Development of large-scale functional networks over the lifespan

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Abstract

The development of large-scale functional organization of the human brain across the lifespan is not well understood. Here we used magnetoencephalographic recordings of 53 adults (ages 18–89) to characterize functional brain networks in the resting state. Slow frequencies engage larger networks than higher frequencies and show different development over the lifespan. Networks in the delta (2–4 Hz) frequency range decrease, while networks in the beta/gamma frequency range (> 16 Hz) increase in size with advancing age. Results show that the right frontal lobe and the temporal areas in both hemispheres are important relay stations in the expanding high-frequency networks. Neuropsychological tests confirmed the tendency of cognitive decline with older age. The decrease in visual memory and visuoconstructive functions was strongly associated with the age-dependent enhancement of functional connectivity in both temporal lobes. Using functional network analysis this study elucidates important neuronal principles underlying age-related cognitive decline paving mental deterioration in senescence.

Keywords: Functional networks; Lifespan; MEG; Cognitive decline

1. Introduction

Healthy aging is the process of growing older in the absence of any clinically measurable pathological processes. Even in this favorable condition, aging is accompanied by lower performance of a large variety of cognitive measures. This age-related decline does not show a uniform pattern across all cognitive abilities and cognitive functions with a large knowledge component, such as verbal ability, decline noticeably later than cognitive functions that require perceptual speed or spatial orientation (Salthouse, 2009; Schaie et al., 2004). In very old age, however, a reliable decline can be detected for all cognitive abilities (Schaie et

al., 2004). Two hypotheses have been proposed to explain this age-dependent decline of cognitive function.

The “cortical noise” hypothesis is based on the fact that even in adulthood, the brain has the ability to change as a result of individual experiences by adding or removing functional connections between neurons (Elbert et al., 1995; Pascual-Leone et al., 1995; Recanzone et al., 1993; Rossi et al., 1998; Rossini et al., 2003; Tecchio et al., 2000; Trachtenberg et al., 2002; Xerri et al., 1999). Maturation, learning, and adaption to physical and environmental changes across the lifespan can trigger maladaptive, negative plasticity, which leads to dedifferentiation of the central nervous system and reduced cortical specialization of the neuronal cell assemblies (e.g., Baltes and Lindenberger, 1997; Mahncke et al., 2006). Accordingly, an increase of “cortical noise” may account for a decline in cognitive function.

The so-called “disconnection” hypothesis (Geschwind, 1965) proposes that the functional disruption of large-scale brain networks accounts for the cognitive decline across the

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lifespan. This view is strongly supported by studies reporting a linear decline of gray matter volume with advancing age (Bartzokis et al., 2001; Hutton et al., 2009) and the work by Sowell and colleagues (Sowell et al., 2003) showing a nonlinear decrease of gray matter density with increasing age. Studies investigating white matter alterations in the human brain also show a general decrease in older age (Head et al., 2004; Pfefferbaum et al., 2000, 2005; Sullivan et al., 2001). However, white matter volume seems to increase until the middle age of about 45 years and to decrease thereafter (Bartzokis et al., 2001; Sowell et al., 2003). Furthermore, functional integration between anterior and posterior brain regions declines with senescence as measured by functional magnetic resonance imaging (fMRI) signal correlation (Andrews-Hanna et al., 2007) while brain atrophy increases (Fjell et al., 2009).

Resting state recordings without any specific task are a useful tool to investigate the large-scale functional organization of the human brain and have been successfully used to analyze the default activity of the functional brain networks (e.g., Greicius et al., 2003; Raichle et al., 2001; Schlee et al., 2009a, 2009b; Tomasi et al., 2011; Vincent et al., 2008). While the brain is at rest without specific cognitive demands, the cortical activity is largely dominated by its intrinsic functional architecture that has been shaped across the lifespan (Albert et al., 2009; Lewis et al., 2009).

Using magnetoencephalography (MEG) this study investigates changes in large-scale functional brain networks of a large frequency range (here: 2–100 Hz) with increasing age. Based on these recordings we analyzed the functional connectivity between brain regions and reconstructed large-scale cortical networks during the resting state. Given the “disconnection” hypothesis, we would expect shrinkage of the functional networks across the lifespan. On the other hand, an increase of the functional networks could be an indicator for elevated intrinsic cortical noise.

2. Methods

2.1. Subjects

A total number of 53 participants ranging in age from 18 to 89 years (mean, 53.1 years, SD, 20.1 years) took part in this study. They were all right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). The ethics committee of the University of Konstanz approved this study. Participants gave written informed consent prior to the assessments and measurements. They received 30 euros for their participation. The participants were recruited via flyers posted at the University of Konstanz, in several residential homes for older adults, the local newspaper, and the local radio station. Exclusion criteria were dementia or probable dementia according to DSM-IV-TR (APA, 2000), current psychiatric disorders, current psychopharmacological medication, left-handedness, metal objects in the body,

as well as a history of severe head injuries or neurological problems.

2.2. Data acquisition

2.2.1. Magnetoencephalographic recording

Neuromagnetic data were recorded with a 148-channel whole-head magnetometer system (MAGNES TM 2500 WH, 4D Neuroimaging, San Diego, CA, USA) while participants lay in a comfortable supine position. The MEG system is installed in a magnetically shielded and quiet room (Vacuumschmelze, Hanau, Germany). The continuous data were recorded with a hard-wired high-pass filter of 0.1 Hz with a sampling rate of 678.17 Hz. The recording duration was set to 5 minutes and the subjects were asked to relax during this time, to stay awake with eyes open and not to engage in deliberate mental activity. Furthermore, they were instructed to fixate on a point on the ceiling of the measuring chamber and to avoid eye movements as well as any body movements.

2.2.2. Neuropsychological assessment

Prior to the MEG recordings, all participants were screened for potential psychiatric disorders using the Mini International Neuropsychiatric Interview (MINI; Ackenheil et al., 1998). Cognitive performance was assessed using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)-NP-plus neuropsychological test battery (Morris et al., 1988), with the subtests verbal fluency (total score of the number of freely generated words of the category “animals” and the number of freely generated words starting with “s” within 1 minute each), word list learning (single trial range, 0–10; total range, 0–30 words), word list delayed recall (range, 0–10 words), word list recognition (range, 0–20 true positives), figure recall (range, 0–14 points), Trail Making Test A (TMT-A; range, 0–180 seconds) and B (TMT-B; range, 0–300 seconds). In addition, the digit symbol substitution test (range, 0–93 correct substitutions within 90 seconds), the mosaic test (range, 0–51 raw points), and the digit span subtests (total range, 0–28 points) of the German version of the Wechsler Adult Intelligence Scale (HAWIE; Tewes, 1991) as well as the revised Benton Visual Retention Test (range for the correct answers, 0–30; Steck, 2005) were conducted. The test scores were used to investigate the behavioral relevance of the changes in the functional network size. Table 1 gives the raw scores (mean, standard deviation, and range) of all neuropsychological tests.

2.3. Data analysis

Data preprocessing and the projection of the signals in the source space were done using the fieldtrip toolbox (FC Donders Centre for Cognitive Neuroimaging; www.ru.nl/fcdonders/fieldtrip) run in a Matlab environment (www.mathworks.com). For the calculation and modeling we closely followed an established procedure described in Schlee et al. (Schlee et al., 2009b). First, all data sets were

Table 1
Raw scores for the neuropsychological test material

Test	Mean	SD	Range
Verbal fluency	52.2	14.2	12–80
Word list learning	23.2	4.1	12–30
Word list recall	8.3	2.1	0–10
World list recognition	19.7	0.7	17–20
Figure recall	11.5	2.6	4–14
Trail making test A	36.9	15.7	19–89
Trail making test B	86.8	50.8	35–270
Digit symbol test	52.2	14.2	21–80
Mosaic test	32.4	10.4	8–50
Digit span test	14.9	3.9	9–23
Benton test	12.4	4.5	4–20

Mean, standard deviation and range are given for all neuropsychological tests conducted.

down-sampled to 600 Hz and cut into epochs of 2 seconds. Epochs containing blinks or muscle artifacts were excluded from further analysis based on visual inspection. Next, an independent component analysis (ICA) was calculated for each individual data set to identify and reject the components that reflect the heart beat (“fastica” algorithm, implemented in eeglab; scn.ucsd.edu/eeglab/). After artifact correction, 90 trials (i.e., 180 seconds in total) were selected randomly from the remaining trials and used for the following analyses. This selection was done to keep the number of trials constant across all subjects. The number of 90 trials reflects a trade-off between cleaning the data from noisy events as much as possible and still having enough data to calculate the autoregressive model.

2.4. Source projection

To project the sensor data into source space, we used a linearly constrained minimum variance (LCMV; Van Veen et al., 1997) beamformer on each individual data set. The LCMV beamformer uses the covariance matrix of the signal data to construct a spatial filter that passes the signals for each time point to a predefined source while minimizing the contribution of other sources. The spatial filters were multiplied with the sensor time series, to derive the single-trial activities. The orientations were rotated such for each trial, that the first orientation accounted for a maximum of the signal. The orientations were then averaged across trials and applied to the single trials. The subsequent analysis steps were performed on the first orientation. A grid of 326 voxels ($2 \times 2 \times 2$ cm) that covered approximately the entire brain volume was used for the beamformer. Even though other beamforming techniques exist that are optimized for the detection of correlated sources (e.g., Diwakar et al., 2011) we decided to use the LCMV beamformer for this study because we were interested in the reconstruction of large-scale functional brain networks in source space rather than on 2 correlated sources.

As suggested by Brookes and colleagues (Brookes et al., 2008) we used a broad frequency band of 1–100 Hz for the beamforming technique in order to minimize distortions of

the source reconstruction, time course, and estimation of the signal strength.

2.5. Partial directed coherence

For each subject, we computed partial-directed coherence (PDC) for the full set of voxels modeling the voxel-by-voxel influence in the frequency range of 2 to 100 Hz in increments of 2 Hz (Baccalá and Sameshima, 2001; Sameshima and Baccalá, 2000). This approach is based on multivariate autoregressive (MVAR) modeling that integrates temporal and spatial information. Here, we model for each voxel the influence by all other voxels for a given time range. The model order p defines this time range of the autoregressive process and describes how many time points—back in time—are used for the modeling the current value. This can be written as

$$y(t) = a_1 \cdot y_{t-1} + a_2 \cdot y_{t-2} + \dots + a_p \cdot y_{t-p} + x_t \quad (1)$$

where $Y(t)$ denotes the predicted value at time t as a vector with 1 entry for each voxel, $A(i)$ denotes a square matrix of regression coefficients and $X(t)$ is called the “innovation process” which equals the difference between the actual value at time t and the estimation of $Y(t)$ based on the linear combination of the previous time points (Schlögl, 2006). In order to find the optimal model parameter p we calculated the Schwarz Bayesian Criterion (SBC; Schneider and Neumaier, 2001) for model orders from 2 to 20. On average, over the whole sample, the minimum of the Schwarz Bayesian Criterion function was located at $p = 3$ which was then taken as the model order for all subjects. For estimation of the autoregressive parameters we used the Vieira-Morf algorithm (Marple, 1987) implemented in the BioSig toolbox (www.biosig.sf.net, Version 2.12), which has been found to provide the most accurate estimates (Schlögl, 2006). The matrix of autoregressive coefficients in the multivariate case can be written as

$$\begin{bmatrix} y_1(t) \\ y_2(t) \\ \vdots \\ y_J(t) \end{bmatrix} = \sum_{k=1}^p \begin{bmatrix} a_{1,1}(k) & a_{1,2}(k) & \dots & a_{1,J}(k) \\ a_{2,1}(k) & a_{2,2}(k) & \dots & a_{2,J}(k) \\ \vdots & \vdots & \dots & \vdots \\ a_{I,1}(k) & a_{I,2}(k) & \dots & a_{I,J}(k) \end{bmatrix} \begin{bmatrix} y_1(t-k) \\ y_2(t-k) \\ \vdots \\ y_J(t-k) \end{bmatrix} + \begin{bmatrix} x_1(t) \\ x_2(t) \\ \vdots \\ x_J(t) \end{bmatrix} \quad (2)$$

where the coefficients a_{ij} represent the linear interaction between voxel i onto voxel j for a given time lag r .

Partial Directed Coherence is a statistical measure that is related to the concept of Granger Causality (Granger, 1969) and is able to detect asymmetric coupling between the compared voxels for a given frequency range. In order to reveal the spectral properties, the autoregressive coefficients are transformed into the frequency domain by

$$\bar{A}(f) = I - \sum_{k=1}^p A(k)e^{-2\pi k(f/f_s)} \quad (3)$$

with the transfer function $\bar{A}(f) = I - A(f)$, and $\bar{a}_{ij}(f)$ being the i, j -th element of the relative coupling strength from voxel j to voxel i at a given frequency f can be written by

$$\pi_{ij}(f) = \frac{\bar{a}_{ij}(f)}{\sqrt{\bar{a}_j^H(f)\bar{a}_j(f)}} \quad (4)$$

The superscript H denotes the Hermitean transpose, which is found by taking the complex conjugate of each entry of the standard matrix transpose. Thus, the PDC value $\pi_{ii}(f)$ indicates how much the activity of voxel i depends on its own past at a given frequency. The value $\pi_{ij}(f)$ denotes how much the frequency specific activity of voxel j depends on voxel i . The PDC estimators were calculated using functions implemented in the BioSig toolbox (www.biosig.sf.net, Version 2.12).

To the best of our knowledge, there is no established way of calculating the statistical significance of the PDC estimators. Thus, we used a permutation approach to estimate thresholds for significant coupling between pairs of voxels (couplings of 1 voxel with itself were excluded from the analysis). Therefore, the following steps (1–3) were repeated 1000 times:

- (1) Shuffle the matrix A of the autoregressive coefficients pseudorandomly. This was done the following way: the matrix A is a square matrix with 326 rows and 326 columns. First, we generated a vector with random numbers between 1 and 326. Second, the columns were shuffled according to the random vector. Third, the rows were shuffled according the same random vector.
- (2) Calculate the PDC estimators as described above.
- (3) Determine the 99%-percentile of the PDC estimator for each frequency and save it. The 99%-percentile was used instead of the maximum to reduce the influence of outliers that might result from the permutation.

The maxima over the 1000 permutations were used as a threshold of significance for each frequency bin. Thresholds were calculated for each participant individually and used to create a binary adjacency matrix for each frequency bin representing the voxel-by-voxel connectivity.

2.6. Size of the functional network

PDC is an asymmetric measure capturing the direction of the information between a full set of voxels. We here concentrated on the size of the functional networks as an indi-

rect measure of the disconnected areas in the brain. First, we calculated the shortest path length from voxel i to j for the full set of voxels. This was done for each frequency bin using functions implemented in the Graph Theory Toolbox (iglin.exponenta.ru). Using the matrix of the shortest path lengths, we were able to investigate the functional network and select those voxels that are not connected to this network in either direction (i.e., not receiving and not sending information). The number of voxels incorporated in the large-scale functional network was counted and used as an operationalization of the network size.

2.7. Statistical analysis

Statistical analysis including the mixed models analysis of variance and correlational analysis was done using the R statistical software package (www.r-project.org, Version 2.7.2). Correction for multiple comparisons was based on Holm's stepwise correction (Holm, 1979).

All relationships between age and the neuropsychological test results or the functional network size were calculated with linear and nonlinear regression models in R and the residual sum of squares of the linear and nonlinear model were compared (analysis of variance). Nonlinear models are reported whenever they improve the statistical regression model significantly (threshold of $\alpha = 0.05$).

3. Results

3.1. Behavioral results

A significant linear decline of cognitive function with advancing age was found for the correct answers in the Benton test ($r = -0.64$; $p < 0.0001$), CERAD word list learning ($r = -0.50$; $p = .0001$), the digit symbol test ($r = -0.67$; $p < .0001$), CERAD word list recall ($r = -0.44$; $p = .001$), the mosaic test ($r = -0.62$; $p < .0001$), the time needed for the TMT-A ($r = 0.51$; $p < .0001$), CERAD figure recall ($r = -0.52$; $p < .0001$), and the time for TMT-B ($r = 0.55$; $p < .0001$). Only the correlations that survived Holm's stepwise correction for multiple comparisons are reported (Fig. 1).

There was no significant correlation between the years of education and the age of the participants ($p = 0.26$; $r = -0.16$) suggesting that the observed results are not driven by participant's education.

3.2. Functional network analysis

For the analysis of the age-dependent changes in the functional networks, we focused on the relative size of the functional networks. Thus, a relative network size of, e.g., 80 would indicate that 80% of all voxels are functionally connected into 1 giant network, while 20% of the voxels are disconnected from it. In general, we found larger network sizes for lower frequencies than for higher frequencies (Fig. 2a). A mixed model analysis of variance (ANOVA) was calculated with the factors frequency and age and a random

intercept per participant. There was a significant interaction of frequency $\times$ age $F(209,539) = 1.62$; $p < 0.0001$ as well as a main effect of frequency with $F(48,539) = 1263.82$; $p < 0.0001$.

To further investigate the frequency $\times$ age interaction, we correlated the relative network size for each frequency bin with the participant's age. The correlation coefficients (Pearson product moment correlations) between age and network size are plotted in Fig. 2b. The frequency bins 2–4 Hz, 16–76, and 84 Hz survived Holm's stepwise correction for multiple comparisons (correction for 50 different frequency bins, frequency range from 2 to 100 Hz in steps of

2 Hz; Fig. 2b). In the low frequency range of 2–4 Hz, the size of the functional network correlated negatively with age. The frequencies of 2 and 4 Hz were collapsed and correlated with age (Fig. 3a). There was a negative correlation of $r = -0.49$; $p = 0.0002$, between the network size and the biological age of the subjects. In the higher frequency range, the frequency bins 16–76, and 84 Hz were positively associated with increasing age. These frequencies were collapsed for the following analysis. In this analysis, the Akaike Information Criterion (AIC) for the nonlinear model was 5 points lower than for the linear model and comparing both models by an analysis of variance, the

Fig. 1. Neuropsychological test results that are significantly correlated with the age of the participant. Correlations with age and the correct scores in Benton Test ($r = -0.64$; $p < 0.0001$), Word List Learning ($r = -0.50$; $p = 0.0001$), the Digit Symbol Test ($r = -0.67$; $p < 0.0001$), Word List Recall ($r = -0.44$; $p = 0.001$), the Mosaic test ($r = -0.62$; $p < 0.0001$), the time to accomplish Trail Making Test A ($r = 0.51$; $p < 0.0001$), Figure Recall ($r = -0.52$; $p < 0.0001$), and the time for Trail Making Test B ($r = 0.55$; $p < 0.0001$).

Fig. 2. (a) The average size of the network across all subjects for the frequency range 2–100 Hz. In general, the network size of higher frequencies is smaller in extent than the network size of lower frequencies. The mean of all participants is drawn in solid lines. To show the interaction between age and frequency, the network size at the 25% and 75% age-quantile is shown in dashed and dot-dashed lines, respectively. (b) The correlation between age and the network size is plotted across frequencies. Significant frequencies that survived Holm's stepwise correction are shaded in gray. Low frequencies (2–4 Hz) correlate negatively, high frequencies (16–76, and 84 Hz) positively with age.

nonlinear model described the data significantly better ($F(50,51) = 6.96$; $p = .01$) with: network size = $87.28 / (1 + e^{-26.98 + 16.89 \cdot \text{age}})$. Changes of network size in the low-frequency range were not correlated with changes in the high-frequency range ($r = 0.01$; $p > 0.9$).

We further examined which brain regions are the most influential for the age-related network changes reported above. A voxel-wise comparison of high-frequency functional connectivity revealed 3 clusters of significant network size increase. They were located in the right frontal region, as well as in the left and the right temporal lobe in older age (Fig. 4). Only small changes were found for the low frequency range (see Supplementary data, Fig. 1).

3.3. Correlation between functional connectivity and cognitive abilities

We calculated Pearson correlations between the functional connectivity of the significant clusters in Fig. 4 (right frontal, left, and the right temporal) and cognitive ability as assessed by our neuropsychological test battery. Functional connectivity from the right temporal region was significantly

correlated with the performance in the Benton test ($r = -0.42$; $p = 0.0017$), CERAD figure recall ($r = -0.51$; $p < 0.0001$), the digit symbol test ($r = -0.51$; $p < 0.0001$), and the mosaic test ($r = -0.44$; $p = 0.0009$). Functional connectivity from the left temporal region was significantly correlated with the performance in the Benton test ($r = -0.42$; $p = 0.002$), CERAD figure recall ($r = -0.43$; $p = 0.001$). All correlations were negative, indicating that cognitive capacities decline with increase in functional connectivity of these regions (see also Table 2 and the scatterplots in the Supplemental data). There were no significant correlations of cognitive abilities with functional connectivity in the right frontal region. All tests were corrected for multiple comparisons.

4. Discussion

To our knowledge, this is the first MEG study to investigate the development of resting state functional brain networks across the lifespan and its relationship to cognitive abilities, which may have important implications for the

Fig. 3. Association of age with the network size for (a) low (2–4 Hz) and (b) high frequencies (16–76, and 84 Hz). (a) The size of the functional network in the low frequency range (2–4 Hz) reveals a negative linear relationship with age ($r = -0.49$; $p = 0.0002$). (b) The relationship between the functional network size for high frequencies and age is best described by a nonlinear regression model with an asymptote of 87.28 and an exponential growth rate of age (exponent $[16.89 \times \text{age}]$).

Fig. 4. Regions that significantly contribute to the increase in high-frequency network size. Functional connectivity of older participants was compared with younger ones. T values are corrected for multiple comparisons. The left temporal lobe, the right temporal lobe, and right frontal regions appear to strongly drive the age-related changes in functional connectivity.

understanding of both normal and pathological brain development. As expected, we found an age-dependent decline in a broad spectrum of cognitive functions. The above results indicate that the development of cortical networks with advancing age is characterized by a decrease of network size in the low frequency range (2–4 Hz) together with an increase in the beta and gamma frequencies above 16 Hz. The increase in the high frequency network might largely be driven by a strengthening of functional connectivity from the left and right temporal lobes and the right frontal region. Increases in the temporal lobes' connectivity were significantly correlated with a decrease in cognitive functioning, in particular with visual-spatial perception and visual-spatial memory (Benton test), with constructive praxis memory (CERAD figure copy) and in the left temporal lobe also with psychomotor speed, concentration (digit-symbol test) and problem solving capability (mosaic test). This study reveals

new insights into the development of cortical networks in normal aging and its behavioral relevance. Two distinct mechanisms for the low and high frequency range need to be distinguished.

The developmental changes of cortical networks were characterized by the size of the large-scale functional brain networks. A general increase of functional connectivity and inclusion of distant brain regions into the network results in an increase of the network size. Disconnection of brain regions, on the other hand, can be measured by a decrease of network size. Using magnetoencephalography we were able to measure cortical connectivity in a broad frequency range of 2–100 Hz. For the lower frequencies below 4 Hz we found evidence for a reduction of functional network size across the lifespan. This result fits well into the “disconnection hypothesis” (Geschwind, 1965) and is consistent with other results demonstrating a disruption of large-scale brain systems as measured by low-frequency fMRI correlations (Andrews-Hanna et al., 2007; Bai et al., 2008; Greicius et al., 2004; Rombouts et al., 2005; Sorg et al., 2007). For the 2–4 Hz frequency range, our results suggest a continuous change of functional connectivity across adulthood between 18 and 89 years rather than a rapid drop in older age. Several factors may account for this age-dependent adaptation of connectivity. The well-documented age-dependent decline of white matter tracts (Head et al., 2004; Pfefferbaum et al., 2000, 2005; Sullivan et al., 2001) can be a good explanation for the changes in functional connectivity reported here. Stereological investigations showing a

Table 2
Correlation between functional connectivity and behavioral test performance

Cluster	Neuropsychological test	Correlation coefficient	p Value
Right temporal lobe	Benton test	−0.42	0.0017
Right temporal lobe	Figure recall	−0.51	< 0.0001
Right temporal lobe	Digit symbol test	−0.51	0.0001
Right temporal lobe	Mosaic test	−0.44	0.0009
Left temporal lobe	Benton test	−0.43	0.002
Left temporal lobe	Figure recall	−0.43	0.001

progression of white matter demyelination in normal aging (Tang et al., 1997) lend further credibility to this interpretation. However, Bartzokis and colleagues (Bartzokis et al., 2001) reported a rather nonlinear development of white matter volume over the life span with the peak around the age of 45 years. Concerning the gray matter, at the other side, morphometric investigations have consistently demonstrated an age-associated decline over the lifespan (Bartzokis et al., 2001; Hutton et al., 2009; Sowell et al., 2003). The interaction between the gray and the white matter degeneration is currently unclear and further research is needed to decipher the interplay between the functional network changes on the 1 side and structural changes of gray and white matter on the other side.

Functional networks of higher frequencies above 16 Hz were in general of smaller size than the low-frequency networks. Here we want to highlight that the functional networks were analyzed over a recording time of 3 minutes. Within this time frame, the 2–4 Hz networks comprised around 97% of the observed voxels, while the networks in the beta and gamma frequency range connected only 80%–90% of the voxels (compare Fig. 2a). Within these smaller boundaries, the higher frequency networks increased significantly with advancing age. Additional analysis showed that this interhemispheric network growth is largely driven by an increased connectivity of the right frontal region and both temporal lobes. The augmented connectivity of the temporal clusters—but not of the right frontal lobe—was associated with reduced performance in neuropsychological tests on visuoconstructive function and visual memory. With Fig. 5 we provide a graphical illustration of this interaction between age, cognitive function measured with the Benton test, and functional connectivity of the temporal lobes. Several interpretations can be found for this increased long-range connectivity in older age. First, an age-dependent decrease of intracortical inhibition may account for the enhanced long-range connectivity in older age. Animal studies on gamma aminobutyric acid (GABA), which is the

most important inhibitory neurotransmitter of the brain, have consistently shown an age-related decrease of GABA effectiveness in the auditory pathways (Casparly et al., 1995, 1999; Ling et al., 2005; Walton et al., 1998, 2002). Similar findings exist for the visual system which also show a decrease of GABA functioning (Liang et al., 2010; Yang et al., 2008). Intracortical inhibition in humans has been studied with short-interval paired-pulse protocols over the motor cortex where the first stimulus is given on subthreshold level and suppresses the motor evoked potential following the second stimulus which is given on a suprathreshold level. Peinemann and colleagues (Peinemann et al., 2001) reported a decrease of the intracortical paired-pulse inhibition with older age. Generalizing these effects of the sensory and motor areas on a cortical-wide level, cortical functions of the aging brain might be characterized by a reduction of neuronal inhibition in sensory areas. This may lead to enhanced neuronal excitability therein and favors the build-up of long-range connectivity between these brain areas, finally leading to a dedifferentiation of specialized cortical networks. Second, it has been proposed that the consequences of negative learning and maladaptive plasticity might further add to the dedifferentiation of cortical networks (Baltes and Lindenberger, 1997; Mahncke et al., 2006). Neuroplastic changes as a result of altered sensory input has been frequently documented in the recent years (Elbert et al., 1995; Pascual-Leone et al., 1995; Recanzone et al., 1993; Rossi et al., 1998; Rossini et al., 2003; Tecchio et al., 2000; Trachtenberg et al., 2002; Xerri et al., 1999). For instance, animal studies have shown that heavy synchronous stimulation of the entire hand leads to plastic reorganization of somatosensory cortex resulting in an undifferentiated representation map with abnormally large and overlapping receptive fields (Allard et al., 1991; Jenkins et al., 1990). Similarly, professional string players with many hours of daily practice are found to have increased cortical representation of the fingers in their left hands (Elbert et al., 1995). The same adaptive mechanisms might take place in the

Fig. 5. Graphical illustration of the association between biological age, temporal lobe connectivity, and performance of the Benton test. The y-axis shows mean partial-directed coherence (PDC) values for the left and right temporal lobe connectivity. Advancing age leads to stronger connectivity of the temporal lobes. Benton Test Performance decreases with advancing age and stronger temporal lobe connectivity.

aging brain by the age-dependent degeneration of the sensory systems: for example, the well-documented degradation of hearing in older age (Cruickshanks et al., 1998) reduces the auditory acuity and frequency tuning, which serves as a complement to the synchronous stimulation in the above-mentioned study. This can lead to an enlargement and overlay of neuronal cell assemblies (NCA) within the sensory cortices. Given the increased long-range functional connectivity in adulthood (Supekar et al., 2009), this NCA enlargement from the sensory areas will be passed on to the cortical-wide network architecture causing dedifferentiation of the NCAs and increasing functional networks. Furthermore, the recruitment of additional brain areas and the functional connectivity among them might also represent a compensatory mechanism that helps to balance the cognitive decline in older age (Cabeza et al., 2002; Rossi et al., 2004) and is, thereby, also a marker for reduced cortical specialization.

Effective cognitive function depends on functional inhibition of task-irrelevant brain regions and the processing in specialized brain areas. Sensory information that is irrelevant to the task needs to be suppressed in order to allow routing of relevant information between specialized brain regions. A decrease of functional inhibition as well as the loss of cortical specialization leads to dedifferentiated information processing and thus to less efficient functioning of cortical networks. On a behavioral level, this failed suppression of irrelevant neuronal activity is probably best described as enhanced distractibility of the participant. Increased distractibility in older age has indeed been demonstrated (Healey et al., 2008) and gives a straightforward explanation for the age-related decline of cognitive function.

Increasing evidence suggests that the neuronal interaction between hippocampus and neocortex also plays an important role in memory formation (Jutras et al., 2009; Sirota et al., 2003) and memory functions degrade after damage to the hippocampus (Manns et al., 2003; Zola et al., 2000). Interestingly, we found that the left and right temporal lobes turn out to be the driving forces for the high-frequency overconnectivity in older age, which is directly related to cognitive decline. Given that this overconnectivity of the temporal voxels is at least partly driven by connectivity of the hippocampal or parahippocampal area, it can be speculated that learning processes and memory formation over the lifespan constantly add new connections to the functional network leading to this rich connectivity of the left and right temporal lobes. Add a certain point, this rich connectivity becomes dysfunctional which is expressed in reduced cognitive function. This speculation, however, is very radical and needs much more critical evaluation in future research projects.

A direct link between the increased network size in beta and gamma frequencies in older age and the cognitive decline, however, cannot be established here and is limited

by the fact that the MEG recordings were done in resting state without any sensory or cognitive stimulation while the neuropsychological assessment was performed outside the scanner. Further research is needed to investigate the functional relevance of the observed changes in long-range connectivity. Even though we found strong correlations between the network changes over the life span and the performance in the neuropsychological tests, further studies are needed to discriminate those changes of clinical relevance from those with no impact on daily functioning in old age. The resting state recordings, however, give us a measure of the brain's baseline activity of functional networks, which is shaped continually by lifelong experience and memory formation (Albert et al., 2009; Lewis et al., 2009). These data suggest an important link between actual cognitive performance and the lifelong development of functional brain networks triggered by biological changes and memory formation as discussed above.

Disclosure statement

The authors disclose no conflicts of interest.

The ethics committee of the University of Konstanz approved this study. Participants gave written informed consent prior to the assessments and measurements.

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