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Functional network reorganization in older adults: Graph-theoretical analyses of age, cognition and sex

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ABSTRACT

Healthy aging has been associated with a decrease in functional network specialization. Importantly, variability of alterations of functional connectivity is especially high across older adults. Whole-brain functional network reorganization, though, and its impact on cognitive performance within particularly the older generation is still a matter of debate. We assessed resting state functional connectivity (RSFC) in 772 older adults (55–85 years, 421 males) using a graph-theoretical approach. Results show overall age-related increases of *between*- and decreases of *within*-network RSFC. With similar phenomena observed in young to middle-aged adults, i.e. that RSFC reorganizes towards more pronounced functional network integration, the current results amend such evidence for the old age. The results furthermore indicate that RSFC reorganization in older adults particularly pertain to early sensory networks (e.g. visual and sensorimotor network). Importantly, RSFC differences of these early sensory networks were found to be a relevant mediator in terms of the age-related cognitive performance differences. Further, we found systematic sex-related network differences with females showing patterns of more segregation (i.e. default mode and ventral attention network) and males showing a higher integrated network system (particularly for the sensorimotor network). These findings underpin the notion of sex-related connectivity differences, possibly facilitating sex-related behavioral functioning.

1. Introduction

Aging is accompanied by a progressive decrease of cognitive abilities, which is variable among individuals and cognitive domains, especially during later decades of life (Grady, 2012; Hedden and Gabrieli, 2004; Salthouse, 2004). Sources of heterogeneity are not fully understood, but seem to be associated with multiple neurobiological substrates (Raz et al., 2005; Whalley et al., 2004). This includes, for example, the architecture of distinct functional networks of the brain. A functional network comprises a set of brain regions exhibiting highly correlated functional BOLD activations accessible via independent component analysis (ICA, Beckmann et al., 2005) and clustering approaches (e.g. Power et al., 2011; Yeo et al., 2011). Regions belonging to the same network share co-varying functional activity patterns and therefore exhibit strong *within*- and less *between*-network resting state functional connectivity (RSFC).

Since functional connectivity among networks plays a major role with respect to cognitive outcomes (Marques et al., 2016; Sadaghiani et al., 2015; Sporns, 2013; Wig, 2017), it has become an important research topic, especially in the field of aging research with cognitive functions declining with different rates. Functional network organization in young subjects is considered as a stable and balanced relation of *within*- and *between*-network RSFC (Bullmore and Sporns, 2012; Sadaghiani et al., 2015; Sporns, 2013; Wig, 2017). In contrast, the adult lifespan was shown to be accompanied by changes of RSFC *within* and *between* brain networks (see Damoiseaux, 2017; Ferreira and Bussato, 2013;

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Sala-Llonch et al., 2015; Wig, 2017; Zuo et al., 2017 for review). Specifically, the segregated, functionally specialized organization of brain networks dissolves, resulting in decreases of *within*- and increases of *between*-network RSFC (Betzel et al., 2014; Cao et al., 2014; Chan et al., 2014; Ferreira et al., 2016; Mowinckel et al., 2012; Tsvetanov et al., 2016; Varangis et al., 2019). Group comparisons between old vs. young subjects revealed similar results, especially in networks involved in higher order cognitive functions such as the default mode, frontoparietal and dorsal attention network (Andrews-Hanna et al., 2007; Geerligs et al., 2015; Goldstone et al., 2016; Grady et al., 2016; Nashiro et al., 2017; Song et al., 2014; Spreng et al., 2016). So, whereas the RSFC within these networks seems to decrease across adulthood, RSFC between networks increases, leading to the question of possible causes and potential behavioral impact.

It has been shown that more segregated functional networks are associated with better cognitive performance (see e.g. Wig, 2017 for review) as well as a higher education level in older adults (Marques et al., 2016). At the same time, the effect of age-related RSFC changes towards more pronounced *between*-network RSFC is ambiguously interpreted. On the one hand, dedifferentiation of brain networks is considered as impaired recruiting of specialized neural mechanisms resulting in performance decline (Chan et al., 2014; Colcombe et al., 2005; Goh, 2011; Nashiro et al., 2017; Park et al., 2004). On the other hand, it is understood as a compensational response, in which additional activation counteracts the age-related decline of brain function in order to maintain successful performance (Cabeza et al., 2002; Heunincks et al., 2008; Reuter-Lorenz and Cappell, 2008; Roberts and Allen, 2016).

The majority of previous research investigated RSFC over the whole adult lifespan or performed comparisons between younger and older adult age-groups. However, especially in the older age group, in which cognitive decline is in progress (Singh-Manoux et al., 2012), evidence of how functional brain networks reorganize and how this might impact cognitive performance in the older subjects is far from being conclusive. A very recent study assessed network-based RSFC differences a in a large cohort of older adults (Zonneveld et al., 2019) and found the age-related shift towards higher network integration, which was found in lifespan studies, to persist also in older subjects. It remained open, though, how this would be associated with cognitive performance. Perry et al. (2017) used a multivariate approach to investigate single connectivity estimates between regions spanning the whole brain in 101 older adults (70–90 years) and found particularly RSFC between regions of primary processing networks to be associated with cognitive performance. Further studies, also focusing on the older age-group and assessing the association between network-level RSFC and behavioral performance in older adults are partly contradictory. For example, in a longitudinal approach, Ng et al. (2016) found an age-related decline of *within*-network RSFC in the default mode as well as in the executive control network without any association of *within*-network RSFC and cognitive performance, but instead a negative correlation between *between*-network RSFC of the default mode network and processing speed. Contrarily, Persson et al. (2014) found intra-individual RSFC within the default mode network to remain stable across a period of six years within a group with comparable age range. In the same study, they found *within*-network RSFC changes of the default mode network to be positively correlated with memory performance, though, hinting at a relevance for cognition beyond age effects. In contrast, in a cross-sectional design, Sala-Llonch et al. (2014) found a high regional clustering coefficient of the default mode network to be associated with worse cognitive performance in verbal and visual memory tasks, pointing at an overall negative correlation between cognitive performance and *within*-network RSFC. Thus, especially at old age discrepant evidence exists regarding RSFC differences and its impact on cognitive performance.

A further issue pertains to the assumed differences in functional connectivity patterns between males and females (Allen et al., 2011; Joel et al., 2015; Satterthwaite et al., 2014; Tomasi and Volkow, 2012b; Zonneveld et al., 2019), particularly when it comes to age-related reorganization (Goldstone et al., 2016; Scheinost et al., 2015). Sex-related differences in RSFC e.g. manifest as females showing higher local connectivity density (Tomasi and Volkow, 2012b), or as higher *within*-network RSFC in females and higher *between*-network RSFC in males (Satterthwaite et al., 2014). Across the lifespan, these differences were found to persist also at older age. Females, e.g., not only exhibited overall higher *within*-network RSFC (Allen et al., 2011), but also showed less age-related decreases of RSFC in the default mode and limbic network (Scheinost et al., 2015). In line with this, Goldstone et al. (2016) assumed the age-related functional network reorganization to be different in males and females, with males showing increasing *between*-network connectivity and simultaneously decreasing *within*-network connectivity as compared to females. Contrarily, a recent cohort study in older adults found overall higher *within*-network RSFC in males (Zonneveld et al., 2019).

Collectively, previous research on particularly older adults hint at the persistence of age-related functional network reorganizations also in older age ranges (Zonneveld et al., 2019). So far, cognitive performance has been related to RSFC of specific networks (Ng et al., 2016; Persson et al., 2014) as well as to specific connections between regions (Perry et al., 2017), or by use of clustering coefficients (Sala-Llonch et al., 2014) showing partly contradictory findings. It remained open, though, how whole-brain RSFC across established brain networks in older adults are related to cognitive performance. It shall be noted, that except for the recent large cohort study in older subjects by Zonneveld et al. (2019), most studies used smaller groups of subjects. Given the considerable amount of interindividual variability in that age group, the question of functional network reorganization in older adults in relation to sex differences and cognitive performance requires large numbers of older subjects to adequately represent the normal variability, as available in large population-based cohorts (Bamberg et al., 2015; Ikram et al., 2015; Miller et al., 2016; van Essen et al., 2012; Völzke et al., 2010). Based on the approaches used in the aforementioned studies, the current study aims at systemically assessing the functional network architecture of the older adult brain with respect to age, sex and particularly cognitive performance across several domains by using a large samples size, a whole-brain approach and additionally addressing associations with neuropsychological performance.

Specifically, we took advantage of a very large population-based sample of older adults of the 1000BRAINS study (Caspers et al., 2014) to disentangle the interplay of *within*- and *between*-networkRSFC differences within whole-brain functionally defined networks using a graph--theoretical approach established for studying whole-brain RSFC differences (Biswal et al., 2010; Bullmore and Sporns, 2009; Bullmore and Sporns, 2012; Rubinov and Sporns, 2010). The aim was to evaluate its impact on cognitive performance in relation to the subjects' education level and to the specifics of network reorganization in males and females. In line with previous research we expected to find overall *within*-network decreases and *between*-network increases of RSFC. Given the non-conclusive evidence on cognition, we tentatively hypothesized lower *within*-network RSFC to be associated with worse cognitive performance. Additional exploratory analyses on this relation will be carried out to allow for a holistic perspective. The latter approach was also favored for the analyses on sex differences, as evidence on those in older subjects was even less conclusive.

2. Materials and methods

2.1. Subjects

The sample of the current study was based on the 1000BRAINS project (Caspers et al., 2014). 1000BRAINS is a population-based study designed to investigate the variability of brain structure, function, and connectivity during aging, and its relation to behavioral, environmental and genetic factors. Participants for 1000BRAINS were drawn from the 10-year follow-up cohort of the Heinz Nixdorf Recall Study, an

epidemiological population-based study for investigating risk factors for atherosclerosis, cardiovascular disease, cardiac infarction, and cardiac death (Schmermund et al., 2002). Since 1000BRAINS aims at characterizing aging at the level of the general population, no exclusion criteria other than eligibility for MR measurements (see Caspers et al., 2014) were applied. At the time of beginning of the present study, the sample of 1000BRAINS comprised 951 older adults (aged 55–85 years) of one measurement time point, as relevant for the current cross-sectional study design. Of these 951 participants, 179 were excluded due to the following reasons: Participants with more than 3 missing values of the neuropsychological assessment (n = 46; see 2.3 for further description), as well as preprocessing failure of structural and/or functional imaging data (n = 101; e.g. artifacts in structural scans, problems during normalization procedure, or AROMA-denoising) were excluded. Additional 21 subjects did not pass a dedicated quality control of the preprocessed functional data checking for potential misalignments and severe intensity drop-outs (n = 21, see 2.2 for description). Lastly, 11 participants with indication for potential cognitive impairment (score of eight or lower) according to the dementia screening test DemTect (Kalbe et al., 2004) were additionally excluded (n = 11). In total, the current study comprises a sample of n = 772 subjects (mean age: 67.1, SD: 6.7, 421 males, see Table 1).

All subjects gave written informed consent prior to inclusion in 1000BRAINS. The study protocol of 1000BRAINS was approved by the Ethics Committee of the University of Essen, Germany.

2.2. Imaging

2.2.1. Image acquisition and preprocessing

Imaging data were collected using a 3T Siemens Tim-TRIO MR scanner with a 32-channel head coil (Erlangen, Germany). Different MR sequences were used for the current study: For the surface reconstruction, a 3D high-resolution T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) anatomical scan was acquired (176 slices, slice thickness 1 mm, repetition time (TR) = 2250 ms, echo time (TE) = 3.03 ms, field of view (FoV) = 256 × 256 mm^2, flip angle = 9°, voxel resolution 1 × 1 × 1 mm^3). Resting-state functional MRI was obtained using a blood-oxygen level dependent (BOLD) sequence with 36 transversally oriented slices, measured using a gradient-echo planar imaging (EPI) sequence (slice thickness 3.1 mm, TR = 2200 msec, TE = 30 msec, FoV = 200 × 200 mm^2, voxel resolution 3.1 × 3.1 × 3.1 mm^3), lasting for ~11 min and producing 300 volumes. During RS image acquisition, participants were instructed to keep their eyes closed, be relaxed, let their mind wander, and not fall asleep. The latter was assured by post-scan debriefing.

Image preprocessing was performed using FSL [FMRIB Software Library: http://www.fmrib.ox.ac.uk/fsl (Jenkinson et al., 2012)]. For each participant, the functional images were motion corrected and coregistered to the individual anatomical scan using FMRIB's Linear Image Registration tool [MCFLIRT and FLIRT (Jenkinson et al., 2002)]. Afterwards, all functional images were slice timing corrected [slicetimer (Parker et al., 2017)], brain extracted [BET (Smith, 2002)], intensity normalized, and spatially smoothed (5 mm at FWHM) [SUSAN (Smith and Brady, 1997)]. Additionally, ICA-based **A**utomatic **R**emoval **O**f **M**otion **A**rtifacts [ICA-AROMA (Pruim et al., 2015)] was applied. ICA-AROMA is a data-driven method to identify and remove motion-related independent components from functional MRI data. According to current suggestions for minimizing the relationship of motion and RSFC (Burgess et al., 2016; Ciric et al., 2017; Parkes et al., 2018), AROMA was combined with global signal regression in the current study. Lastly, all RS-fMRI images were bandpass filtered (0.01–0.1 Hz) and registered to the standard space template (MNI 152) using the Nonlinear Image Registration tool [FNIRT (Jenkinson and Smith, 2001)]. Based on the preprocessed mean AROMA functional data, we checked for potential misalignments by performing the "check sample homogeneity using standard deviation across sample" function analysis provided by the **C**omputational **A**natomy **T**oolbox [CAT12 (Gaser and Dahnke, 2016)]. Participants detected as outlier where manually checked and excluded as the individual image did not match the MNI152 template (n =6). With AROMA particularly focusing on the correction of intensity artifacts induced by head motion, we further on took advantage of an established algorithm by Afyouni and Nichols (2018) to check for each participant volume-wise severe intensity dropouts by generating p-values for spikes (DVARS) on the already preprocessed functional data. In the current study, volumes with corrupted spikes are indicated and participants for which more than 10% of the 300 volumes were detected as dropouts were excluded from further analyses (n =15). To assure an adequate performance of our preprocessing, we checked the correlation between age and motion before as well as after preprocessing and found no remaining significant dependency between age and motion after applying AROMA and excluding the remaining conspicuous participants (age * percentage of corrupted volumes, r = .016, p = .659).

Table 1
Sample distribution of the total group, female and male regarding age, education (Unesco, 1997) and the risk of having dementia: mean (standard deviation).

	%	Age (years)	Education	DemTect
total	100	67.1 (6.7)	6.5 (2.0)	14.9 (2.3)
male	54.5	67.5 (6.7)	6.9 (1.9)	14.4 (2.3)
female	45.5	66.5 (6.6)	5.9 (1.8)	15.5 (2.3)

2.2.2. Functional connectivity analyses

To analyze RSFC within established cortical functional networks, we used the cortical parcellation of Yeo et al. (2011). This parcellation scheme was established based on intrinsic RSFC from 500 participants (collated with a 500 subjects replication cohort). Networks were delineated by clustering the whole-brain RSFC depending on their similarity of functional activation profiles over all subjects. Two network parcellations were established, comprising either seven or seventeen networks. The 7-network parcellation mainly distinguishes known functional RS networks, namely visual-, sensorimotor-, limbic-, frontoparietal-, default mode-, dorsal- and ventral attention networks. Components provided by the 17-network parcellation (83 separate regions with cluster sizes >100 voxels, collapsed over hemispheres) can be allocated to the 7-network scheme, resulting in 7 distinct networks, each consisting of several regions of interest (ROIs, Fig. 1, additional information on label names and MNI-coordinates can be found in Supplementary Table S1). Since the transformation from subject to standard space results in interindividual variance of cluster configuration, all ROIs were eroded using FSL [fslmaths -ero (Smith et al., 2004)] so that voxels close to boundaries with less confidence of network affiliation were discarded.

To estimate graph-theoretical parameters, the individual functional data were translated into a whole brain graph (i.e. connectome, Rubinov and Sporns, 2010). In the current study, each ROI (i.e. node) is represented by a BOLD mean time series spanning 300 time points. Mean time series were extracted node-wise from the preprocessed RS-fMRI data [fslmeants (Smith et al., 2004)] averaging the timeseries of all voxels corresponding to that node. The functional connection between two nodes (i.e. edges) was determined using Pearson's product-moment correlation of the respective average BOLD time series of the two nodes. Consequently, for the 83 selected ROI's in the current study, this resulted in symmetric 83x83 matrices, where each entry represents a Pearson's correlation coefficient between two nodes. This adjacency matrix was then transformed into z-scores by the application of Fishers r-to-z transformation, containing both positive and negative correlations. Due to the fact that integrating both, positive as well as negative weights into the estimation of strength values may possibly lead to a mutual suppression. SSince positive and negative connections can cancel each other out, we performed separate estimations with first, only positive and second, only negative correlations.

Especially in RSFC, where correlations are based on minimal BOLD activity fluctuations, there may be edges that reflect measurement noise

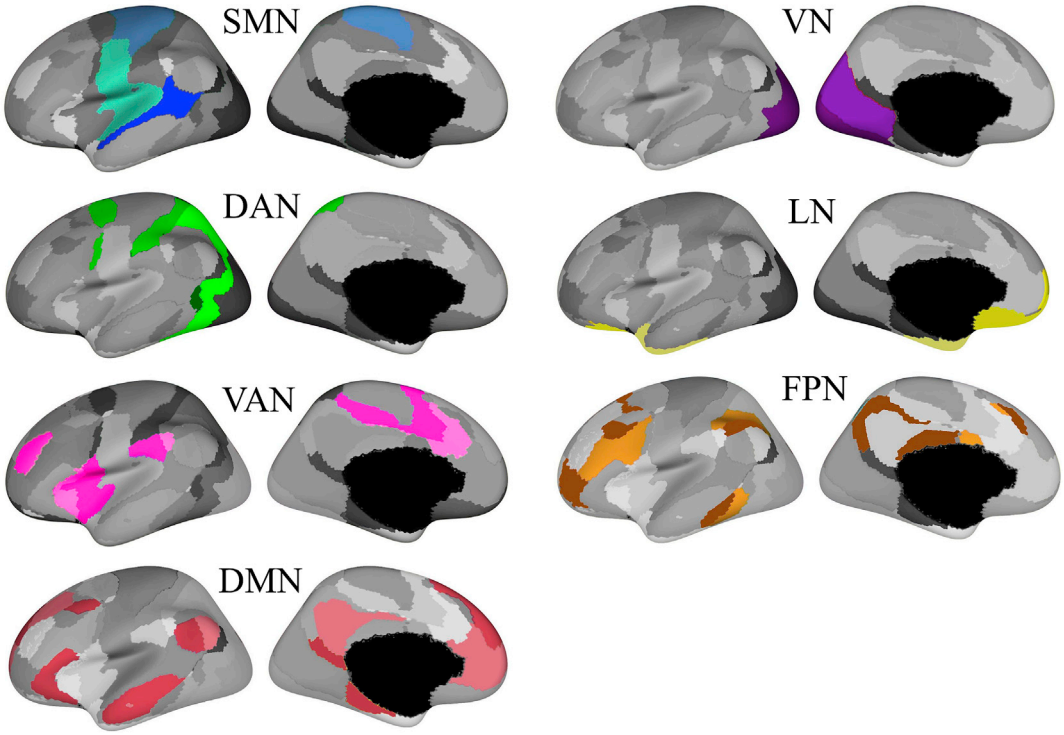


Fig. 1. Functional connectivity-based parcellation of the brain in accordance to Yeo et al. (2011). The cortex was parcellated based on the 17-network scheme, whereupon each region was allocated to the 7-network parcellation: sensorimotor- (SMN), dorsal attention- (DAN), ventral attention- (VAN), default mode- (DMN), visual- (VN), limbic- (LN) and frontoparietal network (FPN).

rather than true signal. To minimize the amount of edges caused by noise, we included the statistical significance of each correlation coefficient as an additional preprocessing step. Therefore, the observed timeseries were randomized by taking its Fourier transform, scrambling its phase and then inverting the transform (Zalesky et al., 2012). This procedure was repeated 1000 times and followed by a permutation test (non-significant edges at $p > .05$ were discarded).

The subject-wise elimination of non-significant edges may potentially result in inter-individual different network sizes (i.e. different amount of edges). Previous research has stated that systematic network differences calculated by graph theoretical parameters can be distorted by differences in the absolute amount of edges in a given network (van Wijk et al., 2010). Therefore, thresholding methods are frequently performed, i.e. reducing the total amount of edges to a set that reach a certain absolute or relative threshold. However, this practice might be prone to false-negatives and may even result in systematic differences of overall RSFC, leading to a more random network characterization in networks with a low overall RSFC (van den Heuvel et al., 2017). Therefore, the current study omitted thresholding methods, but instead focused on network parameters that are not dependent on the varying absolute amount of edges, but additionally address feasible differences resulting from different network sizes.

The software *bctpy* with network parameters as defined in Rubinov and Sporns (2010), was used to quantify the RSFC of networks. First, the whole-brain density was determined. This density represents the ratio of present edges to possible edges between all pairs of nodes, whereby the edge weights are ignored. The network density is an indicator for inter-individually varying network sizes and can be used in order to preclude that systematic differences in network parameters found are not solely based on different network sizes. Second, three different RSFC parameters were calculated for each of the seven networks, all based on the estimation of strength values. The strength of a node is computed by the sum of connectivity weights attached to that node. The strength value has been shown to represent a robust and reliable measure for network quantification as it also enables accurate identification of subjects from a large group on the basis of their connectivity matrices alone (Finn et al., 2015). Additionally, it is not distorted by varying amounts of edges, but captures these as valuable subject-dependent network differences. To limit the number of pairwise comparisons, we calculated composite

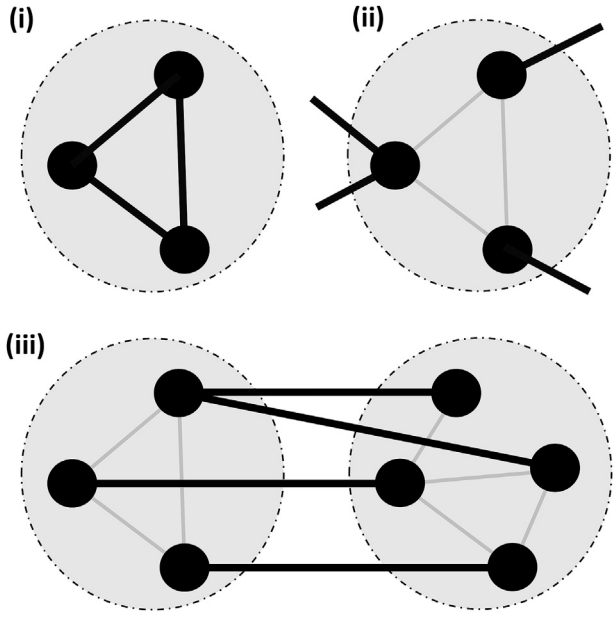


Fig. 2. RSFC. Dashed circles represent brain networks, in which the dots represent its associated brain regions, lines the functional correlation between regions. Black lines indicate edges on which the according RSFC value is based on. (i) *within*-network RSFC, all correlations within one network (ii) *inter*-network RSFC, correlations from one network to all other networks (iii) *between*-network RSFC, correlations between two specific networks.

within- and *between*-network RSFC for each participant, defined as follows and illustrated in Fig. 2..

(i) *Within*-network RSFC comprises the sum of strength values from each node to all nodes within its related network,
(ii) *Inter*-network RSFC is the sum of strength values from each node to all nodes outside the related network,
(iii) *Between*-network RSFC is defined as the sum of connections between two networks.

Further, as previously implemented by Chan et al. (2014), we calculated a combined quantitative parameter, the ratio-score, capturing the *within*-network RSFC in relation to the *inter*-network RSFC. With regard to the current literature showing age-related attenuated *within*-network RSFC and increased *between*-network RSFC, which may at least be partly dependent, we can assume a loss of network segregation during aging. Using a ratio-score which integrates both, the *within*-as well as *inter*-network connectivity, the network's segregation can be quantified as follows:

$$\text{ratio} - \text{score} = \frac{(within - \text{network RFSC} - inter - \text{network RFSC})}{(within - \text{network RFSC} + inter - \text{network RFSC})}$$

Specifically, a ratio-score of 1 implies maximal network segregation (high *within*- and low *inter*-network RSFC), whereas a ratio-score of −1 indicates maximal network integration (low *within*- and high *inter*-network RSFC). A score of zero indicates a balanced system.

2.3. Cognitive performance

All subjects underwent comprehensive neuropsychological assessment addressing a wide range of cognitive functions including the domains of attention, episodic- and working memory, executive functions, as well as language functions (for test description see also Caspers et al., 2014 and Jockwitz et al., 2017 as well as Supplementary Table S2). In the case of one or two missing values in the neuropsychological assessment (>3 missing values led to exclusion, see above), the missing values were replaced by the appropriate median, which was calculated separately for sex and age decades (55–64 years, 65–74 years, 75–85 years). In total, 26 out of the 772 participants included in the current analysis had at least one missing value.

Principal component analysis (PCA) was applied to reduce and classify the neuropsychological data. After transforming all variables into z-scores, data was tested on suitability for PCA, using the Kaiser-Meyer-Olkin (KMO) index (measures the degree of common variability), which reached a value of 0.909 and thus indicated suitability of the data for PCA. PCA was consecutively used to extract neuropsychological components. Finally, Varimax rotation was applied to enhance the interpretability of the extracted components. All steps were performed using IBM SPSS Statistics 24 (http://www-01.ibm.com/software/de/analytics/spss/).

2.4. Statistical analyses

First, we used Multivariate Analysis of Covariance (MANCOVA) as implemented in IBM SPSS Statistics 24 http://www-01.ibm.com/software/de/analytics/spss/to test the relationship between RSFC and age, sex as well as education. To do so, four separate linear models were employed including either *within*-, *inter*-, *between*-network RSFC or the ratio-scores of the given networks as dependent variables and sex, age as well as education level as independent predictors. To account for potential interactions between the predictor variables, we additionally tested interaction effects between age and sex as well as education on all RSFC values. All results were considered significant at $p < 0.05$. Pairwise comparisons within each MANCOVA were Bonferroni-corrected for multiple comparisons (*within*-, *inter*-network RSFC and ratio-scores: $p = 0.05/7$ networks $= 0.007$; *between*-network RSFC: $p = 0.05/21$ network combinations $= 0.002$). To additionally test robustness of effects a bootstrap validation was performed (1000 bootstrap samples, 95% confidence interval) using SPSS Statistics 26. For significant age effects, we conducted regression analyses for slope estimates and variance information.

As post-hoc analyses we addressed the relation between RSFC and cognitive performance. Therefore, partial correlations between all RSFC values (7 *within*- and *inter*-, 21 *between*-network and 7 ratio scores) and each cognitive performance domain were calculated, correcting for age, sex, education as well as the two remaining cognitive domains, respectively. Again, to test the robustness of correlations between cognitive performance and RSFC a bootstrap validation was performed (1000 bootstrap samples, 95% confidence interval). In cases where we found both, associations of RSFC with a cognitive component (results derived from partial correlations, $p < 0.05$) as well as with age (results derived by previous MANCOVAs, $p < 0.05$), we conducted mediation analyses to test whether these concurrent effects may also be significantly related. Specifically, we tested to what extent the age-related decline in cognition is mediated by the age-related differences in RSFC (covariates: sex, education, and the two remaining components, respectively). Comparably, for all RSFC values that where associated with cognitive performance and additionally showed sex-related differences, we tested whether sex-related differences in RSFC significantly mediate the effect of sex on cognition (corrected for age, education, and the two remaining cognitive components, respectively). Mediation analyses were performed using PROCESS (Hayes and Preacher, 2014), implemented in IBM SPSS Statistics 20. The significance of indirect effects was computed using bootstrapping procedures. For 10000 bootstrapped samples unstandardized indirect effects were generated and the 95% confidence interval was computed by determining the indirect effects at the 2.5th and 97.5th percentiles.

Subsequently, we investigated the effect of age and sex on negative strength values, i.e. anticorrelations.

3. Results

In the current study, we found significant age-related differences of *within*- and *between*-network RSFC and the ratio of *within*- and *inter*-network RSFC. Further, results indicate RSFC differences between males and females as well as correlations of network parameters to cognitive performance. Finally, post-hoc analyses revealed age-related differences in RSFC to mediate the cognitive performance decline during aging (RSFC values for the whole group, females and males can be found in Supplementary Tables S4 and S5).

As of note, all networks were tested additionally for effects of the relevant covariates age ($F = 0.909, p = 0.341$), sex ($F = 1.041, p = 0.308$) and education level ($F = 2.376, p = 0.124$) in relation to network density (i.e. number of edges per network). As none of these revealed significant effects, subject-specific differences in network density were not considered further in any of the performed analyses.

Results on negative strength values are described in relation to the results on positive strength values at the end of the sections. Specific information on negative strength values can be found in supplementary material (Supplementary Table S10, Figs. S11 and S12). Of note, in supplementary material all (non-significant) effects regarding the relations between age, education and sex (Supplementary Table S6) as well as cognitive performance (Supplementary Table S9) are denoted. Further, for all significant RSFC effects age-scatter plots as well as sex-boxplots are provided (Supplementary Figs. S7 & S8, respectively).

3.1. Relations between RSFC and age, sex, as well as education

3.1.1. Aging effects on RSFC

Regarding the positive connections, main effects (MANCOVA) revealed age to be significantly related to *within*-network RSFC (F =

6.161, $p < .001$), *between*-network RSFC (F = 2.731, $p < .001$), as well as the ratio between *within*- and *inter*-network RSFC (F = 5.222, $p < .001$) (Fig. 3A, Table 2).

Within-network RSFC was negatively correlated with age. This effect was particularly striking for the visual (F = 12.228, $p < .001$; β = -.125, SE = 0.110) and sensorimotor network (F = 21.056, $p < .001$; β = -.163; SE = 0.017).

In contrast, overall *between*-network RSFC was positively correlated with age. This specifically applied to the connections between the sensorimotor, the frontoparietal (F = 9.716, $p = .002$; β = .112; SE = 0.039) and the limbic network (F = 15.458, $p < .001$; β = .141; SE = 0.011), as well as the connection between the dorsal attention and the limbic network (F = 10.527, $p = .001$; β = .117; SE = 0.012). Only the connection between the sensorimotor and visual network was found to be negatively correlated with age (F = 12.502, $p < .001$; β = -.127; SE = 0.025; Fig. 3A, dashed line; Table 2).

Overall *inter*-network RSFC was not correlated with age, after correcting for multiple comparisons (F = 1.964, $p = .057$). However, the ratio-score of *within*- and *inter*-network RSFC correlated negatively with age indicating the overall balance to be shifted towards predominance of *inter*-network RSFC with increasing age. This effect applied in particular to the sensorimotor (F = 29.561, $p < .001$; β = -.193, SE = 0.001), and dorsal attention network (F = 7.227, $p = .007$; β = -.097, SE = 0.001), the latter however not remaining significant after bootstrap validation.

Concerning negative strength values, we found the inverse effects compared to positive strength values: networks that show age-related

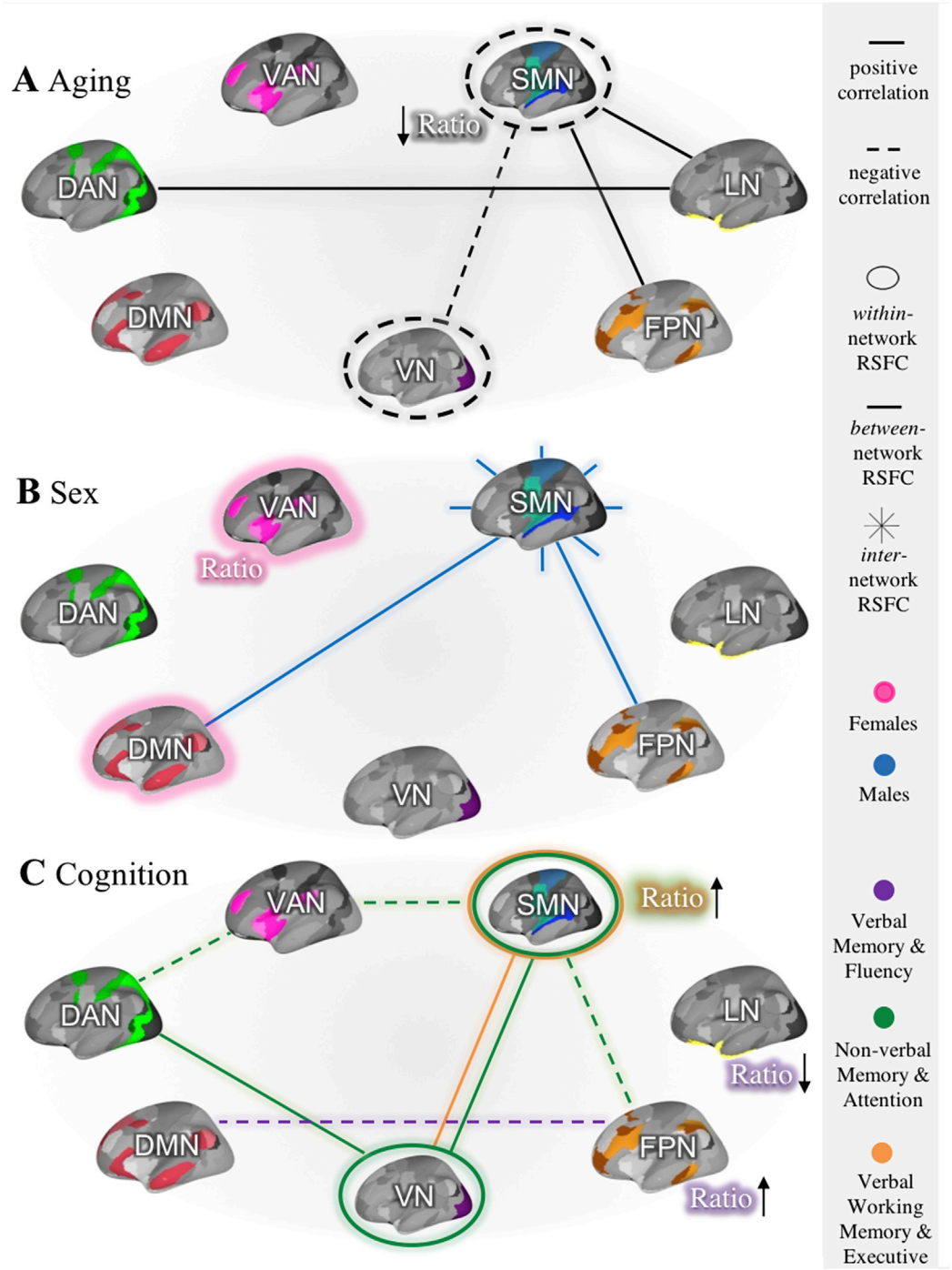


Fig. 3. (A) Age-related differences, (B) sex-related differences and (C) cognitive performance dependent differences of RSFC. Dots stand for differences of *within*-network RSFC, lines for *between*-network RSFC and crosses for *inter*-network RSFC differences (dashed lines negative correlations, solid lines positive correlations and in terms of the ration–scores arrows indicate the direction of correlation: down = negative, up = positive correlation). Pink represent higher values in females, blue in males. Purple represents correlations with the VERBAL MEMORY & FLUENCY, green with the NON-VERBAL MEMORY & ATTENTION, orange with VERBAL WORKING MEMORY & EXECUTIVE component. SMN = sensorimotor, LN = limbic, FPN = frontoparietal, VN = visual, DMN = default mode, DAN = dorsal attention, VAN = ventral attention network.

Table 2
Significant effects (including effect sizes denoted by eta-square) of (a) MANCOVAs with *within*-, *inter*-, the ratios-scores and *between*-network RSFC as dependent variables and age, sex as independent predictors (education as covariate, significance level for *within*-, *inter*-network RSFC, ratio-scores $p < 0.007$ and *between*-network RSFC $p < 0.002$, after Bonferroni-correction) and (b) from partial correlations between *within*-, *inter*-, the ratio-scores, *between*-network RSFC and the three cognitive performance components (1: VERBAL MEMORY & FLUENCY, 2: NON-VERBAL MEMORY & ATTENTION, 3: VERBAL WORKING MEMORY & EXECUTIVE) with age, sex and education level as covariates (significant level: $p < .05$, without correction for multiple comparison). Significant models, that additionally survive post-hoc bootstrap validation, are indicated by an *asterisk (*CI = 95% confidence interval). SMN = sensorimotor, LN = limbic, FPN = frontoparietal, VN = visual, DMN = default mode, DAN = dorsal attention, VAN = ventral attention network. SMN = sensorimotor, LN = limbic, FPN = frontoparietal, VN = visual, DMN = default mode, DAN = dorsal attention, VAN = ventral attention network.

	Networks	*Age*						*Sex*					*Cognition*						
		ß	*p*	*Eta-square*	***Bootstrap CI*** *lower*	*upper*		*p*	*Eta-square*	***Bootstrap CI*** *lower*	*upper*		*component*	*r*	*p*	*Eta-square*	***Bootstrap CI*** *lower*	*upper*	
within	VN	-.125	<.001	.016	-.061	-.016	*						2	.077	.033	.006	.013	.145	*
	SMN	-.163	<.001	.027	-.110	-.048	*						2	.076	.036	.006	.005	.148	*
													3	.101	.005	.01	.035	.174	*
	VAN							.001	.013	-5.953	-1.605	*							
	DMN							.004	.011	-8.772	-1.814	*							
inter	VN												2	.072	.046	.005	-.008	.148	
	SMN							<.001	.017	1.347	3.982	*							
ratio	SMN	-.193	<.001	.037	-.005	-.002	*						2	.095	.008	.009	.027	.162	*
													3	.125	.001	.016	.055	.193	*
	DAN	-.097	.007	.009	-.003	0													
	VAN							<.001	.02	-.076	-.027	*	3	.073	.042	.005	0	.143	
	LN												1	-.082	.023	.007	-.152	-.016	*
	FPN												1	.081	.025	.007	.008	.152	*
between	VN_SMN	-.127	<.001	.016	-.131	-.042	*						2	.099	.006	.01	.032	.163	*
													3	.082	.023	.007	.007	.152	*
	VN_DAN												2	.093	.01	.009	.020	.166	*
	SMN_VAN												2	-.12	.001	.014	-.192	-.042	*
	SMN_LN	.141	<.001	.02	.020	.065	*												
	SMN_FPN	.112	.002	.012	.031	.204	*	.001	.013	.735	2.758	*	2	-.079	.028	.006	-.158	-.005	*
	SMN_DMN							.001	.013	.736	2.771	*							
	DAN_VAN												2	-.11	.002	.012	-.186	-.038	*
	DAN_LN	.117	.001	.014	.031	.064	*												
	FPN_DMN												1	-.093	.01	.009	-.166	-.017	*

decreases in "positive" RSFC values, show age-related increases in "negative" RSFC values, while networks showing age-related increases in "positive" RSFC values, show age-related decreases in "negative" RSFC values. This was in particular applicable to the *within*-network RSFC of the visual and sensorimotor network, the visual-sensorimotor's *between*-network RSFC, respectively. Further, we found age-related increases of negative RSFC within the dorsal attention and frontoparietal network, as well as between the limbic, frontoparietal and default mode network (Supplementary Table S10 and Fig. S11).

3.1.2. Sex and education effects on RSFC

In terms of sex, significant main effects were present for *within*-network RSFC ($F = 2.960$, $p = .005$) as well as the ratio-scores ($F = 3.465$, $p = .001$). Females showed significantly higher *within*-network RSFC in the ventral attention ($F = 10.408$, $p = .001$) as well as the default mode network ($F = 8.335$, $p = .004$; Fig. 3B, red circles; Table 2). Concerning the ratio-scores, females showed a significantly higher ratio of the ventral attention-network, indicating an intensified network's segregation in females ($F = 15.938$; $p < .001$). In contrast, *inter*-network RSFC of the sensorimotor network was significantly greater in males ($F = 13.564$, $p < .001$; Fig. 3B, multiple blue lines; Table 2). Moreover, *between*-network RSFC of the sensorimotor with the default mode ($F = 10.364$, $p = .001$) and frontoparietal network ($F = 10.432$, $p = .001$; Fig. 3B, blue lines; Table 2) were higher in males.

No significant interaction effect between age and sex on any RSFC values was revealed. Further, education and its interaction effects with age and sex showed no significant relations with any RSFC values. Lastly, there were no significant sex-related differences for any negative strength values found (Supplementary Table S10 & Fig. S12).

3.2. Cognitive performance

3.2.1. Principal component analysis

Considering the eigenvalue criterion (eigenvalue >1), three principal components were identified (Figs. 4 and 5 and Supplementary Table S3). The first component majorly comprised performance in verbal memory, phonemic and semantic verbal fluency, figural fluency and vocabulary knowledge (VERBAL MEMORY & FLUENCY component). The second component highlighted performance in (selective) attention, figural memory, visual spatial working memory, and additionally included problem solving (NON-VERBAL MEMORY & ATTENTION component). Component three particularly addressed the participants' capacity of working memory and concept shifting (VERBAL WORKING MEMORY & EXECUTIVE component). All three components showed significant negative correlations with age (VERBAL MEMORY & FLUENCY: $p < .001$, r: -.311; NON-VERBAL MEMORY & ATTENTION: $p < .001$, r: -.371; VERBAL WORKING MEMORY & EXECUTIVE: $p = .007$, r: -.097.; education and sex as covariates), indicating an overall age-related performance decline. The education level was significantly positively correlated with the verbal cognitive performance components (VERBAL MEMORY & FLUENCY: $p < .001$, r: 0.323; VERBAL WORKING MEMORY & EXECUTIVE: $p < .001$, r: 0.263, corrected for sex and age) but not the NON-VERBAL MEMORY & ATTENTION component ($p = .248$, r: -.042; corrected for sex and age). Further, a subsequent MANCOVA revealed males to outperform females in the first two components, but not in the third (VERBAL MEMORY & FLUENCY: $F = 34.489$, $p < .001$; NON-VERBAL MEMORY & ATTENTION: $F = 37.237$, $p < .001$; VERBAL WORKING MEMORY & EXECUTIVE: $F = 0.465$, $p = .495$, age and education as covariates).

3.2.2. Cognitive performance and RSFC

Regarding RSFC, correlations with all three cognitive components were found (Fig 3C, Table 2). The first, VERBAL MEMORY & FLUENCY component, was negatively correlated with the ratio-score ($p = .023$, r: -.082) of the limbic network and the *between*-network RSFC of the frontoparietal and default mode network ($p = .01$, r: -.093; Fig. 3C, purple dashed lines). Further, the ratio-score of the frontoparietal network was positively correlated with the VERBAL MEMORY & FLUENCY component indicating a higher network integration being associated with lower cognitive performance ($p = .025$, r: 0.081). The second, NON-VERBAL

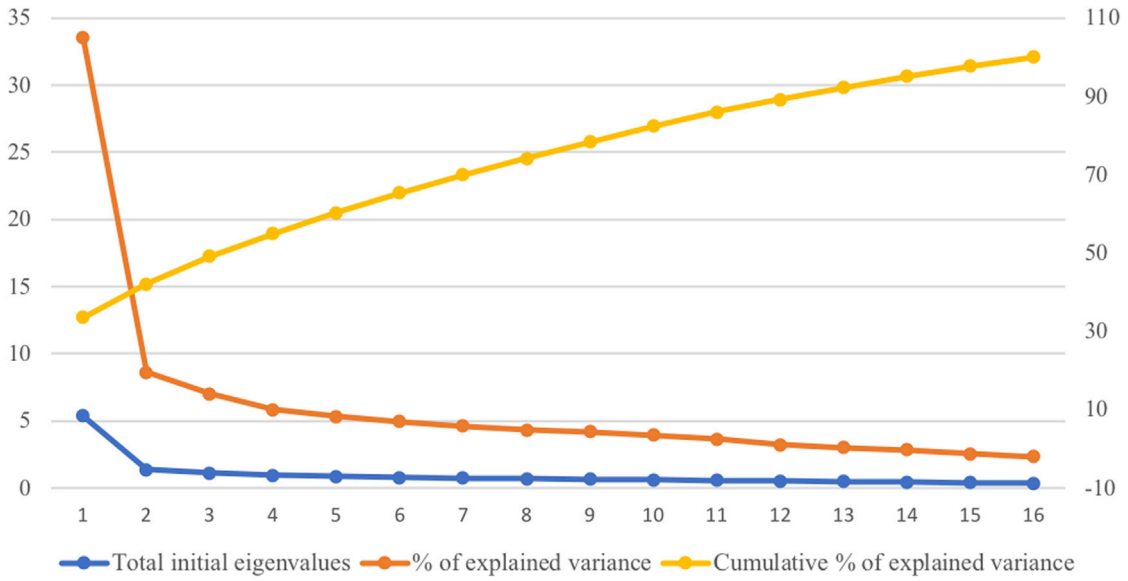


Fig. 4. Screeplot of the initial eigenvalues in the current study estimated PCA. The figure is based on the eigenvalues and explained variance from the PCA shown in Supplementary Table S3. The blue line indicates the total initial eigenvalues, orange line the % of explained variance and the yellow line the cumulative % of explained variance.

Fig. 5. Factor loadings of each cognitive function on each component extracted from PCA analysis (component loading after Varimax rotation). Purple = VERBAL MEMORY & FLUENCY, green = NON-VERBAL MEMORY & ATTENTION, orange = VERBAL WORKING MEMORY & EXECUTIVE.

MEMORY & ATTENTION component, was positively correlated with the visual's *within*-network RSFC (p = .033, r: 0.077; Fig. 3C, green circle) as well as the mutual *between*-network RSFC of the visual, sensorimotor (p = .006, r: 0.099) and dorsal attention network (p = .010, r: 0.093; Fig. 3C, green line). Further, the same component showed a positive correlation with the *within*-network (p = .036, r: 0.076; Fig. 3C, green circle) and ratio-score (p = .008, r: 0.095) of the sensorimotor network, accompanied by a negative correlation with the *between*-network RSFC of the sensorimotor and ventral attention (p = .001, r: -.120), as well as frontoparietal network (p = .028, r: -.079). Lastly, higher RSFC between the dorsal and ventral attention network was significantly related to lower performance in the second component (p = .002, r: -.110; Fig. 3C, green dashed lines). Concerning the third, VERBAL WORKING MEMORY & EXECUTIVE component, positive correlations with the sensorimotor's *within*-network RSFC (p = .005, r: 0.101; Fig. 3C, orange circle), its ratio-score (p = .001, r: 0.125), as well as its *between*-network RSFC with the visual network (p = .023, r: 0.082; Fig. 3C, orange line) were found.

3.2.3. *Mediating effects within and between networks related to cognition*

For some RSFC values we found associations with both, age as well as cognitive performance. For example, the sensorimotor network showed less *within*-network RSFC to be associated with higher age, as well as

worse performance in the VERBAL WORKING MEMORY & EXECUTIVE component. This leads to the question, whether these concurrent effects are also significantly related, hence whether the age-related differences in RSFC mediate the cognitive performance differences across ages or if these are independent processes. Mediation analyses revealed that the age and cognition effects are indeed related (Table 3). While the age-related *within*-network RSFC of the visual network significantly mediated the effect of age on the NON-VERBAL MEMORY & ATTENTION component, the *within*-network RSFC as well as the ratio-score of the sensorimotor network mediated both, the age-related performance in the VERBAL WORKING MEMORY & EXECUTIVE, as well as NON-VERBAL MEMORY & ATTENTION component. The visual-sensorimotor's *between*-network RSFC was found to mediate the effect of age on the NON-VERBAL MEMORY & ATTENTION component.

Since performance in two cognitive components (VERBAL MEMORY & FLUENCY, NON-VERBAL MEMORY & ATTENTION) were also found to be significantly different between males and females, the question arises whether these differences may be mediated by sex-related differences in RSFC. And indeed, we found sex-related differences in RSFC between the sensorimotor and frontoparietal network to significantly mediate the cognitive performance of the NON-VERBAL MEMORY & ATTENTION component (Table 3).

4. Discussion

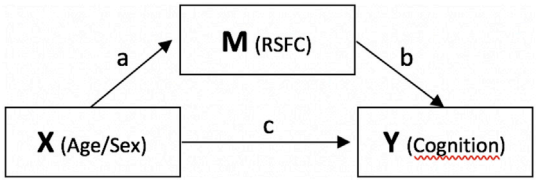
Based on a large population-based sample of older adults, we found age-related decreases of *within*- together with increases of *between*-network RSFC leading to more integrated and less segregated functional brain networks during aging. To examine the mutual dependence of these two effects, we additionally used an integrated parameter of network segregation, calculated as a ratio-score of *within*- and *inter*-network RSFC, which showed considerable decreases in network segregation across aging. Notably, in the old generation, mainly the RSFC of primary processing networks seems to be affected and additionally crucial for cognitive performance as lower RSFC of the according networks are associated with worse cognitive performance. Importantly, we show that age-related differences in RSFC mediate cognitive performance differences. Additionally, when comparing males and females, we found systematic differences in the functional connectivity patterns pointing at a more integrated system in males.

4.1. Aging

Overall *within*-network RSFC decreases and *between*-network RSFC increases have been found in previous findings that focused on age group comparisons (old vs. young) (Geerligs et al., 2015; Grady et al., 2016; Goldstone et al., 2016; Nashiro et al., 2017; Siman-Tov et al., 2017; Spreng et al., 2016) or lifespan trajectories (Betzel et al., 2014; Cao et al., 2014; Chan et al., 2014; Ferreira et al., 2016; Mowinckel et al., 2012; Tsvetanov et al., 2016; Varangis et al., 2019). Therewith, the current study amends such evidence for age-related attenuated network specificity over the lifespan, underpinning the results of Zonneveld et al. (2019) that also within particularly older subjects this trend persists. Importantly, the applied whole-brain approach revealed that RSFC differences in older ages are particularly prominent in the visual and sensorimotor network, which in turn is associated with cognitive performance differences (see section 4.3 for further discussion). Looking at the networks specifically, certain dependencies are of interest.

Age-related *within*-network RSFC decreases were found for the visual as well as the sensorimotor network, thus primary processing networks. These results are in line with Perry et al. (2017), who found especially RSFC of the visual and sensorimotor network to be sensitive to age, as well as cognitive performance using a multivariate approach (n = 101, 70–90 years). Additionally, Zonneveld et al. (2019) could show similar age effects of the sensorimotor network in a comparable age-range to the current study (50–95 years). In contrast to that, former studies investigating the whole adult lifespan, repeatedly found *within*-network RSFC decreases in higher order networks (e.g. attention, frontoparietal, default

Table 3
All cognitive performance components (1: VERBAL MEMORY & FLUENCY, 2: NON-VERBAL MEMORY & ATTENTION, 3: VERBAL WORKING MEMORY & EXECUTIVE) decrease with increasing age and two of the components are significantly different between male and female. For performance components showing an association with age or sex as well as RSFC, we tested (i) whether the age-related cognitive decline is significantly explained by age-related differences in RSFC and (ii) whether the sex-related differences in RSFC significantly cause the sex-related differences in cognition: Mediation Analyses to test the effect of RSFC values on the effect of age or sex on cognition (corrected for sex/age, education and the two remaining components, respectively). Significant models are indicated by an *asterisk*. SMN = sensorimotor, LN = limbic, FPN = frontoparietal, VN = visual, DMN = default mode, DAN = dorsal attention, VAN = ventral attention network. *Between*-network RSFC is indicated by an underscore between the according networks.



		Model		β (p-value)			Effects			Bootstrap confidence intervals		
	X	M (RSFC)	Y (component)	a	b	c	Total	Direct	Indirect	BootSE	lower	upper
*	**Age**	VN	2	-.1260 (.001)	.0697 (.033)	-.4076 (<.001)	-.0626 (<.001)	-.0613 (<.001)	-.0088	.0048	-.0194	-.0010
*		SMN	2	-.1452 (<.001)	.0691 (.036)	-.4063 (<.001)	-.0626 (<.001)	-.0611 (<.001)	-.0100	.0055	-.0221	-.0007
*			3	-.1290 (.002)	.0964 (.005)	-.1609 (<.001)	-.0260 (<.001)	-.0242 (<.001)	-.0124	.0062	-.0266	-.0027
*		VN _SMN	2	-.1065 (.005)	.0899 (.006)	-.4068 (<.001)	-.0626 (<.001)	-.0611 (<.001)	-.0096	.0048	-.0203	-.0016
			3	-.0760 (.064)	.0784 (.023)	-.1673 (<.001)	-.0260 (<.001)	-.0251 (<.001)	-.0060	.0043	-.0161	.0003
		SMN_FPN	2	.1045 (.006)	-.0724 (.028)	-.4088 (<.001)	-.0626 (<.001)	-.0614 (<.001)	-.0076	.0054	-.0204	.0002
*		SMN ratio	2	-.1783 (<.001)	.0881 (.008)	-.4007 (<.001)	-.0626 (<.001)	-.0602 (<.001)	-.0157	.0070	-.0298	-.0041
*			3	-.1578 (<.001)	.1214 (<.001)	-.1541 (<.001)	-.0260 (<.001)	.0232 (<.001)	-.0192	.0075	-.0357	-.0067
*	**Sex**	SMN_FPN	2	-.2409 (.002)	-.0724 (,0279)	-.3838 (<.001)	-.3664 (<.001)	-.3838 (<.001)	.1740	.0104	.0001	.0407

mode network) (Betzel et al., 2014; Chan et al., 2014; Ferreira et al., 2016; Grady et al., 2016; Mowinckel et al., 2012; Siman-Tov et al., 2017; Spreng et al., 2016; Varangis et al., 2019), whereas *within*-network RSFC of primary processing networks were found to remain stable (Betzel et al., 2014; Geerligs et al, 2015; Siman-Tov et al., 2017; Varangis et al., 2019). The latter seemed to hold true when considering linear effects only. Allowing for non-linear effects showed that the sensorimotor network follows an inverted u-shaped trajectory, though, with the inflection point at the age of about 50 years (Betzel et al., 2014; Siman-Tov et al., 2017). Remarkably, as compared to the whole adult lifespan this points at a particular vulnerability of primary processing networks at higher ages and underlines the need for investigating the older age group separately, which was focus of the current study. Regarding *within*-network RSFC differences of higher order networks in older adults, previous results are rather mixed indicating both, *within*-network RSFC decreases, cross-sectionally (Zonneveld et al., 2019) and longitudinally (Ng et al., 2016), as well as longitudinally stable *within*-network RSFC (Persson et al., 2014). Thus, within the current study, we found higher ages to be characterized by *within*-network RSFC decreases of only primary processing networks (e.g. visual and sensorimotor network) while *within*-network RSFC of higher order networks reach a more or less steady level.

Regarding differences of *between*-network RSFC we found overall age-related increases, together with age-related *between*-network RSFC decreases between visual and sensorimotor network, (accompanied by increased anti-correlations *within* as well as *between* the regarding networks). Commonly, the two networks are strongly connected, which is reasonable in terms of e.g. visuomotor integration capabilities (Goodale, 2011). Accordingly, lower *within*-network RSFC as well as *between*-network RSFC found for the visual and sensorimotor network constitute one potential explanation for impaired motor performances in visuomotor tasks in older adults, such as eye-hand coordination or spatially oriented movements (Guan and Wade, 2000; van Halewyck et al., 2014). In turn, age-related *between*-network RSFC increases were found particularly regarding the sensorimotor network. Increases pertain to the connection between the sensorimotor with the limbic and frontoparietal network, networks associated with emotion and memory functions (Frey and Petrides, 2002; Laird et al., 2011; Petrides, 2007; Smith et al., 2009) and attention and executive control mechanisms (Corbetta and Shulman, 2002; Spreng et al., 2010), respectively. Collectively, the sensorimotor's ratio of *within*- to *inter*-network RSFC decreases, indicating an overall reduced segregation and enhanced integration, i.e. higher communication with other networks. Increases of *between*-network RSFC from the sensorimotor network to other networks have previously been shown (Tomasi and Volkow, 2012a; Zuo et al., 2010) and have been interpreted as supporting evidence for compensatory processes, i.e. performance monitoring (Heuninckx et al., 2008; Varangis et al., 2019). Consistent with the compensational theory, increasing *between*-network RSFC to higher order networks could be viewed as the attempt to compensate for e.g. decreasing *within*-network RSFC or impoverished information integration from other networks (Reuter-Lorenz and Cappell, 2008; Reuter-Lorenz and Park, 2010) to counteract behavioral decline. These effects are very much in line with previous studies suggesting that older adults use countervailing cognitive strategies to cope with attenuated perceptual input integration (see Roberts and Allen, 2016 for review) and that reorganization processes within the posterior brain may represent an impetus for restructuring functional organizations in frontal areas (Davis et al., 2007; Goh, 2011; Lee et al., 2015; Seidler et al., 2010). However, since we found no positive association of *between*-network RSFC and cognitive performance, overall decreases of *between*-network RSFC could hint at a dedifferentiation process, further discussed in section 4.3.

Collectively, the results show that the aging process is accompanied by an increase of functional diversity. RSFC decreases are foremost impelled by two specific networks (visual and sensorimotor network) showing *within*-, as well as *between*-network RSFC decreases. Despite the connection between the primary information processing networks, the overall *between*-network RSFC show age-related increases pertaining to a number of different networks including the sensorimotor, frontoparietal, dorsal attention as well as the limbic network and leading to a less segregated and more integrated network system.

Regarding the results on negative correlations, we found both, increases of anti-correlations *between* as well as *within* networks. Previous results on *between*-network anti-correlations mainly pertain to the default mode network indicating age-related decreases of anti-correlations with the frontoparietal (Geerligs et al., 2015), ventral attention (Ferreira et al., 2016; Meier et al., 2012), dorsal attention (Siman-Tov et al., 2017), and sensorimotor network (Meier et al., 2012; Siman-Tov et al., 2017). Since the default mode network is a task negative network, the results may be understood as the reduced ability to suppress the default mode network during task. Regarding task positive networks, decreasing anti-correlations were previously found for the connections between the visual and sensorimotor (Geerligs et al., 2015), frontoparietal and cingulo-opercular (Geerligs et al., 2015; Meier et al., 2012), dorsal attention (Siman-Tov et al., 2017), as well as sensorimotor network (Meier et al., 2012). As anti-correlations between networks have been considered as a marker for network segregation (Fox et al., 2005) previous results point at an increase of network integration from younger to older adults particularly associated with higher order cognitive functions, such as the frontoparietal network. In contrast, in the current study we found increases of anti-correlations between the visual and sensorimotor, limbic and default mode as well as frontoparietal network which may hint at different reorganization processes in older adults compared to the whole adult lifespan. Cognitive performance changes (Hedden and Gabrieli, 2004) as well as RSFC changes (Mowinckel et al., 2012) are found to contain non-linear effects, with a major change deviation from the overall linear trend around the age of 55–60, underpinning the need to account for differences between specific age groups. Further, in the current study we also found increases of anti-correlations within networks (visual, sensorimotor, dorsal attention and frontoparietal network). Especially with regards to the visual and sensorimotor network this is the opposite effect as compared to positive correlations potentially indicating that in older adults, regions of the respective networks not only work less synchronized but even more anticyclical. Previous studies found no (Meier et al., 2012) or only very few (Varangis et al., 2019) anti-correlations within networks. To the best of our knowledge, no other results exist systematically investigating network anti-correlations in particularly older adults. Future studies are warranted to shed further light on systematic changes of anti-correlations during aging.

4.2. Sex differences

Sex-related network differences have previously been demonstrated by task-based fMRI (Weiss et al., 2003; Bell et al., 2006) as well as structural connectivity using diffusion MRI (Ingalhaliker et al., 2014; Tunc et al., 2016). With the current study we can contribute to previously published RS-fMRI results (Allen et al., 2011; Goldstone et al., 2016; Satterthwaite et al., 2014; Scheinost et al., 2015; Tomasi and Volkow, 2012b), showing that also in particularly older adults significant differences in RSFC patterns persist between males and females.

In line with previous research based on RS-fMRI (Allen et al., 2011; Scheinost et al., 2015), females showed higher *within*-network RSFC in the default mode and ventral attention network. Also, the females' ratio of the ventral attention network was higher, indicating a higher segregated system especially concerning a network implicated in reflective and intuitive functions (Buckner et al., 2008; Huo et al., 2018; Vossel et al., 2014). In contrast, males' sensorimotor network was significantly more integrated, showing higher *inter*-network RSFC compared to females. As we additionally found the sensorimotor *between*-network RSFC to mediate sex-related cognitive performance differences, the results potentially indicate a higher relevance of sensorimotor functions during cognitive processing in males (Cassady et al., 2019; Seidler et al., 2015). These findings are very much in line with previous results on RSFC

showing a higher integrated system in males already being present in youth and early adulthood (9–22 years; Satterthwaite et al., 2014) and being intensified during aging (27–74 years; Goldstone et al., 2016). Results based on diffusion MRI show very similar results: higher structural connectivity between networks related to motor, sensory and executive functions in males and higher structural connectivity among networks associated with social motivation, attention, and memory tasks in females (Tunc et al., 2016), which are thought to be structured in order to facilitate a high integration of perception and coordinated action in males and the communication between analytical and intuitive processing in females (Ingalhaliker et al., 2014).

Interestingly, Satterthwaite et al. (2014) examined sex-related RSFC differences in young healthy participants (aged 9–22) and its relation to cognition and found males to outperform females in motor and spatial cognitive tasks, while females were better in tasks of emotion identification and nonverbal reasoning. Remarkably, the cognitive profile of their participants was significantly related to the masculinity or feminity of the according RSFC pattern, stressing the notion that networks may be organized to facilitate sex-related behavioral functioning. Although, very recent studies demonstrate sex to be predictable only based on RSFC patterns (Weis et al., 2019; Zhang et al., 2018), brain patterns in males and females also clearly overlap. Therefore, caution regarding interpretation as findings being completely sex-specific, i.e. 'male brain' vs. 'female brain' is advised (Joel et al., 2015). Nevertheless, interpreting sex-related differences in RSFC patterns in relation to cognitive performance could shed additional light on this phenomenon (Satterthwaite et al., 2014). As the study was focused on general effects of more global cognitive functioning, as operationalized by the PCA components, such mediating effects between sex-specific cognition and RSFC patterns could not be found. Future studies focusing on individual cognitive performance in specific tests known to differ between males and females are needed to advance our understanding of this complex interplay between RSFC patterns, cognition, and sex.

In conclusion, the present results are very much consistent with previously reported sex-related differences in functional as well as structural connectivity patterns and expand the current knowledge about sex-related RSFC differences into the old age group. This stresses the importance of considering sex when examining the functional connectivity architecture of older adults.

4.3. Cognition

The RSFC pattern in older adults was found to reorganize in an age-dependent manner. It is generally assumed that the age-related cognitive performance differences are at least partly associated with functional reorganization processes (Marques et al., 2016; Sadaghiani et al., 2015; Zuo et al., 2017). The present results provide additional evidence for this assumption: the majority of cognitive effects pertain to networks that are also age-related, e.g. visual and sensorimotor network. Further, differences in RSFC were found to mediate cognitive performance differences across ages. In these networks, differences in RSFC were associated with the NON-VERBAL MEMORY & ATTENTION and VERBAL WORKING MEMORY & EXECUTIVE components. While the sensorimotor network was found to mediate age-related differences of both components, the visual network was primarily associated with the NON-VERBAL MEMORY & ATTENTION component. Since this component is endowed with a high proportion of visual functions, one would expect (age-related) decreases of the visual RSFC to be associated with reduced performances, which is exactly what we found. Further, the *between*-network RSFC of the visual and sensorimotor network was positively associated with both components. Accordingly, we found age-related decreases of the visual-sensorimotor's *between*-network RSFC to mediate the cognitive performance differences of the NON-VERBAL MEMORY & ATTENTION component. In contrast, we found negative correlations between cognitive performance and *between*-network RSFC of the sensorimotor and ventral attention, the frontoparietal and default mode as well as the dorsal and ventral attention network. However, none of these connections where found to mediate the age-related decreases in cognitive performance. The other study focusing on whole-brain RSFC differences and its association with cognitive performance in particularly older adults, also found an opposing relationship between age, cognition and the visual as well as sensorimotor network's RSFC (Perry et al., 2017). Although the correlation values as well as the according effect sizes of the current results are small, the consistency to previous results hint at a relevant role of primary processing networks in terms of cognitive differences at higher age, which we will discuss further now.

Until now, two aging theories exist addressing the relation between functional reorganization and cognitive performance: the compensational theory (see section 4.1) and the dedifferentiation theory. As defined in section 4.1, according to the compensational theory, increasing *between*-network RSFC would be the attempt to compensate for decreasing *within*-network RSFC or impoverished information integration from other networks (Grady et al., 2016; Heuninckx et al., 2008; Tsvetanov et al., 2016; Varangis et al., 2019). Within the current study, increased RSFC of the sensorimotor network with networks involved in attention, memory and control are in line with the compensation theory, i.e. RSFC increases may be understood as an adaptive reorganization process to maintain cognitive performance as stable as possible (Cabeza et al., 2002; Park & Reuter-Lorenz, 2009). However, the increasing *between*-network RSFC of the sensorimotor network was rather found to be related to worse performance, e.g. for *between*-network RSFC with the ventral attention and frontoparietal network, which is supportive for the so-called dedifferentiation theory. Here, increasing *between*-network RSFC is associated with a decrease in distinctiveness (i.e. increasing covariance between brain networks) of functional brain networks, which is accompanied by a reduced selectivity of specific cognitive functions, finally resulting in performance decline (Goh, 2011). In line, very recent meta-analyses (Tucker-Drob et al., 2019; Blum and Holling, 2017) not only found cognitive performances to decline, but the shared variance between cognitive abilities to increase with ascending age hinting at a dedifferentiation process not only in terms of functional brain networks but also regarding the cognitive system (for discussion see also de Mooij et al., 2018).

Results of the current study show a relationship between primary processing networks and cognitive components including verbal memory, attention, and executive functions. Interestingly, looking at cognitive functions in a finer subdivision the sensitivity of primary processing networks in older adults was found to be particularly related to lower order cognitive functions (Perry et al., 2017). Since lower level cognitive abilities are suggested to be highly relevant for the performance of also higher order cognitive functions (Baltes and Lindenberger, 1997; Park and Reuter-Lorenz, 2009; Perry et al., 2017), differences in primary processing networks seem to be particularly relevant for cognitive stability in higher ages. Collectively this would suggest that an increase of shared co-varying functional activity patterns of higher order networks (i.e. higher *between*-network RSFC) is associated with a dedifferentiation of the cognitive system affecting many cognitive functions across different domains. In later adulthood, as additionally RSFC of primary processing networks are affected, lower order cognitive functions decline with the additional reinforced impairment of higher order functions (Salthouse, 1996). The current results could reflect both, the compensation and dedifferentiation theory. However, across the lifespan interconnected processes are conceivable with compensational attempts to counteract cognitive decline by the additional inclusion of higher order networks associated with control and monitoring processes. As the neural dedifferentiation increases, i.e. shared variance between functional network activity, *between*-network RSFC may no longer be supportive, but rather result in a dedifferentiated network as well as cognitive system followed by cognitive impairments. Investigations on the interrelation between age-related cognitive and brain differentiation are very limited, but may indeed be promising in uncovering specific patterns of age differentiation between brain and specific cognitive factors as exemplified

by de Mooij et al. (2018).

Altogether, we found age-related RSFC differences to be accompanied by impaired behavioral performances, with a clear distinction of effects in primary as compared to higher-order cognitive networks: lower *within*-network as well as *between*-network RSFC of primary processing networks and higher *between*-network RSFC of higher order networks was associated with lower cognitive performance.

5. Methodological considerations

The present study is based on a cross-sectional design. In order to understand the precise interrelation of RSFC changes and its specific impact on cognitive performance, longitudinal studies are warranted. However, the current cross-sectional design has the advantage of a very large sample size representative and thus largely generalizable for the general older population in West Germany.

A potential limitation of the current study pertains to the implication of a predefined functional network parcellation, which bases on data from younger adults. Methods for such imaging-based brain parcellations improved considerably over the recent decade (Eickhoff et al., 2018). Nevertheless, so far, no whole brain network parcellation based on older adults exists. Within the current study we therefore used an established brain parcellation which has frequently been used across the adult lifespan (Betzel et al., 2014; Fjell et al., 2015, 2017; Ng et al., 2016) enabling direct comparison to previous work.

By using a robust definition of established brain networks as well as performance in general cognitive domains we intended to contribute to the ongoing debate whether systematic age-related differences at the whole-brain level support the compensation or a dedifferentiation theory. Similar to previous large, population-based studies (i.e. Miller et al., 2016), the effect sizes and correlation values in the present study are comparably small. Importantly, particularly at older age, it was shown that there is a rather complex interplay between a variety of influencing factors explaining the total amount of interindividual variability between subjects with each individual factor showing limited effect within such a limited age group (e.g. Caspers et al., 2019; Bittner et al., 2019; Dekkers et al., 2019; Jannusch et al., 2017). However, the current results being very much in line with results from Perry et al. (2017) point at an existing association between primary processing networks and cognitive performance in particularly older adults, not only on single connection but also on network level. Here, we see a potential for more specific underlying mechanisms that might be highly relevant in terms of cognitive differences at higher age. Further studies are warranted to address specific brain-behavior relationships on comprehensive datasets of specifically older adults including very specific connectivity measures as well as functions of specific cognitive domains. Especially multivariate approaches including e.g. different connectivity parameters, additional structural data or specific performance in multiple cognitive domains may be promising in further disentangling the complex interplay between brain phenotypes and cognitive functions (Ferreira et al., 2016; Perry et al., 2017; Tsvetanov et al., 2016). Further, since recent studies from both functional (Schaefer et al., 2018) and anatomical data (Varikuti et al., 2018) hint at useful implementations of finer-grained parcellations (400–600 nodes), changes of the granularity of the parcellations as well as the inclusion of functional parcellations of subcortical structures would be interesting for future studies focusing on specific network-function relations, as well as regional contributions to aging and sex differences.

The current study focused on the estimation of strength values, since it is not dependent on network sizes and therefore circumvents the critical utilization of thresholding (van den Heuvel et al., 2017). Other graph-theory derived measures were not included since the interpretation of measures based on path length or clustering are crucially dependent on apparent direct connections, which is not necessarily the case in RSFC analyses (Honey et al., 2009; Zalesky et al., 2012; Zalesky et al., 2016). This could be addressed by including structural connectivity information in future work on older populations for further understanding the variability of brain network architecture and cognitive abilities in older subjects. Further it should be noted that negative edges imply a qualitatively distinct type of interaction between brain regions, which is not yet clearly interpretable (Chai et al., 2012; Fornito et al., 2013; Murphy and Fox, 2017). Negative correlations may be artificially induced when using global signal regression in functional imaging preprocessing (Fox et al., 2009; Murphy et al., 2009; Murphy and Fox, 2017). Therefore, results on negative weights should be interpreted with caution and should be understood as complementary information underpinning the findings based on positive connections. The evolution of theoretic measures dealing with signed weights or the implementation of multivariate approaches such as partial least squares correlation on the edge level (Mišić et al., 2016; Zimmermann et al., 2016) will help in solving this problem and expand our understanding of functional network dynamics.

6. Conclusion

With the current study we show that the overall trend of decreasing *within*- and increasing *between*-network RSFC shown in previous studies on young and middle-aged subjects is also applicable to older ages. In contrast to younger ages, where mainly changes of higher order networks have been reported, we found RSFC decreases within as well as between primary processing networks, i.e. the visual and sensorimotor network in higher ages. These were additionally found to be relevant for cognitive performance differences, i.e. lower RSFC being associated with lower cognitive performance. Concerning higher order networks, we found age-related increasing *between*-network RSFC especially with the sensorimotor network hinting at a compensational attempt to maintain cognitive functions by the integration of higher order control mechanisms. However, no positive correlations of *between*-network RSFC with higher order networks and cognitive performance were found. Instead, higher *between*-network RSFC was partly even associated with worse cognitive performances, which is in line with the dedifferentiation theory where a less segregated and specialized network system is associated with less differentiated cognitive performances and cognitive decline.

The current study provides additional insight into the potential interconnectedness of the dedifferentiation and compensation processes, where increases in shared variance of network activity could be interpreted as a deliberate additional recruitment of networks for e.g. control mechanisms to maintain behavioral performance. However, the age-related increasing coactivation of networks, i.e. spread of *between*-network RSFC could at some point supersede a beneficial compensation process. The diffuse rather than specific RSFC increases may then lead to an impaired capability of recruiting task-adequate and specific neural mechanism and cognitive functions consequently decline. Finally, the current study emphasizes the need for sex-stratified analyses in studies with older subjects since age-related differences in *within*- and *between*-network RSFC patterns largely differ between males and females, hinting at differential reorganizational processes in older age.

CRediT authorship contribution statement

Johanna Stumme: Investigation, Methodology, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **Christiane Jockwitz:** Methodology, Formal analysis, Writing - review & editing. **Felix Hoffstaedter:** Software, Data curation, Writing - review & editing. **Katrin Amunts:** Resources, Funding acquisition, Writing - review & editing. **Svenja Caspers:** Conceptualization, Supervision, Resources, Funding acquisition, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116756.

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