FDR) procedure (Genovese et al., 2002) was performed to adjust for multiple comparisons (corrected statistical threshold $\alpha = 0.05$). The ANOVA analysis was performed separately on each network parameter (C^w, L^w, C^w/C^w_{rand}, L^w/L^w_{rand} and BC).

Results

Age-related changes in functional connectivity during memory tasks

We found that bilateral homogenous regions demonstrated strongly synchronized fluctuations in both groups and both conditions (Fig. 1), which was consistent with previous studies (Salvador et al., 2005; Achard et al., 2006). Visual inspection revealed that there were similar connectivity patterns in encoding and recognition tasks (left vs. right of Fig. 1C) but differences between the younger and older adults (top vs. bottom of Fig. 1C). Mean functional connectivity obtained from each subject in either the encoding or recognition task showed no significant main effect of group [$F(1, 26) = 1.77$, nonsignificant (NS)], no effect of condition [$F(1, 26) = 0.73$, NS] and no interaction between two factors [$F(1, 26) = 0.25$, NS]. Individual functional connectivity showed a total of 202 pairs of significantly altered connections between the two groups ($P < 0.05$, FDR corrected) as depicted in Fig. 2 and Supplementary Table 1. Specifically, 67 long-range connections (defined as the Euclidian distance between the central positions of brain areas greater than 75 cm) showed significant decreases in older adults, predominantly involving fronto-parietal, fronto-temporal, fronto-occipital and temporal–parietal cortex (blue lines, Fig. 2), whereas 42 long-range connections showed increases, mainly involving the precuneus and orbitofrontal regions (red lines, Fig. 2). Additionally, 50 short-range connections showed significant decreases in older adults, predominantly involving fronto-frontal and fronto-temporal cortex (cyan lines, Fig. 2), whereas 43 short-range connections showed increases, mainly involving the occipital–occipital, parietal–parietal and parietal–subcortical regions (magenta lines, Fig. 2). There was no significant main effect of condition, and no group × condition interaction ($P > 0.05$, corrected), which is consistent with the idea that there is a common factor underlying age-related changes across multiple cognitive domains (Grady et al., 2006).

Age-related changes in network topology during memory tasks

The weighted clustering coefficients C^w and C^w/C^w_{rand} showed no significant effect of group, condition or group-by-condition interaction (Figs. 3A and C). The weighted shortest path length L^w showed a significant effect ($P < 0.05$, FDR corrected) of group in the threshold

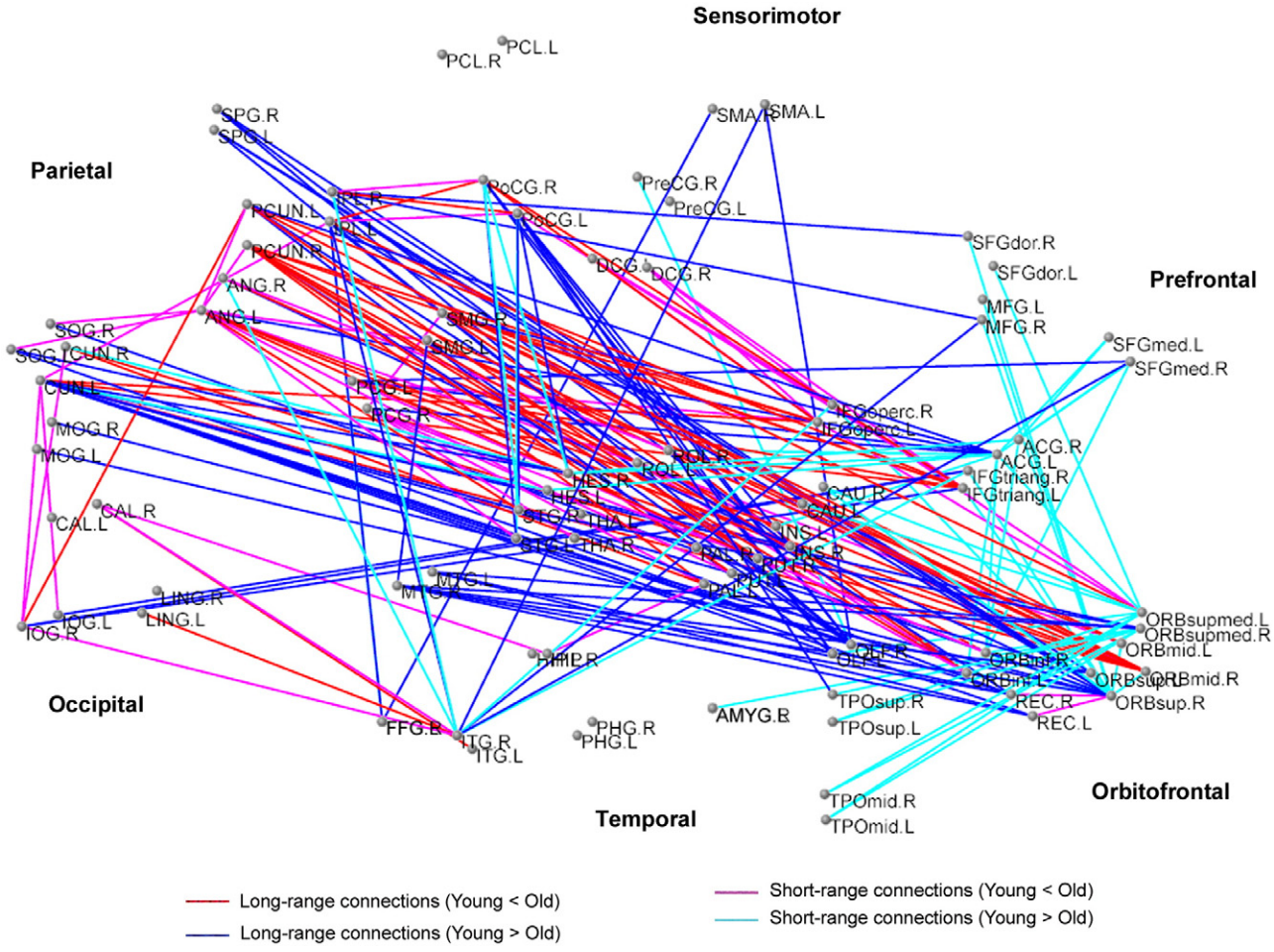

Fig. 2. Age-related changes in functional connectivity. Only the connections with a significant effect of group are shown, highlighted by different color-coded lines for long- and short-range connections. Both left- and right-hemisphere regions are shown in a sagittal view of the brain by locating their y and z centroid coordinates in the standard space. The network was visualized suing the PAJEK program (Batagelj and Mrvar, 1998). The locations of regions have been slightly changed for illustrative purposes. Detailed connections also are seen in Supplementary Table 1. See Table 1 for abbreviations.

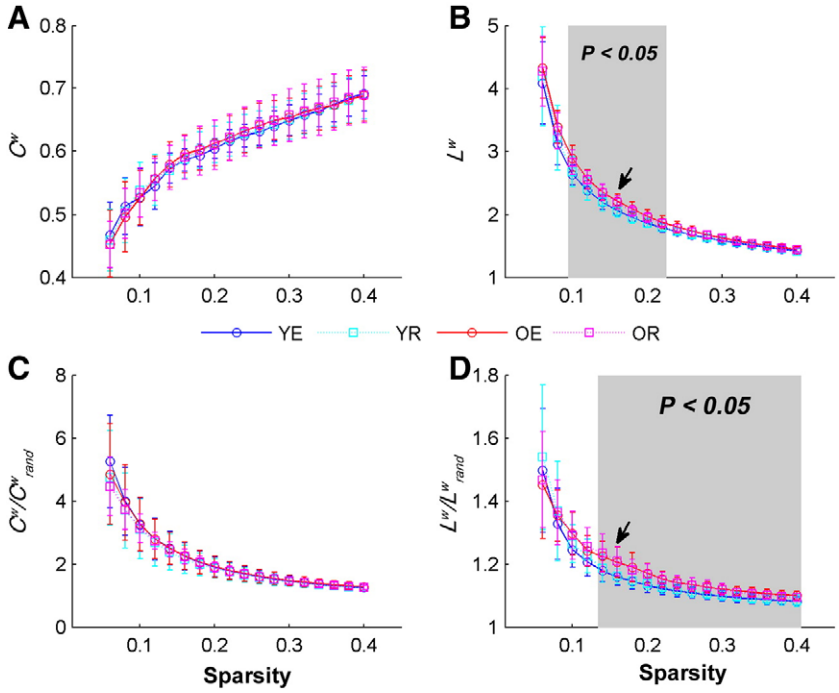

Fig. 3. Measures for brain networks topological organization. Weighted clustering coefficient (C^w) (A) and C^w/C^w_{rand} (C) show no significant changes, whereas significant decreases in weighted shortest path length (L^w) (B) and L^w/L^w_{rand} (D) are observed in both groups in the range of sparsity thresholds covered by the gray area ($p<0.05$, FDR corrected). The abbreviations denote the initial capital letters of each combination in Fig. 1. For example, YE denotes Young (Encoding). The sparsity threshold of 0.16, shown by the arrow, is the most highly significant among all the thresholds with a between-group difference. There was no significant main effect of condition or group × condition interaction using measures of shortest path length. Error bars indicate standard deviation.

range between 0.10 and 0.22 (a gray area in Fig. 3B) but no significant effect of condition or a significant interaction. The detrimental effect of age on the L^w/L^w_{rand} was significant ($P<0.05$, FDR corrected) in the threshold range from 0.14 to 0.4 (a gray area in Fig. 3D) but there was no significant effect of condition and no significant group-by-condition interaction. The most significant between-group difference in L^w and L^w/L^w_{rand} appeared at the threshold of 0.16, as shown by an arrow in the figure. Furthermore, we found that decreases in long-range connections shown previously in the older group were able to predict the changes in L^w/L^w_{rand} (Fig. 4). Achard and Bullmore (2007) have demonstrated that normal aging affected the spontaneously coordinated patterns of brain network activity and led to reduced efficiency of the network, which were in agreement with our findings.

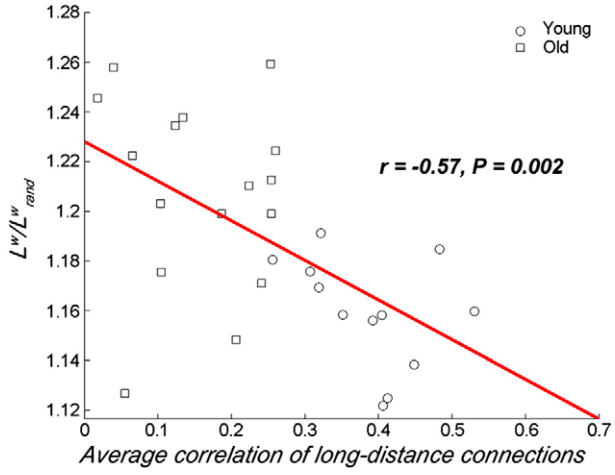

Fig. 4. The relationship between average correlation of long-distance connections and L^w/L^w_{rand}. The values (x-axis) were obtained by averaging the correlation coefficients of the 67 pairs of decreased long-range connections in the older adults. The values (y-axis) correspond to the normalized shortest path length at the sparsity threshold of 0.16.

A recent fMRI study indicated that subject's head motion had a profound influence on functional connectivity between brain regions (Salvador et al., 2008); we addressed this issue by correlating the network parameters with head motion measurements. This analysis

Table 2
The hubs of brain networks in each group during performance of memory tasks.

Region	Side	Classification	*BC*	Region	Side	Classification	*BC*
Young (encoding)				*Young (recognition)*			
THA	L	Subcortical	3.08	MOG	L	Occipital	4.26
MOG	L	Occipital	2.72	PCUN	L	Parietal	2.71
SFGdor	R	Frontal	2.64	STG	L	Temporal	2.57
LING	R	Occipital	2.49	THA	L	Subcortical	2.52
PreCG	L	Frontal	2.43	SPG	L	Parietal	2.44
PCUN	L	Parietal	2.27	PreCG	L	Frontal	2.30
INS	L	Temporal	2.23	MFG	L	Frontal	2.21
STG	R	Temporal	2.11	SMA	R	Frontal	2.08
MTG	R	Temporal	2.02	MFG	R	Frontal	2.05
SFGmed	L	Frontal	1.99	ORBinf	L	Frontal	2.05
PCUN	R	Parietal	1.95	MTG	R	Temporal	2.00
MFG	R	Frontal	1.85	SFGdor	R	Frontal	1.97
PreCG	R	Frontal	1.83	MTG	L	Temporal	1.94
DCG	R	Frontal	1.82	CUN	L	Occipital	1.89
MFG	L	Frontal	1.80				
TPOsup	L	Occipital	1.79				
SMA	R	Frontal	1.73				
Old (encoding)				*Old (recognition)*			
PCUN	L	Parietal	5.15	PCUN	L	Parietal	4.58
PCUN	R	Parietal	3.71	MOG	L	Occipital	3.20
MOG	L	Occipital	3.19	PCUN	R	Parietal	2.68
LING	L	Occipital	2.59	MTG	L	Temporal	2.35
DCG	L	Frontal	2.36	THA	L	Subcortical	2.33
MTG	L	Temporal	2.18	HIP	L	Temporal	2.16
STG	R	Temporal	2.16	DCG	L	Frontal	2.06
THA	L	Subcortical	2.15	HIP	R	Temporal	1.81
HIP	R	Temporal	1.99	INS	L	Temporal	1.73
THA	R	Subcortical	1.96				
CUN	R	Occipital	1.85				

Side: L, left hemisphere; R, right hemisphere. See Table 1 for abbreviations.

revealed no significant correlation between the L^w (and L^w/L^w_{rand}) and head motion (measured by either average absolute values or the first order differences in three translations), suggesting that the observed difference did not result from the influence of head motion. In addition, a lack of alteration in the network topological configuration between encoding and recognition tasks further supported the view that a common factor underlies age-related changes, independent of differences in cognitive functions performed in this experiment (Grady et al., 2006). In general, computing correlations between L^w and behavioral performance (e.g. response times) could contribute to understanding of the relationship between behavior and brain activity. However, in these data there was a significant group difference in average response times for the recognition task ($p=0.02$), indicating that the correspondence between L^w and response times may be due to aging. When this group difference was removed using a linear partial correlation model, the correlation between path length and averaged response times was non-significant ($r=0.27$, $p=0.17$). These findings suggest that the older adults showed reduced global information transfer and preserved local communication across brain regions, but that individual differences in task performance did not correspond with individual differences in path length.

Age-related changes in regional centrality during memory tasks

In this study, we found that many network hubs were found in the association cortices regions in the younger adults [e.g., middle temporal gyrus (MTG), superior temporal gyrus (STG), dorsal superior frontal gyrus (SFGdor), middle frontal gyrus (MFG), supplementary motor area (SMA), precuneus (PCUN), middle occipital gyrus (MOG) and lingual gyrus (LING)] thalamus (THA), as well as limbic/paralimbic regions [e.g. insula, superior temporal pole and inferior orbitofrontal cortex] (Table 2), which is in accordance with previous findings on functional brain networks constructed using resting-state fMRI (Achard et al., 2006; He et al., 2009b). This result reflects a stable property of cortical network architecture across both task-free and goal-oriented states. In the older adults, several network hubs still overlapped with those of the younger participants (e.g., PCUN, MOG, MTG and STG), however the overall number of hubs decreased in the older participants (Table 2). In particular, the hubs that were predominantly located in frontal and temporal regions in younger adults were clearly reduced in the older sample. In contrast, the medial parietal regions (e.g. PCUN) showed increased importance in the functional brain networks of the older

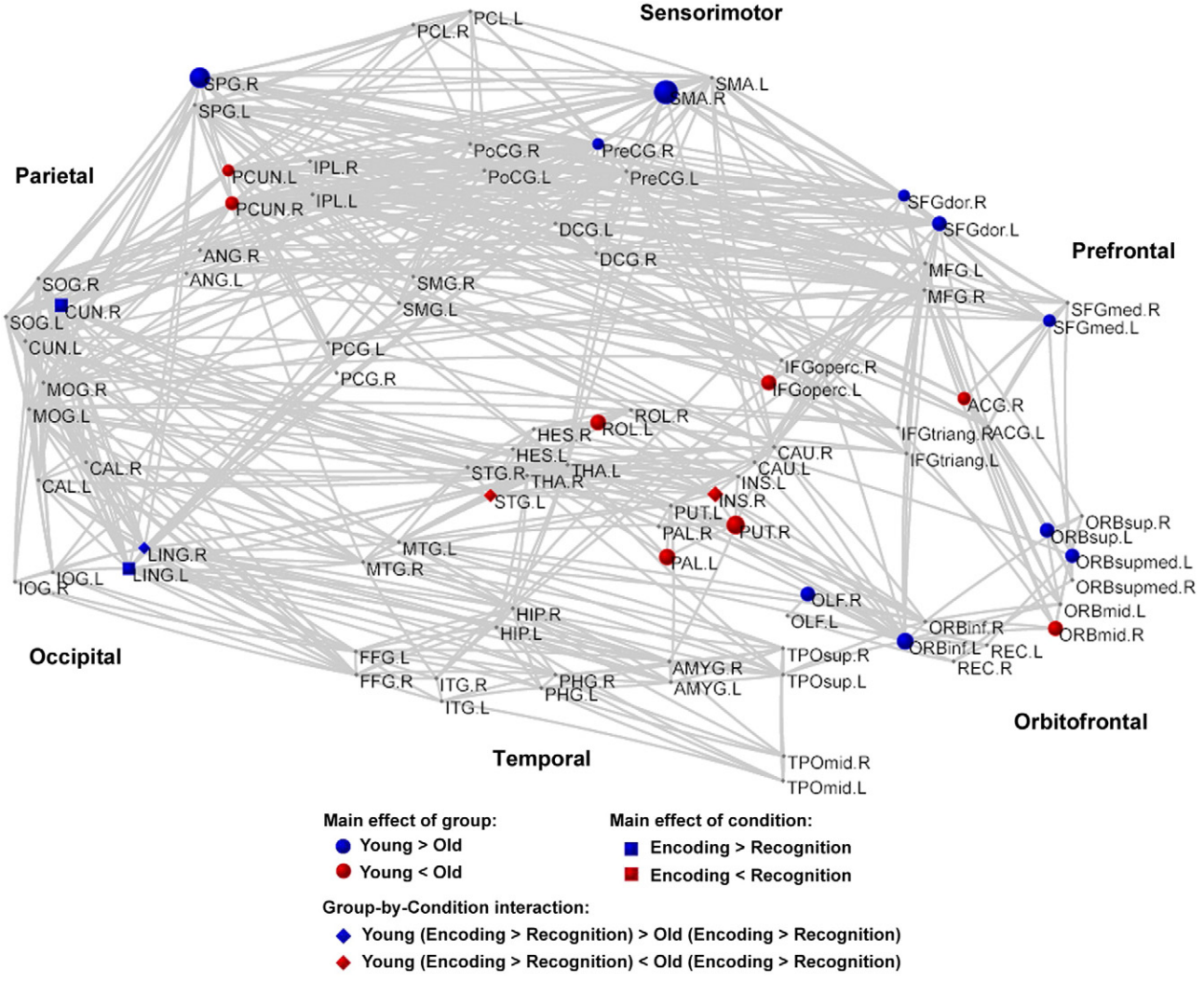

Fig. 5. Significant changes in betweenness centrality. The color-coded nodes show the significant effect of aging and condition; circles denote the main effect of group (between-subject); squares for the main effect of condition (within-subject); diamonds for the interaction of group and condition. The size of colored nodes is proportional to the level of statistical significance. Regions with overlapping effects of interest are only coded by a single color and shape, such as right anterior cingulate gyrus. The rest (smaller gray nodes) are regions with unchanged centrality. The connections shown were obtained from thresholding the correlation matrix in Fig. 1A at a sparsity of 0.16. The network is visualized using the PAJEK program (Batagelj and Mrvar, 1998). The locations of regions have been slightly changed for illustrative purposes. The results of statistical tests are shown in Table 3. See Table 1 for abbreviations.

Table 3
Effects of interest on regional betweenness centrality.

Effect of interest	Side	Classification	$F(1, 26)$	Effect	Hub
Main effect of group					
SMA	R	Frontal	13.62	Y>O	Yes
SPG	R	Parietal	10.29	Y>O	No
ORBinf	L	Frontal	7.32	Y>O	Yes
SFGdor	L	Frontal	5.99	Y>O	No
ORBsup	L	Frontal	5.93	Y>O	No
OLF	R	Frontal	5.90	Y>O	No
SFGmed	L	Frontal	4.78	Y>O	Yes
SFGdor	R	Frontal	4.40	Y>O	Yes
PreCG	R	Frontal	4.23	Y>O	Yes
PUT	R	Subcortical	8.49	O>Y	No
PAL	L	Subcortical	7.05	O>Y	No
ROL	L	Frontal	6.64	O>Y	No
IFGoperc	L	Frontal	6.26	O>Y	No
ORBmid	R	Frontal	6.13	O>Y	No
PCUN	R	Parietal	5.38	O>Y	Yes
ACG	R	Frontal	5.15	O>Y	No
PCUN	L	Parietal	4.40	O>Y	Yes
Main effect of condition					
SFGmed	L	Frontal	5.45	E>R	Yes
LING	L	Occipital	4.98	E>R	Yes
CUN	R	Occipital	4.92	E>R	Yes
PCUN	R	Parietal	4.48	E>R	Yes
Interaction of two factors					
ACG	R	Frontal	4.53	Y (E>R)>O (E>R)	No
LING	R	Occipital	4.42	Y (E>R)>O (E>R)	Yes
ORBsup	L	Frontal	9.10	O (E>R)>Y (E>R)	No
INS	R	Temporal	6.81	O (E>R)>Y (E>R)	No
STG	L	Temporal	5.12	O (E>R)>Y (E>R)	Yes
ROL	L	Frontal	4.78	O (E>R)>Y (E>R)	No

Side: L, left hemisphere; R, right hemisphere. The directions of the effect of interest were determined by post-hoc *t*-tests: Y, young; O, old; E, encoding; R, recognition. In the rightmost column, "Yes" indicates the brain regions identified as network hubs in the brain networks and "No" for the non-hubs (see Table 2). See Table 1 for abbreviations.

adults, which might suggest that an alternate recruitment of neural connectivity was needed to carry out the required tasks. Interestingly, in each of the groups, the hub distribution was similar among both tasks (see Supplementary Fig. 1 for *BC* values of each region in each task), which further supported the functional connectivity findings described above.

Additionally, two-way repeated-measures ANOVAs on regional centrality revealed age-related effects in various brain regions. The decreased centrality in the older adults was found mainly in SMA, SFG and ORB, LING and SPG (blue circles in Fig. 5, and Table 3). Notably, most of these regions had been identified as network hubs in the younger sample, which suggests that the age-related effects were brought about by a preferential impairment of important regions, rather than a non-specific degradation of the entire network. Increased centrality in the older adults was observed in PCUN and ACC (red circles in Fig. 5, and Table 3), which are key components implicated in the "default-mode" network proposed by Raichle et al. (2001). Previous functional imaging studies have suggested that these regions showed altered neuronal activity during memory-related tasks in advanced aging (Lustig et al., 2003; Grady et al., 2006; Miller et al., 2008). In addition, we also observed increased centrality in several subcortical regions (putamen and pallidum) in the older group. Note that most of these areas did not serve as network hubs, indicating that increased centrality may have little influence on the network configuration. In addition, we observed effects of condition or group-by-condition interactions in LING, STG and INS (squares and diamonds in Fig. 5, and Table 3).

Discussion

The current study investigated age-related changes in the coordinated patterns of activity and topology in functional brain networks during performance of encoding and recognition phases of memory tasks. We found that the older adults showed impairments in long-range connections that were associated with decreased topological efficiency of information processing throughout the entire network. Additionally, normal aging was accompanied by reduced nodal centrality in several frontal and parietal areas, and increased nodal centrality in several default-mode and subcortical regions. In contrast, similar network properties were observed in both tasks, indicating that a common network of regions was required for both encoding and recognition. The age-related alteration of the topological organization of functional networks suggests that brain systems underlying cognitive functions can adaptively reorganize during the aging process.

Altered functional connectivity with aging

It is widely believed that most cognitive functions require the active participation of multiple cortical areas, although elementary cognitive operations may be performed by individual brain regions (Bressler and Kelso, 2001). Several studies have suggested that cognitive deficits in normal aging arise from alterations in the functional integration of these coordinated brain systems (Cabeza et al., 1997a; Della-Maggiore et al., 2000; Grady et al., 2003). In this study, we showed an alteration in patterns of functional connectivity during memory tasks in older adults. Notably, many long-range connections between fronto-temporal, fronto-occipital, fronto-parietal and temporal–parietal regions were found to be impaired. These results are consistent with many functional imaging studies showing age-related alterations in fronto-temporal connectivity during resting state (Wink et al., 2006) and task states such as memory encoding (Grady et al., 1995; Grady et al., 2003) and memory for negative stimuli (St Jacques et al., 2008, 2009). Altered fronto-occipital connectivity has also been observed with increasing age (Moeller et al., 1996), and fronto-parietal connectivity has been identified as important in memory function (Buckner, 2004), which has been shown to be impaired in aging using both structural (O'Sullivan et al., 2001; Davis et al., 2009) and functional (Meunier et al., 2009) imaging measures. Several other studies have also shown age-related changes in temporal–parietal connectivity during memory encoding (Dennis et al., 2008) and recognition (Daselaar et al., 2006). Notably, disruptions in long-range functional connectivity combined with impaired short-range connections were found predominantly in frontal-related circuits, which is consistent with previous findings of abnormal frontal functions in older individuals (Buckner, 2004). Similarly, Meunier et al. (2009) found a loss of connectivity between anterior frontal clusters and posterior temporal and parietal clusters in older adults. In contrast, age-related increases in interregional interactions were predominantly observed in several posterior parietal regions, such as angular gyrus and precuneus. These areas have been considered key regions in the default-mode network in younger individuals (Raichle et al., 2001; Greicius et al., 2003) and have been found to show altered activity with aging during task performance (Lustig et al., 2003; Sambataro et al., 2008) and resting state (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008). Our findings of age-related impairments in long-range functional connectivity provide further support for the "disconnection" hypothesis proposed by O'Sullivan et al. (2001).

Altered network topology with aging

In the current study, we showed that the normalized shortest path length of the brain networks exhibited significant increases in the elderly during both encoding and recognition, which provides evidence of less efficient neural processing with normal aging (Grady, 2008). In addition, these increases in normalized shortest path length correlated with the connection weights in the reduced

long-range connections. This finding may reflect a reduction in speed of memory processing in older populations (Grady et al., 1995). This study also provided indications that, compared with young subjects, elderly subjects recruit different functional networks when carrying out the same cognitive task, presumably to compensate for reduced efficiency in brain areas typically recruited in the performance of these tasks (Grady, 2000; Cabeza, 2001). This finding may support the hypothesis that abnormalities in coordinated brain networks drive functional reorganization through changes in processing strategies during advanced aging (Greenwood, 2007). Recently, Achard and Bullmore (2007) examined the efficiency of human brain functional networks in younger and older adults scanned during the resting state. They found that the older adults showed reduced global and local efficiency in these networks. This reduction in global efficiency in aging is compatible with the finding of increased shortest path length in older adults in our study. However, in this study we did not observe between-group differences in local clustering coefficients. The difference between the previous study and our own could be attributable to different experimental designs used: memory encoding and recognition tasks were used in our study but Achard and Bullmore's study used data collected during the resting state. Notably, Meunier et al. (2009) directly compared the community structure of the large-scale functional networks of younger adults to that of older healthy adults to characterize age-related changes in brain modularity and observed marked differences in the composition and topological roles of modules. Even during task performance, network organization depended on whether visual stimuli were remembered or forgotten (De Vico Fallani et al., 2008).

In addition to the age-related changes in network parameters, in this study we also found that functional connectivity, (normalized) clustering coefficient and (normalized) shortest path length overall showed no significant differences between both tasks, providing support of the hypothesis for non-specific task-related brain networks in aging. Several recent studies have examined the relation between brain activity during encoding and subsequently during retrieval phase and demonstrated converging evidence for overlap in brain activation patterns, regardless of type of information (for a review, see Nyberg et al., 2000; Persson and Nyberg, 2000; Nyberg, 2002). Similarly, a recent study indicated a common factor underlying age-related changes in whole-brain patterns of activity by a multivariate analytic technique, independent of specific task tests (Grady et al., 2006). Collectively, our findings were consistent with the evidence and further provided support of the notion that the activation of a memory trace during subsequent retrieval may involve reactivation of processes that were engaged during initial encoding phase (Craik and Lockhart, 1972).

Altered regional centrality with aging

Many studies have suggested that normal aging is accompanied by either decreased (less efficient processing), or increased (functional compensation) neuronal activity in specific brain regions (Grady, 2008). In the present study, we showed that several brain regions exhibited age-related changes in nodal centrality in the functional brain networks. The regions showing reduced centrality with age were mainly located in frontal (e.g., SMA and SFG) and parietal (e.g., SPG) cortices, which are consistent with a recent fMRI study (Achard and Bullmore, 2007) which found a similar pattern of results. Interestingly, these regions were found to be hubs of brain networks in the younger adults, which suggest that the deleterious effects on network structure in older adults are restricted to critically important regions serving as areas of information exchange between different parts of the brain networks. Findings of reduced functional connectivity may account for alterations in relative centrality of these areas (Fig. 2). Many functional neuroimaging studies have also found altered neuronal activity in the frontal and parietal regions in older adults (Grady et al., 1995; Nielson et al., 2006; Kukolja et al., 2009). This dysfunction may lead to cognitive decline and impaired, controlled processing (e.g., strategy formation) during encoding and recognition (West, 1996; Buckner, 2004).

In addition to the age-related decreases in nodal betweenness, we also observed increased centrality with age in several brain regions, such as the precuneus and anterior cingulate gyrus. These brain areas have been described as being part of the default-mode network (Raichle et al., 2001). Default-mode activity is thought to reflect the monitoring and evaluating of external environment and internal milieu as well as self-reference (Gusnard and Raichle, 2001), and is suspended when participants are engaged in goal-directed tasks. Thus, more activity in default-mode regions could reflect a reduced ability to ignore distracting or irrelevant information from the environment (Milham et al., 2002; Gazzaley et al., 2005). This finding of altered default-mode activity in normal aging is compatible with previous studies in aging (Lustig et al., 2003; Grady et al., 2006; Miller et al., 2008), which reported less deactivation in default-mode regions in older adults. In the present study, we also observed age-related changes in nodal centrality in subcortical regions (e.g., putamen and pallidum), which agrees with the findings of a previous study where changes in task-related centrality were detected in the putamen (Beason-Held et al., 2005).

However, this study also contains some methodological limitations. First, we used two cohorts to characterize the age-related alterations in brain functional networks during the performance of memory tasks. However, it is unclear whether such a network topology continuously alters between the younger to older stages used in our study. To address this issue, in future studies it would be beneficial to recruit a large sample of healthy participants over a wide range of ages. Second, a large body of literature has shown that humans show memory losses with age, but that not all types of memory are affected equally (Grady and Craik, 2000). Therefore, it would be worthwhile to utilize other varieties of memory task (e.g. autobiographical memory, working memory), in order to examine whether they display similar age-related impairments. Third, the sample size employed in this study was relatively small, which may have partially contributed to the non-significant correlation between network parameter and performance mentioned above. In future studies, a larger sample would be vital to provide the statistical power necessary to validate these findings. Fourth, we investigated only age-related changes in functional brain networks. However, brain function is always closely associated with its structure (van den Heuvel et al., 2008; Damoiseaux and Greicius, 2009; Honey et al., 2009) and this association has been found to hold during the aging process as well. For instance, Brassen et al. (2009) showed that brain activity alterations correlated with changes in gray matter between younger and older subjects. A recent study has also indicated that, in advanced aging, reduced functional connectivity correlated with a decrease in white matter integrity (Andrews-Hanna et al., 2007). In future studies, it will be vital to investigate how the alterations of functional topology shown here are associated with co-occurring structural changes.

Conclusion

In this study, we provided evidence that changes in cognitive functions in aging are associated with changes in coordination between individual brain regions and their attendant network properties, which was demonstrated as a common factor to underlie the cognitive deficits. The results highlighted age-related alterations in the organization of functional brain networks relevant to goal-oriented tasks, thus potentially contributing, at the systems level, to our understanding how the brain adaptively reorganizes to respond to external stimuli during normal aging.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2010.01.044.

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