Cerebral Cortex August 2008;18:1856–1864
doi:10.1093/cercor/bhm207
Advance Access publication December 5, 2007

Reduced resting-state brain activity in the "default network" in normal aging

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Normal aging is associated with cognitive decline. Functions such as attention, information processing, and working memory are compromised. It has been hypothesized that not only regional changes, but also alterations in the integration of regional brain activity (functional brain connectivity) underlie the observed age-related deficits. Here, we examined the functional properties of brain networks based on spontaneous fluctuations within brain systems using functional magnetic resonance imaging. We hypothesized that functional connectivity of intrinsic brain activity in the "default-mode" network (DMN) is affected by normal aging and that this relates to cognitive function. Ten younger and 22 older subjects were scanned at "rest," that is, lying awake with eyes closed. Our results show decreased activity in older versus younger subjects in 2 resting-state networks (RSNs) resembling the previously described DMN, containing the superior and middle frontal gyrus, posterior cingulate, middle temporal gyrus, and the superior parietal region. These results remain significant after correction for RSN-specific gray matter volume. The relevance of these findings is illustrated by the correlation between reduced activity of one of these RSNs and less effective executive functioning/processing speed in the older group.

Keywords: connectivity, default-mode network, fMRI, ICA, intrinsic brain activity, neuropsychology

Normal aging is related to cognitive decline. Functions such as attention, information processing, and working memory are compromised in elderly (Park et al. 1996; Craik and Salthouse 2000; Salthouse and Ferrer-Caja 2003). Functional and anatomical neuroimaging techniques have been applied to locate specific brain regions affected by aging. For example, imaging studies examining gray matter (GM) volume reported GM reduction mainly in the frontal and parietal cortex (Raz et al. 1997; Good et al. 2001), and functional imaging studies have consistently shown a decrease in occipital lobe activity and an increase in frontal lobe activity across a variety of tasks (Grady et al. 1994; Madden et al. 1996; Cabeza et al. 2004). It has been hypothesized that not only regional changes, but also alterations in the integration of regional brain activity (functional brain connectivity) underlie the observed age-related deficits (O'Sullivan et al. 2001).

For measuring functional brain connectivity, exploration of resting-state connectivity has recently received great interest, for a review see Fox and Raichle (2007), several studies have shown that at "rest" (i.e., in the absence of external stimulation) the brain is organized in multiple active subsystems, resembling specific neuroanatomical systems such as the motor cortex, the visual cortex, and the dorsal and ventral attention systems (Biswal 1995; Beckmann et al. 2005; Damoiseaux et al. 2006; Fox et al. 2006). It has been suggested that these resting-state networks (RSNs) may reflect an intrinsic property of brain functional organization that serves to stabilize brain ensembles, consolidate the past, and prepare us for the future (Buckner and Vincent 2007; Raichle and Snyder 2007). The importance of studying RSNs in the context of clinical exploration has been illustrated by several studies (Greicius et al. 2004; Kennedy et al. 2006; Greicius et al. 2007), suggesting that analysis of intrinsic brain activity may enhance the understanding of disease. All together, fMRI methods to study RSNs have proven to be a powerful approach to study functional brain connectivity.

Here, we investigate whether normal aging affects intrinsic brain activity, and if so whether this is related to the observed decline in cognitive function. Of specific interest to this study is the intrinsic activity of the "default-mode" network (DMN). The DMN is a set of brain regions previously observed to consistently deactivate during active task states (Shulman et al. 1997; Binder et al. 1999). The DMN has been observed to be active in rest and deactivated during active task states. That this network shows resting-state activity is not unique but its response to cognitive tasks is (Fox and Raichle 2007). Previously, less deactivation was found in elderly subjects in the DMN (medial frontal and medial parietal/posterior cingulate regions) during semantic classification (Lustig et al. 2003) and memory (Grady et al. 2006) tasks. According to these findings and the observation of resting-state activity within the DMN, we expect to find an effect of aging on the intrinsic activity of the DMN.

Materials and Methods

Subjects

Two groups, one consisting of 10 younger (age 22.8 ± 2.3, 5 male) and the other of 22 older (age 70.7 ± 6.0, 9 male) healthy right-handed

subjects participated in this study after giving written informed consent in accordance with the VU University Medical Center Medical Ethical Committee. The data of the younger subjects used in this study are the same as used in a previous study (Damoiseaux et al. 2006). All subjects underwent an MRI session of approximately 35 min total. For the "resting-state" scan, which lasted about 10 min, subjects were instructed to lie still with their eyes closed, not to think of any one thing in particular and not to fall asleep. Directly after this scan, the subjects were asked whether they fell asleep, none of the subjects reported they did.

Neuropsychological Assessment

All participants underwent a mini mental status examination, a geriatric depression scale, and the Dutch version of the New Adult Reading test, a test which gives an indication of intelligence quotient measure, followed by an extensive neuropsychological test battery including tests measuring attention/concentration, processing speed, episodic memory, executive functioning, and praxis (see Table 1 for details). Scores on neuropsychological tests were compared between groups by means of *t*-tests.

Imaging Methods

Imaging was performed on a 1.5-T Sonata (Siemens, Erlangen, Germany) scanner. For the functional scan, T_2^*-weighted echo planar images (EPIs) were acquired with the following sequence parameters: time repetition (TR) = 2850 ms, time echo (TE) = 60 ms, flip angle = 90°, 36 axial slices, voxel size = 3.3 mm isotropic. Two hundred volumes were acquired during the resting-state scan. Additionally, a high-resolution T_2^*-weighted EPI and a high-resolution T_1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) images were acquired. The sequence parameters of the high-resolution EPI were TR = 7230 ms, TE = 45 ms, flip angle = 90°, 64 axial slices, voxel size = 1.6 × 1.6 × 2.2 mm. The sequence parameters of the T_1-weighted image were TR = 2700 ms, TE = 3.97 ms, flip angle = 8°, 160 coronal slices, voxel size 1 × 1.5 × 1 mm.

Analysis of Resting-State Data

Preprocessing

The image preprocessing was carried out similarly as in our previously published resting-state study (Damoiseaux et al. 2006), using tools from Oxford Centre for Functional Magnetic Resonance Imaging of the Brain's Software Library (FSL version 3.3 [Smith et al. 2004]). The following prestatistics processing was applied: motion correction (Jenkinson et al. 2002), removal of nonbrain structures (Smith 2002), spatial smoothing using a Gaussian kernel of 6-mm full width at half maximum, mean-based intensity normalization of all volumes by the same factor (i.e., 4-dimensional grand mean scaling in order to ensure comparability between data sets at the group level), high-pass temporal filtering (Gaussian-weighted least squares straight-line fitting, with sigma = 75.0 s), and Gaussian low-pass temporal filtering (half width at half maximum 2.8 s). After preprocessing, the functional scan was first aligned to the high-resolution EPI scan and then to the high-resolution T_1-weighted image, which was subsequently registered to the MNI152 standard space (average T_1 brain image constructed from 152 normal subjects at Montreal Neurological Institute) using affine linear registration (Jenkinson et al. 2002). From the resulting affine transformation matrices, a midspace was defined as the transformation that approximates the average size and shape of the individual subject's spaces, by calculating the geometric mean of the affine transformations that registers the MNI152 standard space template to all subjects' data sets. Within this midspace, the data are kept at the original EPI resolutions, reducing the computational burden of a simultaneous (all subjects) decomposition. Finally, the individual time series data were converted to voxelwise power spectra. Because there is no task in resting-state data to restrict what subjects are doing during a specific time course, we cannot assume a consistent phase for individual RSNs across subjects. Finally, we performed tensor probabilistic independent component analysis (tensor PICA) (Beckmann and Smith 2005) on data of which the temporal domain was transformed into the frequency domain.

Table 1
Participant characteristics and neuropsychological data

	Young	Old	Young vs. Old
	M ± SD	*M* ± SD	*t*
Gender (male/female)	5/5	9/13	0.467
Age	22.80 ± 2.3	70.73 ± 6.0	31.912**
MMSE	29.50 ± 0.5	28.73 ± 1.4	1.695
GDS	0.40 ± 1.0	0.64 ± 1.0	0.61
NLV	99.10 ± 13.1	110.67 ± 18.7	1.753
Attention, concentration, and speed			
Digit span			
Forward span	6.20 ± 1.0	6.23 ± 1.0	0.070
Backward span	5.50 ± 0.7	5.14 ± 0.9	1.137
WAIS symbol substitution/encoding	83.80 ± 13.1	58.73 ± 15.3	4.492**
Trail making test A	26.90 ± 8.8	43.55 ± 15.4	3.162*
Stroop			
Word card	40.30 ± 5.6	46.18 ± 6.4	2.489
Color card	54.40 ± 6.8	60.82 ± 11.0	1.699
Color–word card	79.80 ± 15.8	116.73 ± 37.3	2.988*
Episodic memory			
15-word test			
Total immediate recall	57.90 ± 8.4	42.91 ± 10.7	3.921**
Delayed recall	12.30 ± 2.3	8.41 ± 3.1	3.510*
Visual association test			
A	11.90 ± 0.3	11.50 ± 1.1	1.118
B	11.50 ± 0.7	10.63 ± 1.5	2.155
WAIS symbol substitution/memory			
Cued reproduction	14.60 ± 4.2	9.40 ± 4.0	3.273*
Free reproduction	8.10 ± 1.0	6.41 ± 1.6	3.129*
Memory impairment screen plus			
Direct reproduction	12 ± 0.0	10.95 ± 1.6	2.978*
Delayed reproduction	11.70 ± 0.5	10.41 ± 1.7	3.268*
Executive function			
WISC maze			
Total time	119.50 ± 23.6	217.50 ± 87.8	4.862**
Mistakes	0.50 ± 0.5	2.45 ± 1.6	5.084**
TMTB	53.30 ± 19.0	101.09 ± 44.2	4.276**
TMTB/TMTA	2.04 ± 0.4	2.40 ± 0.8	1.524
Fluency			
Animals 2 min	43.30 ± 5.2	43.25 ± 5.4	2.951*
Insects 1 min	13 ± 2.9	13.75 ± 2.7	3.499*
Praxis			
Rey complex figure			
Copy	34.90 ± 1.0	34.88 ± 1.1	2.981*
Organization	4.20 ± 2.2	4.63 ± 1.8	1.081

Note: MMSE, mini mental status examination; GDS, geriatric depression scale; NLV, the Dutch version of the New Adult Reading test. *Significant at $P = 0.01$/**significant at $P = 0.001$.

Statistical Analyses

A tensor PICA approach, as described previously (Damoiseaux et al. 2006), was used for statistical analyses. In this study, all subjects' data (consisting of 32 data sets) were decomposed into components, which characterize the structured signals in the spatial, subject, and frequency domains. Data were decomposed into 20 components, where the model order was estimated using the Laplace approximation to the Bayesian evidence for a probabilistic principal component analysis model (Beckmann and Smith 2004). Each component consists of a vector of length 32 (subjects) in the subject domain, a vector of length 100 (frequencies) that describes the associated temporal characteristics, and a vector of length 39 165 (voxels) that describes the associated spatial map; for details see (Beckmann and Smith 2005). Final maps were thresholded using an alternative hypothesis test based on fitting a Gaussian/Gamma mixture model to the distribution of voxel intensities within spatial maps and a posterior probability threshold of $P > 0.5$ (Beckmann et al. 2003). The a priori focus of this study was aimed at the DMN. To select the RSN with the best fit to the DMN, a template-matching procedure similar to the one used by Greicius et al. (2004) was used. That is, the best-fit component is the one with the highest value when subtracting the average *z*-score of voxels outside the template from the average *z*-score of voxels inside the

template. Two deactivation maps resulting from a previous study (Rombouts et al. 2007) were added up and served as template. These maps show deactivation in a large sample of healthy elderly subjects, patients with mild cognitive impairment, and patients with Alzheimer's disease while performing an fMRI face-encoding task to assess episodic memory. The resulting template is very similar to the template used in other studies to determine the DMN in resting-state data (e.g., Greicius et al. 2004). In addition to the main between-group comparison of the DMN, exploratory between-group analyses of the remaining 18 components were performed as well. In order to characterize components that differ significantly between the 2 groups (younger and older healthy adults), the 32 values in the subject domain were compared using *t*-tests. To correct for outliers per component, all the values in the subject domain with a standard deviation of more than 3.0 were removed. Seven components did not have any outliers, for 12 components 1 value was removed, and for one component 2. The different values within 1 subject-mode vector show a difference in the relative strength of the associated time by space component within a subjects' data set. That is, a higher value of the subject modes indicates that the subject's data has higher blood oxygen legel–dependent (BOLD) change within the areas indicated by the associated spatial map.

Analysis of GM Volume

To control for possible differences in RSNs that may be explained by differences in GM volume between subjects, we additionally performed an analysis of GM density and used this information as a covariate in our resting-state fMRI analysis, following much of the methodology described by Oakes et al. (2007). Data analysis was performed using FSL version 3.3 (Smith et al. 2004). After removal of nonbrain structures (Smith 2002), the high-resolution images (T_1-weighted MPRAGE) were segmented into GM, white matter, cerebrospinal fluid, and background, and partial volume maps were calculated (Zhang et al. 2001). The GM partial volume maps were transformed into the same final working space as the resting-state fMRI images using affine linear registration (Jenkinson et al. 2002). Per-subject GM volume was averaged separately for each RSN across the brain areas involved in that RSN. These measures were used in the statistical analysis. If the *t*-test (no GM correction) showed that an RSN was different between groups, this RSN was reanalyzed by applying an analysis of variance with RSN values in the subject domain as dependent variable and subjectwise mean GM volume in that specific RSN as additional covariate. To gain information on whether the groups included in our study truly differed in mean GM volume, the mean GM volume of the specific RSNs were compared using a *t*-test. Additional analyses were conducted to compare GM volume voxelwise. Individual GM partial volume maps were compared between younger and older subjects using a general linear model.

Correlations of RSNs with Age and Neuropsychology

The correlation between age and the RSN values in the subject domain (for the older healthy controls only) was calculated using a partial correlation correcting for GM volume, testing 1 tailed. For the correlations between neuropsychological tests and the RSN values in the subject domain (for the older and younger healthy controls), partial correlations were calculated correcting for GM volume and age, testing 1 tailed. The neuropsychological tests used for correlation analyses are those that differ significantly between young and old groups at $P < 0.001$.

Results

Neuropsychology

On most neuropsychological tests, the older healthy subjects perform worse than the young healthy subjects, including tests measuring executive functioning, processing speed, and memory function (when applying a threshold of $P < 0.01$). At a more stringent threshold of $P < 0.001$, older subjects perform worse on 4 tests: the Wechsler Adult Intelligence Scale (WAIS) symbol substitution/encoding, total immediate recall from the 15-word test, the Wechsler Intelligence Scale for Children (WISC) maze, and the Trail Making Test (TMT) part B. The 15-word test measures memory function, the other tests measure attention, processing speed, and/or executive functioning (see Table 1).

Resting-State fMRI Data

Twenty components were estimated, each consisting of vectors that describe underlying signals in the spatial and temporal domains as well as a vector describing the subject-specific contribution to the estimated map. As an example, Figure 1 shows 13 of these spatial maps that were visually identified as being potentially functionally relevant. The remaining 7 components show, among others, head motion, misregistration, and B0 artifacts. Ten of the components (*A–J*) shown in Figure 1 coincide with the RSNs described previously (Beckmann et al. 2005; Damoiseaux et al. 2006; De Luca et al. 2006). These maps show spatial patterns consisting of regions previously known to be involved in visual processing (*A*), the DMN (*B,C*), working memory (*D,E*), motor function (*F*), auditory processing (*I*), and executive functioning (*J*). There are however small differences. In this study, we found one component with a spatial pattern resembling the visual cortex (*A*), whereas in our previous study we consistently found this component to be split into 2 independent spatial patterns (Damoiseaux et al. 2006). Another difference is that in this study, the DMN appears to be split into 2 (*B,C*) or perhaps even 3 (including *M*) components. However, the most interesting difference is the observation of 3 additional potentially interesting spatial patterns. One of these patterns encompasses the thalamus, putamen, insula, and the transverse temporal gyrus (*K*); another consists of the anterior temporal lobe, including the hippocampus (*L*); and the third includes occipitoparietal areas, posterior cingulate, parahippocampal gyrus, and superior frontal (*M*). Because multiple components were visually identified as (possibly) being part of the DMN, a template-matching procedure was applied (see Materials and Methods section) to find the best fit(s) to the DMN. Two components had template-matching scores very close to each other (component *C* of Fig. 1: 1.63 and component *B*: 1.46) and far above the others (score of next best fit was 0.35). Therefore, both these components were included in the between-group comparison. The component in Figure 1*C* contains only the posterior areas of the DMN: the posterior cingulate (Brodmann Area [BA] 23/31; peak 45, 26, 58) and bilateral superior parietal regions (BA 7; peak 23, 31, and 59). The component in Figure 1*B* contains mainly the anterior part of the DMN, encompassing the superior and middle frontal gyrus (BA 9/10/11; *x*, *y*, and *z* peak location = 46, 91, and 35), posterior cingulate (BA 23/31; peak 47, 34, and 51), bilateral middle temporal gyrus (BA 21/38; peak 76, 56, 26), and bilateral superior parietal region (BA 7; peak 71, 29, and 52). The relative contribution of every subject to these 2 components was compared between the older and younger subjects. Both components showed significant change in the relative strength of subjects between the 2 groups (component *B*: $t = 3.28$, $P = 0.007$, inequality in variance; *C*: $t = 2.57$, $P = 0.015$; see Fig. 2). Specifically, these 2 components showed a decrease in the subject-dependent variation in the older subjects compared with the younger subjects. Additionally, exploratory between-group analyses of the relative

contribution of every subject to the remaining 18 components were performed; none of these components showed significant differences between groups ($P < 0.05$ uncorrected).

GM Volume Correction

A significant decrease in GM volume in older subjects compared with younger subjects was found within component *C* (the "posterior" DMN; $t = 2.736$, $P = 0.046$, inequality in variance). An additional voxelwise analysis studying between-group differences in GM volume shows reduced GM volume in the older subjects in the occipital lobe, anterior and posterior cingulate, precuneus, insula, and central sulcus (cluster-corrected $z = 3.1$, $P = 0.05$; see Supplementary Figure). Given the observed GM decrease with aging, we further tested whether the differences in the resting-state components 1*B* and 1*C* could be (partly) explained by group differences in GM volume in the regions included in those components. Therefore, we inserted per subject the mean GM volume within the spatial pattern of the 2 resting-state components as a covariate in the between-group analysis of the 2 resting-state components. After this correction, both components remained significantly different between groups, both showing decreased activity in the older subjects (for 1*B*: $F_{1,29} = 20.76$, $P < 0.0001$; for 1*C*: $F_{1,29} = 6.08$, $P < 0.020$).

Correlations between RSNs, Age, and Neuropsychology

The 2 groups in this study differ greatly in age, and to strengthen our hypothesis that decreased activity in the DMN in both RSNs is indeed related to aging, we correlated age with the subject variation mode of these components (only within the older group). This correlation showed a significant inverse relationship between age and subject variation mode for the "anterior" DMN (1*B*) ($r = -0.58$, $P < 0.003$, 1 tailed; corrected for GM volume within the spatial map of this specific RSN; see Fig. 3 for scatter plot). This shows that the effect of aging on the anterior DMN RSN is not only visible between groups that differ largely in age but also between subjects within the same group (age range 60–81 years). No significant correlation was found for the posterior DMN (1*C*). In addition, we calculated whether the subjects' values on the DMN correlated with scores on the 4 neuropsychological tests showing the strongest effects of aging (in both groups). For the WISC maze and the TMTB, we expected negative correlations with resting-state activity as for these neuropsychological tests a higher score means worse performance. For the WAIS symbol substitution/encoding and the 15-word test, we expect a positive correlation because a higher score means better performance. For the younger subjects, no correlation was found between performance on these neuropsychological tests and the subject values on the 2 RSNs. For the older subjects, a correlation with component 1*B* was found for the TMTB ($r = -0.60$, $P = 0.003$, 1 tailed; corrected for GM volume of the anterior DMN and age; see Fig. 3 for scatter plot). This correlation is significant after correction for multiple comparisons. A correlation with component 1*C* was found for the WAIS symbol substitution/encoding ($r = 0.46$, $P = 0.021$, 1 tailed; corrected for GM volume of the posterior DMN and age), which does not pass the significance threshold after correction for multiple comparisons. The other tests did not show a correlation with either of the DMN components.

Discussion

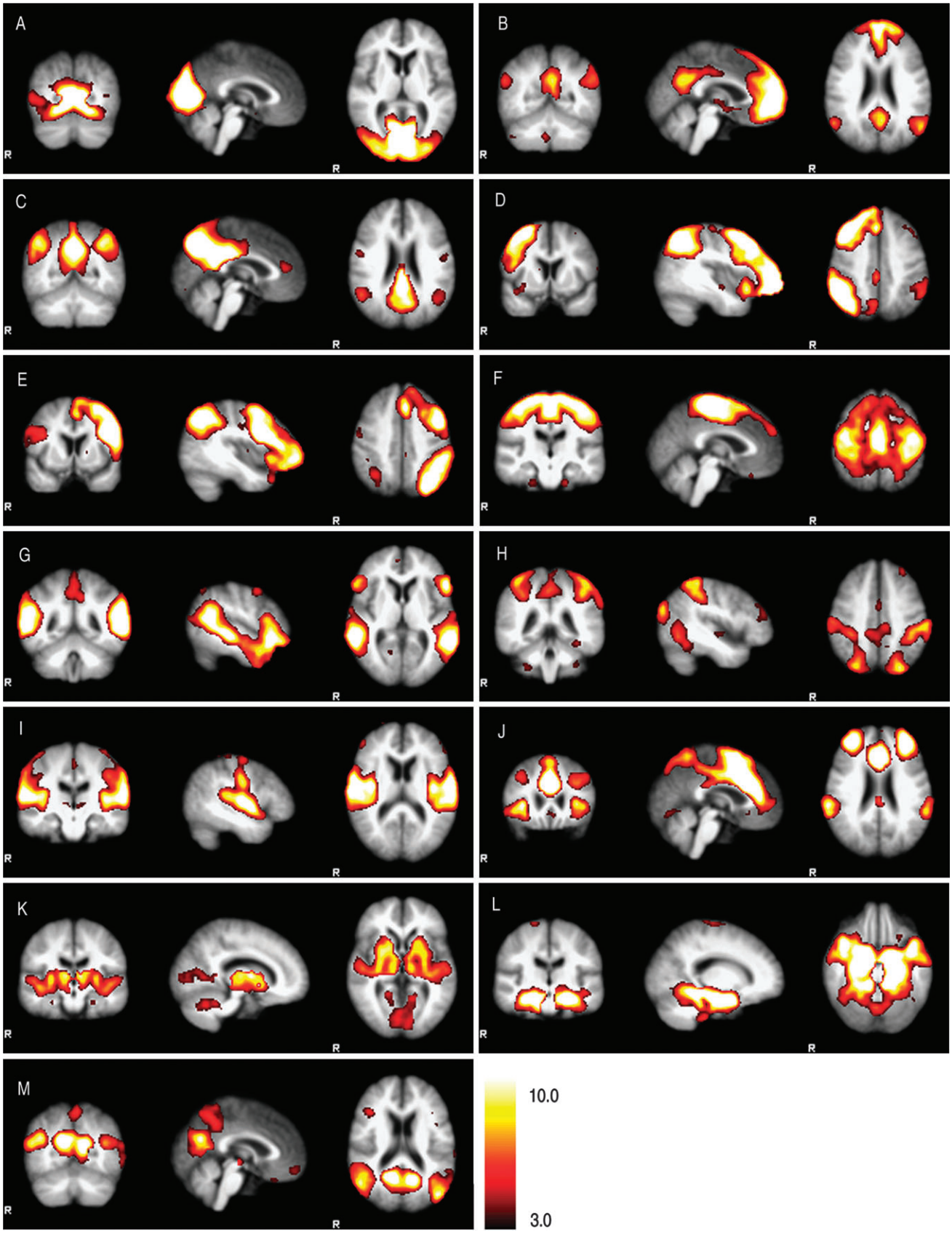
The aim of this study was to explore the effects of normal aging on intrinsic brain activity in the DMN and investigate whether a relationship exists between this activity and cognitive decline. In line with previous research, we found evidence of cognitive decline in older compared with younger subjects in the domains of attention/concentration/processing speed, memory function, and executive functioning. By using tensor PICA, 20 components were estimated out of which 2 components were selected based on a template-matching procedure as representing the DMN. One of these RSNs contained only the posterior areas of the DMN, the other mainly the anterior regions. Between-group differences in activity in both RSNs were observed. The activity expressed in these RSNs was decreased, that is, lower BOLD signal change, in older subjects compared with younger. These results remained significant after correction for GM volume within the areas of these RSNs. These findings confirm our hypothesis; in addition to the previously observed decrease in deactivation of this network during semantic classification and memory tasks (Lustig et al. 2003; Grady et al. 2006), intrinsic activity within the DMN is decreased in the elderly as well.

In this study, we found the DMN to be split in 2 components. Hence, within the DMN, some brain regions behave differently than others. A similar decomposition of the DMN has been observed previously (Damoiseaux et al. 2006; Rombouts et al. 2007). Most resting-state fMRI studies investigating the DMN performed group analyses on one preselected spatial pattern of brain regions identified as being part of the DMN (e.g., on the best fit to the DMN of every single subject) (Esposito et al. 2006; Garrity et al. 2007; Greicius et al. 2007). If in these cases a decomposition of the DMN was present, this would not have been noted due to the methods applied.

The activity of the RSN constituting mainly the anterior part of the DMN (displayed in Fig. 1*B*) correlated with age (within the older group), confirming the inverse relationship between age and the integrity of this network. For the other RSNs (Fig. 1*C*), no correlation with age within the older group was observed. Furthermore, we showed that decreased activity in the "anterior" RSN (1*B*) in the older subjects was indeed associated with cognitive decline, that is, with decreased attention, concentration, processing speed, and/or executive function. For the younger subjects, no correlation between intrinsic activity and cognitive function was found. This can most likely be explained by a lack of statistical power due to the relatively small amount of subjects in this group (10) and little variation within the group.

In the current study, we showed reduced GM volume with aging in the occipital lobe, anterior and posterior cingulate, precuneus, insula, and central sulcus. This is partly in accordance with a previous study, which showed a decline in GM volume in the parietal cortex, central gyrus, insula, anterior cingulate, and cerebellum (Good et al. 2001). It should be noted that Good et al. (2001) examined a large group of subjects across the adult life span and included age as a continuous factor in the analysis, which is different from the approach used in our study.

Furthermore, we found that the average GM volume within the spatial pattern of the posterior DMN RSN was decreased in older subjects compared with younger. However, decrease in GM volume of the posterior DMN RSN was much less



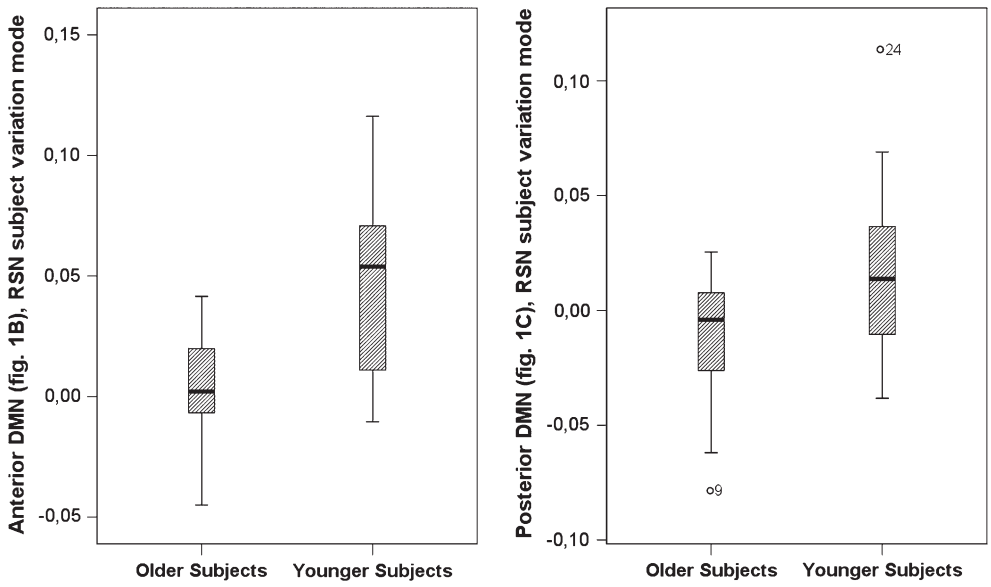


Figure 2. Boxplots showing a group difference on the resting-state components affected by aging**.** The difference between the younger subjects and older subjects on the subject variation mode of both the first and second best-fit default-mode RSNs (see components *C* and *B* in Fig. 1) are displayed in boxplots. The left boxplot shows the posterior DMN (1*C*), consisting of the posterior cingulate (BA 23/31) and bilateral superior parietal regions (BA 7). The right boxplot shows the difference between groups for the the anterior DMN (1*B*), encompassing the superior and middle frontal gyrus (BA 9/10/11), posterior cingulate (BA 23/31), and the superior parietal region (BA 7). The older subjects show decreased activity in both RSNs compared with the younger subjects (component *C*: $t = 2.57$, $P = 0.015$; *B*: $t = 3.28$, $P = 0.007$, inequality in variance). Note that these boxplots show the raw data before correction for GM volume was applied.

significant than decrease in resting state activity in the posterior and anterior DMN RSNs. Nevertheless, because decreased brain activity may be (partly) explained by decreased GM volume, as shown previously (Johnson et al. 2000; Prvulovic et al. 2002; He et al. 2007), it is important to control for GM volumes. For this, we additionally performed an analysis of GM volume and used this parameter as a covariate in our resting-state fMRI analysis. fMRI differences remained significant after correction, showing that decreased resting-state activity in aging is not completely explained by decreased GM volume.

It has been hypothesized that activity of the DMN is related to spontaneous thoughts (i.e., intrinsic attention/information processing) (Raichle et al. 2001). A recent study showed results consistent with this hypothesis, demonstrating an association between the DMN and mind wandering (i.e., spontaneous/stimulus independent/task-unrelated thoughts) (Mason et al. 2007). In that study, subjects' reports on the frequency of mind wandering during the experiment correlated positively with DMN activity. When relating this previous finding with our current results, it could be inferred that decreased integrity of the DMN in older subjects at rest may reflect a decrease in spontaneous thoughts in this group. This idea is in line with a previous observation almost 2 decades ago of an inverse relationship between age and the amount of task-unrelated thoughts (Giambra 1989). In addition, previous work has shown that greater incidence of spontaneous thoughts was related to reduced central executive demand (Teasdale et al. 1995). This suggests that the generation of mind wandering depends on executive function. The relationship that we demonstrate between lower activity of the DMN and decreased performance on tasks measuring attention, concentration, processing speed, and/or executive function therefore could be related to the decrease in spontaneous thoughts.

Besides this proposed relationship with conscious cognitive function, intrinsic brain activity has also been proposed to represent a more fundamental or intrinsic property of brain functional organization that could serve to stabilize brain ensembles, consolidate the past, and prepare us for the future (Buckner and Vincent 2007; Raichle and Snyder 2007). Important here is the recent observation that coherent fluctuations in the BOLD signal are still present under general anesthesia, which suggests that these fluctuations are not merely a reflection of conscious mental activity (Vincent et al. 2007).

In addition to the 10 RSNs described in our previous study (Damoiseaux et al. 2006), we found 3 extra. Theoretically, this could be specifically related to the older subjects, for example, that these RSNs are only, or to a much larger extent, present in the older subjects than in younger. However, this is not likely given the general decline of the areas represented within these networks with aging. For example, a recent study that measured the effect of aging on the efficiency and cost of human brain functional networks using resting-state fMRI

Figure 1. Potentially functionally relevant RSNs. Thirteen out of the 20 estimated components visually identified as being potentially functionally relevant. Ten of these components (*A*–*J*) resemble the RSNs described in our previous study (Damoiseaux et al. 2006), consisting of regions previously known to be involved in visual processing (*A*), the DMN (*B, C*), working memory (*D, E*), motor function (*F*), auditory processing (*I*), and executive functioning (*J*). Three additional potentially functionally relevant components were found, encompassing: the thalamus, putamen, insular, and transverse temporal gyrus (*K*); the anterior temporal lobe, including the (para) hippocampal gyrus (*L*); and occipitoparietal areas, posterior cingulate, parahippocampus, and superior frontal (*M*). Images (coronal, sagittal, and axial views) are *z*-statistics overlaid on the average high-resolution scan transformed into standard (MNI152) space. Black to yellow are *z* values, ranging from 3.0–10.0. The left hemisphere of the brain corresponds to the right side of the image.

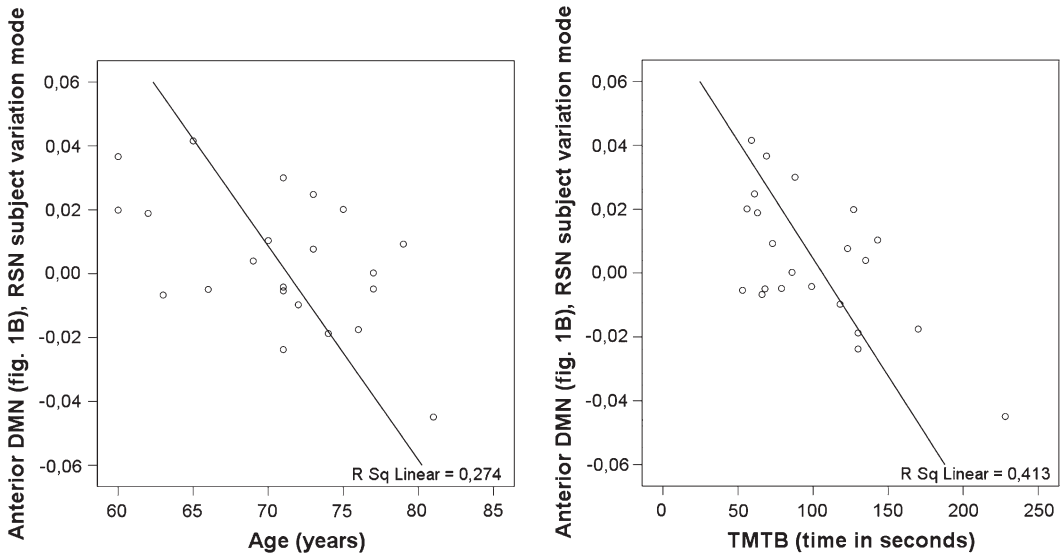


Figure 3. Correlations between resting-state activity, age, and cognitive function. Scatter plots of the correlations between the subject values of the older controls of the anterior DMN (Fig. 1*B*) with age ($r = -0.58$, $P < 0.003$, 1 tailed; corrected for GM volume) and the trail making test B ($r = -0.60$, $P = 0.003$, 1 tailed; corrected for GM volume and age). The values on the *y*-axis are the relative contributions of every subject to RSN 1B. The correlation between resting-state activity of RSN 1*B*, age, and the trail making test B remains significant after removal of the outlier.

found reduced network efficiency in older people in frontal, temporal, limbic/paralimbic, and subcortical brain regions (Achard and Bullmore 2007). Some of these brain regions, such as the (para) hippocampal gyrus, insula, and thalamus, correspond to regions we observed in 2 (Fig. 1*K,L*) of the 3additional RSNs. Even though the concept of "network efficiency" used by Achard (Achard and Bullmore 2007) is quite complex, and translating it to the analysis of the present study is not trivial, these results suggest that it would be more likely to find reduced activity rather than increased activity in these additional RSNs in older subjects. Therefore, these RSNs are more likely the result of increased power due to a larger group of subjects (32 in this study compared with 10 in our previous study) than of older age.

The decreased activity observed in the DMN is largely consistent with the results of the above mentioned resting-state connectivity study by Achard and Bullmore (2007). Other studies that investigated the effect of aging using resting-state fMRI show decreased connectivity in the motor network (Wu et al. 2007) and an increase in the Hurst exponent of fMRI time series in bilateral hippocampus. The latter implies reduced fractal dimension and increased predictability of hippocampal dynamics (Wink et al. 2006). These studies focused specifically on connections of the motor cortex and the hippocampus. The current study focused specifically on the DMN, but changes in other RSNs were explored as well. No alterations in resting-state activity in components encompassing the motor cortex and hippocampus were observed. However, a comparison between these studies and the current study is not straightforward because the previous studies applied a very different approach than the currently applied whole-brain tensor PICA analysis.

Recent studies that examined the effect of aging on functional connectivity during task-related fMRI found both increases and decreases in connectivity (Daselaar et al. 2006; Rowe et al. 2006; Cook et al. 2007). These results appear largely task specific and are difficult to theoretically relate to our present findings. Other task-related fMRI studies into the effects of aging have consistently shown increased frontal and decreased occipital activation (Grady et al. 1994; Madden et al. 1996; Cabeza et al. 2004). The former has been attributed to functional compensation and the latter to insufficient sensory processing in the ventral (occipitotemporal) pathway (Grady et al. 1994; Madden et al. 1996). In addition, age effects on several other brain regions have been reported, such as increased parietal and decreased hippocampal activation (Cabeza et al. 2004; Daselaar et al. 2006), increased (Sharp et al. 2006) and also decreased (Otsuka et al. 2006) anterior cingulate cortex activation, and decreased deactivation of the medial parietal/posterior cingulate region (Lustig et al. 2003). In this study, we found decreased activity in RSNs consisting of a large part of frontal and/or parietal brain areas. Although little is known about the relationship between task-related activation/deactivation and intrinsic brain activity as measured at rest, previous results of increased task-related activation in these regions could concur with our findings. According to our results, intrinsic brain function of these regions, measured at rest, is compromised in the elderly. We hypothesize that, in order to retain adequate performance, the brain compensates this lower intrinsic activity by increasing activation in these regions in response to external stimulation.

Whether the task we found to be related to DMN function (i.e., the TMTB) measures attention/concentration/processing speed or executive function remains a matter of debate. The difference between the cognitive domains' executive function and attention/concentration/processing speed can be quite obscure. In this study, we placed the TMTB under "executive function"; this has been under debate as performance on the TMTB is supposed to be largely affected by concentration and processing speed, functions measured with the Trail making test A. This effect can be corrected by dividing the score on the TMTB by the score on A, resulting in a more pure measure of executive functioning (Corrigan and Hinkeldey 1987). In our study, the values of this more "pure" measure do not differ

between groups (see Table 1); however, they do correlate with the strength of the anterior DMN (Fig. 1*B*; $r = -0.52$, $P = 0.010$, 1 tailed; corrected for GM volume and age). This may suggest that this network is indeed related to executive function as well as to attention, concentration, and processing speed.

A limitation to consider with respect to resting-state fMRI concerns the possible confound of cardiac and respiratory pulsations contributing to between-group differences. It is well known that typical EPI sampling (2.85 s in the present case) renders cardiac or respiratory physiological effects to be aliased. Furthermore, a previous study showed that BOLD signal changes induced by variations in respiratory depth are located in regions resembling the DMN (Birn et al. 2006). This could be especially problematic in studies with possible between-group differences in cardiac and respiratory functions. It is unlikely that this occurred in the present study as no differences in pulse and respiration, which were measured during the resting-state scan, were found between groups (mean heart rate: $t = 0.072$, $P = 0.943$, standard deviation: $t = 0.132$, $P = 0.896$; mean respiration: $t = 1.024$, $P = 0.315$, standard deviation: $t = 1.089$, $P = 0.282$). Moreover, by applying multiple regression techniques like ICA (as was done in this study), it has been shown that these cardiac- and respiratory-induced signal variations have a very specific spatial pattern and can be separated from signal fluctuations of interest, even at low sampling rate (Beckmann et al. 2005; De Luca et al. 2006; Fukunaga et al. 2006). Nevertheless, residual effects of physiological noise might remain present in the data after ICA. However, these effects can only decrease the sensitivity of the detection of group-specific differences unless it is assumed that there is a difference in physiological noise between groups, which is not the case in the current study.

Other limitations to this study are the relatively small number of subjects included, especially in the younger group, and the large difference in age between the 2 groups. The latter makes it impossible to investigate when the age-related decrease in activity occurs. Does it happen gradually or more abruptly after a certain age? For future studies on the influence of aging on intrinsic brain activity, we suggest increasing the number of subjects and including more subject groups across different ages or include age as a continuous factor.

In conclusion, we demonstrate that intrinsic activity of the DMN is related to aging. A previous resting-state fMRI study showed decreased activity in the DMN in Alzheimer's patients compared with age-matched healthy controls (Greicius et al. 2004). The DMN therefore appears to be affected by aging (the current study) but even more by Alzheimer's disease. Increasing evidence suggests that coherent intrinsic brain activity is important for healthy brain function. Changes in intrinsic brain activity have previously been related not only to several different medical conditions such as Alzheimer's disease (Greicius et al. 2004) as mentioned above but also schizophrenia (Zhou et al. 2007), depression (Greicius et al. 2007), and autism (Kennedy et al. 2006). These data suggest that the analysis of intrinsic brain activity may enlarge the understanding of disease and (possibly) cognitive decline.

Supplementary Material

Supplementary figure can be found at: http://www.cercor.oxfordjournals.org/.

Funding

Netherlands Organization for Scientific Research (NWO grant number: 916.36.117).

Notes

Conflict of Intesest: None declared.

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