Flexible Connectivity in the Aging Brain Revealed by Task Modulations

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Abstract: Recent studies have shown that aging has a large impact on connectivity within and between functional networks. An open question is whether elderly still have the flexibility to adapt functional network connectivity (FNC) to the demands of the task at hand. To study this, we collected fMRI data in younger and older participants during resting state, a selective attention (SA) task and an n-back working memory task with varying levels of difficulty. Spatial independent component (IC) analysis was used to identify functional networks over all participants and all conditions. Dual regression was used to obtain participant and task specific time-courses per IC. Subsequently, functional connectivity was computed between all ICs in each of the tasks. Based on these functional connectivity matrices, a scaled version of the eigenvector centrality (SEC) was used to measure the total influence of each IC in the complete graph of ICs. The results demonstrated that elderly remain able to adapt FNC to task demands. However, there was an age-related shift in the impetus for FNC change. Older participants showed the maximal change in SEC patterns between resting state and the SA task. Young participants, showed the largest shift in SEC patterns between the less demanding SA task and the more demanding 2-back task. Our results suggest that increased FNC changes from resting state to low demanding tasks in elderly reflect recruitment of additional resources, compared with young adults. The lack of change between the low and high demanding tasks suggests that elderly reach a resource ceiling. *Hum Brain Mapp 35:3788–3804, 2014.* © 2013 **Wiley Periodicals, Inc.**

Key words: aging; functional network connectivity; eigenvector centrality; working memory; selective attention; resting state; adaptability; graph theory; task dependent connectivity

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INTRODUCTION

Functional connectivity is an important measure that can be used to assess information transfer between brain areas. Numerous studies have demonstrated the existence of different functional networks. These are defined as groups of brain areas that tend to show high functional connectivity and have a particular functional signature (Biswal et al., 1995; Greicius et al., 2003; Sporns et al., 2004). There is ample evidence for a relation between functional connectivity patterns and specific task demands in

young participants. For example, Hampson et al. (2002) showed that functional connectivity between language-related brain areas increased when participants listened to speech compared with resting state. In addition, Shirer et al. (2011) found that connectivity increased between the dorsal attention network (DAN) and the basal ganglia during a subtraction task compared with resting state. These, and similar findings (e.g., Dew et al., 2012; Hare et al., 2010; Sala-Llonch et al., 2012; Sterpenich et al., 2006; Wolbers et al., 2006), illustrate that connectivity within and between (functional) networks is dependent on task demands.

There is strong evidence that connectivity within specific functional networks, that are involved in higher level cognitive functioning, is reduced in elderly (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Grady et al., 2010; Sambataro et al., 2010). However, connectivity between different functional networks tends to increase in older compared with younger adults (Geerligs et al., 2012a). These functional connectivity changes affect cognitive functioning in elderly. For example, a decrease in connectivity within the default mode network (DMN) has been linked to deterioration in performance on processing speed and working memory tasks in elderly (Andrews-Hanna et al., 2007; Sambataro et al., 2010).

Most aging studies so far, have focused on age-related changes in brain activity. These studies have provided evidence that the adaptation of brain activity to task demands proceeds differently in younger and older adults. Older adults often show additional activation compared with young adults, specifically in prefrontal areas, when comparing a task performance to a baseline condition, as well as comparing increasing levels of task demands (Cabeza, 2002; Cabeza et al., 2004; Madden et al., 1999; Mattay et al., 2006; Reuter-Lorenz et al., 2000). It has been suggested that these increased activations reflect the response of the brain to processing inefficiencies, leading to the recruitment of additional or "reserve" resources (Reuter-Lorenz and Cappell, 2008; Stern et al., 2005). The downside of this additional recruitment is that older adults appear to reach a resource ceiling as the task demands increase further. At this point, activation does not increase anymore and might even decrease, which is associated with a drop in task performance (Reuter-Lorenz and Cappell, 2008).

Although many studies have demonstrated the differences between younger and older groups in adaptation of brain activation to task demand, it is not known whether elderly are able to adapt the connectivity between different brain networks to the demands of the task at hand, in a similar manner as young adults. This question is especially important in the context of the age-related changes in connectivity both within and between functional networks that have been observed. Previous work by Spreng and Schacter (2011) has provided a first indication that flexibility of interactions between networks is reduced in older adults. They demonstrated that in younger adults the

fronto-parietal control network (FPCN) was flexibly coupled to either the DMN or the DAN, depending on the task demands (involving autobiographical memory or visuo-spatial planning, respectively). In older adults, this flexibility was reduced and the FPCN was coupled with the DMN in both task conditions.

In this study, we focus on connectivity between functional networks, that is, functional network connectivity (FNC). A procedure to study FNC was first described by Jafri et al. (2008). This procedure is based on the identification of different functional networks, using spatial independent component analysis (ICA). ICA can be applied to decompose fMRI data into a set of maximally spatially independent voxel-wise maps and their corresponding time-courses (Calhoun et al., 2001). Although the resulting spatial maps of independent components (ICs) are maximally independent, their corresponding time-courses can show considerable temporal correlations. Therefore, the temporal correlations between different ICs or "functional networks" can be computed and compared between different conditions (Arbabshirani et al., 2012). It should be noted that there is no fixed number of functional networks in the brain. The number of networks that is identified in a given study depends on the scale on which these networks are investigated. If one were to investigate on a smaller scale, functional networks can generally be split again into distinct sub networks (Meunier et al., 2009, 2010).

This method allows testing whether functional connectivity between pairs of ICs is modulated by particular task demands. However, a disadvantage of this approach is that it requires a large number of multiple comparisons. Alternatively, task related modulations of functional connectivity can be indexed by looking at centrality (Lohmann et al., 2010); a class of graph theoretical measures that can be used to assess the prominence or functional importance of each IC, within the complete graph of ICs. A graph is a schematic representation of a network, which consists of a set of nodes (in this case the ICs) and edges (the connections between them). Depending on the number and positioning of the edges, one IC can be more central in the graph than another. Task related changes in centrality can be used as an index of adaptations to task demands. The centrality of an IC can be measured in a number of different ways. The simplest way to define centrality of an IC is to look at its degree, defined as the number of connections an IC has with other ICs. Degree defines an IC with many connections as more central in the graph than an IC with few connections (Freeman, 1979). However, the degree is not able to measure the influence of an IC throughout the graph. Therefore, we instead used the eigenvector centrality, to capture not only the direct connections of an IC but also its influence throughout the graph (Bonacich, 1972, 2007). Eigenvector centrality can be seen as a sum of all direct connections, weighted by the centrality of indirect connections, thereby taking into account the entire connectivity pattern.
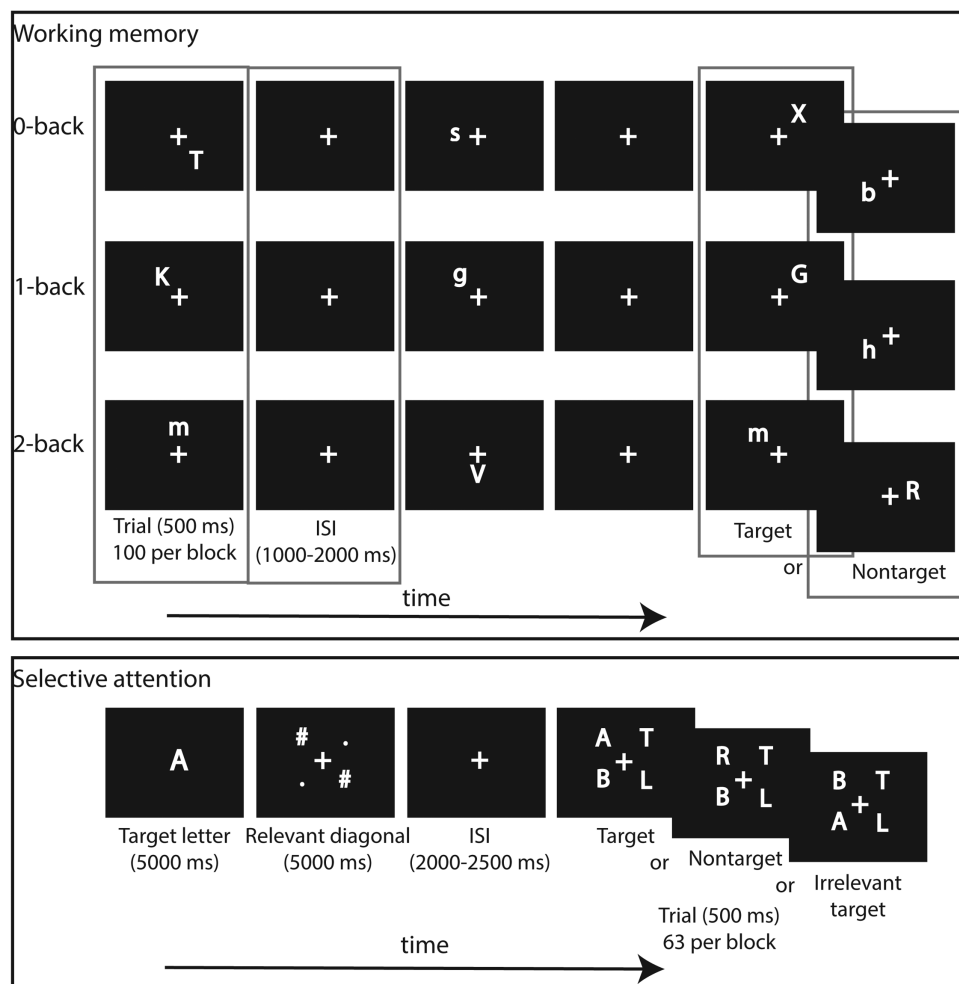
Figure 1.
Schematic description of the *n*-back and the selective attention tasks.

In this study, fMRI was recorded in both younger and older participants during eyes closed resting state, during a selective attention (SA) task and during a working memory task. Functional networks are each involved in certain (cognitive) functions. It is likely that depending on the demands of the task as hand, different ICs will play a more central role in the graph of ICs. Therefore, it is expected that the pattern of eigenvector centrality over ICs will change depending on the task at hand. To this end, we used correlations to investigate the similarity of eigenvector centrality over all ICs between different experimental conditions. For example, if the FNC is independent of a specific task, we would expect the eigenvector centrality pattern in the tasks to be similar, that is, we would expect a high correlation over ICs. On the other hand, low correlations would reflect a task or condition dependent change in eigenvector centrality. The main aim of our study was to assess whether condition-related changes in eigenvector centrality patterns were dependent on age; are elderly able to flexibly adapt FNC to the demands of the task at hand, similar to young adults? Based on effects of aging on brain activity as discussed above, it is could be hypothesized that older participants adapt FNC patterns to the task demands in a different way than young. By comparing the similarity of eigenvector centrality patterns between younger and older participants across conditions, we can assess differences in the age-related modulation of FNC. In addition, we examined these changes in more detail by investigating the age- and condition-related changes in eigenvector centrality, separately for each IC.

METHODS

Participants

Forty younger (21 males, $M_{age} = 20.6$ years, range: 18–26 years) and 40 older adults (24 males, $M_{age} = 64.9$ years, range: 59–74 years) participated in the experiment after giving

informed consent. All participants were right handed and had no history of neurological or psychiatric disorders. They had normal or corrected-to-normal visual acuity. All participants scored 26 or higher on the Mini Mental State Examination (MMSE, Folstein et al., 1975) and below 16 on both subscales of the Hospital Anxiety and Depression Scale (HADS, Zigmond and Snaith, 1983). The study adhered to the Declaration of Helsinki and was approved by the local ethics committee of the University Medical Center Groningen, the Netherlands. Data of one young and one older participant were lost due to technical problems. One older participant was excluded because a brain abnormality was detected.

Procedure and Cognitive Tasks

fMRI data was recorded in three different runs, in which participants performed an *n*-back task, a SA task and 10-min of resting state. A schematic display of the SA as well as the *n*-back task is presented in Figure 1. During resting state, participants were instructed to keep their eyes closed, but not to fall asleep. Results on each of these conditions separately will be reported elsewhere. The order of the tasks was randomized over participants. For both tasks, stimulus generation and response collection were controlled using E-prime 1.2 (Psychology Software Tools, Sharpsburgh, PA). Participants viewed the stimuli via a mirror mounted on the head coil. In both tasks, a fixation cross remained on screen throughout the task presentation. Responses were given by pressing a button with the right index or middle finger. The specific association between the button and the response finger was randomized over participants.

N-Back Task

The *n*-back task had three load conditions; 0-, 1-, and 2-back. Each block started with the presentation of task instructions. Subsequently, in each trial participants were presented with a single stimulus letter (500 msec). Each letter was randomly positioned in one of eight possible locations (horizontal X axis, vertical Y axis and the lower and upper position of both diagonals). The inter trial interval varied randomly between 1,000 and 2,000 msec. In the 0-back load condition, the target was the letter "x." In the 1-back load condition, the target was any letter identical to the letter immediately preceding it. In the 2-back load condition, the target was any letter identical to the letter presented two trials ago. The visual input was identical for all loads and the conditions could only be differentiated through the instructions received. Each load condition was presented twice, resulting in a total of six task blocks, with 100 trials each. In each block, targets occurred randomly in 50% of the trials. Blocks were followed by a 30 sec fixation cross. The order of the task loads was semi-randomized between participants. Letters were randomly presented either in upper-case (50%) or lower-case (50%). Participants were instructed to ignore the case of the letter

and to focus on its identity. The letters were chosen from a set of 18 consonants derived from the Dutch alphabet (all consonants except the letters Q, Y, and J).

Selective Attention Task

After general task instructions, six experimental blocks, each containing 63 trials were presented. At the start of a block, participants were presented with a target letter (5 sec), followed by a cue frame, indicating on which diagonal (right-up, left-up) relevant information would be presented. In each trial, the stimuli, consisting of four letters positioned at the end points of both diagonals, were presented for 300 msec followed by an interstimulus interval varying randomly between 2,000 and 2,500 msec. Participants were required to press the "yes" button when the target letter was presented on a relevant diagonal position [target]. In all other cases [i.e., target letter on irrelevant diagonal positions (irrelevant target) or no target letter presented (nontarget)] they should press 'no'. Relevant target trials made up 33% of the total number of trials. There were never two target letters present in one stimulus frame. Stimulus letters were randomly chosen from the alphabet, excluding the letters g, i, o, q, u, x, and y. Each block was followed by a 30 sec fixation cross.

Behavioral Data

Participants were excluded based on behavioral data if there were indications that they did not understand/follow the task instructions. Data of three younger participants and one older participant were excluded because their accuracy on the SA task was around or below chance level (below 60%) in one or more task conditions (targets, nontargets, and/or irrelevant targets). For the *n*-back task, all participants performed the 0- and 1-back task with over 70% accuracy, indicating that the task instructions were clear. On the 2-back task, four participants performed around or below chance level (below 60% accuracy). However, this likely reflects the difficulty of the task and not the lack of understanding of task instructions. Therefore, data of these participants were included in the analysis. Thus, the behavioral and ICA analyses were performed on the data of 36 younger and 37 older participants. For each participant and each task, the median reaction time for correct responses and the mean accuracy scores were used in subsequent analyses. Fast guesses (responses faster than 200 msec) and responses slower than the minimum interstimulus interval (1,500 msec for the *n*-back task and 2,000 msec for the SA task) were regarded as incorrect responses.

Image Acquisition

FMRI scans were obtained with a 3 Tesla MR scanner (3T Achieva, Philips Medical Systems, Best, Netherlands), with echo planar imaging (EPI) capability and an eight

channel SENSE head coil. Functional images were obtained with the following pulse sequence parameter settings: single shot EPI; 37 slices; slice thickness = 3.5 mm; no gap; field of view = 224 mm; matrix scan size 64 by 64; transverse slice orientation; repetition time (TR) = 2000 msec; echo time (TE) = 30 msec; minimal temporal slice timing = 1836 msec; flip angle 70°. A 3-D T1-weighted anatomical scan of the entire brain was obtained for each participant using the following pulse sequence parameters: field of view = 256 mm; matrix scan size 256 by 256; 170 slices; slice thickness 1 mm; transverse slice orientation; TE = 3.6 msec; TR = 9 msec; flip angle 8°.

fMRI Data Analysis

Offline processing was performed using the statistical parametric mapping software package (SPM 8; http://www.fil.ion.ucl.ac.uk/spm/software). The functional images were motion-corrected and coregistered to the anatomical scan. The co-registration was checked visually and adjusted manually when required. Bias regularization (SPM 8) was used to reduce signal intensity variations due to field inhomogeneities in both structural and functional images. For functional images, the regularization was initially applied to the first and the last functional scan within each run. Based on these two corrections, an average correction factor was computed for each voxel, which was applied to all scans in each run. A group specific anatomic template was created (for young and elderly participants together), using Diffeomorphic Anatomical Registration Exponentiated Lie algebra (DARTEL), to optimize inter-participant alignment (Ashburner, 2007). Data were smoothed with an 8 mm full-width half maximum (FWHM) Gaussian kernel.

Independent Component Analysis

Data were decomposed into functional networks using a group-level spatial ICA as implemented in the GIFT toolbox (version 2.0e, http://mialab.mrn.org/software/gift/). The data from the two tasks and resting state were entered as separate runs in the analysis. Before ICA decomposition, voxel time series were z-scored to normalize variance across space (similar to Allen et al., 2012). This procedure is aimed at minimizing a possible bias in subsequent variance-based data reduction steps due to variance differences between tasks and participants. The number of components in each run of each participant was estimated by the minimum description length (MDL) criterion (Li et al., 2007). The mean estimated number of components was 38; therefore, the data was decomposed into 38 functional networks. To monitor the reliability of the ICA decomposition, we repeated the Infomax ICA algorithm (Bell and Sejnowski, 1995) 10 times in the ICASSO toolbox within GIFT (http://www.cis.hut.fi/projects/ica/icasso). With each repetition, the ICA algorithm was initialized with a different start point. Generally, these results showed com-

pact clusters, validating the reliability of component estimation. After IC components had been established on the group-level, part of the dual regression procedure was applied to estimate participant- and run specific time-courses (Filippini et al., 2009). This was done by regressing the group spatial maps into the 4D dataset of each subject and each run. This procedure ensures that the IC time-course for each participant and each run is based on the same spatial map. A subset of 25 ICs was visually selected for further analysis, based on the expectation that ICs should exhibit peak activations in grey matter and low spatial overlap with known vascular, ventricular, motion, or susceptibility artifacts.

Functional Connectivity Analysis

Before the functional connectivity analysis, we applied a number of additional processing steps to the time-courses of each participant and each run to remove variance in the data related to participant motion and scanner drifts (Van Dijk et al., 2010). A flow chart of the analysis procedure is presented in Figure 2. The default procedure in GIFT is to detrend the linear, quadratic and cubic trends in the time-courses. Subsequently, residual effects of motion were corrected by regression with the six realignment parameters and their temporal derivatives. In addition, variance associated with stimulus presentation was removed in the SA-task and the n-back task, to make sure that connectivity is not dominated by synchronized stimulus-evoked responses (Al-Aidroos et al., 2012; Geerligs et al., 2012a). For the SA task, target, non-target and irrelevant target trials were modeled as separate regressors. In addition, regressors related to task instructions and error trials were modeled in separate regressors. For the n-back task, 0-back, 1-back, and 2-back trials were modeled as separate regressors in addition to regressors for the task instructions. In both tasks, we convolved all regressors with the canonical hemodynamic response function (HRF), as well as the temporal derivative and the dispersion derivative to account for local variability in the shape of the HRF. The residuals of this procedure were used to compute functional connectivity. The resulting functional connectivity reflects background connectivity, which can be used to assess how the cognitive state of a participant affects the functional architecture of the brain (Al-Aidroos et al., 2012).

An additional movement correction procedure was performed to make sure that the effects of age and task condition on functional connectivity were not due to spurious effects of motion. To this end, we used part of the procedure applied by Power and colleagues (2012). The first step in this correction procedure was to calculate the total displacement per scan. The rotational parameters were transformed to millimeters (mm) displacement by assuming affected voxels were at a distance of 65 mm from the origin of the rotation. The total displacement per scan was computed using the procedure in the ArtRepair
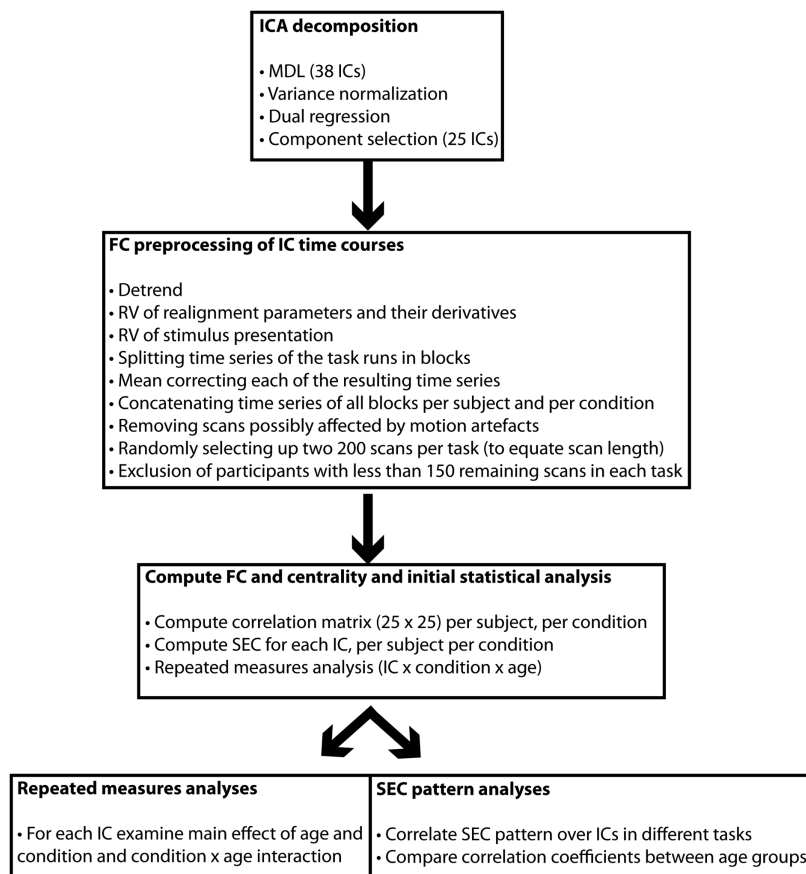
Figure 2.

Flow chart of all steps in the analysis procedure after the initial, standard preprocessing steps. RV = removal of variance, SEC = scaled eigenvector centrality, FC = functional connectivity, ICA = independent component analysis, MDL = minimal description length.

toolbox http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html. Scans in which the displacement compared with the previous scan was larger than .5 mm were flagged. The flagged scans as well as two scans before and one scan after this scan were not taken into account in the computation of the correlation matrix.

In addition to movement differences, a bias might be introduced due to the differing numbers of scans in each task condition; 300 resting state scans, ± 200 scans per n-back load condition and ± 480 scans for the SA task. Therefore, we randomly selected up to 200 scans (depending on the number of scans left after movement correction) out of all scans for both the resting state and the SA condition, to make the number of scans equivalent to each n-back load condition. These scans were then used to compute the correlation matrix. Those participants (four younger and two older) for which fewer than 150 scans remained in one or more conditions due the movement correction procedure were excluded from the FNC analysis. Thus, the FNC analysis was performed on the data of 32 younger and 35 older participants.

Condition specific time series were generated by segmenting time-courses from each IC into separate condition blocks. Each block started three scans after the first stimulus onset and ended at the final stimulus onset of that block. For the n-back task, there were two 0-back blocks, two 1-back blocks, and two 2-back blocks. For the SA task, there were six experimental blocks. The time course of each block segment was mean centered and concatenated with segments of the same condition. Subsequently the correlation coefficient was computed between the time-courses for each pair of ICs for each participant and each condition. The Spearman rank correlation was used to reduce the effect of outliers on the correlation estimate.

Eigenvector Centrality

To determine the functional importance of each IC, we used a graph theoretical approach. The ICs are taken as the separate nodes in a graph, whereas the functional connections between ICs represent the graph's edges. Eigenvector centrality was computed for each node, for each

condition and each participant separately (Lohmann et al., 2010). A node is considered to be central if it has many connections as well as high connectivity strengths to other nodes, particularly when these other nodes have a large number of connections, preferably with a high connectivity themselves (Bonacich, 1972). Eigenvector centrality can be seen as a weighted sum of the direct and the indirect connections of a node (Bonacich, 2007), that is, it takes the entire pattern of connections within a graph into account. Moreover eigenvector centrality does not depend on a pre-specified threshold for correlation values, unlike other centrality measures such as degree or betweenness centrality.

Eigenvector centrality is based on an eigenvector decomposition of the adjacency matrix (A). If we define λ_{max} as the largest eigenvalue and x_{max} as the corresponding eigenvector then $Ax_{max} = \lambda_{max}x_{max}$. The eigenvector centrality of a node i is then defined as $x_{max,i}$. The eigenvector centrality represents the relative influence of a node on all other nodes. Therefore, a graph with a higher average correlation coefficient will not always result in higher centrality values. Because we were interested in the total influence of a node on all other nodes, we applied an additional scaling by the largest eigenvalue λ_{max}. Here, we employed that the largest eigenvalue λ_{max} of a positive correlation matrix is closely related to the mean of this positive correlation matrix (Friedman and Weisberg, 1981). Scaling the relative contribution per node (eigenvector centrality) with the total influence all nodes have on each other (λ_{max}), thus results in a measure of the total influence per node, the scaled eigenvector centrality (SEC): $SEC_i = x_{max,i}\lambda_{max}$.

To calculate the eigenvector centrality, it is required that the eigenvector decomposition has a unique solution. To achieve this, all values in the adjacency matrix must be positive. Lohmann et al (2010), proposed two methods to meet this requirement: either to add a constant to the correlation values, using $\tilde{r} = r + 1$ or to use the absolute values of the correlation coefficient $\tilde{r} = |r|$, where r is the correlation and $\tilde{r}$ is the adapted version. Using the first alternative will result in a low eigenvector centrality for nodes with high negative correlations, underestimating the strength of the influence of these nodes. The second alternative, on the other hand, takes only the strength of the correlation into account and not the sign. However, since a node with a strong negative correlation can be regarded as a node with a high influence on other nodes in the graph, we chose this second approach.

Statistical Analysis

The main aim of this study was to investigate whether elderly are able to flexibly change patterns of functional connectivity between networks (FNC) depending on task demands. General changes in FNC patterns were measured by correlating the SEC over all ICs in one condition with the SEC over all ICs in another condition. This results in one Spearman rank correlation coefficient per partici-

pant, per comparison between conditions. These correlation values were transformed to a normal distribution using Fisher r to z' transformation (Fisher, 1921). For each combination of conditions, the transformed scores were then compared between age groups using an independent samples t-test in SPSS. To reduce the number of comparisons, analyses were initially restricted to the resting state, SA and 2-back conditions, as these are most distinct in terms of the cognitive processes they require. The 0-back and 1-back task conditions were used for post hoc testing to confirm specific patterns observed in the data.

To examine the effects of age groups and task on SEC, repeated measures analysis were used. Initially, we used a model with the within subject factors task (rest, SA-task and 2-back task) and IC and the between subject factor age group. Subsequently, repeated measures analyses were created per IC, with the within subject factor task and the between subject factor age group. As this resulted in 25 different models, the reported P-values of this analysis were corrected for multiple comparisons, using the FDR correction (Benjamini and Hochberg, 1995). P-values were adjusted for violations of the sphericity assumption using the Greenhouse-Geisser correction (Greenhouse and Geisser, 1959). Only results with an FDR corrected $P \leq 0.01$ are reported. This stringent threshold was chosen to limit the number of false positives resulting from the 75 tests performed. For clarity, uncorrected degrees of freedom values are presented in the results section. Paired and independent samples t-tests were used for post hoc testing. Before the analyses, SEC values were transformed as described by van Albada and Robinson (2007) to ensure that they obey a Gaussian normal distribution, maintaining the mean and standard deviation of the original distribution.

To explore whether the SEC is related to task performance, we created regression models for each of the ICs for which an interaction effect between task and age group was observed. For each of the task conditions (SA and 2-back), the accuracy and reaction times during task performance were used as the dependent variables in separate models. Age group and the SEC of the respective IC were used as the independent variables, along with the interaction between the two. This resulted in a total of 16 regression models. No correction for multiple comparisons was applied to these post hoc tests.

RESULTS

Behavioral Data

In all tasks, older participants responded slower than younger participants [$F(1,71) = 116.6$, $P < 0.001$], however, the differences between age groups varied with condition [$F(3,213) = 19.83$, $P < 0.001$, see Table I]. Differences between age groups were largest in the 2-back task condition (237 msec), smaller in the 1-back task condition (161 msec) and the SA task (154 msec) and smallest in the 0-

TABLE I. Averages and standard deviations for response times (RT) and accuracy (ACC), separately for each age group and task (condition)

	0-back	1-back	2-back	SA
RT young (msec)	483 (50)	534 (60)	650 (104)	506 (68)
RT old (msec)	600 (54)	695 (81)	888 (108)	660 (80)
ACC young (%)	94 (3)	90 (5)	86(4)	95(3)
ACC old (%)	94(3)	90(4)	73 (12)	95 (4)

back task condition (116 msec). In both age groups, participants were faster in the 0-back than the 1-back task condition [$t(72) = 14.04$, $P < 0.001$] and faster in the 1-back than the 2-back task condition [$t(72) = 14.48$, $P < 0.001$]. In the SA task, participants were faster than in the 0-back task condition [$t(72) = 7.59$, $P < 0.001$] but slower than in the 1-back task condition [$t(72) = 5.22$, $P < 0.001$].

In the 2-back task condition, older participants had significantly lower accuracy scores than young participants [$t(71) = 6.08$, $P < 0.001$], whereas there were no significant differences between the age groups in the other tasks and conditions [age × condition; $F(3,242) = 30.77$, $P < 0.001$]. In both age groups, accuracy scores were higher in the 0-back than the 1-back task condition [$t(72) = 7.63$, $P < 0.001$] and higher in the 1-back than in the 2-back task condition [$t(72) = 8.07$, $P < 0.001$]. Accuracy scores in the SA task were slightly higher than in the 0-back task condition [$t(72) = 2$, $P = 0.049$].

Independent Components

From the 38 estimated IC components, 25 components were selected as non-artifactual, relevant networks. These components were derived from all the rest and task data together. Figure 3 illustrates the spatial maps of these components. For clarity and ease of display, these ICs were grouped based on function, using a similar approach as Allen et al. (2012). A description of the ICs can be found in the caption of Figure 3.

For each IC, we used the scaled eigenvector centrality (SEC) to investigate its centrality or importance in the graph. SEC reflects the total influence of an IC in the graph of ICs, by capturing both the correlation strength and the number of connections of that IC to other ICs, as well as the centrality of the neighboring (i.e., connected) ICs. To investigate whether SEC changes in different ICs depend on age-group and condition, a repeated measures analysis was performed. We observed a main effect of IC [$F(24,3120) = 28.6$, $P < 0.001$], a main effect of task [$F(2, 3120) = 11.49$, $P < 0.001$] and a main effect of age group [$F(1,65) = 12.36$, $P = 0.001$], as well as, significant interactions between task and IC [$F(48,3120) = 9.08$, $P < 0.001$], age and IC [$F(24,3120) = 6.09$, $P < 0.001$], and age, task, and IC [$F(48,3120) = 4.16$, $P < 0.001$]. To elucidate these effects we created a repeated measures model for each IC, with the

within subjects factor task and the between subjects factor age group. This allowed us to investigate differences in SEC between the two age groups, differences between the conditions as well as interactions between age and condition, separately for each IC. Averages and standard deviations for the SEC can be found in Supporting Information Table I, separately for each IC, condition, and age group.

Effects of Age on SEC

Older participants had higher SEC values than younger participants in four of the 25 identified ICs, indicating that connectivity between functional networks was increased in older compared with younger participants. In particular in two of the four visual ICs, the basal ganglia, and the anterior cingulate IC, older participants had higher SEC values than younger participants. Note that this description of results only takes into account the ICs in which there was no interaction between age and condition. Younger participants had a higher SEC than older participants in the medial frontal IC. In Table II, all main effects of task and age are described.

Effects of Task on SEC

In the majority of ICs, the SEC was smaller in task conditions compared with resting state, indicating that between network connectivity was stronger during resting state than during task performance. In particular in the ICs related to visual or auditory information processing, as well as ICs related to sensorimotor functions and the basal ganglia IC, the SEC was larger in resting state than during task performance. Specifically in the inferior frontal IC we found that centrality was increased in the 2-back task compared with resting state. The SA task showed an increase in SEC compared with resting state in the angular gyrus IC and the inferior frontal IC. In other ICs, the effect of task was specific to one of the age groups; these results are discussed in the next section.

Interactions Between Task and Age Per IC

The averages in different tasks and age groups are visualized in Figure 4 for those ICs that showed a significant interaction between task and age group. An interaction between task and age was observed in the *somatosensory IC* (IC 9). In younger participants, SEC was not significantly different between conditions, whereas in old participants the SEC increased from rest to the SA task [$t(34) = 2.63$, $P = 0.013$] and from the SA task to the 2-back task condition [$t(34) = 2.93$, $P = 0.006$]. Therefore, in rest elderly had a lower SEC than young adults [$t(65) = 2.11$, $P = 0.039$], whereas in the 2-back task condition elderly had a higher SEC than young participants [$t(65) = 2.62$, $P = 0.011$].

For older adults, the SEC in the *precuneus IC* (IC 14) was larger in the 2-back task condition than in the SA
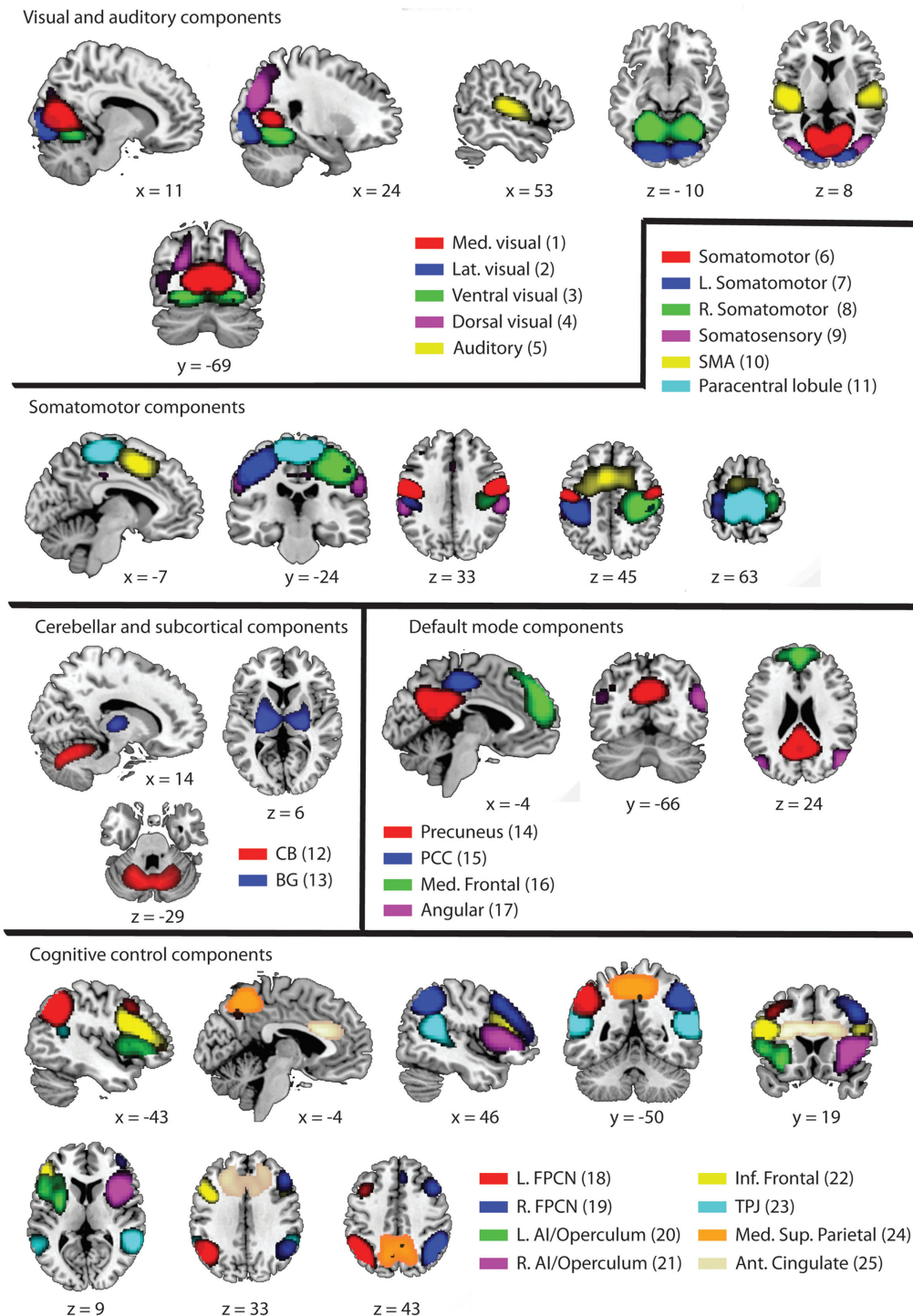
Figure 3.

Identified independent components (ICs), grouped by location and function. The number between brackets indicates the IC number. Within the identified ICs, there were four visual components, representing the medial (IC1), lateral (IC 2), ventral (IC3), and dorsal (IC4) parts of the visual system. In addition, one auditory component (IC 5) was identified. Six different components were identified that are related to sensorimotor functions (IC 6-11). Separate ICs were identified for the cerebellum (IC 12) and the basal ganglia (IC 13). The classical default mode network was represented in four separate components (IC 14-17). Separate left and right fronto-parietal components were identified (IC 18 and 19, respectively) as well as left and right anterior insula/opercular networks (IC 20 and 21, respectively). Bilateral inferior frontal (IC 22) and temporo-parietal junction components (IC 23) were identified as well as medial superior parietal (IC 24) and anterior cingulate components (IC 25). R = right, L = left, Ant = anterior, Inf = inferior, Sup = superior, Lat = lateral, Med = medial, SMA = supplementary motor area, CB = cerebellum, BG = basal ganglia, PCC = Posterior Cingulate Cortex, FPCN = fronto-parietal control network, AI = anterior insula, TPJ = temporo-parietal junction.

task [$t(34) = 3.88$, $P < 0.001$] and in rest [$t(34) = 3.17$, $P = 0.003$], while in young adults SEC was higher in the SA task than the 2-back task [$t(31) = 2.23$, $P = 0.033$] while both tasks were not significantly different from rest. In the 2-back task condition, the SEC in the precuneus was significantly larger in older than young adults [$t(65) = 4.31$, $P < 0.001$].

Another interaction between task and age group was observed in the *right FPCN IC* (19). The SEC was significantly larger in young than older participants during the 2-back task condition [$t(65) = 3.84$, $P < 0.001$], but not in rest or during the SA task. In young adults, SEC was largest in the 2-back task condition compared with the SA task [$t(31) = 5.47$, $P < 0.001$] and rest [$t(31) = 3.84$, $P = 0.001$]. In the older adults, no significant differences were observed between the tasks.

In the temporo-parietal junction (*TPJ*) *IC* (23), similar SEC values were observed in both age groups in rest, while the SEC was larger in older than young adults in both the 2-back task condition [$t(65) = 3.31$, $P = 0.002$] and the SA task [$t(65) = 5.35$, $P < 0.001$]. In young participants, SEC was smaller in the SA task compared with the 2-back task condition [$t(31) = 5.5$, $P < 0.001$] and rest [$t(31) = 2.5$, $P = 0.018$]. In contrast, SEC in the older participants was larger in the 2-back task condition compared with the SA task [$t(34) = 2.52$, $P = 0.017$] and larger in the SA task compared with rest [$t(34) = 4.63$, $P < 0.001$].

We have performed additional analyses in which we have tested the effects of removing the variance associated with stimulus presentation before the computation of the connectivity matrix. The results of this procedure are described in the Supporting Information. They show that the main findings described above are robust and are only minimally affected by the specific approach used. In addition, to demonstrate the effect of the specific threshold selected for the analysis, results of the analyses are also presented for a lower significance threshold ($p_{fdr} < 0.05$) in Supporting Information Table II.

Effects of Age on Changes in SEC Patterns With Changing Task Demand

In the second approach to shed more light on the IC × age × task interaction, we focused on the relation between different ICs. Specifically, we examined the change in the SEC patterns across ICs between different task conditions and the effects of aging on this change. Correlation analyses were used to investigate the similarity of SEC patterns over all ICs between different conditions. Little change between two conditions would be reflected in high correlation values (high similarity), whereas a large change between two conditions would results in low correlations (low similarity). Correlations were compared between age groups to see how changes between conditions are affected by aging.

Differences in SEC Patterns Between Resting State and Task Performance

The relative importance of nodes, that is, the SEC pattern, was similar in resting state and the SA task in young participants (z-transformed correlation: $M = 0.46$, $SD = 0.26$), whereas this similarity was reduced in older participants ($M = 0.17$, $SD = 0.28$; $t(65) = 4.35$, $P < 0.001$). For both younger and older adults there was little similarity between the SEC patterns in the 2-back task condition and rest [young: $M = 0.19$, $SD = 0.28$; old: $M = 0.12$, $SD = 0.22$; $t(65) = 1.03$, $P = 0.31$]. The relatively high accuracy levels and the fast responses in the SA task suggest that the levels of cognitive demand required by this task are lower than the cognitive demand required in the 2-back task condition. Therefore, the results suggest that the change in SEC pattern is larger in older than younger participants only from resting state to low demanding tasks. To confirm this, we additionally considered the 0- and the 1-back task conditions. The accuracy levels and response times indicate that task demand in the 0-back task condition is similar to that in the SA task, while demand in the 1-back task condition is higher than in the 0-back task condition, but lower than in the 2-back task condition. Based on the effect of aging in the SA-task compared with resting state, we would expect the largest age group differences in the change in SEC pattern for the 0-back task condition versus resting state and a smaller age difference for the 1-back task condition versus resting state. Indeed, we found that the SEC pattern in the 0-back task condition was more similar to the resting state condition, in young ($M = 0.44$, $SD = 0.26$) compared with older adults ($M = 0.15$, $SD = 0.29$; $t(65) = 4.17$, $P < 0.001$). Similarly, the SEC pattern in the 1-back task condition was more similar to the resting state, in young ($M = 0.30$, $SD = 0.26$) compared with older adults [$M = 0.17$, $SD = 0.21$; $t(65) = 2.16$, $P = 0.035$]. In Figure 5, the age group differences in absolute changes in SEC between tasks and resting state are visualized per IC.

Differences in SEC Patterns Between the Selective Attention Task and n-Back Task Conditions

In addition to the decreased similarity in SEC pattern between resting state and low demanding task conditions in elderly compared with young individuals, we observed an increased similarity in SEC pattern between different tasks in the elderly. The SEC patterns in the 2-back task condition and SA task were similar in older ($M = 0.44$, $SD = 0.29$) and less similar in younger adults [$M = 0.27$, $SD = 0.21$; $t(65) = 2.7$, $P = 0.009$]. In line with this result, elderly showed a more similar SEC pattern between the 0-back and the 2-back task condition [young $M = 0.25$, $SD = 0.30$; old $M = 0.58$, $SD = 0.33$; $t(65) = 4.16$, $P < 0.001$] and showed a trend toward the same effect in the 0-back and the 1-back task condition [young $M = 1.51$, $SD = 0.33$;

TABLE II. Results of repeated measures analysis; effects of condition, age group and the interaction of age group and condition on SEC

IC	Main effect task		Post hoc			Main effect age		Post hoc	Interaction Task * Age	
	F	p	RE-SA	R-2B	SA-2B	F	p	O-Y	F	p
Med. Visual (1)	7.23	0.004	RE > SA		2B > SA	19.6	<0.001	O > Y		
Lat. Visual (2)	5.98	0.007	RE > SA							
Ventral visual (3)	12.95	<0.001	RE > SA	RE > 2B						
Dorsal visual (4)						10.27	0.009	O > Y		
Auditory (5)	19.28	<0.001	RE > SA	RE > 2B	2B > SA					
Somatomotor (6)	24.66	<0.001	RE > SA	RE > 2B	2B > SA					
L. Somatomotor (7)	13.70	<0.001	RE > SA	RE > 2B	SA > 2B					
R. Somatomotor (8)	19.31	<0.001	RE > SA	RE > 2B						
Somatosensory (9)									8.36	0.004
SMA (10)										
Paracentral lobule (11)	10.81	<0.001	RE > SA		2B > SA					
CB (12)										
BG (13)	5.39	0.011	RE > SA			50.35	<0.001	O > Y		
Precuneus (14)									10.32	0.004
PCC (15)										
Med. Frontal (16)	5.49	0.010			SA > 2B	16.49	<0.001	Y > O		
Angular (17)	12.39	<0.001	SA > RE		SA > 2B					
L. FPCN (18)										
R. FPCN (19)									7.74	0.007
L. AI/Operculum (20)										
R. AI/Operculum (21)	7.23	0.002	RE > SA	RE > 2B						
Inf. Frontal (22)	24.67	<0.001	SA > RE	2B > RE	2B > SA					
TPJ (23)									12.95	<0.001
Med. Sup. Parietal (24)										
Ant. Cingulate (25)	6.23	0.005	RE > SA	RE > 2B		48.30	<0.001	O > Y		

Y = young, O = old, RE = rest, SA = selective attention task, 2B = 2-back task, R = right, L = left, F = F-value, p = p-value, Ant = anterior, Inf = inferior, Sup = superior, Lat = lateral, Med = medial, SMA = supplementary motor area, CB = cerebellum, BG = basal ganglia, PCC = Posterior Cingulate Cortex, FPCN = fronto-parietal control network, AI = anterior insula, TPJ = temporoparietal junction, degrees of freedom for the F-test of the task and the interaction effect were 2 and 130, degrees of freedom for the F-test of the age effect were 1 and 65. Main effects of age and task are not displayed for those ICs that demonstrated a significant interaction of task*age.

old $M = 0.67$, SD = 0.34; $t(65) = 1.96$, $P = 0.054$]. However, the age groups did not show a difference in SEC pattern similarity between (a) the 1-back and the 2-back task condition, (b) the 0-back task condition and the SA task, and (c) the 1-back task condition and the SA task [a: young $M = 0.53$, SD = 0.26; old $M = 0.60$, SD = 0.31; $t(65) = 1.0$, $P = 0.32$; b: young $M = 0.57$, SD = 0.32; old $M = 0.50$, SD = 0.33; $t(65) = 0.83$, $P = 0.41$; c: young $M = 0.49$, SD = 0.32; old $M = 0.48$, SD = 0.34, $P = 0.93$]. The differences between age-groups in SEC changes between task conditions are visualized in Figure 5.

Relation With Behavior

Of the four ICs that showed an interaction between condition and age group, only the precuneus IC (14) showed a significant correlation with behavior. In the SA task, increased SEC of the precuneus IC (14) was related to increased accuracy [$B = 0.01$, $t(63) = 2.10$, $P = 0.04$], whereas no significant effect of age [$B = 0.007$, $t(63) = 0.70$,

$P = 0.49$] and no interaction between age and SEC was observed [$B = 0.001$, $t(63) = 0.07$, $P = 0.95$]. However, it should be noted that no correction for multiple comparisons was applied and that the F-test for the complete regression model was not significant [$F(3,63) = 1.63$, $P = 0.19$]. Therefore, the observed relation could be a false positive result.

DISCUSSION

To truly understand the effects of aging on brain function, it is important to know if elderly are able to adapt FNC in response to changing task demands. In this study, we investigated how aging affects the adaptation of functional connectivity between functional networks (FNC) to the demands of the task at hand. We have used a brain-wide approach to show that elderly can indeed adapt functional connectivity. However, the results show that the impetus to change FNC patterns changes with age;
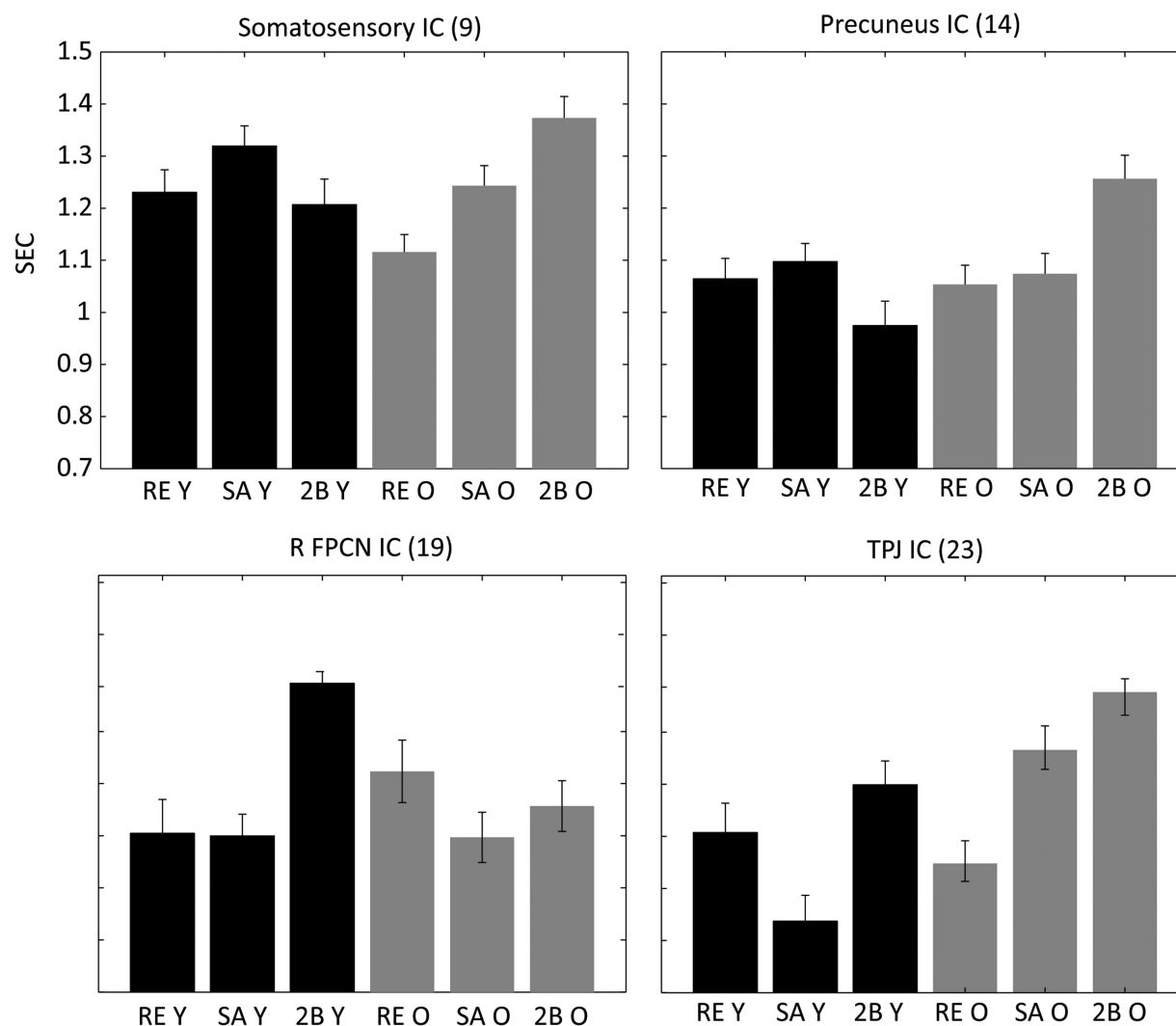
Figure 4.

SEC for the different conditions and age groups, displayed for those ICs showing a significant interaction between age and task. Black bars show the mean and standard error of the SEC in younger participants, gray bars show the SEC in older partici- pants. RE = rest, SA = selective attention task, 2B = 2-back task, Y = young, O = old, FPCN = fronto-parietal control network, TPJ = temporo-parietal junction.

whereas young participants show the maximal change in connectivity patterns from less demanding to more demanding task conditions, older participants showed maximal change from rest to low demanding tasks.

Previous studies have shown that during task perform- ance, functional connectivity increases between specific areas that are involved in execution of the task at hand (e.g., Dew et al., 2012; Hampson et al., 2002; Hare et al., 2010; Sala-Llonch et al., 2012; Shirer et al., 2011; Sterpenich et al., 2006; Wolbers et al., 2006). Since, the SEC incorpo- rates both direct and indirect functional connectivity from an IC to all other ICs, we would expect that, similar to functional connectivity, the SEC will increase in ICs that

are functionally relevant to the task at hand. Indeed, the results of the current study demonstrate an increase in centrality of ICs that play an important role in task per- formance. During the 2-back task, we found that in both age groups, centrality was increased in the inferior frontal IC compared with resting state, an area that has been sug- gested to play an important role in working memory (Nagel et al., 2009; Owen et al., 2005). In addition, another network important for working memory, the right FPCN, showed increased centrality in young participants during the 2-back task. Another study by Lohmann et al. (2010) has also shown that the eigenvector centrality increases in areas that are important in the condition at hand. More
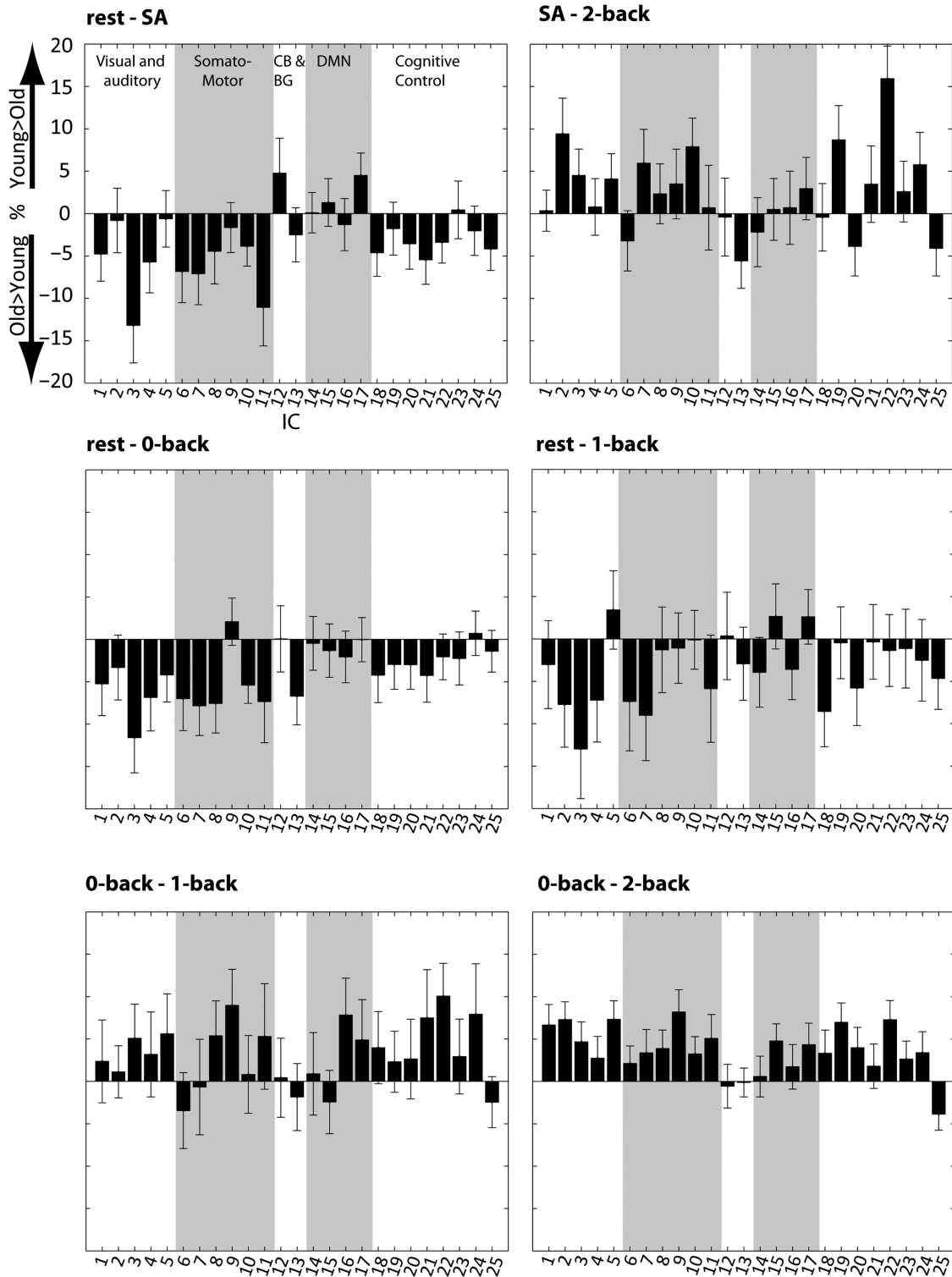
Figure 5.

Visualization of the differences between age-groups in absolute change in SEC between task/rest conditions per IC. The bars represent differences between older and younger adults in absolute SEC change per IC. Differences are expressed as a percentage of the total difference between older and younger adults. The standard error of the mean is indicated by the error bars.

specifically, they found that the eigenvector centrality of the ventral striatum, a key region implicated in reward such as food, increased in a sated compared with a hungry condition. Note that the direction of correlations was not taken into account in the current analysis. Therefore it is unclear whether a SEC increase reflects an increase in negative correlations or an increase in positive correlations.

Especially in the visual and somatomotor ICs, functional connectivity to other ICs was decreased during task performance compared with resting state. These results are in line with those of Arbabshirani et al (2012), who found a general decrease in FNC during performance of an auditory oddball task compared with resting state. These authors suggested that performance of an active task may be facilitated by higher activation within specialized brain networks rather than collaboration between different networks. This idea is further supported by findings of Nir et al. (2006). They compared visual stimulation to periods of eyes closed resting state and showed that during visual stimulation; functionally related visual areas were more strongly connected, while functionally dissimilar visual regions became de-correlated. Together with our results, this suggests that most networks show decreased connectivity to other functional networks with increasing levels of task demands.

As visual and somatomotor networks are essential for adequate performance in the SA and working memory tasks, it is puzzling why these networks showed a decrease as opposed to an increase in SEC during task performance compared with resting state. First of all, it should be noted that in the current study, participants closed their eyes during the resting state condition, while performance of the two tasks was dependent on the processing of visual input. This difference in visual input might have aggravated the observed effects of task compared with resting state on the SEC of visual ICs. Alternatively, it might be the case that increases in SEC with increasing task demand are limited to those networks that play the most central role in the task. For example, working memory of visual items is thought to rely on the maintenance of sensory representations in the visual cortex as well as on the manipulation of these items. Therefore, especially areas involved in maintaining and manipulating this representation, such as the inferior frontal gyrus, would need to increase FNC during working memory tasks to enable adequate performance. A limitation of this study is that these two alternatives cannot be disentangled with this dataset. Future studies using an eyes open baseline period could investigate whether the observed FNC changes are truly related to task performance or to the difference between eyes open during task performance and eyes closed during resting state.

Our findings indicate an age-related difference in the modulation of FNC with condition. Whereas young participants show the maximal change in SEC patterns from less demanding to more demanding task conditions, older participants showed maximal change from rest to a low demanding task. It is important to note that this result cannot be due to the difference between eyes closed–eyes open in rest versus task, as there was no difference between older and younger adults in the comparison between resting state and the high demanding two-back task. This result fits well with previous literature on BOLD activation differences in elderly compared with young participants. In working memory studies, for example, it has been found that elderly show increased prefrontal activation compared with young participants in low working memory loads, whereas the opposite pattern is observed during high working memory loads (Mattay et al., 2006). According to Reuter-Lorenz and Cappell (2008), processing inefficiencies cause the aging brain to recruit more neural resources to achieve computational output equivalent to that of a younger brain. They argued that as demand increases, elderly can reach a resource ceiling (Grady, 2012). In turn this can lead to age-related declines in performance in more demanding tasks. In the context of the current results, the larger change in SEC patterns from resting state to the less demanding cognitive tasks in elderly compared with young adults, could reflect the recruitment of additional neural resources necessary to cope with task demands. The limited adaptation of centrality in case of additional task demands in elderly might be a sign of elderly reaching a resource ceiling. These results show that the theories of age-related change, mainly based on changes in brain activation, are in line with observed connectivity changes in the aging brain.

In addition, we observed that the functional connectivity to other ICs was larger in older compared with younger participants in a number of ICs (i.e., the visual ICs, the basal ganglia IC and the anterior cingulate IC). This age-related increase in connectivity between functional networks is in line with results from a previous study, in which we found that connectivity between functional networks was increased during a visual oddball task in older compared with younger participants (Geerligs et al., 2012a). Tomasi and Volkow (2012) also found indications that connectivity between functional networks increases with age; they showed that long range connectivity from areas in the somatomotor network, thalamus, and cerebellum was increased in elderly during resting state. Previous studies have demonstrated that besides increases in between network connectivity, connectivity within specific functional networks is decreased with age (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Grady et al., 2010; Rieckmann et al., 2011; Sambataro et al., 2010). Together, these age-related changes result in decreased segregation of functional networks. This is in line with the dedifferentiation theory of aging that suggests that areas in the older brain may become less functionally distinct (Baltes and Lindenberger, 1997; Carp et al., 2011; Park et al., 2004). Moreover, it shows that dedifferentiation is not limited to brain areas but extends to functional networks as well (Geerligs et al., 2012a).

In four ICs, we found significantly different task dependent changes in centrality between older and

younger participants (i.e., right FPCN, TPJ, somatosensory, and precuneus IC). In the right FPCN, younger participants showed increased centrality during the 2-back task compared with resting state and the SA task. This is well in line with expectations, as the main constituents of the right FPCN, the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex, are often found to be active during working memory tasks (Cabeza et al., 2008; Owen et al., 2005). However, in the elderly, the centrality of the right FPCN was not increased during performance of the 2-back task compared with resting state. In addition, the centrality was significantly smaller in older than younger participants in the 2-back task. Previous studies have demonstrated that the connectivity from the right DLPFC was decreased in elderly especially under conditions of high working memory load. Nagel et al. (2011), for example, showed that in young but not older participants, connectivity between the left and the right DLPFC increased with increasing working memory load. Furthermore, Rieckmann et al. (2011) showed that functional connectivity from the right DLPFC to parietal areas and the occipito-temporal sulcus was reduced in older compared with younger participants during a working memory task. Implications of the reduced connectivity/centrality of the right FPCN in old relative to younger adults remains elusive at this moment. We, for example, did not observe a correlation between 2-back performance and SEC of this IC.

A second IC in which we observed task dependent changes of centrality between older and younger participants, was the TPJ. During the SA task, the centrality of the TPJ was increased in elderly compared with young participants. Whereas the dorsal parietal cortex is related to attentional top–down control, the TPJ plays an important role in the capture of bottom–up attention by an external stimulus (Cabeza et al., 2012; Corbetta and Shulman, 2002; Corbetta et al., 2008). Although older participants performed as accurate on this task as younger participants, we have shown in a previous study that older participants have trouble suppressing the information that is presented on the irrelevant spatial positions (Geerligs et al., 2012b). This is in line with a large body of research that has shown that elderly generally suffer more from distraction of irrelevant information than younger adults (see also: de Fockert et al., 2009; Gazzaley et al., 2005, 2008; Haring et al., 2013; Hasher and Zacks, 1988; Hasher et al., 1999; Mager et al., 2007). Wen et al. (2012) showed that increased connectivity directed from the ventral attention network (including the TPJ), to the DAN, was associated with slower and less accurate performance in a visual spatial attention task. The increased centrality of the TPJ during the SA task might be related to an increased likelihood of attentional capture by (irrelevant) external stimuli in the elderly. However, as no direct link to performance was observed, it is important that this interpretation is tested in future studies.

Whereas most visual and somatomotor ICs showed a decrease in centrality in task performance compared with resting state, elderly showed an increase in the centrality in the somatosensory IC with increasing task demand. In younger participants there was no effect of task on somatosensory IC centrality. Similarly, in the precuneus IC (part of the DMN), centrality did not change between tasks in young participants while older participants showed a higher centrality in the 2-back task than in the SA task or resting state. Previous research has shown that older adults often have trouble with the suppression of activity as well as connectivity within the DMN, which is related to decreased task performance (Grady et al., 2006; Persson et al., 2007; Sambataro et al., 2010). Although we can only speculate about the more specific implications of the current findings, they do show that with age, the functional networks that are recruited for task performance change.

In this study, we set out to study functional connectivity between networks and how the change in connectivity with changing task demands is affected by aging. It is important to note that the answer to this question heavily depends on the definition of networks. Here, we used ICA to identify different brain networks. The recommended approach to use the minimal description length (MDL) procedure to find a suitable number of components resulted in a large number (38) of components (Li et al., 2007). Decomposing the data into these 38 components resulted in a quite regional decomposition, in which areas that are generally regarded as one functional network (e.g., the DMN) were split into subcomponents. This is in line with previous literature that has shown that functional networks can be identified at different levels of hierarchy (Meunier et al., 2009, 2010). It would be important for future studies to investigate whether these results would be similar when different methods are used to define functional networks.

In conclusion, elderly are able to adapt FNC to task demands. However, the impetus for FNC change is different in young and elderly. Whereas young participants showed the maximal shift in FNC patterns between the less demanding SA task and the more demanding 2-back task, older participants showed the maximal connectivity shift between resting state and the SA task. The observed increases in FNC from rest to task were found to be limited to those ICs that are involved in central functions related to the demands of the task at hand, whereas FNC decreases in the other ICs. We argued that the age-related changes reflect the previously reported recruitment of additional resources in elderly.

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