Functional Network Reorganization in older Adults:

Structural relations and its impact on sex and cognitive performance

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Johanna Stumme

aus Hamburg

Berichter: Univ.-Prof. Dr. Dr. Klaus Mathiak
Univ.-Prof. Dr. Dr. Svenja Caspers

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Ich widme diese Arbeit meinen Eltern
Karin und Rudolf Stumme

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Abbreviations

APM	Anisotropic Power Maps
AROMA	Automatic Removal Of Motion Artifacts
BOLD	Blood Oxygen Level Dependent
CAT	Computational Anatomy Toolbox
CSD	Constrained Spherical Deconvolution
CI	Confidence Interval
DAN	Dorsal Attention Network
DMN	Default Mode Network
DWI	Diffusion Weighted Imaging
EPI	Gradient-Echo Planar Imaging
FC	Functional Connectivity
fMRI	functional Magnetic Resonance Imaging
FoV	Field of View
FPN	Frontoparietal Network
ICA	Independent Component Analysis
KMO	Kaiser-Meyer-Olkin
lCI	lower Confidence Interval
LN	Limbic Network
MANCOVA	Multivariate Analysis of Covariance
MNI	Montreal Neurological Institute and Hospital (MNI) coordinate system
MPRAGE	Magnetization-Prepared Rapid Acquisition Gradient-Echo
MRI	Magnetic Resonance Imaging
NIPALS	Nonlinear Iterative Partial Least Squares Algorithm
PCA	Principal Component Analysis
PLSR	Partial Least Square Regression
RMSEP	Root Mean Squared Error of Prediction
ROI	Region of Interest
RSFC	Resting-state Functional Connectivity
$RSFC_{neg}$	Resting-state Functional Connectivity based on negative correlations
$RSFC_{pos}$	Resting-state Functional Connectivity based on positive correlations
SC	Structural Connectivity
SD	Standard Deviation
SE	Standard Error
SMN	Sensorimotor Network

TE	Echo Time
TR	Repetition Time
TPM	Tissue Probability Maps
uCI	upper Confidence Interval
VAN	Ventral Attention Network
VN	Visual Network

1 Introduction

1.1 Aging Process

In the course of normal aging, cognitive functions progressively decrease, for reviews see (Grady, 2012; Hedden & Gabrieli, 2004; Salthouse, 2004). Thereby is the performance decline variable among cognitive domains with some showing considerable decreases across age (i.e. working and episodic memory, processing speed, reasoning), while others remain rather stable (i.e. language functions, emotional processing) (Hedden & Gabrieli, 2004; Salthouse, 2004). Importantly, across individuals the progression of cognitive functions is highly variable with some individuals showing an early and steep age-related decline while others maintain their cognitive abilities up to high ages. In fact, the variability of performance between individuals increases with ascending age resulting in a particularly high heterogeneity during later decades of life (Hedden & Gabrieli, 2004; Salthouse, 2004; Ylikoski et al., 1999).

With regard to the continuing demographic change, the health of older adults is becoming increasingly important. Preserving cognitive abilities is crucial for autonomy and independent living. In turn, cognitive decline is accompanied by the increasing need for support and assistance which will become increasingly challenging regarding the aging population (Ulrich, 2004).

A promising aspect in handling the aging population is to understand potential sources of the high inter-individual cognitive variability in older adults. Sources of heterogeneity are far from being fully understood, but have been associated with a variety of neurobiological substrates including the brain's cortical structure and function (Raz et al., 2005; Whalley et al., 2004). The present work aimed at contributing to this highly important issue of identifying potential neurobiological sources for the highly inter-individual variability in higher age by particularly looking at the relation between age and the brain's functional connectivity (FC), i.e. how different areas of the brain are inter-connected. In 1.2. previous work on the relation between age and local brain properties will be described leading to the promising potential of inspecting the brain's whole-brain FC.

1.2 Neurobiology of Aging

The technological evolution of non-invasive magnetic resonance imaging (MRI) enormously increased the possibilities to study the aging process. Here, the human brain can be measured *in-vivo* which has yielded a great abundance of brain research in recent years also regarding the field of aging (MacDonald & Pike, 2021). In fact, aging has been found to influence the brain in a holistic way showing multiple neurobiological changes including the brain's cortical structure and functional activity, introduced in the following.

Brain Structure

Structural MRI provides insights into the size of cortical structures, typically measured by the volume of grey and white matter. Across the aging process, the brain atrophies showing considerable age-related decreases of the grey matter volume (Good et al., 2001; Raz et al., 2005; Resnick et al., 2003; Salat et al., 2005). Thereby, previous work on cross-sectional as well as longitudinal data found the rate of shrinkage to be region specific with frontal and temporal regions being more vulnerable as compared to parietal and occipital regions (for review see Fjell and Walhovd (2010)). Importantly, not only results from cross-sectional studies (Ferreira et al., 2014; Fjell & Walhovd, 2010; Manard et al., 2016; Seidler et al., 2010), but also longitudinal studies (Aljondi et al., 2019; Oschwald et al., 2019) indicate that age-related changes of regional grey matter volume impact the performance of the regions' associated cognitive functions. For example, Ferreira et al. (2014) found age-related grey matter volume changes of several brain regions to mediate cognitive performance differences in visuospatial functions, reaction time, mental flexibility and executive functions. Meanwhile, atrophy rates of e.g. the medial temporal cortex are considered as a valid diagnostic marker for mild cognitive impairment states (Frisoni et al., 2010; McDonald et al., 2009). A very recent study even found baseline grey matter volume differences in frontal and temporal brain regions to predict the cognitive performance changes in verbal episodic memory and executive functions over a 10-year follow-up period (Aljondi et al., 2019). Although a variety of studies has shown that grey matter volume differences indeed relate to cognitive performance differences, age-related changes of grey matter seem to not explicitly determine the rate of age-related cognitive decline. There is a substantial proportion of seniors which can tolerate greater amounts of grey matter changes than others without showing obvious cognitive impairments (Bartres-Faz & Arenaza-Urquijo, 2011; Valenzuela & Sachdev, 2006).

The Brain's Functional Activity

A factor which is sensitive to brain aging and may at least partly account for the different relations between cortical structure and performance, is the brain's functional activity. Using functional MRI (fMRI), functional activity can be measured *in-vivo* and reflects differences in the oxygenation of the cortical structures' regional blood flow which is indicative for the activation state of brain regions.

Measuring functional activity during the performance of a behavioral task (task-based fMRI) revealed differences in the activation pattern between younger and older adults. For example, previous work compared functional activation patterns between younger and older adults during the performance of the same memory task and found left prefrontal activations in younger adults while older adults activated prefrontal regions of both hemispheres (Cabeza et al., 1997; Reuter-Lorenz et al., 2000). Interestingly, in older adults, the bilateral activation pattern was associated with better memory performance. The additional recruitment of regions located in the contralateral hemisphere led to a better maintenance of cognitive performance in the older adults. In fact, common aging theories suggest the functional recruitment of additional brain areas to picture a compensation strategy in which age-related differences in cortical structure may be compensated by functional adaptations (Cabeza et al., 2002; Marstaller et al., 2015; Pistono et al., 2021; Reuter-Lorenz & Cappell, 2008). The flexible usage of brain structures is thereby considered to countervail cognitive performance decline (Bartres-Faz & Arenaza-Urquijo, 2011; Stern, 2002; Stern, 2009).

A limitation of task-based fMRI is that conclusions on functional differences can only be related to the specific cognitive function induced local brain activations. As aging was shown to affect multiple cognitive functions at once (Hedden & Gabrieli, 2004; Salthouse, 2004), the focus on a specific task may underestimate concurrent aging effects in other brain regions that are not associated with the specific task performance. Furthermore, behavioral functions require the communication, i.e. integration and coordination of multiple regions across the whole brain (Bassett & Sporns, 2017; Sporns et al., 2004). Therefore, to understand age-related variability of brain function in a more comprehensive manner, the capture of simultaneously occurring age effects across the whole brain depicts a promising approach.

A highly prevalent method that omits task-related activations and allows the investigation of functional activities across the whole brain is resting-state fMRI (Biswal et al., 2010; Margulies et al., 2010). Here, spontaneous low frequency fluctuations of the

blood oxygen level dependent (BOLD) signal are measured that occur independent of any task performance. Brain regions that share similar time dependent low frequency fluctuations in their BOLD signal can be allocated to brain networks (Damoiseaux et al., 2006; Smith et al., 2009; Yeo et al., 2011). Although functional activity during rs-fMRI is not induced by task performances, resting-state networks were found to show a very high overlap to task-induced functional activity patterns (Damoiseaux et al., 2006; Smith et al., 2009). Hence, with resting-state data, behavioral factors such as age or cognitive performances can not only be related to specific task-induced activations but to brain function in a holistic perspective capturing simultaneous aging-effects across the whole brain (Biswal et al., 2010).

Collectively, age has been found to influence local properties of cortical structure and function. Importantly, behavioral functions also require an integration and coordination of multiple regions across the whole brain underpinning the promising potential to investigate whole brain interaction and communication across aging rather than focusing on specific regions in isolation. Investigating whole brain interactions in relation to any behavioral factor requires a deliberate representation and organization of the data which is the particular purpose of the concept of a brain connectome, discussed in the next chapter.

1.3 The Whole-Brain Connectome

The brain is a complex and highly integrated system in which multiple regions are simultaneously coordinated in order to accomplish behavioral tasks (Bassett & Sporns, 2017). Therefore, modeling the brain as a whole system is highly expedient, i.e. how the integration and coordination of regions covering the whole brain are influenced by behavioral factors such as age. Investigating a whole brain system in relation to any behavioral factor, though, requires a deliberate representation and organization of the data which is purposed by the concept of a brain connectome (Bullmore & Sporns, 2009, 2012; Sporns et al., 2004). A connectome is understood as the collection of multiple brain regions (nodes) and the connections (edges) between them (Fornito et al., 2013). Accordingly, the determination of a connectome is first and foremost dependent on the definition of brain regions (1.3.1) and the connectivity between them (1.3.2).

1.3.1 Parcellation

The definition of nodes is a key factor determining the scale (macro- or microscale) on which brain connectivity is examined. Whereas investigations at the microscale focus on the basic elements of brain architecture, i.e. neurons and their dendritic and axonal projections, analyses on the macroscale address the organization of large-scale pathways allowing the incorporation of regions across the whole brain.

At the macroscale different atlases can be used parcellating the brain into regions by using anatomical information such as anatomical landmarks (sulci and gyri) (Desikan et al., 2006) or cytoarchitectonic segmentations, the latter considering different arrangements of cells, i.e. their distribution and composition across the brain (Amunts et al., 2020). Furthermore, the brain can be parcellated into regions by considering its functional properties, i.e. the varying functional BOLD activations (Power et al., 2011; Schaefer et al., 2018; Yeo et al., 2011). As described above, networks defined on the similarity of resting-state BOLD activations were found to show a very high overlap to functional activity patterns that are activated during task (Damoiseaux et al., 2006; Smith et al., 2004; Yeo et al., 2011). For example, the very well-known and highly established functional network parcellation from Yeo et al. (2011) divides the brain into seven distinct functional networks. This parcellation scheme was established based on intrinsic resting-state functional activity "from 500 participants (collated with a 500 subjects replication cohort). Networks were delineated by clustering the whole-brain depending on their similarity of functional activation profiles over all subjects" (Stumme et al., 2020, page 3). Of these seven resting-state networks, two networks are associated with processing

primary functions including the visual network (VN) related to the processing of visual functions and the sensorimotor network (SMN) related to motor performance. Furthermore, the parcellation scheme comprises five networks supporting higher-order cognitive functions: two networks are associated with attention (dorsal- (DAN) and ventral attention network (VAN)), the limbic network (LN) is related to memory performance and the frontoparietal network (FPN) with processing executive functions. Lastly, the default mode network (DMN) is especially activated when a person rests and is internally focused (reflective and emotional processing) and deactivated as the person is externally focused, i.e. due to attention or goal-directed tasks. Hence, parcellations based on functional BOLD activations can be used to directly link brain networks to the processing of behavioral tasks while regions defined by e.g. anatomical landmarks provide no or only little insight to cognitive processing.

Based on the definition of brain regions (nodes), the connectivity between them (edges) can be estimated resulting in a whole brain connectome that indicates how each pair of regions is interconnected.

1.3.2 Connectivity

There exist multiple possibilities to define connectivity between regions. For example, while FC is a statistical dependency defined by the correlation of regions' functional activations, structural connectivity (SC) refers to the white matter fiber tracts physically connecting brain regions via many axons between neural cells. Focus of the current work was the whole brain FC and its relation to age. As SC is the underlying construct to exchange information between regions, the second study additionally addressed the relation of whole brain functional to SC. Therefore, procedures of defining FC and SC will be explained in more detail.

Functional connectivity

FC depicts the time dependent coactivation pattern between regions. The regions' activation pattern is measured by differences in the oxygenation of the regional blood flow across time (BOLD signal) indicating the regions' activation state across time (Damoiseaux et al., 2006; Logothetis & Wandell, 2004). For each of the defined regions in a connectome, BOLD timeseries can be extracted reflecting the mean timeseries across all voxels belonging to the defined region. FC is then defined as the (Pearson's) correlation of regions' BOLD timeseries, with a high correlation indicating a high shared coactivation pattern and therewith a strong functional connection strength between regions (Fornito et al., 2010). Besides positive correlations (FC_{pos}), i.e. the coherent

activity states across time, brain regions can also be anticorrelated (FC_{neg}). In this case, brain regions are depicted by anticyclical activity states meaning that if region A is activated, region B is deactivated and vice versa. With negative correlations implying a qualitatively distinct type of the brain region's interaction and these being not yet clearly interpretable (Chai et al., 2012; Fornito et al., 2013; Murphy & Fox, 2017), most studies omit anti-correlations and focus on the investigation of FC_{pos}.

Structural connectivity

SC refers to white matter fiber tracts physically connecting brain regions and measured *in-vivo* using diffusion weighted imaging (DWI) (Bammer, 2003; Hagmann et al., 2006). Using DWI, the diffusion properties of water molecules can be characterized for each voxel in the white matter. Since water molecules diffuse preferentially in directions free of barriers, they move rather along than perpendicular to axons which results in an anisotropic diffusion pattern reflecting the orientation of fibers (Beaulieu, 2002; Pierpaoli et al., 2001). Based on local (voxel-wise) estimates on the white matter fiber orientations white matter pathways can be reconstructed using fiber tracking algorithms that propagate streamlines according to the water diffusion preference (Behrens et al., 2003; Jeurissen et al., 2014). Thereby, the number of streamlines connecting two regions is indicative of the connection strength.

Based on the compiled connectome which represents the brain as a collection of brain regions (nodes) and the connections between them (edges) quantitative parameters can be estimated using a graph-theoretical approach allowing the characterization and comparison of individual connectomes.

1.3.3 Characterizing the Whole-Brain Connectome

As described above, a brain connectome is comprised by multiple nodes and edges. In order to compare individual connectomes across subjects or in relation to behavioral factors, the multitude of data within the connectome can be compiled to meaningful quantitative parameters that optimally characterize the composition of a connectome. Therefore, graph-theoretical approaches can be used (Bassett & Sporns, 2017; Bullmore & Sporns, 2009, 2012; Fornito et al., 2013). Graph theory is a mathematical approach to study complex systems of interacting elements. With regards to brain connectivity, the connectome is a graph comprising a number of nodes (elements) and their combining edges (interactions). Graphs can be constructed including different levels of information. While binary graphs only represent the presence or absence of connections (i.e. interactions), weighted graphs additionally give information about the strength of existing

connections (Figure 1 i,ii). Furthermore, it can be differentiated between undirected or directed graphs, the latter giving additional information on the origin and destination of a connection, i.e. whether information transfers from region A to B or vice versa (Figure 1 iii).

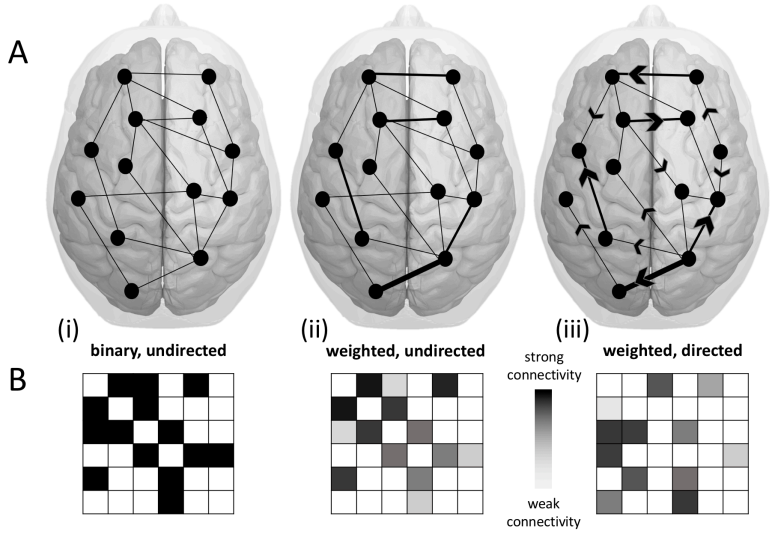


Figure 1: Brain connectome visualized as graphs and matrices.
Columns and rows represent nodes, elements represent connections between pairs of regions: (i) binary (symmetric) graph in which lines (A) and painted elements (B) represent existing edges; (ii) weighted (symmetric) graph in which thickness of lines (A) and color of elements (B) indicate connections strength; (iii) directed (asymmetric) graph in which errors additionally indicate directionality of connections.

Based on a compiled graph, different features of interest can be combined to quantitative parameters which allow a characterization and comparison of graphs also in relation to behavioral factors (Fornito, 2016; Rubinov & Sporns, 2010). For example, with regards to the brain connectome, connectivity parameters can be estimated that combine all connections within a given network (Figure 2, solid lines) or those between networks (Figure 2, dashed lines). Thereby, intra-network connectivity comprises connections between nodes belonging to the same network (Figure 2, A). The connectivity with nodes outside its related network can either comprise connections with nodes of any other network (inter-network, Figure 2, C) or more specifically with nodes belonging to one specific other network (between-network, Figure 2, B). By the determination of intra-, inter-, or between-network connectivity, one can consider how many connections exist between nodes (binary graph) or even how strong the connections between them are (weighted graph). Quantitative parameters that were chosen to be a meaningful representation of the brain's connectome are described in more detail in the study-specific methods.

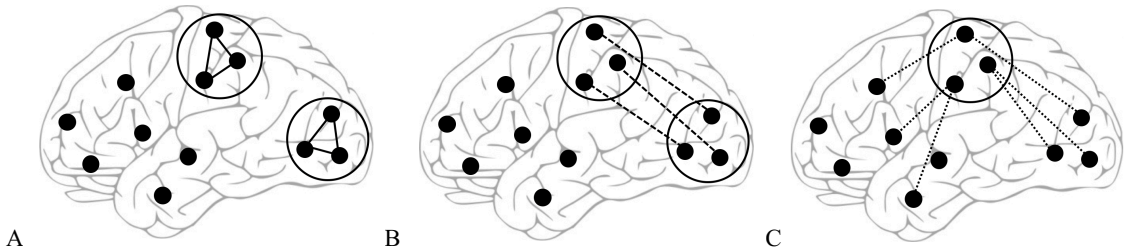


Figure 2: Visualization of quantitative graph parameters for a brain connectome.
Dots represent brain regions and are circled if they belong to the same network. Lines represent connections between regions with solid lines indicating edges within a network (intra-network, A), dashed lines between two specific networks (between-network, B) and dotted lines from network nodes to nodes belonging to any other than its respective network (inter-network, C).

After explaining how a brain connectome can be defined and characterized, focus of the next chapter is to review the current state of research regarding the functional brain connectome in the aging process, its impact on cognitive performance and the relation to sex and the structural connectome (1.4).

1.4 Whole-Brain Functional Connectivity

Results of recent years have not only shown that the whole-brains' resting-state functional connectivity (RSFC) organization measured by rs-fMRI data (functional connectome) is indicative for behavioral performances in various diseases including Alzheimer's disease (Lin et al., 2018), Parkinson's disease (Wu et al., 2009) or epilepsy (Zhang et al., 2010), but can also be used to predict gender (Zhang et al., 2018). These results are highly promising and hint at an existing relation also between RSFC and age which may potentially also explain differences in cognitive performance of older adults. In the following sections the current state of research regarding the relation between RSFC and age (1.4.1), cognitive performance (1.4.2) and sex (1.4.3) will be given. Furthermore, results on a potential relation between RSFC and SC are described (1.4.4) unveiling open issues and leading to the aim of the current work.

1.4.1 Age-related Differences in Functional Connectivity

In young adults, an efficient functional network configuration associated with high cognitive performance is characterized by a balance between connections of regions belonging to the same (intra-network RSFC) and other networks (inter-network RSFC) (Bullmore & Sporns, 2012; Sadaghiani et al., 2015; Sporns, 2013; Wig, 2017). Across the lifespan, however, this modulated and specialized network configuration decomposes showing decreasing intra-network RSFC and increasing inter-network RSFC (Betzel et al., 2014; Cao et al., 2014; Chan et al., 2014; Ferreira et al., 2016; Jockwitz & Caspers, 2021; Mowinckel et al., 2012; Tsvetanov et al., 2016; Varangis et al., 2019). Similar effects have been identified when comparing groups of younger adults to older adults, which is especially applicable to networks involved in higher-order cognitive functions such as the DMN, FPN and DAN (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). Hence, while within these networks, RSFC decreases across adulthood, the RSFC between networks increases. This leads to the open question of underlying causes and a possible behavioral impact. Previous research analyzing age-related RSFC differences, mainly included participants across the whole adult lifespan or performed group comparisons between younger and older adults. Very recently, a large cohort study of only older adults indeed found the age-related shift towards higher network integration (Zonneveld et al., 2019). This, however, was not related to the participants cognitive performance. As the older age group is particularly vulnerable in terms of cognitive decline and depicted by highly variable cognitive performance (Hedden & Gabrieli, 2004;

Salthouse, 2004; Singh-Manoux et al., 2012), investigating the interrelation between RSFC and cognition in older adults may be highly promising. So far, the older adults functional brain network reorganization and its association with cognitive performance is still an unsolved issue.

1.4.2 Relation between Functional Connectivity and Cognitive Performance

Cognitive abilities are assumed to be optimal in cases of a balanced functional system between network segregation and integration, for review see e.g. Wig (2017). Similarly, a higher education was found to be associated with a higher segregated network system (Marques et al., 2016). Interestingly, the impact of an age-related shift towards a higher network integration as described in 1.4.1, is differentially interpreted. On the one hand, the dedifferentiation theory considers the age-related shift to represent an 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). In contrast, the compensation theory suggest an over-recruitment of brain regions, i.e. additional activations, to represent a compensational response that counteracts the age-related decline of brain function to maintain successful performance (Cabeza et al., 2002; Heuninckx et al., 2008; Marstaller et al., 2015; Reuter-Lorenz & Cappell, 2008; Roberts & Allen, 2016). By the use of a multivariate approach, Perry et al. (2017) analyzed single RSFC estimates between pairs of regions across the whole brain in older adults (70-90 years) and found especially connections within primary processing networks to be associated with cognitive performance. Studies focusing on the relation between network-level RSFC and cognitive performance, though, show contradictory results. For example, "in a longitudinal approach, Ng et al. (2016) found an age-related decline of intra-network RSFC in the DMN as well as in the executive control network which was not found to be associated with cognitive performance. Instead, they found a negative correlation between inter-network RSFC of the DMN and processing speed." (Stumme et al., 2020, page 2). On the other side, "Persson et al. (2014) found intra-individual RSFC within the DMN to remain stable across a period of six years within a group with comparable age range. In the same study, they found intra-network RSFC changes of the DMN 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 DMN to be associated with worse cognitive performance in verbal and visual memory tasks, pointing at an overall negative correlation between cognitive performance and intra-network RSFC." (Stumme et al., 2020, page 2). In summary, in particularly older adults, there exists inconsistent

evidence regarding the relation between network-based RSFC differences and cognitive performance.

1.4.3 Sex-related Differences in Functional Connectivity

A variety of studies indicate that males and females are significantly different in terms of their cognitive abilities. For example, while females outperform males in functions regarding verbal and episodic memory, males typically perform better in visual memory tasks (de Frias et al., 2006; Mansouri et al., 2016; McCarrey et al., 2016). In older adults, a very recent work found cognitive profiles to be different for males and females pointing at different processing styles to exist also in old age (Jockwitz et al., 2021). With regards to these sex-related behavioral differences, differences in the functional brain architecture may be assumed. And indeed, FC patterns have been found to show differences between males and females (Allen et al., 2011; Joel et al., 2015; Satterthwaite et al., 2015; Tomasi & Volkow, 2012b; Zonneveld et al., 2019). For example, while females were found to show higher local connectivity density (Tomasi & Volkow, 2012b) and higher intra-network RSFC, males are depicted by higher inter-network RSFC (Satterthwaite et al., 2015). Furthermore, considering age-related reorganizations, there have been sex-related differences found: "Across the lifespan, females not only exhibited overall higher intra-network RSFC (Allen et al., 2011), but also showed less age-related decreases of RSFC in the DMN and LN (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 more increasing inter-network connectivity and simultaneously decreasing intra-network connectivity as compared to females." (Stumme et al., 2020, page 2). Conclusively, previous results hint at RSFC differences between males and females in younger adults. Furthermore, the age-related progressions of RSFC were found to be sex-specific raising the question of how sex-related differences manifest in particularly older adults.

1.4.4 Relation between Functional and Structural Connectivity

Given the fact that structural connections represent the underlying construct for functional communication, age-related differences in RSFC may be related to differences in SC. In fact, SC was also found to change across the aging process. Previous lifespan studies found inverted U-shaped trajectories of SC, characterized by integrity increases during childhood and adolescence (Imperati et al., 2011; Yeatman et al., 2014), with a peak at middle adulthood (about 30-40 years) and followed by decreases at older age spanning the whole brain with a particular vulnerability of regions located within the frontal lobe

(Antonenko & Floel, 2014; Betzel et al., 2014; Gunning-Dixon et al., 2009; Puxeddu et al., 2020; Yeatman et al., 2014; Zhao et al., 2015).

So far, age-related differences in brain function cannot be directly linked to SC decline. While there exist many studies characterizing age-related differences of functional and structural networks in isolation, for reviews see (Damoiseaux, 2017; Wig, 2017; Zuo et al., 2017), much less is known about their mutual relationship in aging. Studies investigating this structure-function relation found overall positive correlations between SC and RSFC, although the existence of SC is more highly indicative for existing RSFC than vice versa, for reviews see (Damoiseaux, 2017; Damoiseaux & Greicius, 2009; Park & Friston, 2013; Straathof et al., 2019; Wang et al., 2015). In cases of strong SC, the RSFC between regions was also found to be high. In turn, RSFC was found to be less directly related to SC, in the way that RSFC might also be high between regions that are not directly physically connected, potentially explained by indirect connections (Greicius et al., 2009; Honey et al., 2009; Jung et al., 2017; Misic et al., 2016; van den Heuvel et al., 2009; Zimmermann et al., 2016). Across the adult lifespan, decreasing SC was found to be accompanied by functional reorganizations at the network level (Betzel et al., 2014). The relation between SC and RSFC was found to strengthen with increasing age hinting at RSFC to more strongly rely on stable SC in older adults (Zimmermann et al., 2016). This is an interesting aspect especially with regards to the uncertainty of potential sources for age-related RSFC differences (1.4.1). Although RSFC differences are thought to picture strategic adaptions to maintain cognitive performance on the one hand, there is a large quantity of studies showing age-related RSFC reorganizations to be associated with worse performance. This raises the question what other factors explaining age-related RSFC changes exist, and underpins the need to investigate RSFC in relation to SC in older adults.

2 Aim of the Study

Aim of the current work was to contribute to the highly important prerequisite of identifying potential neurobiological sources for the high inter-individual variability of cognitive performance in older adults. Thereby, main objective of the present work was to investigate the age-related reorganization of RSFC. To the current state of research, a great quantity of studies exists pointing at age-related differences of RSFC across the adult lifespan. In fact, these age-related differences have been associated with differences in cognitive performance. So far, however, the majority of studies focused on RSFC changes across the whole adult lifespan. Especially in the older age group, in which cognitive decline is particularly variable, evidence of how functional brain networks reorganize and how these relate to cognitive performance is inconclusive and will be focus of the first study. Furthermore, since previous studies on younger adults indicate that sex differences do not only exist in cognitive performance, but also regarding RSFC (including different progressions across age), the open question on how the network configuration in older adults differs between males and females is additionally addressed.

Sources of age-related RSFC differences are still a matter of debate. On the one hand, it is understood as a compensation strategy to cope neurodegenerative decline by functional adaptions to maintain cognitive performance. However, increasing of non-network specific activations have been associated with worse performance leading to the question what other underlying factors there may be explaining the depicted RSFC changes. As SC represents the underlying construct for functional communication, a high relation between them would be expected. So far, however, very little is known about their mutual relationship. Relating RSFC to SC may unveil potential sources for RSFC differences in the older population and was therefore focus of the second study. Using a multivariate approach considering whole-brain region-wise connectivity estimates of both modalities within one statistical model, differences between RSFC and SC were assessed that are together characteristic for the older adult's brain.

Hence, to contribute to the understanding of the so far unsolved issue of highly inter-individual variable aging processes in older adults, the current work implemented two studies: Within the first study, whole-brain RSFC differences in older adults, its relation to sex and potential impact on cognitive performance were investigated. Building upon these results, the second study aimed at identifying potential sources of the depicted age-related RSFC differences and analyzed its relation to SC.

3 Data Basis for both Studies

3.1 Study Population

Participants of the current work were based on the 1000BRAINS project (Caspers et al., 2014), a population-based study which was designed to investigate brain structure and function. Particularly, 1000BRAINS aims at investigating the brains variability during aging as well as its relation to behavioral, environmental and genetic factors. The sample of 1000BRAINS (n = 1314, 18-87 years, 582 females) were drawn from the 10-year follow-up cohort of the Heinz Nixdorf Recall Study, which is an epidemiological population-based study elaborating risk factors for atherosclerosis, cardiovascular disease, cardiac infarction, and cardiac death (Schmermund et al., 2002), as well as the associated Multi-Generation Study. For 1000BRAINS, there were no exclusion criteria other than eligibility for MRI measurements applied as the study aims to characterize aging at the level of the general population (Caspers et al., 2014). These included cardiac pacemakers, coronary artery stents, surgical implants or prostheses in head or trunk, tattoos or permanent make-up on the head or any history of neurosurgery. Further, MR imaging was stopped as participants experienced claustrophobia or dental implants were found to cause artefacts in the brain images. Prior to the inclusion in 1000BRAINS, all subjects gave written informed consent. The study protocol of 1000BRAINS was approved by the Ethics Committee of the University of Essen in Germany.

3.2 MRI Acquisition

MRI was performed using a 3T Siemens Tim-TRIO MR scanner with a 32-channel head coil (Erlangen, Germany) located at the Forschungszentrum Jülich in Germany. For the investigation of SC and RSFC, different sequence images were included in the current work (for detailed description of the 1000BRAINS study protocol also see Caspers et al. (2014)): "For 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). For rs-fMRI, a BOLD gradient-echo planar imaging (EPI) sequence was with 36 transversally oriented slices (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) was used, lasting for ~11 minutes and producing 300 volumes. During rs-fMRI 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." (Stumme et al., 2020, page 3). And lastly, diffusion tensor images were acquired using the following parameters: (60 directions, HARDI subset) EPI, TR = 6.3s, TE = 81ms, 7 b0-images (interleaved), 60 images with b = 1000s/mm2, voxel resolution = 2.4×2.4×2.4mm3; HARDI (120 directions) EPI, TR = 8s, TE = 112ms, 13 b0-images (interleaved), 120 images with b = 2700s/mm2, voxel resolution = 2.4×2.4×2.4mm3.

4 Study 1: Functional Network Reorganization

With the first study, the current work aimed at assessing systematic functional network differences in older adults, how these differ across age and sex and potentially relate to cognitive performance differences. With the results it was targeted to contribute to the understanding what neurobiological sources there may be for the highly variable age-related performance decline in older adults.

In the current work, a large sample of older adults from the 1000BRAINS study (Caspers et al., 2014) was used to disentangle the interplay of RSFC differences within and between functionally defined whole-brain networks. For the quantification of whole-brain RSFC differences (Bassett & Sporns, 2017; Biswal et al., 2010; Bullmore & Sporns, 2009, 2012; Rubinov & Sporns, 2010) a graph-theoretical approach was utilized (described in 1.3.3). As suggested by previous research (1.4.1), overall intra-network decreases and between-network increases of RSFC were expected. Given the non-conclusive evidence on cognition (1.4.2), only a tentative hypothesis was made expecting intra-network RSFC being positively related to cognitive performance. To allow for a holistic perspective, exploratory analyses on this relation was carried out. This was also favored to analyze sex-related differences, as evidence in older subjects is yet inconclusive (1.4.3).

4.1 Material & Methods

4.1.1 Sample

At the time of beginning of the first study, "the sample of 1000BRAINS comprised 951 older adults (aged 55-87 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 three missing values of the neuropsychological assessment" (Stumme et al., 2020, page 3) (n = 46; see section 4.1.5 for further description) were excluded. Further, participants with preprocessing failure of structural T1 and/or functional imaging data were excluded (n = 101; e.g. artifacts in structural scans, problems during normalization procedure or denoising, see section 4.1.2 for further description). "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). 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." (Stumme et al., 2020, page 3) (see Table 1).

Table 1: Sample distribution of the first study.

Whole group, female and male regarding age, education and the risk of having dementia: mean (sd).

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

4.1.2 Image Preprocessing

Functional "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 (5mm at FWHM) [SUSAN (Smith & Brady, 1997)]. Additionally, [**I**ndependent **C**omponent **A**nalysis-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 & Smith, 2001)]." (Stumme et al., 2020, page 3). Based on the preprocessed mean AROMA functional data, quality control was performed to detect potential misalignments by performing the "check sample homogeneity using standard deviation (SD) across sample" function provided by the **C**omputational **A**natomy **T**oolbox [CAT12 (Gaser & Dahnke, 2016)]. Participants that were considered as outlier were additionally manually checked and excluded from further analyses as the individual image did not match the MNI152 template. AROMA particularly focuses on the correction of intensity artifacts that are induced by head motion. To further check for each participant volume-wise severe intensity dropouts, the established algorithm by Afyouni and Nichols (2018) was performed. Here, p-values for spikes (called DVARS) on the already preprocessed functional data are generated indicating volumes that show corrupted spikes. Participants were excluded as 10% of their functional volumes were detected as dropouts.

4.1.3 Functional Connectome

To analyze RSFC within established functional networks, the cortical parcellation of Yeo et al. (2011) was used. In fact, building upon the 7-network parcellation distinguishing the known functional resting-state networks previously described in 1.3.1 (VN, SMN, DAN, VAN, LN, FPN and DMN), Yeo et al. (2011) additionally subdivided the brain into a 17-network parcellation scheme depicting more fine-grained classification of brain regions. In fact, the 17-network parcellation provides 83 separate regions (with cluster sizes >100 voxels, collapsed over hemispheres), that in turn can be allocated to the 7-network scheme (Figure 3, additional information on label names and MNI-coordinates can be found in Supplementary Table 1). "Since the transformation from subject to standard space results in interindividual variance of cluster configuration, all regions of interests (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." (Stumme et al., 2020, page 3).

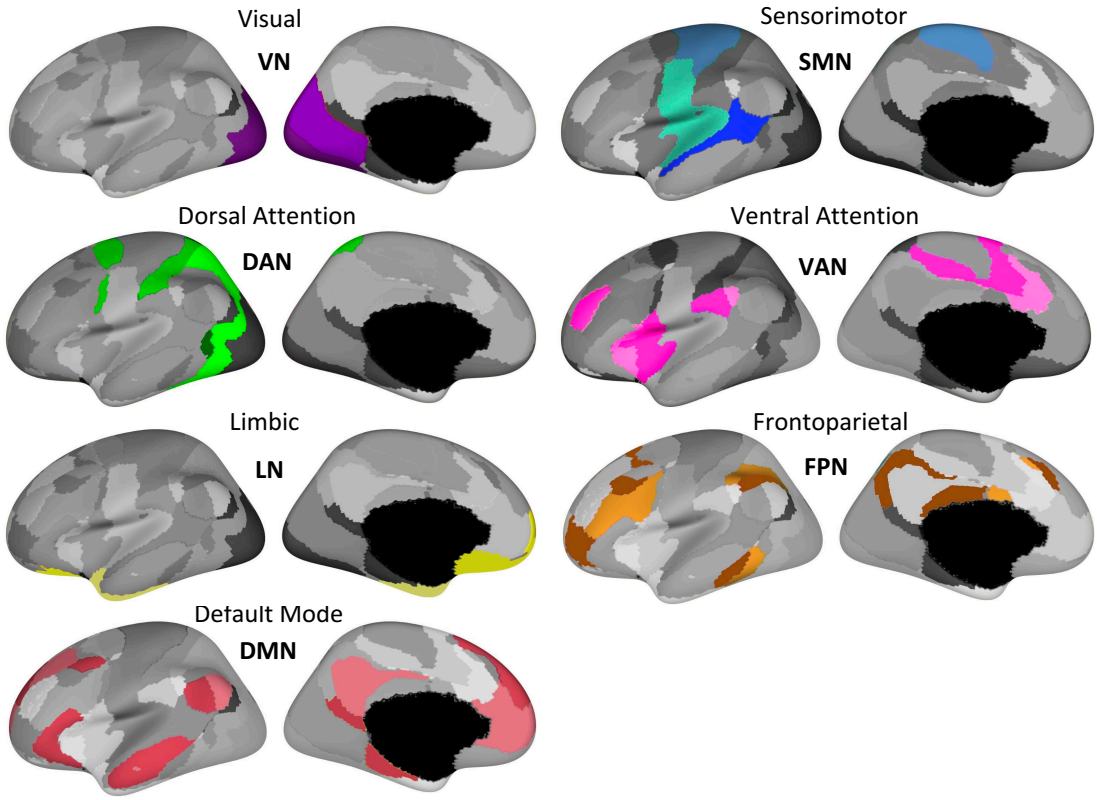


Figure 3: Functional network parcellation in accordance to Yeo et al. (2011).
(VAN = violet, SMN = blue, DAN = green, VAN = pink, LN = yellow, FPN = orange, DMN = red).

For FC, mean time series spanning 296 time points (discarded first four of in total 300 volumes) were extracted node-wise [fslmeants (Smith et al., 2004)], i.e. from each defined brain area of the preprocessed rs-fMRI data by averaging the time series across all voxels corresponding to that node. Pearson's product-moment correlation was used to estimate the RSFC between nodes by correlating the respective average BOLD time series. Performing this for each pair of node resulted in a symmetric n*n matrix (n = 83 nodes), each entry (i.e. edge) representing a Pearson's correlation coefficient between the respective nodes. In RSFC, correlations are based on minimal BOLD activity fluctuations enhancing the possibility that edges may reflect measurement noise rather than true signal. Therefore, an additional preprocessing step was included to minimize the amount of edges that are caused by noise: "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 1,000 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-individually different network sizes (i.e. different overall 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 size." (Stumme et al., 2020, page 4).

By applying a Fishers r-to-z transformation, the adjacency matrix was transformed into z-scores. Lastly, integrating positive and negative correlations into the estimation of connectivity parameters (i.e. strength value, see 4.1.4) may lead to a mutual suppression by canceling each other out. Therefore, separated RSFC matrices were generated, one only including positive correlations ($RSFC_{pos}$) and the second one only including absolute values of negative correlations ($RSFC_{neg}$).

4.1.4 Network Parameters

The software bctpy (a python version of the Brain Connectivity Tollbox, brain-connectivity.toolbox.net) with "network parameters as defined in Rubinov and Sporns (2010) was used to quantify the FC 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." (Stumme et al., 2020, page 4). Composite intra-, inter- and between-network RSFC were calculated for each participant and are defined as follows, illustrated in Figure 2:

(i) *Intra-network* RSFC: sum of strength values from each node to all nodes within its related network,

(ii) *Inter-network* RSFC: sum of strength values from each node to all nodes outside the related network,

(iii) *Between-network* RSFC: sum of connections between two specific networks.

Furthermore, a combined quantitative parameter was calculated, capturing the intra-network RSFC in relation to the inter-network RSFC. This ratio score can be understood as an index of the network's segregation (also see Chan et al. (2014)) and is quantified as follows:

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

While a ratio-score of 1 is indicative for a maximally high network segregation (high intra- and low inter-network RSFC), a ratio-score of -1 characterizes a maximally high network integration (low intra- and high inter-network RSFC). A score of zero represents a balanced system.

4.1.5 Neuropsychological Variables and Principle Component Analysis

"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 Table 2). In the case of one, two or three missing values in the neurological assessment (>3 missing values led to exclusion, see above), the missing values were replaced by the 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 .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 (Abdi, 2003). All steps were performed using IBM SPSS Statistics 24 (http://www-01.ibm.com/software/de/analytics/spss/)." (Stumme et al., 2020, page 5).

Table 2: Test descriptions of all neuropsychological tests used within the first study.

Further descriptions can also be found in Caspers et al. (2014), Jockwitz et al. (2017) as well as Stumme et al. (2020). Factor loadings and components are results of the performed PCA (described in 4.2.3). Bold printed numbers indicate the according component affiliation.

Test (Reference)	Function	mean(SE)	Description	Factorloadings			
				1	2	3	Components
Regensburger Wortflüssigkeitstest (Aschenbrenner et al., 2000)	Semantic verbal fluency	24.10 (0.24)	Total number of generated words belonging to the category "Berufe (job)" (2min.)	**0.749**	0.107	0.026	**Verbal Memory & Fluency**
Regensburger Wortflüssigkeitstest (Aschenbrenner et al., 2000)	Phonemic verbal fluency	18.74 (0.23)	Total number of generated words beginning with the letter B (2min.)	**0.681**	-0.072	0.226	
Verbaler Gedächtnistest (Lux et al., 2012)	Verbal episodic memory	41.8 (0.38)	Total number of free recalled words from a list comprised by 15 words (sum score of 5 trails)	**0.573**	0.133	0.189	
Wortschatztest (Schmidt & Metzler, 1992)	Vocabulary	31.06 (0.17)	Total number of correctly identified real words within rows of pseudo words	**0.554**	0.022	0.483	
Fünf-Punkte-Test (Jülich version; similar to: Regard et al., 1982)	Figural fluency	26.69 (0.27)	Total number of unique designs created by connecting 5 dots (3min.)	**0.494**	0.41	0.185	**Non-verbal Memory & Attention**
Block-Tapping-Test (Schelling, 1997)	Visual spatial working memory	5.44 (0.03)	Total number of correctly repeated blocks given in a sequence (sum score forward)	-0.087	**0.682**	0.088	
Visual pattern (Jülich version; similar to: Della Sala et al., 1997)	Visual working memory	7.79 (0.06)	Total number of correctly memorized matrix patterns of black and white squares with increasing complexity	0.131	**0.653**	0.298	
Block-Tapping-Test (Schelling, 1997)	Visual spatial working memory	4.70 (0.04)	Total number of correctly repeated blocks given in a sequence (sum score backward)	0.043	**0.632**	0.127	
Benton-Test (Benton et al., 2009)	Figural memory	16.29 (0.29)	Total number of errors made during the free recall of 20 previously presented figures	0.421	**0.53**	0.39	
Alters-Konzentrations-Test (Gatterer, 2008)	Selective attention	34.20 (0.39)	Time (sec.) to cancel target figures out of similar distractor figures	0.48	**0.526**	0.024	
Trail Making Test (part A) (taken from CERAD-Plus; Morris et al., 1989)	Processing speed	39.82 (0.49)	Time (sec.) to connect randomly arranged numbers in ascending order (part A)	0.447	**0.512**	-0.039	
Leistungsprüfungssystem 50+ (Subtest 3) (Sturm et al., 1993)	Problem solving	20.78 (0.18)	Total number of correctly tagged irregularities in serials of geometric figures (5min.)	0.373	**0.489**	0.46	
Zahlennachsprechen (from Nürnberger Alters-Inventar; Oswald and Fleischmann, 1997)	Verbal short term memory	6.1 (0.04)	Total number of correctly repeated sequences of numbers (sum score forward)	0.041	0.045	**0.741**	**Verbal Working Memory & Executive Functions**
Zahlennachsprechen (from Nürnberger Alters-Inventar; Oswald and Fleischmann, 1997)	Verbal working memory	4.7 (0.04)	Total number of correctly repeated sequences of numbers (sum score backward)	0.094	0.208	**0.691**	
Trail Making Test (part B-A) (taken from CERAD-Plus; Morris et al., 1989)	Concept shifting	53.52 (1.33)	Time difference (sec.) between connecting alternately numbers and letters in ascending order (part B) and (part A)	0.371	0.223	**0.484**	
Farb-Wort-Interferenztest (Jülich version; similar to: Bäumler, 1985; Stroop, 1935)	Susceptibility to interference	43.21 (0.82)	Time difference (sec.) between naming the ink in which color words were printed (part 3) and naming the color of squares (part 2)	0.323	0.204	**0.394**	

4.1.6 Statistical Analysis

First, to test how RSFC is related to age as well as sex, Multivariate Analysis of Covariance (MANCOVA) were performed as implemented in IBM SPSS Statistics 23 (http://www-01.ibm.com/software/de/analytics/spss/). Thereby, four separate linear models were employed with RSFC estimates as dependent variables (either intra-, inter-, between-network RSFC or the ratio-scores of the given networks), and age as well as sex as independent predictors (corrected for education level). "To account for potential interactions between the predictor variables, interaction effects between age and sex as well as education on all $RSFC_{pos}$ values were tested. All results were considered significant at $p < 0.05$. Pairwise comparisons within each MANCOVA were Bonferroni-corrected for multiple comparisons (intra-, inter-network $RSFC_{pos}$ and ratio-scores: p = 0.05 / 7 networks = 0.007; between-network $RSFC_{pos}$: p = 0.05 / 21 network combinations = 0.002). To additionally test robustness of effects a bootstrap validation was performed (1,000 bootstrap samples, 95% confidence interval [(CI)])." (Stumme et al., 2020, page 5). For significant age effects, regression analyses were conducted to obtain slope estimates and variance information.

As post-hoc analyses the relation between $RSFC_{pos}$ and cognitive performance was assessed. Therefore, "partial correlations between all $RSFC_{pos}$ values (7 intra- 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. To test the robustness of correlations between cognitive performance and $RSFC_{pos}$ a bootstrap validation was performed (1,000 bootstrap samples, 95% CI). In cases where both, associations of $RSFC_{pos}$ with a cognitive component (results derived from partial correlations, $p < 0.05$) as well as with age (results derived by previous MANCOVAs, $p < 0.05$) were found, a mediation analysis was conducted to test whether these concurrent effects may also be significantly related [(Figure 4)]. Specifically, it was tested to what extent the age-related decline in cognition is mediated by the age-related differences in $RSFC_{pos}$ (covariates: sex, education and the two remaining components, respectively). Comparably, for all $RSFC_{pos}$ values that where associated with cognitive performance and additionally showed sex-related differences, it was tested whether sex-related differences in $RSFC_{pos}$ 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 & Preacher, 2014), implemented in IBM SPSS Statistics 23. The significance of indirect effects was computed using bootstrapping procedures. For 1,000 bootstrapped samples

unstandardized indirect effects were generated and the 95% CI was computed by determining the indirect effects at the 2.5th and 97.5th percentiles [(Table 5)].” (Stumme et al., 2020, page 5).

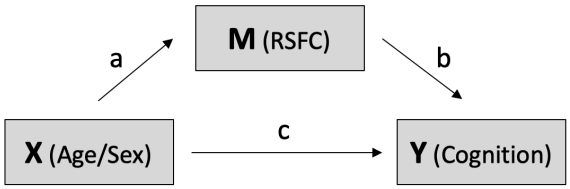


Figure 4: Visualization of the mediation analyses performed.
Statistical approach to test die mediation effect of RSFC differences (M) on the relation between age or sex (X) and cognition (Y).

Subsequently, also the effect of age and sex on negative strength values was investigated, i.e. anticorrelations ($RSFC_{neg}$), using the same procedure as described for $RSFC_{pos}$.

4.2 Results

In the first study, the older adults' whole-brain functional network architecture and its relation to age and sex as well as its potential impact on cognitive performance was assessed. Before inspecting any network parameters, the network density was related to age ($F = 0.909$, $p = 0.341$), sex ($F = 1.041$, $p = 0.308$) and the educational level ($F = 2.376$, $p = 0.124$) to preclude that systematic differences in network parameters found are solely based on different network sizes. With the results revealing no significant relations, all subsequently reported effects can be attributed to systematic network differences rather than the network sizes per se. And indeed, results revealed age to be associated to not only intra- and between-network $RSFC_{pos}$ but also the ratio of intra- and inter-network $RSFC_{pos}$ (described in 4.2.1). Importantly, age-related differences in $RSFC_{pos}$ were found to mediate the cognitive performance differences in older adults (described in 4.2.2). Regarding sex-related differences, results indicate males and females to indeed exhibit a diverging $RSFC_{pos}$ network architecture (described in 4.2.3). All significant effects regarding the relation between RSFC and age, its association to sex as well as cognitive components are collectively visualized in Figure 5. To complete the understanding of whole-brain RSFC differences, results on $RSFC_{neg}$ are additionally described in relation to the results on $RSFC_{pos}$ at the end of each section.

Further worthy of note, in Supplementary Material all network-wise $RSFC_{pos\&neg}$ estimates (standard error, SE) are denoted for males, females and the whole group (Supplementary Tables 2, 3). Further, additional information can be found regarding the effects between education and $RSFC_{pos}$ (Supplementary Table 4). Lastly, the effects between $RSFC_{neg}$ and age and sex are denoted in Supplementary Table 5, and visualized in Supplementary Figures 1 and 2, respectively.

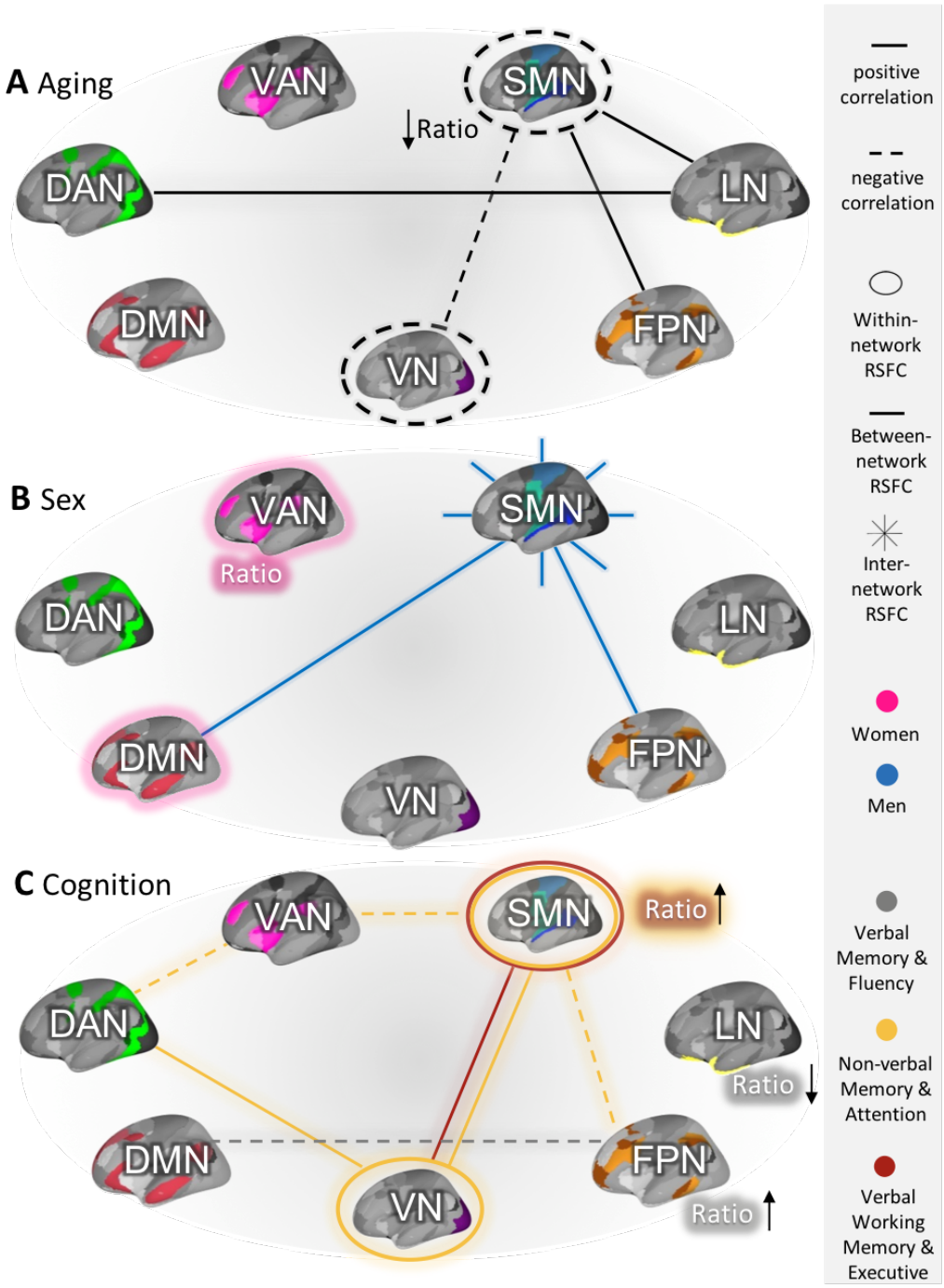


Figure 5: Schematic visualization of (A) age-related differences, (B) sex differences and (C) cognitive performance dependent differences of $RSFC_{pos}$.

Circles stand for differences of intra-network $RSFC_{pos}$, lines for between-network $RSFC_{pos}$ and crosses for inter-network $RSFC_{pos}$ differences. Dashed lines = negative correlations, solid lines = positive correlations. For ratio-scores, the arrows indicate the direction of correlation: down = negative correlation, 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.

4.2.1 Relations between RSFC and Age

In older adults, the whole-brain functional connectome was found to differ across age. Main effects (MANCOVA) revealed the older adults chronological age to not only be related to the connectivity within networks (intra-network $RSFC_{pos}$: $F = 6.161$, $p < .001$), but also the connectivity between networks (between-network $RSFC_{pos}$: $F = 2.731$, $p < .001$) as well as the rate of networks segregation ($RSFC_{pos}$ ratio-score: $F = 5.222$, $p < .001$). Importantly, age-related $RSFC_{pos}$ differences seem to be network specific with primary processing networks showing different age-relations as compared to higher-order networks. In the following section aging effects are more specifically described for the intra-network RSFC, inter-network RSFC, the between-network RSFC as well as the ratio-scores. All results regarding the age – $RSFC_{pos}$ relations are denoted in Table 3 and visualized in Figure 5A.

Table 3: Results of all relations between network-wise $RSFC_{pos}$ estimates and age.
Regression coefficients (ß) and from the MANCOVAs derived *p*-values and F-stats. Significant values (intra-, inter-network $RSFC_{pos}$, ratios < 0.007 and between-network $RSFC_{pos}$ < 0.002 after Bonferroni-correction), that additionally survived post-hoc bootstrap validation are indicated by an *asterisk* and highlighted in grey. For significant effects, also effect sizes (eta-square) are denoted.

		Age – RSFC						
		VN	SMN	DAN	VAN	LN	FPN	DMN
Within	ß	-.125	-.163	-.073	-.057	.021	.009	.051
	p	<.001 *	<.001 *	.042	.115	.569	.809	.154
	F	12.228	21.056	4.161	2.492	0.324	0.059	2.033
	eta	.016	.027					
Inter	ß	-.032	.061	.059	.071	.055	.092	.075
	p	.382	.093	.102	.047	.13	.011	.037
	F	0.765	2.822	2.676	3.946	2.303	6.515	4.385
Ratio	ß	-.056	-.193	-.097	-.095	-.009	-.071	-.010
	p	.119	<.001 *	.007	.008	.801	.049	.775
	F	2.44	29.561	7.059	7.227	.064	3.893	.081
	eta		.037	.009				
Between								
VN		*1*						
SMN	ß	-.127	*1*					
	p	<.001 *						
	F	12.502						
	eta	.016						
DAN	ß	-.037	-.036	*1*				
	p	.301	.322					
	F	1.072	.98					
VAN	ß	.039	.072	.049	*1*			
	p	.284	.046	.175				
	F	1.147	3.993	1.844				
LN	ß	.026	.140	.116	.076	*1*		
	p	.477	<.001 *	.001 *	.036			
	F	0.505	15.458	10.527	4.404			
	eta		.065	.064				
FPN	ß	.055	.112	.046	.011	-.040	*1*	
	p	.127	.002 *	.204	.768	.264		
	F	2.33	9.716	1.619	0.087	1.249		
	eta		.012					
DMN	ß	-.006	.034	.039	.046	.002	.104	*1*
	p	.862	.345	.276	.201	.947	.004	
	F	.03	.893	1.189	1.639	.004	8.457	

With increasing age, the $RSFC_{pos}$ within networks (intra-network) was found to decrease. Specifically, on network level this effect was significant for the VN ($F = 12.228$, $p < .001$; ß = -.125, SE = 0.11, lCI = -.061, uCI = -.016) and SMN ($F = 21.056$, $p < .001$; ß = -.163; SE = 0.017, lCI = -.110, uCI = -.048), visualized in Figure 6.

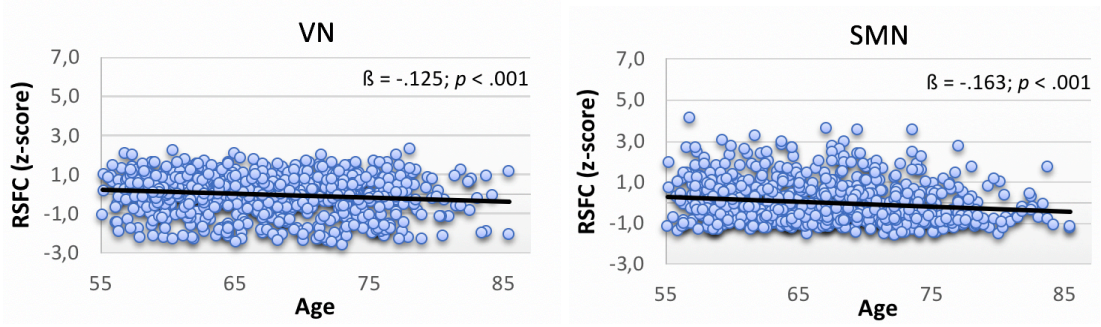


Figure 6: Scatterplots of significant relations between age and intra-network $RSFC_{pos}$ estimates. The visualized results (z-scores) showed a significant age effect and additionally survived post-hoc bootstrap validation.

Overall inter-network $RSFC_{pos}$, i.e. the connection of one network to the rest of the brain, was not related to age when correcting for multiple comparisons ($F = 1.964$, $p = .057$)., Looking at the connectivity between certain networks more specifically, though, significant relations with age appeared. In contrast to age-related decreases in intra-network RSFC, the overall between-network $RSFC_{pos}$ was positively correlated with age indicating a higher connectivity between networks in older adults. Specifically, this effect pertained to the connectivity between the SMN, the FPN ($F = 9.716$, $p = .002$; ß = .112; SE 0.039, lCI = .031, uCI = .204) and the LN ($F = 15.458$, $p < .001$; ß = .141; SE = 0.011, lCI = .020, uCI = .065) and additionally to the between-network RSFC of the DAN and the LN ($F = 10.527$, $p = .001$; ß = .117; SE = 0.012, lCI = .031, uCI = .064), visualized in Figure 7. Remarkably, the only negative age – connectivity relation pertains to the connection between the two primary processing networks (VN and SMN) indicating age-related connectivity decreases between them ($F = 12.502$, $p < .001$; ß = -.127; SE = 0.027, lCI = -.131, uCI = -.042).

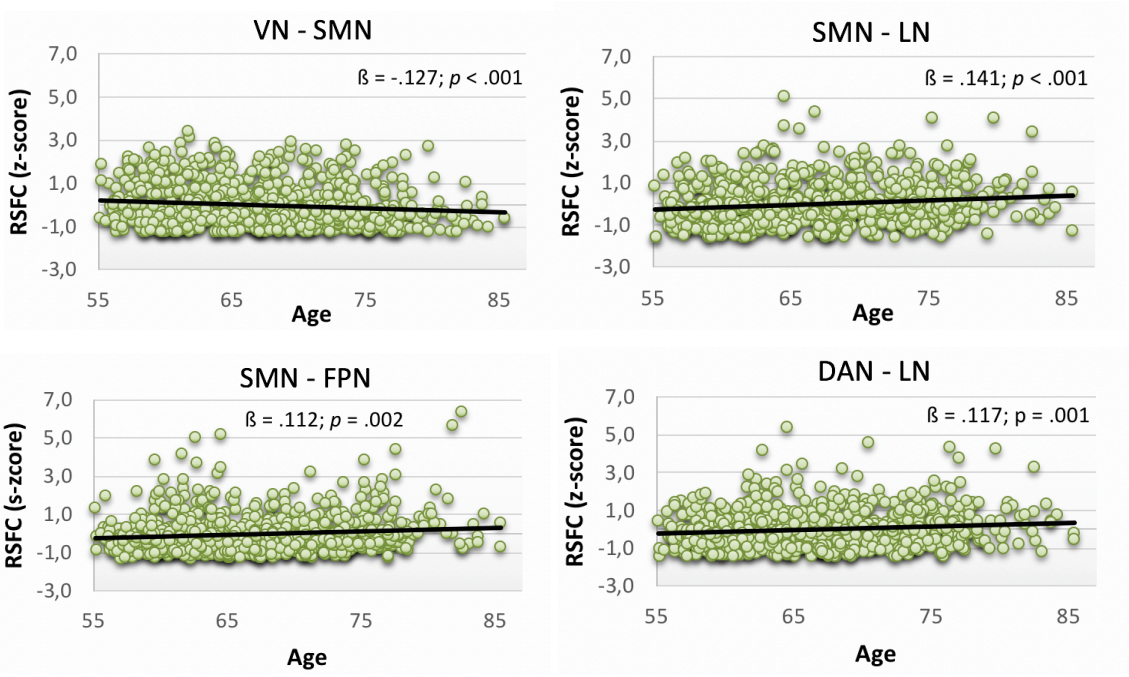


Figure 7: Scatterplots of significant relations between age and between-network $RSFC_{pos}$ estimates. The visualized results (z-scores) showed a significant age effect and additionally survived post-hoc bootstrap validation.

Combining the connectivity within and between networks to a ratio-score revealed a negative correlation with age. A decreasing ratio-score indicates a shift of $RSFC_{pos}$ from segregated networks to more integrated networks which is depicted by an increasing predominance of connectivity between networks rather than within networks. This effect particularly applied to the SMN ($F = 29.561$, $p < .001$; ß = -.193, SE = 0.001, lCI = -.005, uCI = -.002, visualized in Figure 8) and DAN ($F = 7.227$, $p = .007$; ß = -.097, SE = 0.001, lCI = -.003, uCI = 0). However, the latter did not remain significant after bootstrap validation.

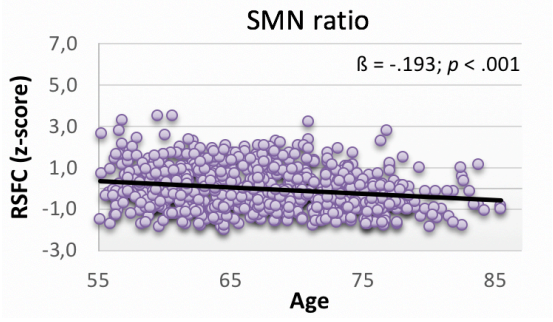


Figure 8: Scatterplots of significant relations between age and the network's $RSFC_{pos}$ ratio scores. The visualized results (z-scores) showed a significant age effect and additionally survived post-hoc bootstrap validation.

As of note, the inverse effects for $RSFC_{neg}$ were found as compared to $RSFC_{pos}$: networks that depicted by age-related decreases in $RSFC_{pos}$, show age-related increases in $RSFC_{neg}$

and vice versa (Supplementary Table 5, visualized in Figure 5A and Supplementary Figure 1). This particularly pertained to the intra-network RSFC of the VN and SMN and the VN-SMN between-network RSFC, respectively. Furthermore, age-related increases of $RSFC_{neg}$ were found within the DAN and FPN as well as between the LN, FPN and DMN.

4.2.2 Relations between RSFC and Sex

With regards to sex, results revealed males and females to have significant differences in their whole-brain RSFC architecture (Table 4 and visualized in Figure 5B and Figure 9). In fact, differences regard to the connectivity within networks (intra-network $RSFC_{pos}$: F = 2.960, p = .005) as well as the networks ratio-scores, i.e. indicating how segregated a network is (F = 3.465, p = .001).

Table 4: Results of all relations between network-wise $RSFC_{pos}$ estimates and sex.

From the MANCOVAs derived *p*-values and F-stats. Significant values (intra-, inter-network $RSFC_{pos}$, ratios < 0.007 and between-network $RSFC_{pos}$ < 0.002 after Bonferroni-correction), that additionally survived post-hoc bootstrap validation are indicated by an *asterisk* and highlighted in grey. For significant effects, also effect sizes (eta-square) are denoted.

		Sex - RSFC						
		VN	SMN	DAN	VAN	LN	FPN	DMN
Within	*p*	.983	.963	.937	.001 *	.016	.106	.004 *
	F	0	0.002	0.006	10.408	5.861	2.624	8.335
	eta				.013			.011
Inter	*p*	.048	<.001 *	.044	.098	.744	.615	.325
	F	3.923	13.564	4.065	2.738	0.107	0.253	0.971
	eta		.017					
Ratio	*p*	.158	.022	.279	<.001 *	.041	.116	.011
	F	1.995	5.281	1.174	15.938	4.206	2.476	6.544
	eta				.02			
Between								
VN		1						
SMN	*p*	.345	1					
	F	0.893						
	eta							
DAN	*p*	.271	.014	1				
	F	1.214	6.053					
	eta							
VAN	*p*	.824	.18	.931	*1*			
	F	0.05	1.802	0.008				
	eta							
LN	*p*	.523	.775	.742	.307	*1*		
	F	0.409	0.082	0.109	1.045			
	eta							
FPN	*p*	.039	.001 *	.639	.481	.506	*1*	
	F	4.266	10.432	0.221	0.498	0.442		
	eta		.013					
DMN	*p*	.003	.001 *	.020	.055	.522	.220	*1*
	F	8.677	10.364	5.392	3.704	0.411	1.505	
	eta		.013					

Regarding the intra-network $RSFC_{pos}$, females were found to have significantly higher connectivity within the VAN (F = 10.408, p = .001, lCI= -5.953, uCI= -1.605) as well as within the DMN (F = 8.335, p = .004, lCI = -8.772, uCI = -1.814). Females were additionally found to show a significantly higher ratio of the VAN, indicating a more segregated network in females (F = 15.938; p < .001, lCI = -.076, uCI = -.027). In contrast, the functional network architecture of males was found to be depicted by a significantly higher inter-network $RSFC_{pos}$ of the SMN indicating a higher integration of the SMN in males (F = 13.564, p < .00, lCI = 1.347, uCI = 3.982). Looking at the $RSFC_{pos}$ between networks more specifically, higher $RSFC_{pos}$ in males particularly pertained to the connection between the SMN and the DMN (F = 10.364, p = .001, lCI = .736, uCI = 2.771) as well as FPN (F = 10.432, p = .001, lCI = .735, uCI = 2.758). "No significant interaction effect between age and sex on any $RSFC_{pos}$ values was revealed. Further, education and its interaction effects with age and sex showed no significant relations with any $RSFC_{pos}$ values. Lastly, there were no significant sex-related differences for any negative strength values found." (Stumme et al., 2020, page 7) (Supplementary Table 5, Supplementary Figure 2).

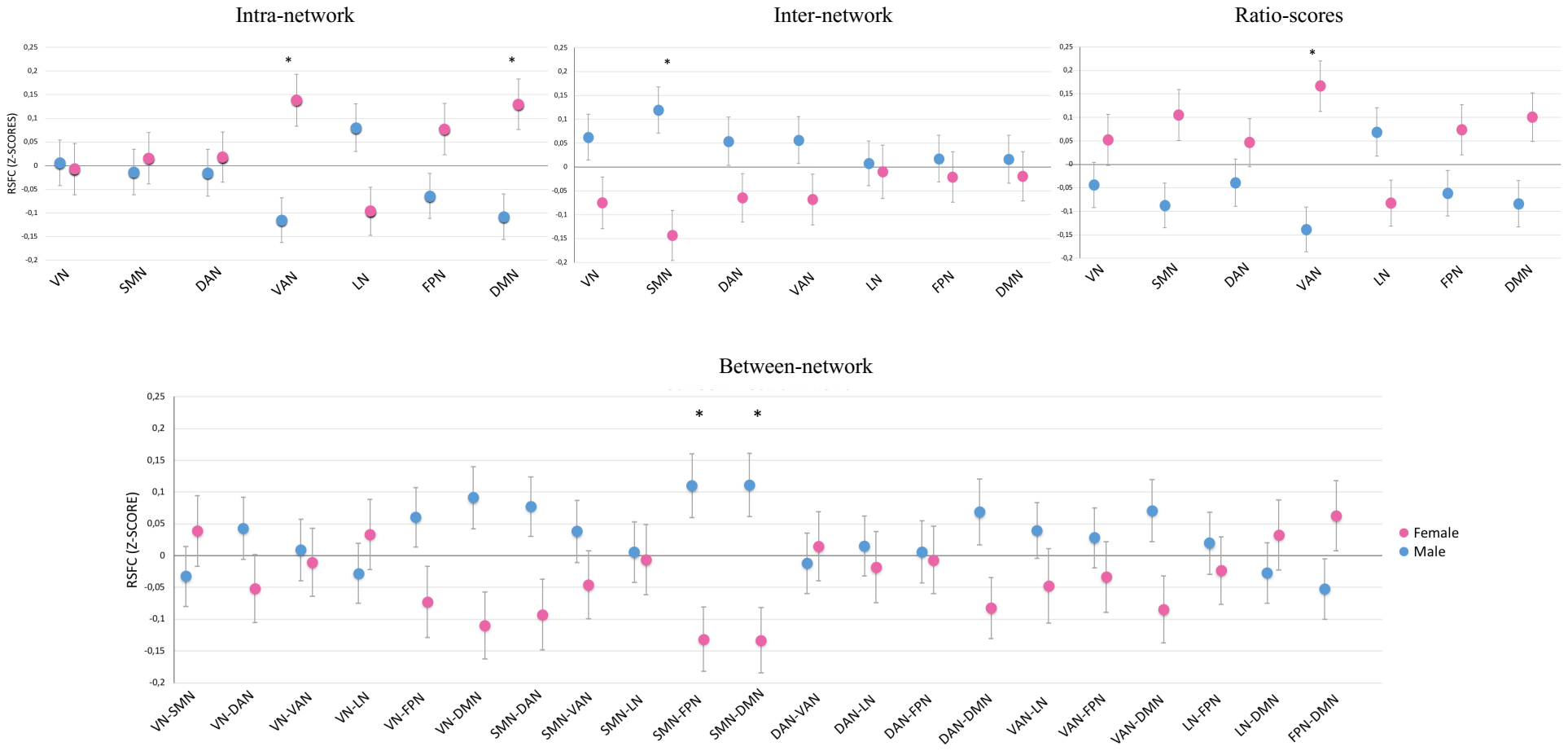


Figure 9: Network-wise sex-related $RSFC_{pos}$ differences.

Visualized intra-network $RSFC_{pos}$, inter-network $RSFC_{pos}$, the ratio-scores and between-network $RSFC_{pos}$ differences (z-scores, including error bars) between male (blue dots) and female (pink dots). Significant values (< 0.007 after Bonferroni-correction for intra-, inter-network and the ratio-scores & < 0.002 after Bonferroni-correction for between-network $RSFC_{pos}$), that additionally survived post-hoc bootstrap validation, are indicated by an *asterisk*.

4.2.3 Relation between RSFC and Cognitive Performance

To examine the relation between whole-brain RSFC and cognitive performance, cognitive performance variables were first decomposed to principal components (PCA) and subsequently related to RSFC estimates using a two-step approach. First, the relation between the cognitive components and $RSFC_{pos}$ was assessed using partial correlations and correcting for the effect of age, sex and education. Second, to investigate whether the depicted relations between $RSFC_{pos}$ and cognitive performance may be explained by age- and sex-related $RSFC_{pos}$ differences, mediation analyses were performed.

Principal Component Analysis

Conducting a PCA on the 16 cognitive variables included in the present study revealed three principal components with an eigenvalue of >1, covering 49% of overall variance (Table 5).

Table 5: Eigenvalues and explained variance from PCA.

Initial eigenvalues, eigenvalues after extraction, and eigenvalues and percentage of explained variance after Varimax rotation.

Component		Initial eigenvalues			Rotation sums of squared loadings		
		Total	% of variance	Cumulative %	Total	% of variance	Cumulative %
1	Verbal Memory & Fluency	5.364	33.527	33.527	2.93	18.313	18.313
2	Non-verbal Memory & Attention	1.381	8.633	42.16	2.691	16.816	35.129
3	Verbal Working Memory & Executive	1.124	7.028	49.188	2.25	14.059	49.188
4		0.933	5.833	55.021			
5		0.853	5.332	60.354			
6		0.791	4.941	65.295			
7		0.74	4.624	69.92			
8		0.692	4.323	74.242			
9		0.669	4.183	78.425			
10		0.63	3.938	82.363			
11		0.587	3.667	86.03			
12		0.517	3.233	89.263			
13		0.48	2.997	92.261			
14		0.454	2.84	95.1			
15		0.41	2.563	97.663			
16		0.374	2.337	100			

The composition of the three identified components (eigenvalue criterion of >1) are visualized in Figure 10 and now described in more detail. “The first component majorly comprised performance in verbal memory, phonemic and semantic verbal fluency, figural fluency and vocabulary knowledge (VERBAL MEMORY & FLUENCY). The second component highlighted performance in (selective) attention, figural memory, visual spatial working memory and additionally included problem solving (NON-VERBAL MEMORY & ATTENTION). Component three particularly addressed the participants’ capacity of working memory and concept shifting (VERBAL WORKING MEMORY &

EXECUTIVE)." (Stumme et al., 2020, page 7). Relating the cognitive components to age, sex and education revealed significant differences across age, sex as well as the education level. "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: .323; VERBAL WORKING MEMORY & EXECUTIVE: $p < .001$, r: .263, corrected for sex and age) but not the NON-VERBAL MEMORY & ATTENTION component ($p = .248$, r: -.042; corrected for sex and age). Further, males were found 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)." (Stumme et al., 2020, page 7).

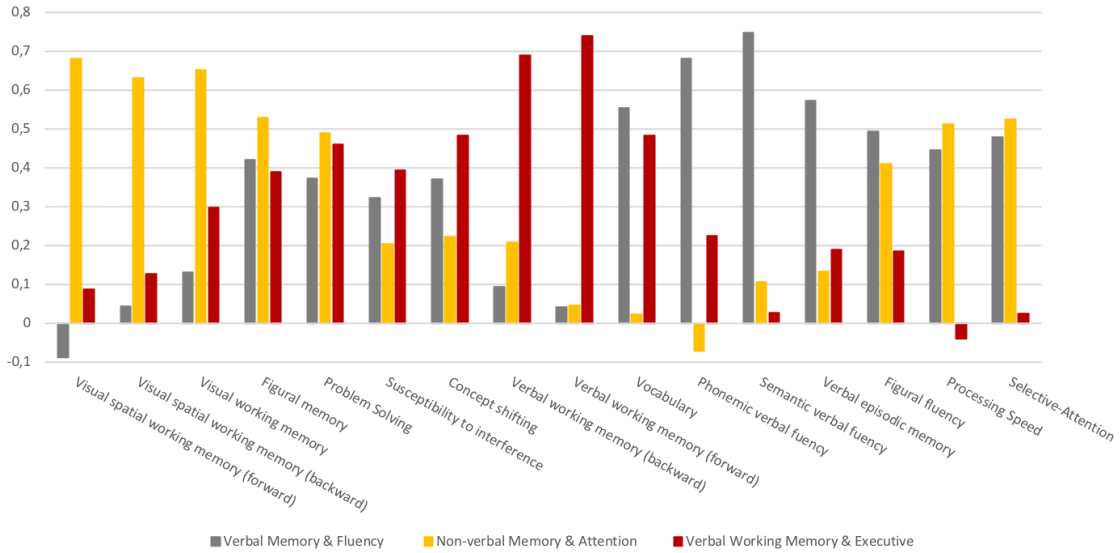


Figure 10: Factor loadings of each cognitive function on each component extracted from PCA. The respective values are also denoted in Table 2. Grey = VERBAL MEMORY & FLUENCY, yellow = NON-VERBAL MEMORY & ATTENTION, brown = VERBAL WORKING MEMORY & EXECUTIVE.

Cognitive Performance and RSFC

To relate differences in the functional whole-brain architecture to the participants cognitive performance, the three identified principal components were related to $RSFC_{pos}$ estimates using partial correlations (corrected for age, sex and education). In fact, results

revealed $RSFC_{pos}$ the be related to all three cognitive components (Table 6 and visualized in Figure 5C).

The first cognitive component (VERBAL MEMORY & FLUENCY) was found to be significantly related to connectivity estimates including the LN, FPN and DMN (Figure 11). The between-network $RSFC_{pos}$ of the FPN and DMN (p = .01, r: -.093, lCI = -.166, uCI = -.017) was negatively related to the VERBAL MEMORY & FLUENCY component. While the ratio-score of the LN also showed a negative correlation with the first component (p = .023, r: -.082, lCI = -.152, uCI = -.016), a higher FPN's ratio-score was associated with higher performance in the VERBAL MEMORY & FLUENCY component (p = .025, r: .081, lCI = .008, uCI = .152).

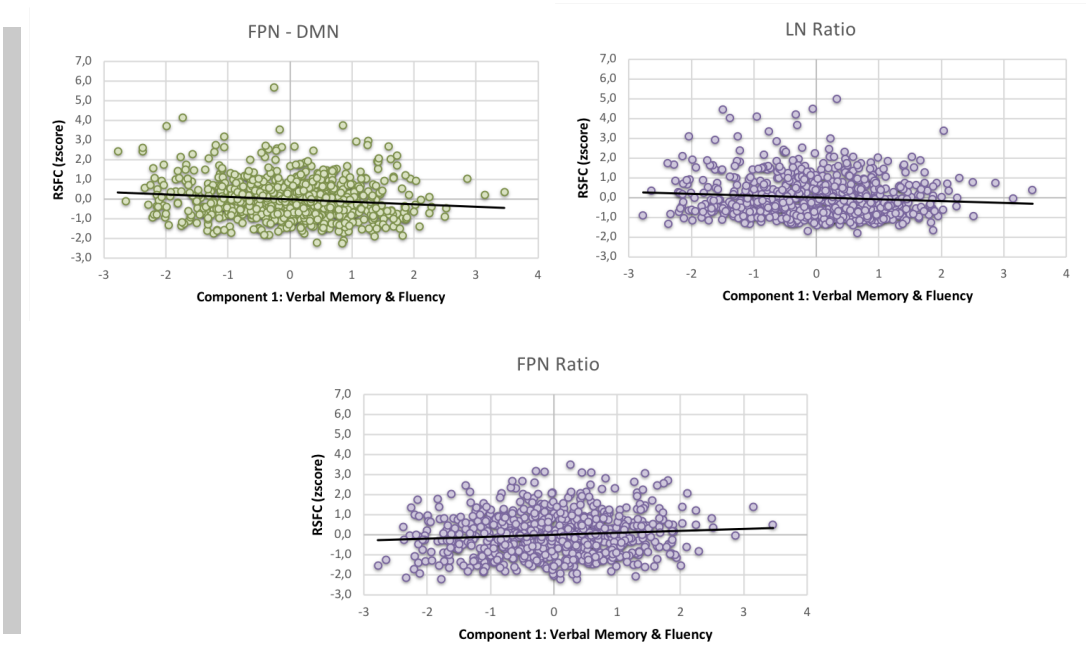


Figure 11: Scatterplots of significant correlations between $RSFC_{pos}$ and cognitive component one. The visualized results (z-scores) showed a significant correlation between the cognitive component one (VERBAL MEMORY & FLUENCY) and $RSFC_{pos}$ estimates (green = between-network RSFC, purple = ratio scores). Grey bar indicating the VERBAL MEMORY & FLUENCY component.

The second component (NON-VERBAL MEMORY & ATTENTION) showed associations with the $RSFC_{pos}$ between networks including the VN, SMN, DAN, VAN and FPN (Figure 12). Specifically, higher intra-network $RSFC_{pos}$ of the VN (p = .033, r: .077, lCI = -.008, uCI =.148) was associated with better cognitive performances. Although this effect did not remain significant after bootstrap validation, the more specific between-network $RSFC_{pos}$ of the VN with the SMN (p = .006, r: .099, lCI = .032, uCI = .162) and DAN (p = .010, r: .093, lCI = .020, uCI = .166) showed significant positive relations with the second component. Further, the SMN showed positive and

negative associations with the cognitive performance in NON-VERBAL MEMORY & ATTENTION: while the intra-network $RSFC_{pos}$ (p = .036, r: .076, lCI = .005, uCI = .148) and ratio-score (p = .008, r: .095, lCI = .027, uCI = .162) of the SMN were positively correlated with the performance, the between-network $RSFC_{pos}$ of the SMN and VAN (p = .001, r: -.120, lCI = -.192, uCI = -.042) as well as FPN (p = .028, r: -.079, lCI = -.158, uCI = -.005) were negatively correlated. Lastly, a lower performance of the second component was found to be related to a higher $RSFC_{pos}$ between the DAN and VAN (p = .002, r: -.110, lCI = -.186, uCI = -.038).

Figure 12: Scatterplots of significant correlations between $RSFC_{pos}$ and cognitive component two. The visualized results (z-scores) showed a significant correlation between the cognitive component two (NON-VERBAL MEMORY & ATTENTION) and $RSFC_{pos}$ estimates (blue = intra-network $RSFC_{pos}$,

green = between-network $RSFC_{pos}$, purple = ratio scores). Yellow bar indicating the NON-VERBAL MEMORY & ATTENTION component.

The third, i.e. VERBAL WORKING MEMORY & EXECUTIVE component, was found to be positively related to the SMNs intra-network $RSFC_{pos}$ (p = .005, r: .10, lCI = .035, uCI = .174), its ratio-score (p = .001, r: .125, lCI = .055, uCI = .198) and its between-network $RSFC_{pos}$ with the VN (p = .023, r: .082, lCI = .007, uCI = .152), visualized in Figure 13.

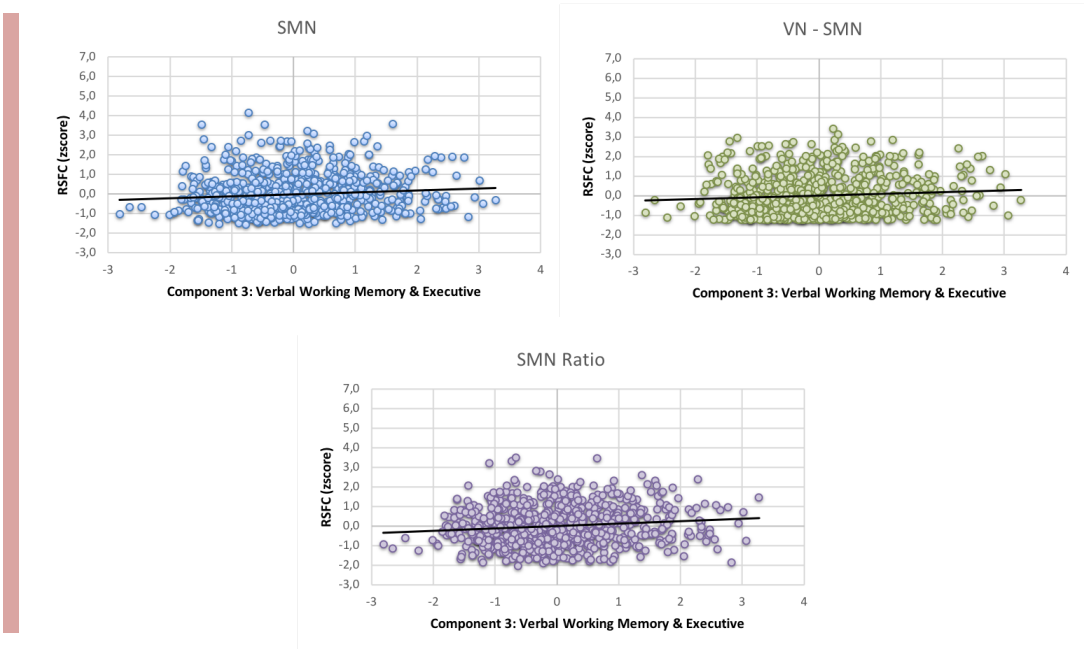


Figure 13: Scatterplots of significant correlations between $RSFC_{pos}$ and cognitive component three. The visualized results (z-scores) showed a significant correlation between the cognitive component three (VERBAL WORKING MEMORY & EXECUTIVE) and $RSFC_{pos}$ estimates (blue = intra-network $RSFC_{pos}$, green = between-network $RSFC_{pos}$, purple = ratio scores). Red bar indicating the VERBAL WORKING MEMORY & EXECUTIVE component.

Table 6: Results of all partial correlations between network-wise $RSFC_{pos}$ estimates and cognitive performance components.

Partial correlations between intra-, inter-, the ratio-scores, between-network $RSFC_{pos}$ and the three cognitive performance components (age, sex and education level as covariates): r and p-values. Significant values ($p < 0.05$, without Bonferroni-correction), that additionally survived post-hoc bootstrap validation, are indicated by an *asterisk* and highlighted in grey. For significant effects, also effect sizes (eta-square) are denoted.

		Verbal Memory & Fluency							**Non-verbal Memory & Attention**							**Verbal Working Memory & Executive Functions**						
		VN	**SMN**	**DAN**	**VAN**	**LN**	**FPN**	**DMN**	**VN**	**SMN**	**DAN**	**VAN**	**LN**	**FPN**	**DMN**	**VN**	**SMN**	**DAN**	**VAN**	**LN**	**FPN**	**DMN**
Within	r	.008	.042	.033	.029	-.062	.046	-.021	.077	.076	.041	-.023	.027	.009	-.064	.014	.101	-.038	.04	.042	.027	-.001
	p	.818	.246	.365	.428	.087	.207	.555	.033 *	.036 *	.253	.521	.458	.802	.077	.69	.005 *	.294	.266	.243	.447	.968
	eta								.006	.006							.01					
Inter	r	.007	.006	-.007	-.001	.051	-.062	-.018	.072	-.067	-.051	-.064	.002	-.032	-.03	.013	-.04	-.042	-.058	-.019	-.033	-.045
	p	.846	.861	.842	.989	.162	.084	.618	.046 *	.063	.158	.078	.965	.383	.409	.714	.264	.241	.105	.594	.354	.211
	eta								.005													
Ratio	r	.005	.025	.051	.028	-.082	.081	-.006	-.01	.095	.051	.024	.022	.022	-.047	-.01	.125	.002	.073	.051	.049	.046
	p	.89	.495	.158	.443	.023 *	.025 *	.858	.792	.008 *	.155	.511	.545	.546	.195	.785	.001 *	.946	.042 *	.16	.177	.207
	eta					.007	.007			.009							.016		.005			
Between																						
VN		1							1							1						
SMN	r	.056	1						.099	1						.082	1					
	p	.123							.006 *							.023 *						
	eta								.01							.007						
DAN	r	-.003	.005	1					.093	.033	1					.05	.031	1				
	p	.927	.887						.010 *	.356						.165	.384					
	eta								.009													
VAN	r	.01	-.029	-.014	1				-.017	-.12	-.11	1				-.038	-.051	-.035	1			
	p	.781	.425	.703					.644	.001 *	.002 *					.292	.16	.334				
	eta									.014	.012											
LN	r	.032	.008	.002	.004	1			-.046	-.023	-.029	-.031	1			-.066	-.061	-.061	.023	1		
	p	.378	.818	.95	.916				.201	.52	.431	.392				.069	.093	.091	.522			
	eta																					
FPN	r	-.021	-.016	.028	.032	.032	1		.019	-.079	-.028	.008	.008	1		-.017	-.066	-.042	-.046	-.01	1	
	p	.555	.658	.445	.379	.371)			.59	.028 *	.443	.817	.827			.629	.068	.248	.204	.786		
	eta									.006												
DMN	r	-.026	.026	-.039	-.016	.06	-.093	1	.01	-.037	-.002	.003	.043	-.048	1	-.028	-.042	-.042	-.022	.007	-.015	1
	p	.472	.477	.28	.657	.096	.01 *		.791	.306	.953	.937	.23	.181		.433	.241	.245	.534	.843	.679	
	eta						.009															

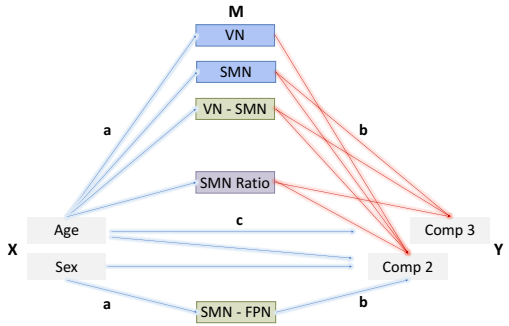
4.2.4 Mediating Effects of RSFC Differences related to Cognition

For some $RSFC_{pos}$ values, associations were found with both, age as well as cognitive performance. For example, the intra-network $RSFC_{pos}$ of the SMN showed negative relation to not only age, but a positive relation to the 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 $RSFC_{pos}$ mediate the cognitive performance differences across ages or if these are independent processes.” (Stumme et al., 2020, page 9). To test this effect, mediation analyses were performed and revealed that age indeed influences the relation between $RSFC_{pos}$ and cognitive performance (Table 6 and Figure 14). “While the age-related intra-network $RSFC_{pos}$ of the VN significantly mediated the effect of age on the NON-VERBAL MEMORY & ATTENTION component, the intra-network $RSFC_{pos}$ as well as the ratio-score of the SMN mediated both, the age-related performance in the VERBAL WORKING MEMORY & EXECUTIVE as well as NON-VERBAL MEMORY & ATTENTION component. The VN-SMNs between-network $RSFC_{pos}$ 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 raised whether these differences may be mediated by sex-related differences in $RSFC_{pos}$. And indeed, sex-related differences in $RSFC_{pos}$ between the SMN and FPN were found to significantly mediate the cognitive performance of the NON-VERBAL MEMORY & ATTENTION component.” (Stumme et al., 2020, page 9) (Table 7).

Table 7: Mediating effects of $RSFC_{pos}$ values on the effect of age or sex on cognition.

Mediation analyses to test the effect of RSFC values (M) on the effect of age or sex (X) on cognition (Y) (corrected for sex/age, education and the two remaining components, respectively). Significant models are indicated by an *asterisk*. Comp = component.



	Model			ß (*p*-value)			Effects			Bootstrap confidence intervals		
	X	M	Y	a (*p*)	b (*p*)	c (*p*)	Total	Direct	Indirect	BootSE	LLCI	ULCI
*	**Age**	VN	Comp 2	-.1260 (.001)	.0697 (.033)	-.4076 (<.001)	-.0626 (<.001)	-.0613 (<.001)	-.0088	.0048	-.0194	-.0010
*		SMN	Comp 2	-.1452 (<.001)	.0691 (.036)	-.4063 (<.001)	-.0626 (<.001)	-.0611 (<.001)	-.01	.0055	-.0221	-.0007
*			Comp 3	-.1290 (.002)	.0964 (.005)	-.1609 (<.001)	-.0260 (<.001)	-.0242 (<.001)	-.0124	.0062	-.0266	-.0027
*		VN-SMN	Comp 2	-.1065 (.005)	.0899 (.006)	-.4068 (<.001)	-.0626 (<.001)	-.0611 (<.001)	-.0096	.0048	-.0203	-.0016
			Comp 3	-.0760 (.064)	.0784 (.023)	-.1673 (<.001)	-.0260 (<.001)	-.0251 (<.001)	-.006	.0043	-.0161	.0003
		SMN-FPN	Comp 2	.1045 (.006)	-.0724 (.028)	-.4088 (<.001)	-.0626 (<.001)	-.0614 (<.001)	-.0076	.0054	-.0204	.0002
*		SMN Ratio	Comp 2	-.1783 (<.001)	.0881 (.008)	-.4007 (<.001)	-.0626 (<.001)	-.0602 (<.001)	-.0157	.007	-.0298	-.0041
*			Comp 3	-.1578 (<.001)	.1214 (<.001)	-.1541 (<.001)	-.0260 (<.001)	.0232 (<.001)	-.0192	.0075	-.0357	-.0067
*	**Sex**	SMN-FPN	Comp 2	-.2409 (.002)	-.0724 (,0279)	-.3838 (<.001)	-.3664 (<.001)	-.3838 (<.001)	.174	.0104	.0001	.0407

Figure 14: Visualized mediating effects of $RSFC_{pos}$ values on the effect of age or sex on cognition.

Significant mediation effects of $RSFC_{pos}$ (M) on the relation between age or sex (X) and cognition (Y). Blue lines = negative relation, red lines = positive relation. Blue boxes = intra-network RSFC, green boxes = between-network RSFC and purple boxes = ratio scores.

4.3 Discussion: Network-based RSFC differences

In order to contribute to the understanding what neurobiological sources there may be for the highly variable age-related performance decline in older adults, the first study assessed systematic functional network differences and related these to age and sex and cognitive performance.

Collectively, the results of the first study indicated the whole-brain functional network architecture to indeed be sensitive to age, sex as well as cognitive performance. Specifically, aging was found to be accompanied by a combination of age-related decreases in intra- together with overall increases in between-network RSFC leading to more integrated and less segregated functional brain networks. This effect was underpinned by the results of the ratios-scores, i.e. a parameter integrating the intra- and inter-network RSFC, indicating considerable increases in the network integration across aging. Remarkably, in the here examined older generation, mainly RSFC of primary processing networks were found to be affected. Importantly, particularly the RSFC of primary processing networks seem to be additionally crucial for cognitive performance as age-related differences in RSFC were found to mediate cognitive performance differences. Furthermore, inspecting sex and its relation to RSFC, systematic differences were found pointing at a more integrated system in males. Results based on functional network differences in relation to age (4.3.1), cognitive performance (4.3.2) and sex (4.3.3) will be discussed in detail in the following.

4.3.1 Age-related RSFC differences

Overall, results of previous studies that either compared groups of younger to older adults (Geerligs et al., 2015; Goldstone et al., 2016; Grady et al., 2016; Nashiro et al., 2017; Siman-Tov et al., 2016; Spreng et al., 2016) or investigated 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) indicate age-related decreases in intra-network RSFC and increases in between-network RSFC. Results of the here conducted first study amend these evidences by showing that the trend of an age-related attenuated network specificity also persists within particularly older subjects. Remarkably, the applied whole-brain approach revealed that age-related RSFC differences in older adults seem to be particularly prominent in primary processing networks, i.e. the VN and SMN. Importantly, these networks were additionally found to be especially relevant for cognitive performance differences (see 4.3.2 for further discussion). Certain interrelations are of interest when looking at the networks more specifically, discussed in the following.

Age-related intra-network RSFC decreases which were found for the VN as well as the SMN are very much in line with Perry et al. (2017), who used a multivariate approach in older adults (n = 101, 70-90 years) and also found RSFC of primary processing networks to not only be age-sensitive but also related to cognitive performance. Perry et al. (2017) found very similar age effects in the SMN using a comparable age-range as used within the current study (50 – 95 years). In contrast to that, "former studies investigating the whole adult lifespan, repeatedly found intra-network RSFC decreases in higher-order networks (e.g. attention, FPN, DMN) (Betzel et al., 2014; Chan et al., 2014; Ferreira et al., 2016; Grady et al., 2016; Mowinckel et al., 2012; Siman-Tov et al., 2016; Spreng et al., 2016; Varangis et al., 2019), whereas intra-network RSFC of primary processing networks were found to remain stable (Betzel et al., 2014; Geerligs et al., 2015; Siman-Tov et al., 2016; Varangis et al., 2019). The latter seems to hold true when considering linear effects only. Allowing for non-linear effects showed that the SMN 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., 2016)." (Stumme et al., 2020, page 10). Hence, comparing the effects in older adults to those across the whole adult lifespan, a particular vulnerability of primary processing networks at higher ages appears which stresses the need to examine age-related RSFC differences with respect to different age-groups. In terms of higher-order networks age-related RSFC differences in older adults, previous results are inconclusive indicating intra-network RSFC decreases on the one hand, cross-sectionally (Zonneveld et al., 2019) and longitudinally (Ng et al., 2016), but longitudinally stable intra-network RSFC on the other hand (Persson et al., 2014). In conclusion, for intra-network RSFC, results of the current study indicate higher age to be characterized by decreases of only primary processing networks (e.g. VN and SMN) while higher-order remain rather stable.

Age-related differences of the between-network RSFC were two-fold. On the one hand, similar to the results of the intra-network RSFC, the connectivity between primary processing network was found to decrease with ascending age. This, however, was accompanied by overall age-related increases of the between-network RSFC, particularly applicable to connections of the SMN with the LN and FPN. Given the two primary processing networks facilitating efficient visuomotor integration capabilities (Goodale, 2011), age-related decreases in intra-network RSFC as well as between-network RSFC may present a possible explanation for the impaired motor performances in older adults, i.e. visuomotor tasks including eye-hand coordination or spatially oriented movements (Guan & Wade, 2000; Van Halewyck et al., 2014). Increases of the SMN's between-

network RSFC have previously been shown (Tomasi & Volkow, 2012a; Zuo et al., 2010) and may be understood as a compensational attempt to recruit additional networks that are implicated in the processing of memory functions (LN, (Frey & Petrides, 2002; Laird et al., 2011; Petrides, 2007; Smith et al., 2009)), attention and control mechanisms (Corbetta & Shulman, 2002; Spreng et al., 2010) to increase performance monitoring to maintain cognitive performance (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 intra-network RSFC or impoverished information integration from other networks (Marstaller et al., 2015; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008) 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., 2008; Goh, 2011; Lee et al., 2015; Seidler et al., 2010)." (Stumme et al., 2020, page 10). There were, however, no positive associations between the between-network RSFC and cognitive abilities found in the current study, which may rather hint at a dedifferentiation process. Increasing between-network RSFC are thereby associated with a reduced distinctiveness of functional brain networks resulting in a worse selectivity of specific cognitive functions (Goh, 2011), further discussed in 4.3.2.

In summary, across the aging process the functional diffusivity increases. Age-related RSFC decreases are foremost driven by two specific networks (VN and SMN) showing decreases within as well as between networks. Besides the primary processing networks showing between-network RSFC decreases, the overall RSFC between networks increases which leads to a less segregated and more integrated network system in higher ages.

For negative correlations, increases were found between as well as within networks. "Previous results on between-network anti-correlations mainly pertain to the DMN indicating age-related decreases of anti-correlations with the FPN (Geerligs et al., 2015), VAN (Ferreira et al., 2016; Meier et al., 2012), DAN (Siman-Tov et al., 2016) and SMN (Meier et al., 2012; Siman-Tov et al., 2016)." (Stumme et al., 2020, page 10). Since the DMN is a task negative network, i.e. principally anti-correlated with other networks, increasing between-network RSFC may reflect a reduced capacity to suppress the DMN during task. With regards to task positive networks, lower anti-correlations were found

for the connections between primary processing networks (Geerligs et al., 2015), the FPN with the cingulo-opercular (Geerligs et al., 2015; Meier et al., 2012), DAN (Siman-Tov et al., 2016) as well as the SMN (Meier et al., 2012). “As anti-correlations between networks have been considered as a marker for network segregation (Fox et al., 2009) previous results point at an increase of network integration from younger to older adults particularly associated with higher-order cognitive functions, such as the FPN. In contrast, in the current study increases of anti-correlations between the VN and SMN, LN and DMN as well as FPN were found, which may hint at different reorganization processes in older adults compared to the whole adult lifespan. Cognitive performance changes (Hedden & 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.” (Stumme et al., 2020, page 10). Furthermore, in the present study increases of anti-correlations within networks were found for the VN, SMN, DAN and FPN. Especially in terms of the VN and SMN these results build the exact opposite effect as compared to positive correlations. Potentially, in older adults, regions within primary processing networks work not only less synchronized but even more anticyclical. Previous studies addressing the effects of anti-correlations within networks found either no (Meier et al., 2012) or only very few correlations with age (Varangis et al., 2019). Until now, there are no other results systematically evaluating network specific anti-correlations in older adults pointing at the need for future research.

4.3.2 Impact on Cognitive Performance

Results of the current study indicate the whole-brain RSFC pattern in older adults to reorganize in an age-dependent manner. This functional reorganization process is assumed to be at least partly related to the cognitive performance variability in aging (Marques et al., 2016; Sadaghiani et al., 2015; Zuo et al., 2017). Results of this first conducted study indeed underpin this assumption by showing that the majority of RSFC-cognition relations pertain to networks that are also related to aging, e.g. the VN and SMN. Testing these associations statistically revealed differences in RSFC to significantly mediate the cognitive performance differences in aging.

Specifically, within primary processing networks, “differences in RSFC were associated with the NON-VERBAL MEMORY & ATTENTION and VERBAL WORKING MEMORY & EXECUTIVE components. While the SMN was found to mediate age-related differences of both components, the VN 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 VN intra-network RSFC to be associated with reduced performances, which is exactly what was found." (Stumme et al., 2020, page 11). Furthermore, regarding the between-network RSFC of the primary processing networks, higher RSFC was associated with better performance in both components, i.e. the NON-VERBAL MEMORY & ATTENTION and VERBAL WORKING MEMORY & EXECUTIVE. Accordingly, differences in the VN and SMN's between-network RSFC significantly mediate the age-related differences in the NON-VERBAL MEMORY & ATTENTION performance. In terms of between-network RSFC including higher-order networks, only negative relations were found with cognitive performance, whereas none of these connections significantly mediated age-related decreases in cognitive performance. So far, there exist one more study addressing whole-brain functional reorganizations in older adults and its association with cognitive performance. Their results are based on single connectivity estimates rather than network-based analyses, but indicate a very similar relationship between age, cognition and the VN as well as SMN's RSFC (Perry et al., 2017). Together with the results of the current work, this very much hints at a relevant role of primary processing networks in terms of cognitive differences at higher age, which will be discussed further now.

Two aging theories exist, i.e. the compensational theory (also see 1.2) and the dedifferentiation theory, that address functional reorganizations and its impact on cognitive performance. First, the compensational theory suggests increasing between-network RSFC to characterize a compensational attempt that integrates information from other networks in order to counteract age-related decline resulting from e.g. decreasing intra-network RSFC (Grady et al., 2016; Heuninckx et al., 2008; Tsvetanov et al., 2016; Varangis et al., 2019). The here depicted increased RSFC of the SMN with networks involved in memory, attention and control mechanisms could indeed point an adaptive reorganization process that aims to maintain cognitive performance despite the impoverished information integration from the VN (Cabeza et al., 2002; Reuter-Lorenz & Cappell, 2008). However, increasing between-network RSFC of the SMN with the VAN and FPN were rather found to be related to worse cognitive abilities leading to the second aging theory, i.e. the dedifferentiation theory. Here, increasing covariance between brain networks is associated with a constantly higher recruitment of brain region resulting in a lower functional diversity of functional brain networks (Lou et al. 2019). This potentially goes along with a reduced capacity to select specific cognitive functions and may finally result in cognitive performance decline (Goh, 2011). In line, "very recent

meta-analyses not only found cognitive performances to decline, but the shared variance between cognitive abilities to increase with ascending age (Blum & Holling, 2017; Tucker-Drob et al., 2019), hinting at a dedifferentiation process not only in terms of functional brain networks but also regarding the cognitive system (de Mooij et al. (2018)). 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).

Results could indeed be interpreted as evidence for the compensation as well as dedifferentiation theory. Presumably, interconnected processes are conceivable (Figure 15). First, the additional inclusion of higher-order networks associated with control and monitoring processes may indeed represent compensational attempts trying to counteract a starting cognitive decline. As the recruitment of additional brain region more and more increases, however, increasing between-network RSFC may no longer be supportive, but rather result in a decreased functional diversity of brain networks. This dedifferentiated network system may then be followed by a reduced selectivity of cognitive functions resulting in cognitive decline.

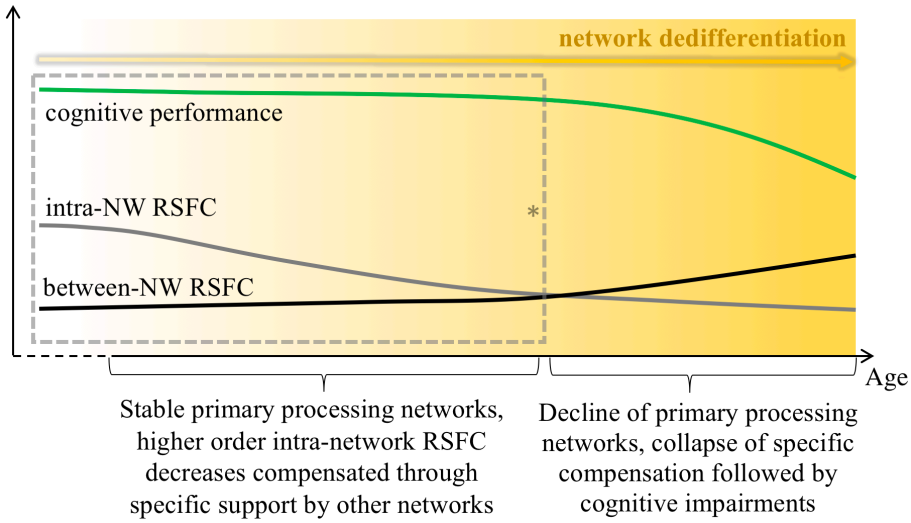


Figure 15: Modelled lifespan trajectories of RSFC differences and cognitive performance. Between-network RSFC (black), intra-network RSFC (grey) and cognitive performance (green) differences. While in younger age decreases of intra-network RSFC may be successfully compensated by specific increases of between-network RSFC, showing only minor cognitive impairments, constant increases of RSFC between networks may at some point supersede a target-oriented compensation, resulting in cognitive decline. Interpretations on younger age base on previous work (indicated by an asterisk), as the current study focuses on older age. NW = network.

Altogether, age-related RSFC differences were found to be accompanied by a cognitive performance decline. Thereby, a clear distinction can be made between the effects regarding primary processing networks as compared to higher-order networks: While the intra-network as well as between-network RSFC of the VN and SMN were positively associated with cognitive performance, the higher-order between-network RSFC was negatively related to cognitive performance.

4.3.3 Sex-related differences in RSFC

To the current state of research, sex-related network differences been demonstrated by task-based fMRI (Bell et al., 2006; Dumais et al., 2018; Filkowski et al., 2017; Spets & Slotnick, 2020; Subramaniapillai et al., 2019; Weiss et al., 2003) and SC using diffusion MRI (Ingalhalikar et al., 2014; Tunc et al., 2016). Results of the current study show that in particularly older adults, there exist significant differences in RSFC patterns between males and females. This is very much in line with previously published rs-fMRI results (Allen et al., 2011; Goldstone et al., 2016; Satterthwaite et al., 2015; Scheinost et al., 2015; Tomasi & Volkow, 2012b) and will be discussed in more detail in the following.

The in the current work depicted results of higher intra-network RSFC in females regarding the DMN and VAN are very much in line with previous rs-fMRI based research (Allen et al., 2011; Scheinost et al., 2015). Furthermore, "the females' ratio score of the VAN 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' SMN was significantly more integrated, showing higher inter-network RSFC compared to females." (Stumme et al., 2020, page 10). Interestingly, the SMN's between-network RSFC was found to mediate sex-related cognitive performance differences. These results potentially indicate sensorimotor functions to be more highly relevant for cognitive processing in males as compared to females (Cassady et al., 2019; Seidler et al., 2015). Previous results on RSFC have also found a higher integrated network system in males, which was already present in youth and early adulthood (9-22 years) (Satterthwaite et al., 2015) and was even intensified during the aging process (27-74 years) (Goldstone et al., 2016). For SC based on diffusion MRI, results show a very similar pattern (Tunc et al., 2016). Males were found to show a significantly higher SC between networks related to motor, sensory and executive functions, while the female's network system was more strongly connected among networks associated with social motivation, attention and memory tasks. This has been considered beneficial to facilitate sex-specific functioning, i.e. "a high integration of perception and coordinated action in males and the communication between analytical

and intuitive processing in females (Ingalhalikar et al., 2014). Interestingly, Satterthwaite et al. (2015) 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 femineity of the according RSFC pattern, stressing the notion that networks may be organized to facilitate sex-related behavioral functioning." (Stumme et al., 2020, page 11).

Similarly, a very recent study on a subset of the 1000BRAINS dataset found significant differences in the cognitive profiles between older males and females (Jockwitz et al., 2021). Here, males were found to show a more holistic cognitive profile with stronger interrelations between performances while females were depicted by more decomposed, i.e. specific cognitive profiles. In fact, this is very much in line with the results of the current study, where males were found to show a more integrated whole-brain functional system. Mediating effects of RSFC patterns on the relation between sex and cognition, though, could not be found which may be explained by the rather general effects of global cognitive functioning, as operationalized by the PCA components.

In summary, results of this work are "in line with previous sex-related differences in functional as well as SC patterns of previous studies and expand the current knowledge about sex-related RSFC differences into the old age group. This stress the importance of considering sex when examining the functional connectivity architecture of older adults." (Stumme et al., 2020, page 11). As of note, although there is a variety of studies indicating sex-specific differences to exist and even demonstrating that sex can be predicted based on rs-fMRI patterns (Weis et al., 2020; Zhang et al., 2018), caution is advised concerning the interpretation of these findings (Joel et al., 2015). Functional brain network patterns also clearly overlap between males and females and terms such as "male-brain" or "female-brain" should be avoided.

4.4 Conclusion

Results of the first study within this current work indicate that the whole-brain functional connectome of older adults indeed undergoes a reorganization process with increases in RSFC between networks, while the RSFC within networks decrease. Age-related differences in RSFC were most prominent within and between primary processing networks. This is highly important as these results are different as compared to previous results on lifespan studies, where predominantly higher-order networks were found to change. Hence, in the older adult's population, it seems that especially primary processing networks are sensitive to aging. This is particularly interesting as the current results additionally indicate that age-related decreases in cognitive performance are mediated by differences in the SMN's and VN's RSFC. Hence, in older age a shift towards overall higher network integration seems to be characteristic, but more importantly also decreases of RSFC in primary processing networks, the latter additionally associated with cognitive performance decline. Therewith, the results of the first study potentially unveiled a neurobiological factor accounting for the high inter-individually variable performances in older adults, i.e. RSFC differences of particularly primary processing networks.

What still remains unclear is what sources there may be for the depicted RSFC aging patterns, i.e. less RSFC in primary processing networks accompanied by an overall higher network integration. As discussed above, theories exist suggesting compensation processes to be the impelling motive for RSFC changes. However, results on the relation between higher inter-network connectivity and cognitive performance are mixed, some studies rather pointing at dedifferentiation processes (i.e. higher between-network RSFC resulting in cognitive performance decline). In fact, sources of age-related RSFC differences are still a matter of debate. One potential factor that may influence age-related RSFC differences could be SC as it is the underlying construct to exchange information between regions. To test the relation between RSFC and SC, a second study was conducted that aimed at identifying age-related whole-brain RSFC differences that concurrently occur with whole-brain SC differences (see 5).

5 Study 2: Structural and Functional Connectivity Relation

With the first study, RSFC differences were calculated network-wise and successfully linked to age, sex and cognitive performance. Building upon the results of the first study, the second study went one step further and aimed at unveiling potential sources for the depicted RSFC differences. Therefore, RSFC differences were related to SC. As SC is the underlying construct for brain regions to exchange information, a high relation between RSFC and SC could be expected. However, so far, especially in older adults, the relation between RSFC and SC is inconclusive (as discussed in 1.4). Therefore, by investigating RSFC and SC differences that concurrently occur across age, aim of the second study was to identify SC-RSFC relations which may potentially depict sources for the age-related RSFC differences as found in the first study.

For the purpose of the second study, the resolution from the network level was increased to the investigation of nodal (region-wise) RSFC differences. By zooming from network level to more specific nodal-wise RSFC differences, age effects could be attributed to more specific brain regions. To relate RSFC differences to SC, it was taken advantage of an age prediction model. In recent years, an increasing number of studies have used different neuroimaging data, i.e. different brain features, to predict the participants' biological age. Thereby, age prediction models unveil and therewith support our understanding of brain features that are particularly indicative for the aging process. For example, Jiang et al. (2020) used structural MRI to predict the biological age of participants (aged between 18 and 90 years) and found networks to vary in their prediction accuracy with particularly the FPN, DAN and DMN to have highest prediction values and therewith being most characteristic for the aging process. The majority of age prediction studies used structural MRI data and successfully predicted age with mean average errors between predicted and measured age of around 5 years (Cole & Franke, 2017; Cole et al., 2017; Franke et al., 2010; Liem et al., 2017). Studies based on connectivity data have also demonstrated feasibility of RSFC (Dosenbach et al., 2010; La Corte et al., 2016; Li et al., 2018; Vergun et al., 2013) as well as SC (Han et al., 2014; Richard et al., 2018) for age prediction, though with prediction accuracies that not fully achieve those of structural MRI data. Building upon previous work on age prediction based on either SC or RSFC lifespan data, aim of this work was to build models of brain age in particularly older adults that incorporate whole-brain region-wise RSFC and SC data. Thereby, the intended purpose was to provide both, prediction accuracies but more

importantly, find SC and RSFC differences that are together characteristic for the older adults' age.

With respect to previous studies on age-related SC and RSFC differences, the frontal lobe was assumed to be particularly age-characteristic in terms of SC and the SMN in terms of RSFC. Given the non-conclusive evidence on the structure-function relation, an exploratory analysis on this relation was carried out to allow for a holistic perspective.

5.1 Material & Methods

5.1.1 Sample

From the first to the second study, another 18 participants aged between 55 and 87 years were scanned for 1000BRAINS resulting in a total of 969 older participants of one measurement time point. From this basic sample, 725 participants had both, functional rs-fMRI as well as structural DWI data available (see section 3.1), as relevant for the current multimodal cross-sectional study design. Of these 725 participants, 74 had to be excluded due to either preprocessing failure or insufficient quality of either functional data (n = 22) or structural data (n = 52, see 5.1.2 for description of quality control). Lastly, participants with missing information of education (n = 1) or the dementia screening test (n = 13, DemTect (Kalbe et al., 2004)) or those scoring low on the dementia screening test (score of eight or lower, n = 1) were excluded. In total, the current study comprises a sample of n = 636 subjects (Table 8).

Table 8: Sample distribution of the second study.
Whole group, female and male regarding age and education: mean (sd).

	%	**Age (years)**	**Education**
total	100	67.1 (6.8)	6.5 (2.0)
male	51	67.7 (7.0)	7.0 (1.9)
female	49	66.4 (6.6)	6.0 (1.8)

5.1.2 Image preprocessing

Functional image preprocessing

For each participant, the first four echo-planar imaging (EPI) volumes were discarded. Using a two-pass procedure all functional images were corrected for head movement by fist aligning all volumes to the first image and second to the mean image using affine registration. By the use of the "unified segmentation" approach (Ashburner & Friston, 2005), all functional images were spatially normalized to the MNI152 template (Holmes et al., 1998). This was preferred to normalization based on T1 weighted images as previous studies indicated increased registration accuracies (Calhoun et al., 2017; Dohmatob et al., 2018). Additionally, ICA-based Automatic Removal Of Motion Artifacts [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). Subsequently, to check for each participant for volume-wise severe intensity dropouts, the established algorithm by Afyouni and Nichols (2018) was used that generates p-values for spikes (DVARS) based on the preprocessed functional data. Participants for whom more than 10% of the 300 volumes were detected as dropouts were excluded from further analyses (n = 8). Lastly, the "check sample homogeneity was performed using SD across sample" function analysis provided by the CAT12 toolbox (Gaser & Dahnke, 2016) to check for potential misalignments. Participants detected as outlier where manually checked and excluded as the individual mean AROMA functional image did not align to the MNI152 template (n = 8).

Structural diffusion image preprocessing

For each participant, tissue probability maps (TPM) for grey matter, white matter as well as corticospinal fluid (CSF) were computed from T1 data using the CAT12 (Gaser & Dahnke, 2016) implemented in SPM12 (Ashburner, 2009). To optimally extract the brain from the T1 data, brain masks were used created by superimposing the three probability maps and thresholding them at 0.5 (small enclosed holes were filled). The T1 brain image was bias field corrected, rigidly aligned to MNI152 template space and resampled to 1.25 mm isotropic voxel size serving as a coregistration image for the subsequent alignment of the similarly resampled diffusion data (see below) to the MNI152 template (in accordance to standard pipelines as used in e.g. the human connectome project (www.humanconnectomeproject.org) or the UK Biobank (www.ukbiobank.ac.uk)). Diffusion MRI data were corrected for eddy current and motion artifacts including interpolation of slices with signal dropouts (Andersson et al., 2016; Andersson & Sotiropoulos, 2016). Visual quality control was performed to check for ghosting, remaining signal dropouts or very noisy data. Suboptimal datasets were removed from further analysis (n = 69). For diffusion MRI - T1 alignment, the first b0 images from each diffusion MRI data with b1000 and b2700 were extracted and rigidly aligned to T1 dataset using mutual information as cost function (Wells et al., 1996). Based on the corresponding transforms, all diffusion MRI data were registered to the individual T1 space, separately for the two b-values. The realignment implicitly resampled the data to 1.25mm and b-vectors were rotated according to the transformations. To account for susceptibility artefacts and optimize image registration, Anisotropic Power Maps (APM) were computed (Dell'Acqua et al., 2014) from the b2700 diffusion MRI data. Since the APM contrast is very similar to the T1 image, they provide an optimal basis for image registration. Accordingly, APMs were used to compute the non-linear transformation

from diffusion to anatomical space additionally taking EPI induced distortions into account using ANTs (https://stnava.github.io/ANTs/). The derived non-linear transformations were then used to transform the TPMs to diffusion space. Finally, the two datasets with b1000 and b2700 were merged into one single file and corrected for different ETs. This correction was computed by a voxel-wise multiplication of the b2700 data with the ratio of the non-diffusion-weighted data respectively for the two datasets. Subsequently, local modelling and probabilistic streamline tractography were performed using the MRtrix software package (Tournier et al., 2012) version 0.3.15. The constrained spherical deconvolution (CSD) local model was computed using multi-tissue CSD of multi-shell data (Jeurissen et al., 2014) using all shells and a maximal spherical harmonic order of 8. Ten million streamlines were computed with dynamic seeding in the grey-white matter interface for every subject using the probabilistic iFOD2 algorithm with a maximal length of 250 mm and a cut-off value at 0.06.

5.1.3 Connectome

Within the second study a continued development of the parcellation from Yeo et al. (2011) with a finer-grained subdivision of brain networks into a total of 400 regions was utilized (Schaefer et al., 2018), visualized in Figure 16. This was done according to recent studies, which found a resolution of 400-600 nodes to be optimal for functional (Schaefer et al., 2018) and structural analyses (Varikuti et al., 2017). This cerebral cortex parcellation was created based on resting-state images from 1489 participants integrating both, a local gradient and a global similarity approach. Thereby, the capability of a local gradient approach to detect abrupt changes in voxels' RSFC was combined with a global similarity approach which clusters areas across the whole brain with similar RSFC patterns into parcels sharing high covarying rs-fMRI signals. Comparing the results to four previously published parcellations, they found their generated parcellations to be depicted by a very great functional and connectional homogeneity and additionally achieved a comparable agreement with architectonic boundaries (Schaefer et al., 2018).

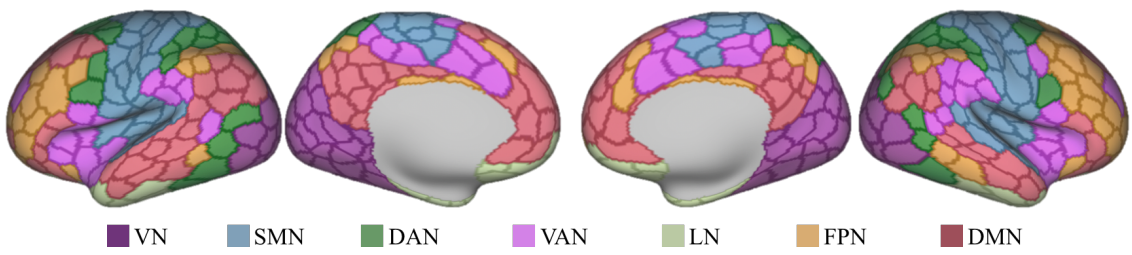


Figure 16: Functional network parcellation in accordance to Schaefer et al. (2018).

Functional Connectome

Comparable to the first study, from the preprocessed rs-fMRI data, mean time series were extracted node-wise spanning 296 time points [fslmeants (Smith et al., 2004)]. Pearson's product-moment correlation was used to estimate the correlation coefficient between nodes' average BOLD time series resulting in a symmetric 400*400 matrix, each entry indicating the connection between regions with a high correlation indicating a high connection between the respective nodes. To account for the potential existence of correlations caused by noise, the statistical significance of each correlation coefficient was tested. 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 1,000 times and followed by a permutation test (non-significant edges at $p > .05$ were discarded). Finally, the adjacency matrix was transformed into z-scores by applying a Fishers r-to-z transformation. Lastly, to avoid that negative and positive correlations cancel each other out in the estimation of strength values, RSFC matrices were separated, one only including positive correlations ($RSFC_{pos}$) and the second one only including absolute values of negative correlations ($RSFC_{neg}$).

Structural Connectome

For SC, the parcellation template first had to be warped to individual diffusion space. This was done by combining the non-linear warps of the spatial T1 registration to MNI152 and the distortion correction with the APMs. Since streamlines are generated seeding from the grey-white matter interface and the predefined parcellation scheme only covers cortical grey matter, the template was expanded adding voxels towards the grey-white matter boundary so that all regions also include the seeding points. To increase the biological accuracy of SC, the SIFT-2 method was applied (Smith et al., 2015). Here, each streamline is weighted with an estimate of its effective cross-sectional area, so that the streamline density matches the white matter fiber density computed directly from the diffusion signal. Finally, to adjust for normal distributions the derived 400*400 matrix was log10 transformed.

5.1.4 Node-wise Connectivity Parameters

Based on the structural connectome and the positive as well as negative functional whole-brain connectomes (i.e. three different 400x400 connectivity matrices) two different parameters for each node were calculated:

(i) *Intra-network* connectivity estimate comprising the sum of weights (i.e. connectivity values) of edges from that node to all nodes within its

corresponding network divided by the number of all edges in the network (n nodes, there are n*(n-1)/2 possible edges in a fully connected network)

(ii) *Inter-network* connectivity estimate comprising the sum of edge weights from that node to all nodes outside its corresponding network divided by the number of all edges in the network.

These estimates resulted in 6 different strength values for each node (intra-network: SC, $RSFC_{pos}$, $RSFC_{neg}$ and inter-network: SC, $RSFC_{pos}$, $RSFC_{neg}$), in total comprising 2400 (3*2 strength values * 400 parcels) connectivity values for each subject.

5.1.5 Statistical Analysis

To unveil SC and RSFC differences that are together characteristic for the older adults' age, a multivariate statistical analysis was performed which can be subdivided into two sections. First, a prediction model was built and its accuracy to predict age also in comparison to random data was validated (Figure 17, A). Building upon the validated model the composition of RSFC and SC differences were analyzed, i.e. how they are combined within the components to predict age (Figure 17, B). For the prediction model, partial least square regression was used (PLSR (Mevik et al., 2020)) with whole-brain region-wise SC, $RSFC_{pos}$ and $RSFC_{neg}$ values as predictor variables (corrected for sex and education) and biological age as the response variable.

PLSR is a multivariate statistical approach that has the advantage to incorporate multiple predictor variables potentially even extending the amount of observations and depicting high collinearity (Haenlein & Kaplan, 2004; Krishnan et al., 2011; McIntosh & Lobaugh, 2004). With PLSR, predictor variables are decomposed into a smaller set of independent components (nonlinear iterative partial least squares algorithm, NIPALS) on which a least square regression is performed to define covariates that are maximally correlated with the response variable. Hence, with regards to the current dataset, within one component a unique amount of variance of the connectivity estimates (predictors) was used to explain the highest possible amount of variance in age (response). Therefore, PLSR assigned all connectivity estimates (SC, $RSFC_{pos}$, $RSFC_{neg}$) different weights (indicated by their loading values) such that a maximally high correlation with age is achieved. Inspecting the loading values within one component is then informative on which connectivity estimates particularly contribute to the age prediction. To define a model with an appropriate number of components that has good predictive ability, i.e. explaining sufficient amount of variability without overfitting the model, PLSR performed a permutation approach with cross-validation (Mevik & Wehrens, 2015; Mevik et al., 2020). Thereby, the model for age prediction was repeatedly calculated with

different numbers of components, each run omitting one individual and determining cross-validated residual values (leave one out cross-validation to depict the difference between the actual response and predicted response value). Root mean squared error of prediction (RMSEP) were calculated by summing all squared prediction errors indicating the model's predictive ability. Based on the RMSEP curve (i.e. one RMSEP for each number of included components), a permutation test was performed assessing the models' performance. Starting at the minimum RMSEP, it successively excluded components until there is no further significant drop in performance found ($\alpha = .01$) (for detailed description of PLSR also see Mevik and Wehrens (2015) and Mevik et al. (2020)).

To validate the model's predictive ability in the current study, the PLSR model was built on a training data set (n = 382, 60% of the initial sample) and subsequently applied to a test dataset (n = 254, remaining 40% of the initial sample) (Figure 17, A). Thereby, age of the test dataset was predicted and subsequently compared to the individuals' chronological age. To assure model performance across different training and test datasets to be comparable, the age prediction procedure was repeated 5,000 times randomly resampling the training and test datasets. Finally, the prediction model's legitimacy was validated by comparing the RMSEP based on real data to the RMSEPs of 5,000 null models. Null models were created by randomly scrambling age and connectivity estimates and reperforming the age prediction procedure (i.e. dividing data into training and test dataset, train the model on the training dataset and predict age of the test dataset).

After validating the model's prediction ability, focus of the analysis was the investigation of the defined components (Figure 17, B). As described above, in PLSR connectivity estimates are combined in a way such that they show the highest possible correlation with age. The direction of correlation between age and the component is indicated by the component's score values. Score values represent the degree to what extent a subject is expressed by this specific component. As an example, within the current study, a negative correlation between age and the score values of a component can be interpreted as age-related decreases of connectivity estimates. Thereby, loading values indicate how the correlation between age and the component's score value is applicable for the particular connectivity estimate: Connectivity estimates with positive loading values are in line with the overall component's correlation, i.e. showing the same direction of correlation with age as the components' score values. In turn, negative loading values show the opposite association with age as compared to the score values, i.e. age-related increases with whole component decreases and vice versa. For this second

step of the analyses, the training and test dataset were reassembled and the predefined and validated PLSR model was conducted on the whole group. This was done in order to maximize the representativeness of interpretation on the component's composition for the largest group of older adults. Finally, to enhance reliability of the connectivity estimates' loading values, a bootstrap procedure was included estimating CIs for loading values of the connectivity estimates (90% sample size, 5,000 iterations). Loading values that did not reliably contribute to age prediction were set to zero.

For each component, PLSR calculated a loading value for each connectivity estimate resulting in 2,400 loading values for each component (400 values for each modality: intra- and inter-network for SC, $RSFC_{pos}$, $RSFC_{neg}$). For the purpose of interpretability, network-wise mean loading values (the average across all loading values within one network) were additionally calculated to make the strength of loading values also comparable across networks. Network-wise loading values were visualized for each component separately for intra- and inter-network SC, $RSFC_{pos}$ and $RSFC_{neg}$ as bar plots. Additionally, node-wise loading values were plotted onto the brain surface to also allow the distribution of loading values to be interpretable (node-wise loading values are additionally depicted as bar plots in Supplementary Figures 3 & 4). With regards to previous literature indicating frontal regions to show different age-related decreases as compared to the rest of the brain, loading values between frontal regions and the rest of the brain were additionally compared. Therefore, mean average loading values of regions located within the frontal lobe were calculated and compared these to the mean average loading values located in the rest of the brain using an undirected two-sample t-test.

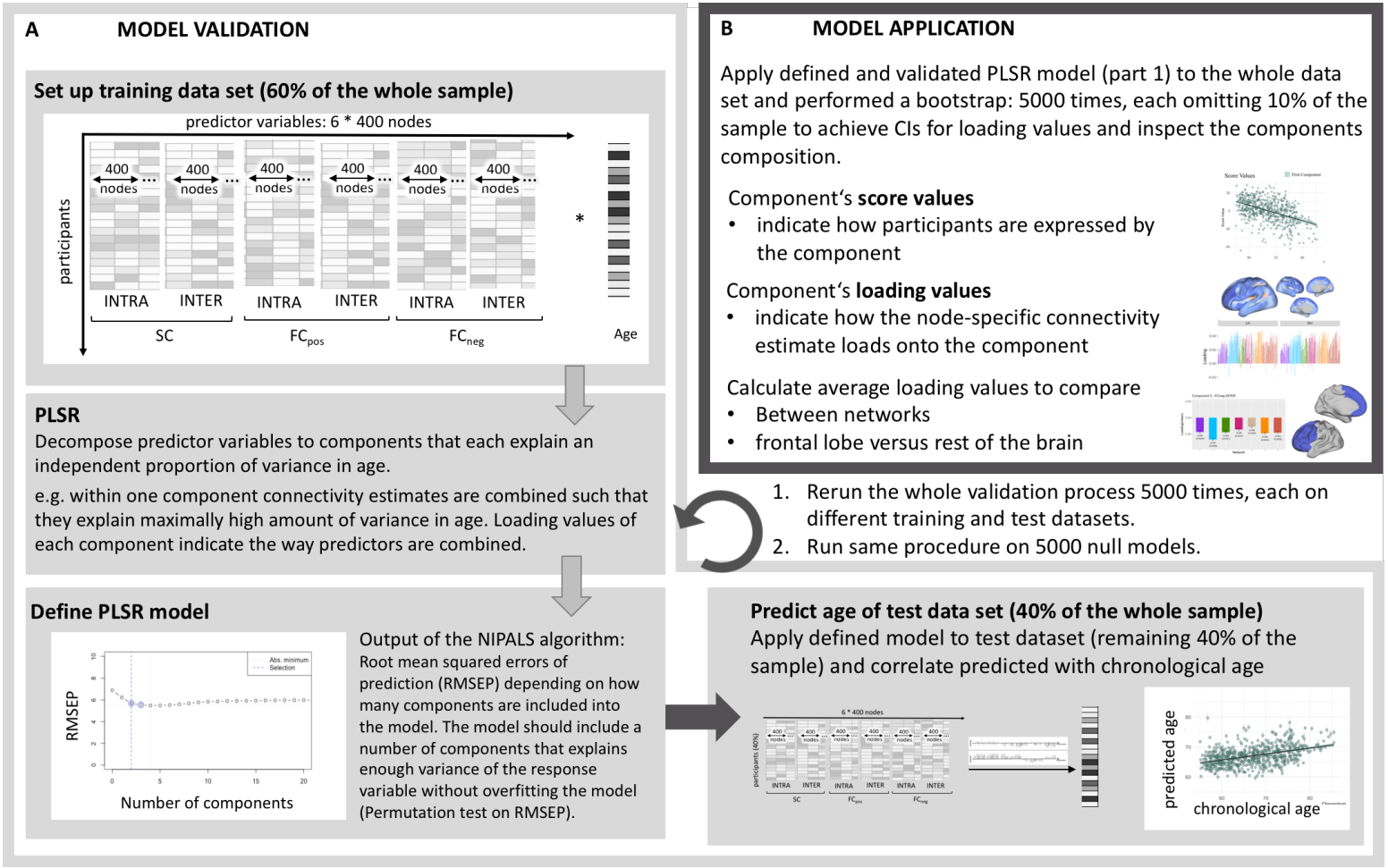


Figure 17: Illustration of the second's study statistical procedure.

A) the PLSR model validation process B) the model application. PLSR = Partial Least Square Regression. CI = Confidence Interval.

5.2 Results

Aim of the second study was to relate RSFC to SC differences and to unveil RSFC and SC differences that are together age-characteristic. Results showed that region-wise patterns of SC and RSFC estimates are indeed predictive of older adults' age. Furthermore, they appear to be interdependent with the frontal lobe's SC and SMN network's RSFC being particularly age-characteristic. Results are discussed in more detail in the following, first describing the results of the model validation, i.e. whether connectivity estimates are indeed predictive for older adults' age. Second, the component compositions are described, i.e. indicating which connectivity estimates were found to be particularly age-characteristic.

The model validation process indicated two components to be optimal for age prediction, explaining sufficient variance without overfitting the model (Table 9, Figure 18).

Table 9: PLSR model validation: Results of the cross-validated permutation approach.
Cross-validated permutation approach was performed on the training dataset (n=382) indicating the calculated RMSEP, the % variance in brain connectivity explaining the % of variance of age by including up to 10 components.

Component		1	**2**	3	4	5	6	7	8	9	10
RMSEP		6.229	**5.676**	5.54	5.483	5.497	5.526	5.601	5.679	5.775	5.830
% variance explained	age	8.355	**11.09**	19.95	22.78	25.34	28.26	29.67	30.98	32.20	33.23
	connectivity	24.44	**54.38**	60.52	72.61	82.16	86.19	91.71	94.59	96.79	98.11

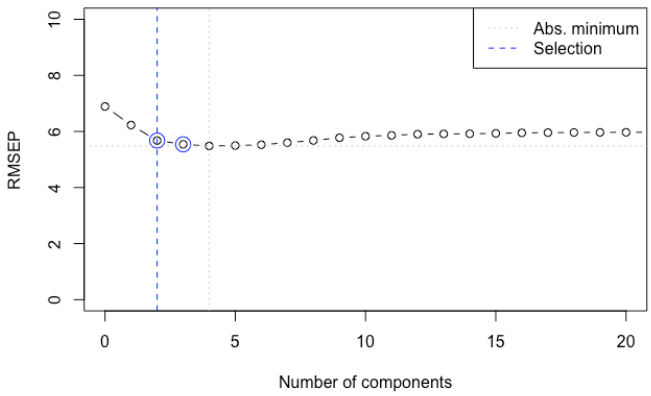


Figure 18: PLSR model validation: RMSEPs of the cross-validated permutation approach.
Cross-validated permutation approach performed on a training data set (n= 382) revealed two components (blue dashed line) to be optimal for age prediction.

Applying the defined prediction model on 5,000 different combinations of training and test datasets, not only correlations between predicted and chronological age were estimated, but additionally their CIs. Including one component into the prediction model (RMSEP = 6.19, sd = .112), a correlation of r_{mean} = .426 (sd = .048) between predicted and chronological age was obtained explaining 8.29% variance of age (sd = .48), visualized in Figure 19 (A and B, green). Including additionally the second component into the prediction model (RMSEP = 5.78, sd = .138) revealed a considerable increase of prediction accuracy explaining 12.72% of age variance (sd = 1.36) and resulted in a correlation of r_{mean} = .540 (sd = .050) between predicted and chronological age (Figure 19, A and B, violet). Importantly, both models (i.e. with one as well as with two components) revealed a significantly better prediction accuracy for prediction as compared to null models. Thus, intra- and inter-network SC and RSFC estimates of 400 brain regions was found to be predictive of older adults' age (1st component: $RMSEP_{mean}$: 6.19, $RMSEP_{nullmodel}$: 7.27, $p < .001$, 2nd component: $RMSEP_{mean}$: 5.78, $RMSEP_{nullmodel}$: 7.69, $p < .001$), visualized in Figure 19, C.

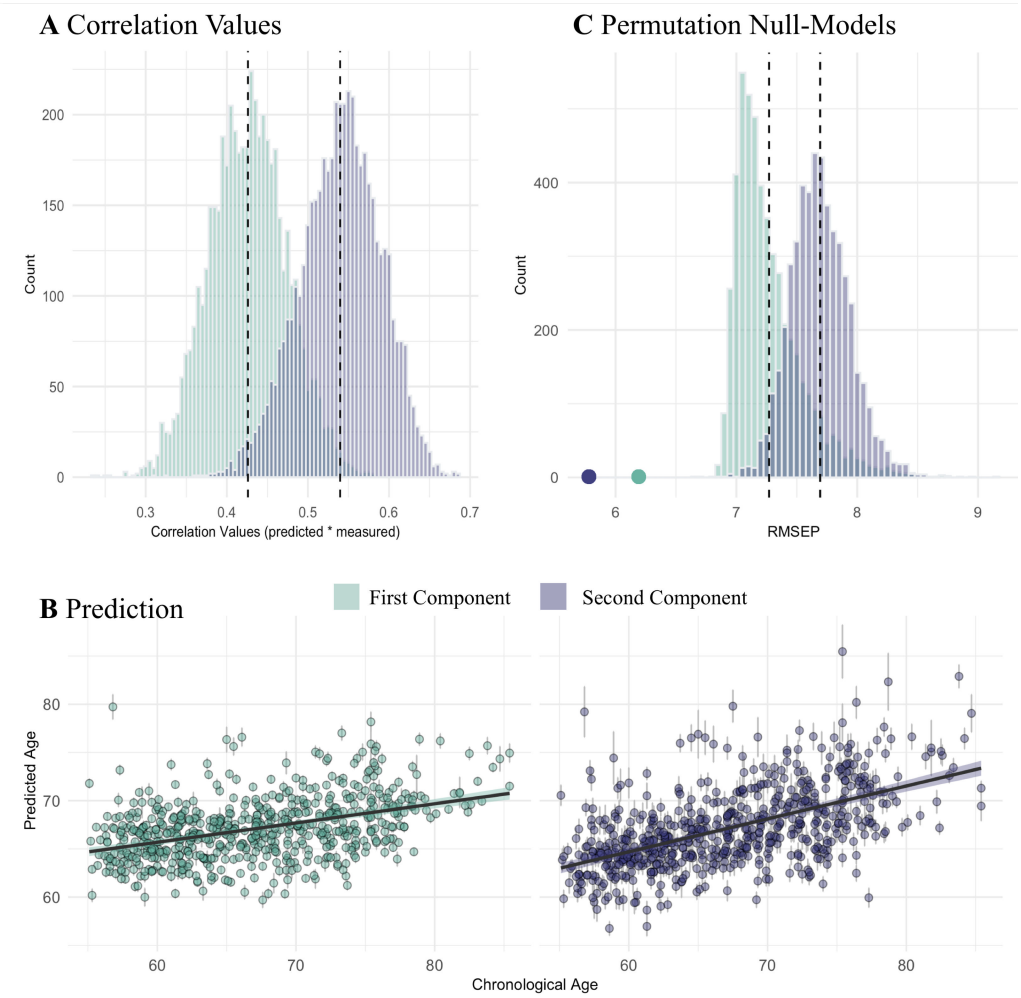


Figure 19: Results of the PLSR model validation process.

(A) Distribution of correlation values between chronological and predicted age based on 5000 different training and test splits including one component (green: r_{mean} = .426, p > .001, lCI = .425, uCI= .427) and two components (violet: r_{mean} = .540, p > .001, lCI = .538, uCI= .541). (B) Scatterplot of the correlation between predicted and chronological age including one component (green) or two components (violet): predicted values depict mean values (errorbars: +/- 1*sd) from 5000 different training and test splits. (C) Distribution of RMSEP from 5000 created null models including one component (green: $RMSEP_{nullmodel}$ = 7.27) and two components (violet: $RMSEP_{nullmodel}$ = 7.69). Colored points indicate the RMSEP of the real model (green: $RMSEP_{1comp}$ = 6.19, violet: $RMSEP_{2comp}$ = 5.78).

With the model's validation, RSFC and SC estimates can be assumed to be predictive of older adults' age. Main objective of this second study was then to relate RSFC to SC and analyze SC and RSFC differences that are together characteristic for the older adults' age. Therefore, the prediction model was applied to the whole group particularly focusing on the composition of the defined components which can be derived from the components specific score and loading values (as described in 5.1.5).

Applying the prediction model to the whole dataset, component one was found to comprise a unique aspect of the overall variance in brain connectivity of 8.2% explaining

21.9% of the variance in age ($RMSEP_{comp1}$= 6.172, mean average prediction error = 5.0 years). Component two, comprising another 4.9% of variance in brain connectivity explained further 20.3% of variance in age ($RMSEP_{comp2}$= 5.728, mean average prediction error = 4.2 years). For both components, lower score values with increasing age were found ($r_{comp1:}$ -.47, r_{comp2}: -.45, both $p < .001$), visualized in Figure 20. Based on this negative correlation between age and the components' score values, positive loading values of connectivity estimates can be interpreted as age-related connectivity decreases, while negative loading values indicate connectivity increases. Additionally, higher loading values indicate a stronger association with age.

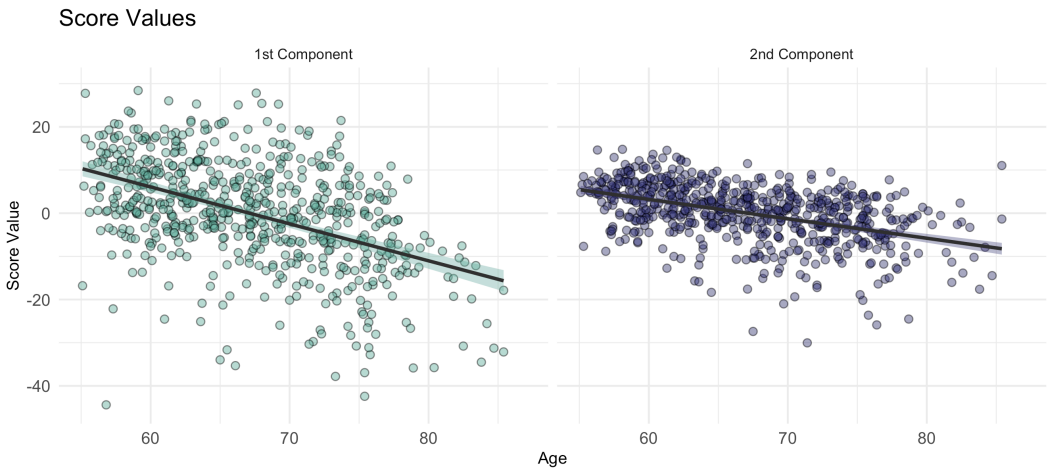


Figure 20: Individual PLSR score values across age based on the whole sample.
Score values of the first (green: r= -.47, $p < .001$, 21.9% explained variance) as well as second (violet: r= -.45, $p < .001$, 4.5% explained variance) component decrease with increasing age.

In the following sections, loading values will be successively described for component one and component two. For each component, this will include 2,400 loading values comprising 400 node-wise intra- and inter-network connectivity estimates for each modality (SC, $RSFC_{pos}$ as well as $RSFC_{neg}$). Node-wise loading values are plotted onto the brain surface to demonstrate the loadings' distribution across the brain (Figures 21, 22). As described in the Methods section (5.1.5), network-wise mean loading values ($network_{mean}$(sd)) were additionally calculated to make the strength of loading values more easily interpretable across networks. They are visualized as bar plots in Figures 21 and 22. As of note, node-wise loading values for each component and modality are additionally visualized as bar plots in Supplementary Figures 3 and 4 which can be informative for the variability of loading values within a network.

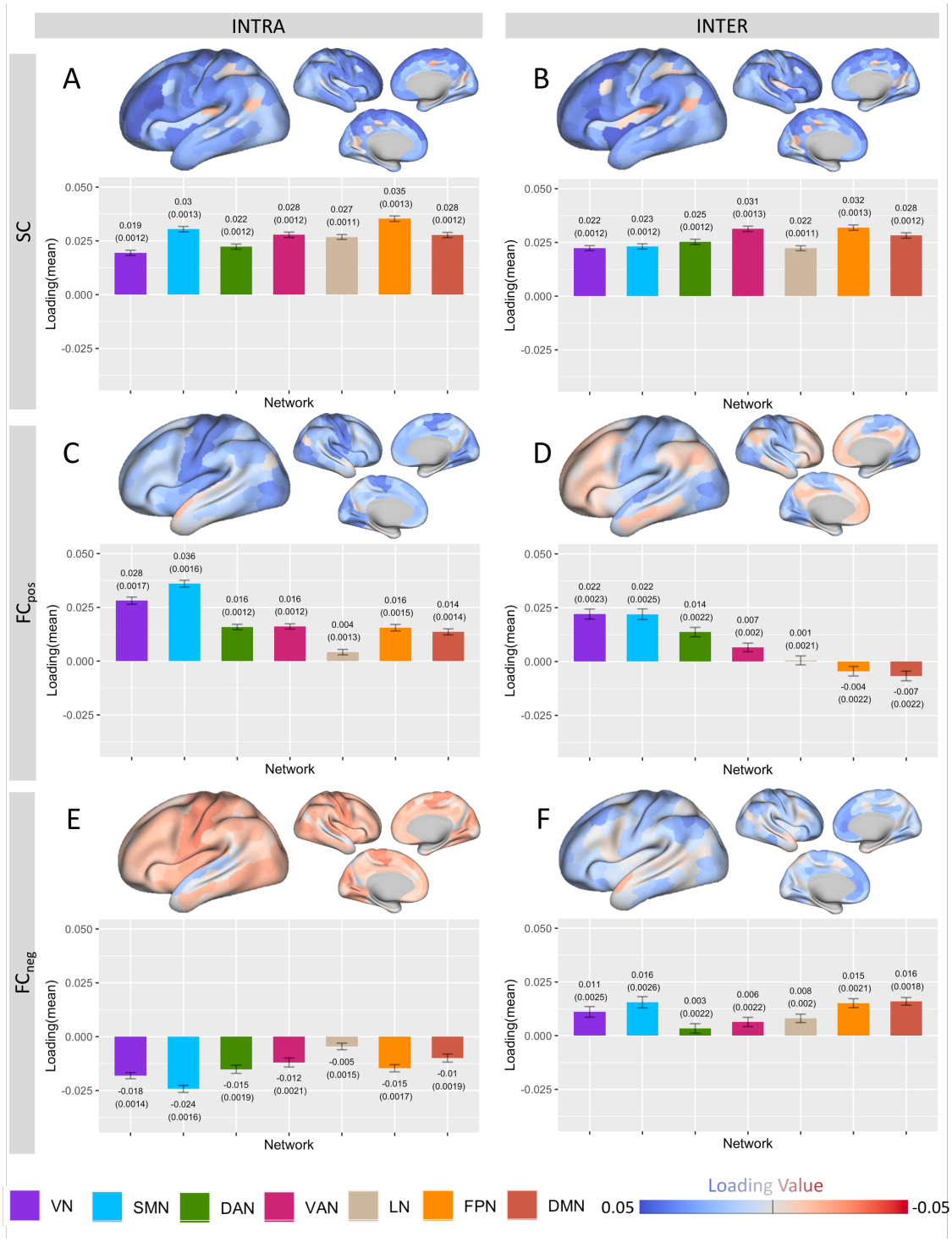


Figure 21: Visualized region- and network-wise loading values of PLSR component one. Node-wise loading values of the 1st component for intra- (A, C, E) and inter-network (B, D, F) connectivity. Loading values for SC (A, B), RSFC$_{pos}$ (C, D) and RSFC$_{neg}$ (E, F) are projected onto an inflated average surface (Q1-Q6_R440, available under https://db.humanconnectome.org) where positive loadings are colored in blue and negative values in red (for node-wise bar plots see Supplementary Figure 3). Network-wise mean loading values (SD) are visualized as bar plots (colored according to their respective network).

Within the first component, positive loading values for the intra-network $RSFC_{pos}$ of all networks were found (Figure 21, C), i.e. higher age being associated with lower intra-network $RSFC_{pos}$. Particularly, loading values of regions within primary processing networks were found to be prominently high (VN_{mean}=.028(.002), SMN_{mean}=.036(.002)) indicating the highest informative value for the prediction of the older adults age, i.e. strongest correlations with age. Regarding the inter-network $RSFC_{pos}$ (Figure 21, D), positive loading values were found for the VN, SMN and DAN, while the FPN and DMN showed overall negative loading values. In fact, looking at the node-specific loading values (Supplementary Figure 3, D), regions within the LN, VAN, FPN and DMN showed divergent directions with both positive and negative loading values.

In terms of negative correlations, negative loading values for the intra-network $RSFC_{neg}$ were found regarding all networks (Figure 21, E & Supplementary Figure 3, E) and positive loading values for the inter-network $RSFC_{neg}$ regarding all networks (Figure 21, F and Supplementary Figure 3, F). Therewith, in the first component higher anticorrelations within networks and lower anticorrelations between networks are associated with higher age.

Notably, comparing $RSFC_{pos}$ and $RSFC_{neg}$, intra-network RSFC showed very much opposing effects across all networks with overall positive loading values for $RSFC_{neg}$ and negative loading values for $RSFC_{pos}$ (Figure 21, C & E and Supplementary Figure 3, C & E). In contrast, for inter-network RSFC, FPN and DMN showed contrasting effects, while the VN and SMN showed positive loading values in both, $RSFC_{pos}$ as well as $RSFC_{neg}$ (Figure 21, D & F and & Supplementary Figure 3, D & F).

Concurrent to the depicted age-related RSFC differences, positive loading values for SC concerning all networks distributed across the whole brain were found (Figure 21, A & B and Supplementary Figure 3, A & B) indicating an overall age-related decrease in SC. Positive loading values pertained to both, intra- and inter-network SC, indicating SC decreases between nodes within their respective networks (Figure 21, A & Supplementary Figure 3, A) as well as between nodes belonging to different networks (Figure 21, B and Supplementary Figure 3, B). Specifically, the contribution of each region's SC for age prediction was found to vary across the brain (indicated by the strength of loadings) showing particularly high loading values for regions within the frontal lobe (intra-network: $Frontal_{mean}$=.033(.001), $Rest_{mean}$=.024(.001); inter-network: $Frontal_{mean}$=.032(.001), $Rest_{mean}$=-.024(.001)). Comparing loading values between brain areas within the frontal lobe as compared to the rest of the brain revealed significant higher loading values in the frontal lobe for intra-network SC (t=4.8, p<.001) as well as

inter-network SC (t=5.6, p<.001) (Figure 22). Thus, SC differences in frontal brain regions seem to be most highly characteristic for the participants' age with lower SC being associated with higher age.

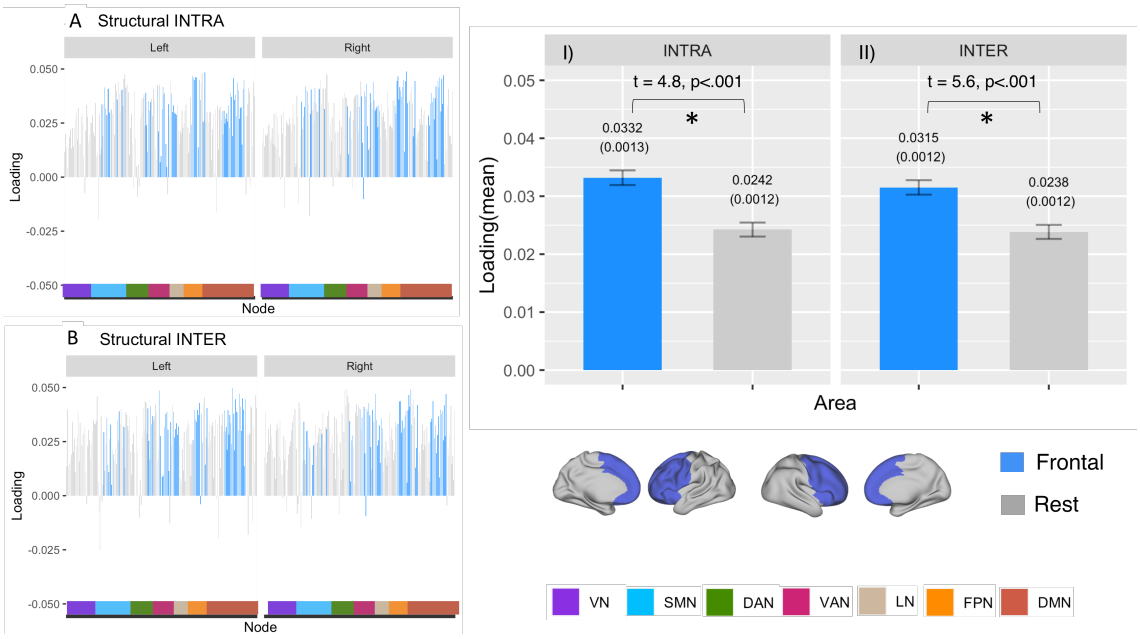


Figure 22: The 1st component's SC loading values within the frontal lobe and the rest of the brain. Node-wise loading values for intra- (A) and inter-network (B) are network-wise ordered and colored blue as its location is within the frontal lobe. Additionally, mean loading values (SD) across all regions within the frontal lobe (blue) or the rest of the brain (grey) are depicted for intra- (I) and inter-network (II) SC and statistically compared (t-test: significant at p<.05, indicated by an *asterisk*).

Cohesively, within the first component a combination of low SC, $RSFC_{pos}$ and high anticorrelations within all networks was found to be indicative for higher age. Between networks, higher $RSFC_{pos}$ was associated with higher age only for higher-order networks (particularly including the FPN and DMN). Concurrently, higher age was associated with higher $RSFC_{neg}$ between all networks. Particularly, within the first component, higher age was predicted by (and is therewith associated with) low intra-network $RSFC_{pos}$ of primary processing networks, high inter-network $RSFC_{pos}$ of higher-order networks and low SC within and across all networks (with an emphasis of regions located within the frontal lobe).

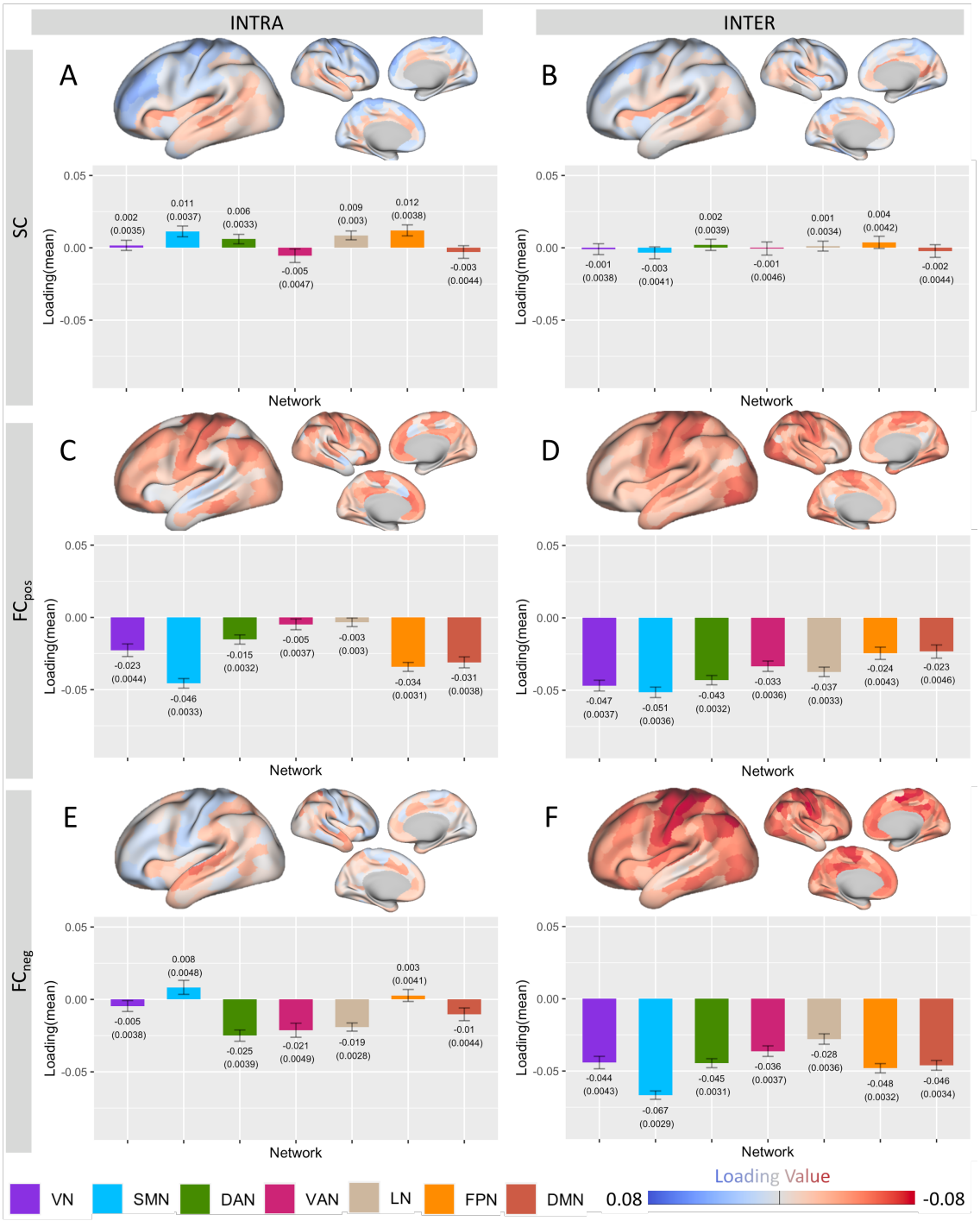


Figure 23: Visualized region- and network-wise loading values of PLSR component two.

Node-wise loading values of the second component for intra- (A, C, E) and inter-network (B, D, F) connectivity of SC (A, B), $RSFC_{pos}$ (C, D) and $RSFC_{neg}$ (E, F) projected onto an inflated average surface (Q1-Q6_R440, available under https://db.humanconnectome.org) where positive loadings are colored in blue and negative values in red (for node-wise bar plots see Supplementary Figure 4). Network-wise mean loading values (SD) are visualized as bar plots (colored according to their respective network).

Regarding the second component's intra-network RSFC, for $RSFC_{pos}$ negative loading values were applicable to all networks and particularly prominent for the SMN (SMN_{mean}=-.046(.003)), FPN (FPN_{mean}=-.034(.003)) and DMN (DMN_{mean}=-.031(.004))

(Figure 23, C & Supplementary Figure 4, C). For intra-network $RSFC_{neg}$, positive loading values for the SMN and FPN were found, while all other networks showed negative loading values. Comparing the intra-network $RSFC_{neg}$ loading distribution across the brain to these of $RSFC_{pos}$ (Figure 23 and Supplementary Figure 4, C & E), opposing effects were apparent: in regions, where the intra-network $RSFC_{pos}$ was low, $RSFC_{neg}$ was high and vice versa.

Regarding the inter-network RSFC, higher $RSFC_{pos}$ as well as higher $RSFC_{neg}$ were found to be indicative for higher age (Figure 23, D & F). This was applicable to all networks with especially strong negative loading values within the SMN (SMN_{mean}=-.051(.004)).

Regarding the second component's SC, positive as well as negative loadings were found for both, the intra- as well as inter-network SC. As of note, all networks comprised both, regions that show positive as well as negative loading values (Supplementary Figure 4, A & B). Looking at the loading distribution across the brain, loading values for inter- and inter-network SC were again found to be similarly distributed across the brain (Figure 23, A & B and Supplementary Figure 4, A & B). Also within this component, positive loadings pertained significantly more to the frontal lobe as compared to the rest of the brain (intra-network: $Frontal_{mean}$=.01(.004), $Rest_{mean}$=.001(.004), t=2.9, p=.004; inter-network: $Frontal_{mean}$=.002(.004), $Rest_{mean}$=-.002(.004), t=3.4, p<.001), visualized in Figure 24. Thus, lower intra- as well as inter-network SC of particularly the frontal lobe were associated with higher age. In contrast, negative loading values particularly pertained to regions located in posterior and temporal parts of the brain (Figure 23, A & B).

Noticeable, comparing the node-wise intra-network SC with $RSFC_{pos}$ (Supplementary Figure 4, A & C), contrasting effects were found particularly for the SMN and FPN: in regions where SC showed positive loadings, $RSFC_{pos}$ showed negative loadings indicating regions with low SC showing rather high $RSFC_{pos}$ and vice versa (Figure 23, B & D and Supplementary Figure 4, B & D).

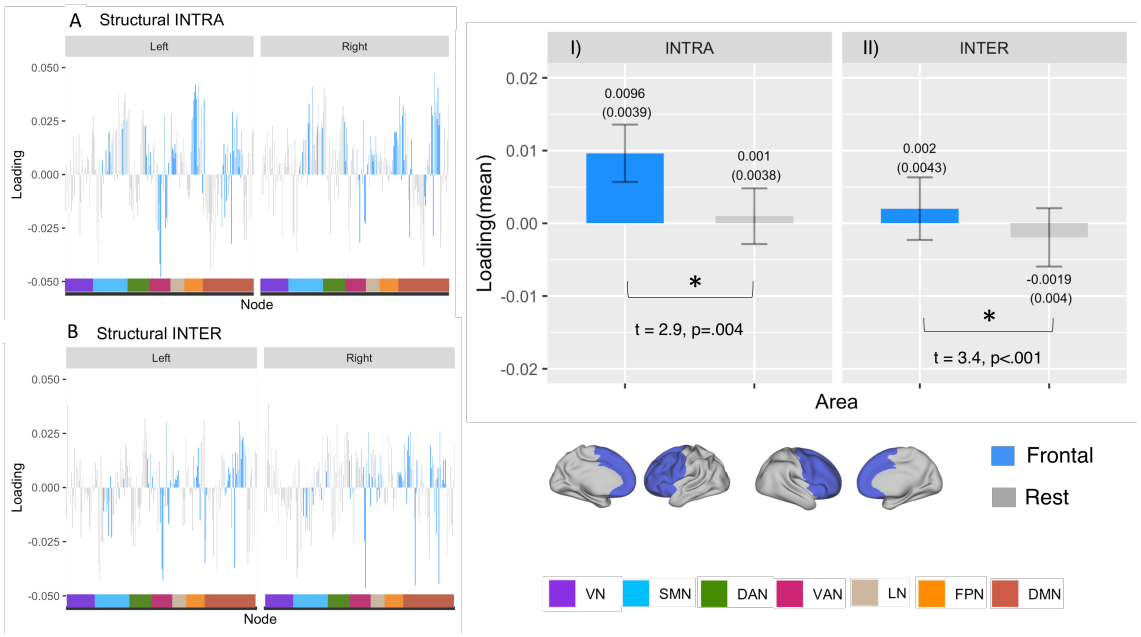


Figure 24: The 2nd component's SC loading values within the frontal lobe and the rest of the brain. Node-wise loading values for intra- (A) and inter-network (B) are network-wise ordered and colored blue as its location is within the frontal lobe. Additionally, mean loading values (SD) across all regions within the frontal lobe (blue) or the rest of the brain (grey) are depicted for intra- (I) and inter-network (II) SC and statistically compared (t-test: significant at p<.05, indicated by an *asterisk*).

In summary, within the second component higher age was characterized by a combination of high intra- and inter-network $RSFC_{pos}$ accompanied by pronounced $RSFC_{neg}$ across networks especially regarding the SMN. Within this component, SC decreases particularly affected frontal regions, while posterior and temporal parts remained rather stable. Remarkably, the second component comprised inverse effects regarding the intra-network SC, $RSFC_{pos}$ and $RSFC_{neg}$: Low SC was accompanied by high $RSFC_{pos}$ and low $RSFC_{neg}$. In turn, regions with high SC showed rather low $RSFC_{pos}$ (Figure 23, A & C & E).

5.3 Discussion: Structural and Functional Connectivity Relation

Using the multivariate approach of PLSR, aim of the second study was to identify regional RSFC and SC differences, that concurrently occur and are therefore together characteristic for the older adult's brain. Therewith, the study aimed at relating RSFC differences to SC differences to unveil potential sources for the depicted age-related RSFC differences as found within the first study. Results demonstrated that combined whole-brain RSFC and SC estimates of 400 brain regions can be used to predict the chronological age of older adults. Thereby, the contributions to age prediction were found to be different among modalities (RSFC or SC) and across brain regions, which provides insights into the relation between SC and RSFC, discussed in the following.

Functional connectivity

In terms of positive intra-network RSFC, overall lower connectivity (especially regarding the VN and SMN) were found to be characteristic for higher age within the first component. Interestingly, the opposite pattern was found for the second component, such that higher positive intra-network RSFC was indicative for higher age, which was particularly applicable to the SMN. These results are accompanied by complementary effects of negative RSFC indicating that in older adults, regions of the respective networks not only work less synchronized but even more anticyclical as comprised by the first component. In turn, if the positive intra-network RSFC is rather high in older adults, captured by the second component, regions of the respective networks seem to work more coherently with only little anticorrelations. As worked out and discussed in the first study, the SMN has been shown to play a particular role in older adults. While in younger adults, aging effects seem to predominantly affect higher-order networks (Betzel et al., 2014; Chan et al., 2014; Ferreira et al., 2016; Grady et al., 2016; Mowinckel et al., 2012; Siman-Tov et al., 2016; Spreng et al., 2016; Varangis et al., 2019), age-related differences in older adults were found to particularly affect primary processing networks (see 4.2.1 and Perry et al. (2017); Zonneveld et al. (2019)). Importantly, lower intra-network RSFC of primary processing networks are associated with lower cognitive performances (see 4.2.3 and Perry et al. (2017)). Therewith, the first component may reflect the typical aging pattern in older adults that is associated with a cognitive performance decline. In turn, preserved $RSFC_{pos}$ in primary processing networks as captured by the second component may hint at a less accelerated aging process potentially showing less severe cognitive decline.

In terms of inter-network $RSFC_{pos}$, for higher-order networks a similar effect was found for both components indicating higher network integration in higher age. This is in line with previous results suggesting positive RSFC between higher-order networks to increase across the lifespan (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) and also within older adults (see 4.2.1 and Zonneveld et al. (2019)). While higher-order networks show similar effects in both components, primary processing networks were again found to show the opposite effects across the components with lower $RSFC_{pos}$ within the first and higher $RSFC_{pos}$ within the second component being indicative for higher age. Overall higher positive inter-network RSFC may hint at a compensational attempt, as an additional functional recruitment of other networks is thought to counteract brain damages to maintain behavioral functions as stable as possible (Cabeza et al., 2002; Heuninckx et al., 2008; Iraji et al., 2016; Marstaller et al., 2015; Park & Reuter-Lorenz, 2009; Pistono et al., 2021). However, for compensational purposes one would suggest specific minor coactivations of networks as discussed in 4.3.2 (Figure 15). While the first component is depicted by inter-network $RSFC_{pos}$ increases of only higher-order networks, the second components inter-network $RSFC_{pos}$ increases affect the whole brain and are concurrently accompanied by higher negative inter-network RSFC, i.e. anticorrelations. The combination of increasing positive as well as negative RSFC may point at a dedifferentiation process in which an uncoordinated, diffuse activation pattern may not be conducive for behavioral performances (Chan et al., 2017; Chan et al., 2014; Colcombe et al., 2005; Goh, 2011; Nashiro et al., 2017; Park et al., 2004).

Subsuming, RSFC shows very much opposing effects between the two components, less applicable to the inter-network $RSFC_{pos}$ of FPN and DMN, but very much driven by the SMN. This may indicate that there exist two aging patterns particularly defined by the acceleration of $RSFC_{pos}$ in the SMN. As lower RSFC of the SMN was shown to be characteristic for an age-related decline in older adults and additionally important for cognitive performance (see 4.2.4 and Madden et al. (2017); Perry et al. (2017)), the first component may reflect the typical aging pattern in older adults that is associated with a cognitive performance decline. In contrast, the second component with overall preserved RSFC may characterize a less pronounced aging process or at least a different aging strategy, potentially picturing compensational attempts. The contrasting effects in RSFC between the two components are especially interesting when looking at the concurrently occurring SC effects, discussed in the following.

Structural connectivity

Regarding SC, in both components lower SC particularly within the frontal lobe was found to be characteristic for higher age. These effects were found to be very similar not only regarding the two hemispheres but also for intra- and inter-network connectivity indicating that SC not only decreases between regions belonging to the same network but also between regions of different networks. Previous investigations on SC are not as comprehensive as for RSFC, but results based on lifespan studies overall show consistent effects, for reviews see (Antonenko & Floel, 2014; Damoiseaux, 2017; Gunning-Dixon et al., 2009; Zuo et al., 2017). Across the lifespan, inverted U-shaped trajectories of white matter integrity were found (i.e. increases in SC from childhood to early adulthood followed by decreases in SC until late adulthood) using different measures such as fractional anisotropy or mean/axial/radial diffusivity (Bartzokis et al., 2012; Betzel et al., 2014; Burzynska et al., 2010; Damoiseaux & Greicius, 2009; Imperati et al., 2011; Mwangi et al., 2013; Westlye et al., 2010). Multiple studies used graph-theoretical estimates to quantify age-related differences and found overall decreasing connectivity from adulthood onwards, i.e. indicated by lower local and global efficiency (Betzel et al., 2014; Gong et al., 2009; Zhao et al., 2015; Zuo et al., 2017). Previous results on lifespan development indicate white matter of the frontal lobe to be particularly vulnerable to the aging process showing the greatest deteriorations across age, while white matter of temporal and occipital regions was found to be relatively preserved (Antonenko & Floel, 2014; Gunning-Dixon et al., 2009; Rojkova et al., 2016; Salat, 2011; Salat et al., 2005; Zhao et al., 2015). This is very much in line with the current results showing frontal regions being most affected and thereby highly characteristic for age. In fact, within the current study SC decreases of temporal and occipital regions are also seen, though only within the first component. As previous lifespan studies found temporal and occipital regions to be relatively preserved across age (Zhao et al., 2015), a decline of SC in these regions may be a specific effect within particularly older adults. This may hint at a more accelerated age-related decline affecting the whole brain captured by the first component. With regards to RSFC, the effects are very much in line in the way that the first component captures connectivity patterns that may be associated with advanced aging showing more widely affected SC decline and $RSFC_{pos}$ decreases of particularly the SMN. In contrast, the second component is characterized by preserved SC in temporal and occipital regions and overall high $RSFC_{pos}$ potentially hinting at a less accelerated aging process with lower cognitive decline.

Relation of functional and structural connectivity

Results of the current study indicate RSFC and SC to be both important for age prediction, each showing age-related differences that are predictive of older adults' age. In the following section the relation between these differences will be addressed by comparing the strengths of loadings between modalities, from which the importance for age prediction and simultaneous occurrence can be derived.

Within the first component, SC was found to have overall higher loading values (applicable to all networks with a slight emphasis on the FPN) as compared to positive and negative RSFC pointing at the highest relevance of SC for age prediction, i.e. being most characteristic for aging differences. This is in line with previous results showing that region-wise SC has a stronger negative age-connectivity correlation as compared to RSFC (Zimmermann et al., 2016). The importance of SC for age prediction is closely followed by positive intra-network RSFC of primary processing networks underpinning the idea of a central role of particularly the SMN during older age (Madden et al., 2017; Perry et al., 2017; Stumme et al., 2020; Zonneveld et al., 2019). Regarding the second component, high loading values in SC only pertain to a small number of regions, while the majority of regions have small loading values. Here, RSFC shows overall high loading values regarding both, positive and negative RSFC pointing at a significant role of RSFC for age prediction in a situation when SC is rather stable.

Remarkably, looking at the second component more specifically, very much opposing effects were found for the intra-network SC and RSFC, especially applicable to sensorimotor, frontal and superior temporal regions. Here, lower SC at higher age is accompanied by higher positive RSFC, while regions that are rather stable over age in terms of SC (particularly temporal regions) show lower positive RSFC at higher age. Since SC is the structural framework for functional cross-talk between brain regions, one would rather expect a positive relation between SC and RSFC and therefore RSFC to also decrease in regions with lower SC as it is the case within the first component. RSFC is constrained by the large-scale anatomical structure of the cerebral cortex (Davis et al., 2012; Salat, 2011) and previous work investigating the SC-RSFC relation indeed found SC to mediate the according RSFC of brain networks (Jung et al., 2017). Still, since RSFC reflects coherent activity of two regions described by correlational values, a functional connection can also indirectly exist without a direct structural linkage, i.e. via a third "connector" region. Detours of RSFC including connector regions could be interpreted as a beneficial strategy to cope for the age-related SC decline, potentially picturing the attempt to maintain behavioral performance (Cabeza et al., 2002; Marstaller et al., 2015; Park & Reuter-Lorenz, 2009; Pistono et al., 2021). A higher recruitment of brain regions

may be accompanied by increasing wiring costs but may also result in a higher cognitive reserve, i.e. performance maintenance (Franzmeier et al., 2018). Hence, SC decline of a white matter pathway may be compensated by higher positive RSFC using alternative pathways, resulting in regional SC decreases accompanied by increases of positive RSFC which is expressed in the second component. This is in line with Zhu et al. (2014) who found lower SC to be accompanied by stronger RSFC, which was associated with lower performance in network specific behavioral functions. Further, Reijmer et al. (2015) also focused on older adults and found RSFC and SC to be related, with a higher relation being indicative for better cognitive performance. Differences become apparent, though, when comparing results based on older adults to those on lifespan samples. Across the lifespan, the age-specific decline of SC and RSFC was found to be not or only weakly related and cognitive performance was predominantly explained by reductions in SC, less so by RSFC (Fjell, Sneve, Grydeland, Storsve, Amlien, et al., 2017; Fjell, Sneve, Grydeland, Storsve, & Walhovd, 2017; Hirsiger et al., 2016; Tsang et al., 2017). In turn, the relationship between RSFC and cognitive performance was strongest in cases where the rate of reduction of SC was lowest, implying a rather independent impact of SC and RSFC on cognitive performance (Fjell et al., 2016; Hirsiger et al., 2016). With regards to the current results, this underpins the significant role of RSFC differences in cases where SC is stable. Hence, there may be a different relation of RSFC and SC applicable in older adults as compared to the whole lifespan. For older adults, future studies on RSFC-SC relations are essential to investigate what its potential impact on cognitive performance may be.

5.4 Conclusion

To the current state of research, there exist a variety of studies showing that across the aging process not only the brain's RSFC changes, but also the SC. What is still a matter of debate is how these differences may be related. For the current work this relation was of particular interest as it may unveil origins of the age-related RSFC differences as depicted by the first study. Therefore, this second study focused on the interdependency of region-wise SC and FC differences and how these are together characteristic for older adults' age. Results revealed that while the SC of the frontal lobe was found to be highly age characteristic, differences in the RSFC of the SMN are predominantly indicative for older peoples' chronological age. The results additionally pointed at two differential age progressions, in which the combination of low SC across the whole brain and low $RSFC_{pos}$ of particularly primary processing networks in older adults may be understood as an accelerated aging process. Instead, older adults with overall higher $RSFC_{pos}$ (especially preserved intra-network $RSFC_{pos}$ of the SMN) paired with less SC decreases in posterior and temporal brain regions potentially experience a more attenuated aging process. Further multimodal studies are warranted to investigate the interrelation of SC and RSFC in older adults with its impact on cognitive performance to evaluate different progressions of age-related connectivity changes.

In the following section (6) the results of the first and second study will be related to each other and collectively discussed. After addressing some limitations of this work (7), a summary will be given to finalize the present work (8).

6 Cross-study Discussion and Outlook

With regards to the demographic change, healthy aging is becoming increasingly important allowing an independent living and autonomy up to high age. However, the older adult population is depicted by highly inter-individually variable age progressions with some adults showing earlier and steeper cognitive decline as others (Hedden & Gabrieli, 2004; Salthouse, 2004). Unveiling neurobiological sources for this high heterogeneity depicts a great potential for e.g. the development of diagnostic and therapeutic possibilities and the determination of risk and protective behavioral factors. With the current work it was aimed to contribute to the discovery of neurobiological sources that may account for differences in age progressions. Building upon previous results that suggest cognitive decline to be associated with local properties of brain structure and functional activity (Raz et al., 2005; Whalley et al., 2004), the current work investigated how brain regions are interconnected across the whole brain and how this whole-brain interconnectivity is related to age, sex and cognitive performance. Therefore, two studies were conducted on particularly the older adults' population in which a high inter-individual variability in cognitive performance is prevalent.

Within the first study, whole connectivity was estimated based on resting-state FC (RSFC). Resting-state has the great advantage that neural activations are measured in rest, independent to any task performance, which allows to look at the brain in a holistic perspective including activity (differences) across the whole brain at once. Based on the whole-brain RSFC pattern, graph-theoretical parameters were estimated network-wise, indicating how strong brain regions are connected within their according networks or between different networks. With regards to previous literature on lifespan studies (Betzel et al., 2014; Cao et al., 2014; Chan et al., 2014; Ferreira et al., 2016; Jockwitz & Caspers, 2021; Mowinckel et al., 2012; Tsvetanov et al., 2016; Varangis et al., 2019), it was hypothesized that with increasing age the RSFC between networks would increase while the RSFC within networks decreases. And indeed, this is exactly what the results of the first study depicted indicating an age-related shift from rather specialized and segregated networks towards a higher network integration. Therewith, the current work not only underpins the results based on lifespan studies, but additionally expands the current state of research by showing that this trend also persists into older adults. Moreover, as compared to lifespan studies, results of the current work indicate different networks to be affected in older adults: While predominantly higher-order networks were found to change across the lifespan (for review see Jockwitz and Caspers (2021)), in older adults particularly the primary processing networks seem to be age-sensitive. This is particularly

interesting with regards to the high cognitive performance differences that is characteristic for the older adult population.

In terms of cognitive performance differences, the current state of research suggests lower RSFC within networks to be associated with lower performance (for review see Wig (2017)). In fact, results of this work underpin these suggestions showing a positive correlation between the intra-network RSFC and cognitive performance. Importantly, this effect is related to the same networks that have also shown the highest age-sensitivity (VN and SMN) insistently pointing at a high relevance of primary processing networks for older adults' age progressions. Testing these coinciding effects statistically revealed that the primary processing networks' RSFC indeed influence the cognitive performance differences in aging. While the current state of research allowed a rather conclusive hypothesis regarding the association between intra-network RSFC and cognitive performance, it is still a matter of debate whether the age-related shift towards a higher network integration would be associated with higher or lower performances, i.e. a compensation or dedifferentiation process. Accordingly, results of the current work showed both: while lower performances were positively associated with the RSFC between primary processing networks, it was negatively associated with the RSFC including higher-order networks. Hence, while the decline of RSFC within and between primary processing networks is found to be insistently bad for cognitive performance, increases to higher-order networks seem to also be non-beneficial in terms of cognitive maintenance in older adults, rather pointing at a dedifferentiation process. In fact, the current work introduced a schematic model in which compensation and dedifferentiation processes are not mutually exclusive but rather a merging process, in which a minor recruitment of additional brain areas may be initially beneficial (in younger adults) but superseded by increasingly diffuse coactivations (in older adults) eventually resulting in cognitive decline. Finally, the first study additionally addressed sex-related RSFC differences and found males and females to be depicted by significant differences in their network architecture. Interestingly, with males showing a significantly higher network integration as compared to females, the results very well match those of the very recent study (also based on the older adults' 1000BRAINS cohort) indicating that the cognitive profile of males is rather globally organized, meaning that cognitive performance in males are significantly more interrelated as compared to those in females (Jockwitz et al., 2021).

With the first study, the current work identified a potential neurobiological factor that may account for the highly variable cognitive performances in older adults, i.e. a reorganization process which is particularly driven by RSFC decreases of primary

processing networks. Building upon these results, the second study went one step further and aimed at unveiling potential origins for the depicted RSFC differences. In fact, as prerequisite to actually exchange information, brain regions have to be connected via physical connections, i.e. axons. Physical connections can indirectly be measured by DWI which similar to the whole-brain RSFC, allows the investigation of SC between brain regions across the whole brain. Although SC is the underlying construct for brain regions to exchange information, RSFC cannot yet be directly linked to SC, for review see Straathof et al. (2019). Though, by investigating RSFC and SC differences that concurrently occur across age, dependencies between RSFC and SC may be uncovered that contribute to the understanding of age-related RSFC differences as found within the first study. Therefore, in the second study the relation between whole-brain RSFC and SC was analyzed based on a subset of the 1000BRAINS participants that had both, resting-state data as well as diffusion data available.

As statistical method to unveil the SC – RSFC relation, an age-prediction approach was utilized. Thereby, a prediction model was built based on RSFC and SC estimates of a training dataset and subsequently used to predict the chronological age of a test dataset. Given the model succeeds in predicting the age of the unknown dataset, which indeed was the case within the current work, the prediction model can be further analyzed revealing which connectivity estimates are important for age-prediction, i.e. particularly characteristic for the aging process. Thereby, SC and RSFC differences that concurrently occur across age can be detected. The age-prediction approach revealed differences of the SMN to be most age-characteristic in terms of RSFC, again pointing at the central role of primary processing networks' RSFC in older adults and additionally aggravating the relevance to particularly the SMN. Interestingly, RSFC decreases within the SMN were found to be accompanied by whole-brain SC decreases. Concurrently, inter-network RSFC increases only pertained to small parts of higher-order networks (FPN and DMN). With regards to first, the results of the first study indicating lower intra-network RSFC of the primary processing networks to be associated with cognitive decline and second, results of previous work indicating SC decreases of temporal and occipital regions to only occur at later stages of the aging process (Zhao et al., 2015), these effects may be understood as a proceeded aging process. In contrast, in cases where the RSFC of the SMN was rather stable or even showed age-related intra-network RSFC increases, SC decreases only pertained to regions located within the frontal lobe. Hence, a less severe SC decline was found to be accompanied by higher RSFC, not only related to the SMN but to the whole brain. All together, these results suggest RSFC to increase in cases

where the decline of SC is not yet advanced. This may be understood as the attempt to maintain cognitive performance by a functional overactivation and recruitment of additional intact (structurally well connected) regions. Though, as the SC decrease further proceeds, RSFC may also overall decrease potentially resulting in cognitive decline. Future studies are warranted to investigate how the SC-RSFC relation in older adults are associated with cognitive performance.

Altogether, results of this work point at a highly relevant role of primary processing networks (especially the SMN) in older adults: RSFC decreases within primary processing networks were found to be associated with cognitive performance decline. An overactivation and additional recruitment of brain networks (potentially to maintain cognitive performance) only occurs in cases where the SC decline is not yet highly progressed. Possibly, the functional recruitment of additional brain areas particularly occurs as the underlying structural connectome allows an efficient compensation. For example, RSFC may increase in order to compensate a loss of local functionality e.g. as a result of grey matter volume decline (Park & Reuter-Lorenz, 2009; Pistono et al., 2021; Reuter-Lorenz & Cappell, 2008). With intact structural connections, the consultation of additional brain regions indeed could be beneficial. However, with proceeding SC decline, the underlying construct to exchange information between regions diminishes restricting the possibility for successful compensation.

Particularly with regards to the efficiency of compensation and information transfer, it may be valuable to also consider fiber length distributions. Recent work found that fiber tract lengths systematically differ across the cortex and importantly also in relation to the functional complexity of brain networks (Bajada et al., 2019). While more complex functional networks (i.e. higher order networks) comprise tracts of various lengths, primary processing networks rather imply short range fibers. This could hint at a relation between the structural integration of these networks and the susceptibility to aging: with lower tract lengths, the capability of compensation may be more limited as compared to regions being integrated across the whole brain, i.e. by a wide repertoire of tract lengths. Fundamentally, to directly link SC (potentially also tract lengths) to RSFC changes as well as their behavioral consequences, longitudinal research is highly desired.

Besides the great potential of longitudinal studies, a recently emerging and highly promising field of research is the computational neuroscience. Here, computational simulations are used to solve and validate mathematical models that underlie brain dynamics e.g. across the aging process (Naik et al., 2017; Surampudi et al., 2018). Computational modelling is particularly valuable for the integration of data across

different modalities, e.g. not only linking structural and functional connectivity data, but also the system level to the neuron level (Einevoll et al., 2019). Further, brain simulations have been found to uncover model parameters that quantify mechanisms underlying an emergent behavior, which would not be traceable from direct observations (Breakspear, 2017). In this regard, relating the 1000BRAINS structural and functional connectomes by the use of a computational neuroscience approach could be promising to assess the impact of SC on RSFC in a causal sense.

Lastly, to finish this work with a positive outlook, the concept of the so-called cognitive reserve should be addressed: Although nobody can prevent oneself from aging, there exist studies indicating that specific lifetime experiences can positively influence the maintenance of cognitive functions in older adults (Antonenko & Floel, 2014; Marques et al., 2016; Pettigrew & Soldan, 2019; Stern, 2009). For example, second language learning was found to delay the onset of symptoms associated with neurodegeneration by several years (Bak, 2016). With regards to cognitive reserve, proxy variables (such as second language learning) are assumed to beneficially influence the efficiency, capacity, or flexibility of brain networks across the lifetime which then, during the aging process, allow a better coping of age-related brain changes (Pettigrew & Soldan, 2019). With the current work indicating RSFC of primary processing networks being so highly relevant for cognitive maintenance in older adults, training and preservation of primary processing functions may be highly significant and conducive for healthy aging. This could be considered for e.g. aging preservation programs or lifestyle consultations. Future research is warranted to first, detect behavioral interventions that positively stimulate primary processing networks and second, investigate how these potentially influence their progression across aging.

With the results of the current work, relevant neurobiological factors were identified that may contribute the highly variable aging process. The inter-relation between SC and RSFC and its causal link to behavioral performance is still far from being conclusive. With regards to the increasing importance of healthy aging, computational neuroscience approaches as well as longitudinal research are highly promising in further uncovering the dynamics between SC and RSFC as well as their interrelation with behavioral performance.

7 Methodological Considerations

The present work, including both studies, "is based on a cross-sectional design. In order to understand the precise interrelation of RSFC changes, its specific impact on cognitive performance [as well as changes of the relation between SC and RSFC], 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." (Stumme et al., 2020, page 12).

The implication of predefined functional network parcellations may depict a potential limitation of the current work, as these are not based on data from specific older adults. In fact, methods to create imaging-based brain parcellations improved over the recent years (Eickhoff et al., 2018) and has very recently yielded a whole-brain network parcellation also for particularly older adults (Doucet et al., 2021). For the first study, it was decided on an established brain parcellation which has frequently been used across the adult lifespan (Betzel et al., 2014; Fjell et al., 2015; Fjell, Sneve, Grydeland, Storsve, & Walhovd, 2017; Ng et al., 2016) to enable a direct comparison to previous work. In accordance to very recent results indicating a parcellation into 400-600 nodes to be optimal for functional and structural analyses (Schaefer et al., 2018; Varikuti et al., 2017), the granularity of the parcellation from the first to second study was increased to allow for the detection of finer-grained regional effects. The majority of studies investigating whole-brain connectivity focus on cortical brain regions. However, resting-state networks are known to also encompass subcortical structures (Ji et al., 2019). For a complete picture of SC-RSFC relations as well as its associations with aging, cognitive performance and sex, the inclusion of subcortical structures will be an essential and promising factor for future studies.

Regarding the first study, aim was "to contribute to the ongoing debate whether systematic age-related differences at the whole-brain level support the compensation or a dedifferentiation theory. Therefore, a robust definition of established brain networks and the performance in general cognitive domains was used. Similar to previous large, population-based studies (i.e. Miller et al. (2016)), the effect sizes and correlation values between RSFC and age or the cognitive components 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 (Bittner et al., 2019; Caspers et al., 2020; 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 could be potential for more specific underlying mechanisms, i.e. specific node or edge differences, 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.

The current work 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 [and are therefore also not applicable for SC - RSFC relations] (Honey et al., 2009; Zalesky et al., 2012; Zalesky et al., 2016).” (Stumme et al., 2020, page 12) Further it should be noted that negative correlations 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 & Fox, 2017). “Negative correlations may be artificially induced when using global signal regression in functional image preprocessing (Fox et al., 2009; Murphy et al., 2009; Murphy & Fox, 2017). Therefore, results on negative weights should be interpreted with caution and should be understood as complementary information without demanding clear interpretability on its own but rather underpinning the findings based on positive connections. The evolution of theoretic measures dealing with signed weights will help in solving this problem and expand our understanding of functional network dynamics.” (Stumme et al., 2020, page 12).

SC evolves, rearranges and strengthens in developmental stages, after brain injuries as well as across the lifespan as a result of e.g. learning processes (Fields, 2005; Salat, 2011; Yeatman et al., 2014). At high age, however, increases in SC are rather unlikely and may point at yet unresolved methodological constraints. In addition, tractography on diffusion imaging data is not a direct measurement but only an estimation of anatomical connectivity (Sotiropoulos & Zalesky, 2019) and known to under-represent long-distance white matter connections (de Reus & van den Heuvel, 2013). Across the aging process the paucity of long-distance connections even increases which may foster increasing short-range connections (Puxeddu et al., 2020; Zhao et al., 2015). This is especially important as recent work found the fiber length distribution to systematically

vary across the cortex (Bajada et al., 2019). Ground truth for structural connectomes has not yet been evolved.

8 Summary

Results of the current work show that the previously reported trend of decreasing intra- and increasing between-network RSFC in studies on young and middle-aged subjects is also applicable in particularly older adults. Importantly, while in younger age mainly changes of higher-order networks have been reported, the current results on older adults indicate RSFC decreases within and between particularly primary processing networks, i.e. the VN and SMN. Here, lower RSFC were additionally associated with lower cognitive performance indicating primary processing networks to be particularly relevant for cognitive performance differences. Furthermore, age-related increases of the SMN with higher-order networks was found which may hint at a compensational attempt to maintain cognitive functions despite the loss of intra-network coherence. However, higher between-network RSFC was rather associated with worse cognitive performance underpinning the dedifferentiation theory in which a less segregated and specialized network system in aging is associated with cognitive decline. In this work, insights into a potential interconnectedness of the compensation and dedifferentiation processes are provided. Thereby, compensational attempts, i.e. specific and task-adequate co-activations, may at some point during the aging process be superseded by a dedifferentiated, diffuse activation pattern followed by cognitive decline. With regards to sex, results of this work emphasize the need for sex-stratified analyses in studies with older subjects as sex-specific RSFC differences were found, potentially facilitating sex-related behavioral functioning. Furthermore, in the second study older adults' chronological age was demonstrated to be predictable by combined whole-brain region-wise RSFC and SC, though showing a differential importance of brain regions and modalities for age prediction. While for RSFC regions of the SMN were found to be age-characteristic, the frontal lobes SC seems to be particularly indicative for older peoples' chronological age. Additionally, the results point at two differential age progressions: In cases where age-related differences in SC only affect the frontal lobe, RSFC of the SMN is relatively preserved. In contrast, if age-related decreases in SC pertain to the whole brain, the SMN shows overall RSFC decreases potentially hinting at a more accelerated aging process.

In conclusion, the age-related RSFC reorganization in older adults particularly affects the SMN. Here, differences are not only related to cognitive performance decline, but also dependent on whole-brain SC differences underpinning the necessity to integrate multiple modalities for a comprehensive understanding of the cognitive aging in older adults.

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10 Supplement

Supplementary Table 1: Anatomical information on the functional network parcellation in accordance to Yeo et al. (2011) used within the first study. Regions are subdivided into left and right hemisphere according to their respective networks. Each regions‘ macro-anatomical label name (according to Tzourio-Mazoyer et al., 2002) as well as its center of gravity (COG) in x, y and z direction are denoted (also see Stumme et al., 2020).

NETWORK	LEFT HEMISPHERE					RIGHT HEMISPHERE				
	ROI	Label	COG (X)	COG (Y)	COG (Z)	ROI	Label	COG (X)	COG (Y)	COG (Z)
VISUAL	1	Lateral occipital Cortex	-25.9	-86.8	-2.2	43	Lateral Occipital Cortex	28.4	-82.3	-2.0
	2	Intracalcarine Cortex	-11.3	-73.5	12.2	44	Intracalcarine Cortex	13	-70.4	11.6
SOMATOMOTOR	3	Precentral Gyrus	-22.4	-25.7	62.8	45	Precentral Gyrus	23.1	-24	61.4
	4	Central Opercular Cortex	-50.4	-15.4	17.4	46	Central Opercular Cortex	51.9	-12.3	15.3
	5	Superior Temporal Gyrus. posterior division	-56.8	-32.8	5.6	47	Superior Temporal Gyrus. posterior division	55.3	-27.4	1.8
DORSAL ATTENTION	6	Lateral occipital Cortex. superior division	-33.5	-65.5	22.8	48	Lateral occipital Cortex. superior division	36.4	-62.0	23.3
	7	Precentral Gyrus	-26.8	-5.07	55.7	49	Precentral Gyrus	26.7	-4.7	57.8
	8	Superior Parietal Lobule	-35.3	-40.5	53	50	Superior Parietal Lobule	31	-40.1	54.7
						51	Precentral Gyrus	54.9	7.6	30.3
						52	Middle Temporal Gyrus	58	-57.9	3.4
VENTRAL ATTENTION	9	Cingulate Gyrus. anterior division	-8.3	-9	48.3	53	Cingulate Gyrus. anterior division	8.45	-6.3	48.7
	10	Insular Cortex	-42.5	0.6	2.1	54	Insular Cortex	43.5	2.8	0.6
	11	Supramarginal Cortex. anterior division	-58	-31.4	25.8	55	Supramarginal Cortex. anterior division	60.4	-27.9	25.7
	12	Frontal Pole	-31.4	44.3	26.4	56	Precentral Gyrus	51.7	-0.9	47.1
	13	Paracingulate Gyrus	-4.8	23.3	33.4	57	Frontal Pole	34.9	45.4	22.4
	14	Insular Cortex	-36	19.1	0.2	58	Insular Cortex	40.1	20.8	0.6
	15	Frontal Orbital Cortex	-26.5	42	-12.1	59	Paracingulate Gyrus	7.8	20.8	41.8
	16	Supramarginal Gyrus. posterior division	-60.7	-41.4	34.8	60	Supramarginal Gyrus. posterior division	61.2	-38.8	34.9
LIMBIC	17	Temporal Fusiform Gyrus. anterior division	-35.6	-4.9	-33	61	Temporal Fusiform Gyrus. anterior division	36.4	-3.0	-34
	18	Frontal Medial Cortex	-12.1	37	-17.6	62	Frontal Medial Cortex	12.4	37.8	-17.9
FRONTO-PARIETAL	19	Precuneous Cortex	-7.27	-63.5	43.9	63	Precuneous Cortex	8.0	-60.1	42.6
	20	Cingualte Gyrus. poterior division	-4.65	-25	27.4	64	Cingualte Gyrus. poterior division	5.1	-25.1	28.3
	21	Angular Gyrus	-47.3	-53.6	48.7	65	Frontal pole	31.6	54.6	-1.0
	22	Middle Frontal Gyrus	-41.1	22.1	39.9	66	Middle Frontal Gyrus	37.9	19	46.5
	23	Superior Frontal Gyrus	-27.2	13.2	58.3	67	Superior Frontal Gyrus	4.7	33.5	42.9

	Supplementary Table 1: Anatomical information on the functional network parcellation – continued								
	24	Frontal Pole	-32.7	54.9	-1.8	68	Angular Gyrus	51.3	-52.1	45.5
	25	Middle Temporal Gyrus. poterior division	-59.5	-40.1	-14.2	69	Middle Temporal Gyrus. poterior division	62.5	-30.7	-16.3
	26	Superior Frontal Gyrus	-2.9	31.5	42.6	70	Middle Frontal Gyrus. anterior division	54.3	-6.1	-21.8
	27	Middle Temporal Gyrus. poterior division	-55.6	-13.3	-18.4	71	Frontal Orbital Cortex	46.2	27.3	-6.5
	28	Frontal Orbital Cortex	-45.4	26.5	-2.2	72	Frontal Pole	10	46.6	41.2
	29	Angular Gyrus	-51.6	-55.4	27.9					
	30	Superior Frontal Gyrus	-8.9	44.1	40.6					
	31	Middle Frontal Gyrus	-39.9	13.6	49.6					
DEFAULT MODE	32	Middle Frontal Gyrus	-43	21.9	23.3	73	Middle Frontal Gyrus	42.4	18.7	28
	33	Supramarginal Gyrus	-38.3	-50.8	44.1	74	Angular Gyrus	40.7	-50.6	45.2
	34	Superior Frontal Gyrus	-25.6	6.7	57.3	75	Middle Temporal. temporooccipital part	60.2	-47.8	-12.3
	35	Inferior Temporal Gyrus	-53.1	-52.3	-10.4	76	Parahippocampal Gyrus. posterior division	26.5	-28.3	-19.7
	36	Precuneous Cortex	-13.1	-57.1	13	77	Precuneous Cortex	13.7	-54.1	13.6
	37	Parahippocampal Gyrus. posterior division	-25.3	-32.5	-17.3	78	Lateral occipital Cortex. superior division	47.8	-70.6	26.4
	38	Lateral occipital Cortex. superior division	-38.5	-78.8	30.9	79	Paracingulate Gyrus	7.5	49.8	5.74
	39	Cingulate Cortex. posterior division	-6.0	-50.3	30.9	80	Cingulate Cortex. posterior division	6.3	-50.2	29.9
	40	Paracingulate Gyrus	-7.6	50.7	5.53	81	Angular Gyrus	50.7	-57.7	29.2
	41	Superior Frontal Gyrus	-22.0	29.9	46.1	82	Superior Frontal Gyrus	22.9	35.2	43.2
	42	Lateral occipital Cortex. superior division	-43.8	-67.8	36.6	83	Middle Frontal Gyrus. anterior division	61	-7.4	-17.6

Supplementary Table 2: Network-wise $RSFC_{pos}$ values (+/- SE) for the whole group, only females and only males.

		VN	SMN	DAN	VAN	LN	FPN	DMN
All	**within**	6.25(0.07)	7(0.11)	13.35(0.18)	51.82(0.56)	2.05(0.04)	70.67(0.67)	90.88(0.89)
	inter	16.37(0.24)	32.51(0.35)	45.16(0.41)	75.13(0.71)	19.97(0.23)	111.19(1.07)	81.37(0.82)
	ratio	-0.42(0.01)	-0.64(0)	-0.18(0.01)	-0.54(0)	-0.81(0)	-0.22(0.01)	0.05(0.01)
Female	**within**	6.23(0.11)	7.05(0.17)	13.44(0.27)	53.96(0.85)	1.95(0.05)	72.1(1.01)	94.08(1.32)
	inter	15.87(0.36)	31.12(0.51)	44.41(0.58)	73.79(1.06)	19.91(0.36)	110.57(1.58)	80.93(1.17)
	ratio	-0.4(0.01)	-0.63(0.01)	-0.16(0.01)	-0.54(0.01)	-0.81(0.01)	-0.21(0.01)	0.07(0.01)
Male	**within**	6.26(0.1)	6.96(0.15)	13.27(0.25)	50.03(0.73)	2.13(0.05)	69.48(0.89)	88.21(1.18)
	inter	16.77(0.31)	33.66(0.47)	45.77(0.58)	76.25(0.97)	20.02(0.3)	111.71(1.46)	81.73(1.15)
	ratio	-0.43(0.01)	-0.65(0.01)	-0.21(0.01)	-0.55(0.01)	-0.8(0.01)	-0.23(0.01)	0.04(0.01)
All	**VN**		5.6(0.17)	7.89(0.19)	4.47(0.14)	1.19(0.05)	5(0.14)	8.57(0.2)
	SMN			12.92(0.23)	21.47(0.32)	3.15(0.07)	9.53(0.26)	12.35(0.26)
	DAN				28.91(0.48)	3.12(0.08)	24.5(0.42)	12.96(0.3)
	VAN					7.69(0.16)	55.96(0.74)	31.76(0.65)
	LN						9.83(0.19)	14.96(0.24)
	FPN							99.85(1.03)
Female	**VN**		5.78(0.25)	7.62(0.29)	4.43(0.21)	1.24(0.08)	4.72(0.22)	7.96(0.29)
	SMN			12.32(0.36)	21.06(0.48)	3.14(0.11)	8.58(0.36)	11.37(0.38)
	DAN			1.00	29.11(0.73)	3.08(0.12)	24.42(0.62)	12.28(0.4)
	VAN					7.48(0.26)	55.27(1.14)	30.22(0.96)
	LN						9.71(0.28)	15.17(0.36)
	FPN							101.64(1.57)
Male	**VN**		5.45(0.22)	8.12(0.26)	4.51(0.19)	1.16(0.07)	5.24(0.18)	9.08(0.27)
	SMN			13.42(0.3)	21.81(0.44)	3.16(0.1)	10.32(0.36)	13.16(0.36)
	DAN				28.75(0.64)	3.15(0.1)	24.57(0.57)	13.53(0.43)
	VAN					7.86(0.19)	56.53(0.97)	33.04(0.89)
	LN						9.93(0.26)	14.78(0.31)
	FPN							98.35(1.36)

Supplementary Table 3: Network-wise $RSFC_{neg}$ values (+/- SE) for the whole group, only females and only males.

		VN	SMN	DAN	VAN	LN	FPN	DMN
All	**within**	0.02(0)	0.81(0.04)	1.09(0.05)	5.35(0.21)	0.33(0.02)	15.22(0.36)	18.08(0.4)
	inter	32.33(0.37)	41.48(0.44)	56.09(0.5)	96.64(0.83)	22.18(0.24)	105.66(0.78)	132.31(1.11)
Female	**within**	0.03(0.01)	0.76(0.06)	0.95(0.07)	4.86(0.31)	0.35(0.03)	14.21(0.54)	16.97(0.53)
	inter	32.64(0.56)	42.03(0.7)	55.78(0.81)	97.82(1.26)	21.89(0.36)	104.62(1.18)	133.69(1.65)
Male	**within**	0.02(0.01)	0.85(0.06)	1.21(0.08)	5.77(0.28)	0.32(0.02)	16.05(0.48)	19(0.58)
	inter	32.08(0.48)	41.03(0.56)	56.35(0.62)	95.65(1.09)	22.41(0.31)	106.53(1.05)	131.17(1.5)
All	**between**							
	VN		2.28(0.09)	3.14(0.1)	14.35(0.27)	3.3(0.08)	22.54(0.35)	19.04(0.31)
	SMN			4.64(0.12)	11.57(0.27)	3.32(0.08)	30.96(0.45)	30.19(0.41)
	DAN				15.12(0.35)	5.4(0.11)	33.13(0.48)	50.74(0.58)
	VAN					9.48(0.19)	50.23(0.73)	92.51(1.22)
	LN						12.57(0.21)	10.27(0.19)
	FPN							61.87(0.88)
Female	**VN**		2.21(0.13)	3.2(0.16)	14.23(0.45)	3.28(0.12)	22.93(0.54)	19.43(0.46)
	SMN			4.59(0.19)	11.32(0.42)	3.2(0.12)	31.77(0.71)	30.97(0.63)
	DAN				14.35(0.54)	5.29(0.15)	32.62(0.78)	51.5(0.89)
	VAN					9.6(0.29)	50.16(1.09)	95.98(1.88)
	LN						12.34(0.3)	10.07(0.29)
	FPN							59.42(1.3)
Male	**VN**		2.34(0.12)	3.1(0.13)	14.46(0.34)	3.32(0.11)	22.22(0.46)	18.72(0.42)
	SMN			4.68(0.16)	11.78(0.34)	3.42(0.11)	30.3(0.56)	29.54(0.55)
	DAN				15.76(0.45)	5.49(0.15)	33.56(0.61)	50.11(0.78)
	VAN					9.38(0.25)	50.3(0.99)	89.62(1.59)
	LN						12.76(0.29)	10.44(0.25)
	FPN							63.91(1.17)

Supplementary Table 4: Results of the relations between network-wise $RSFC_{pos}$ and education.

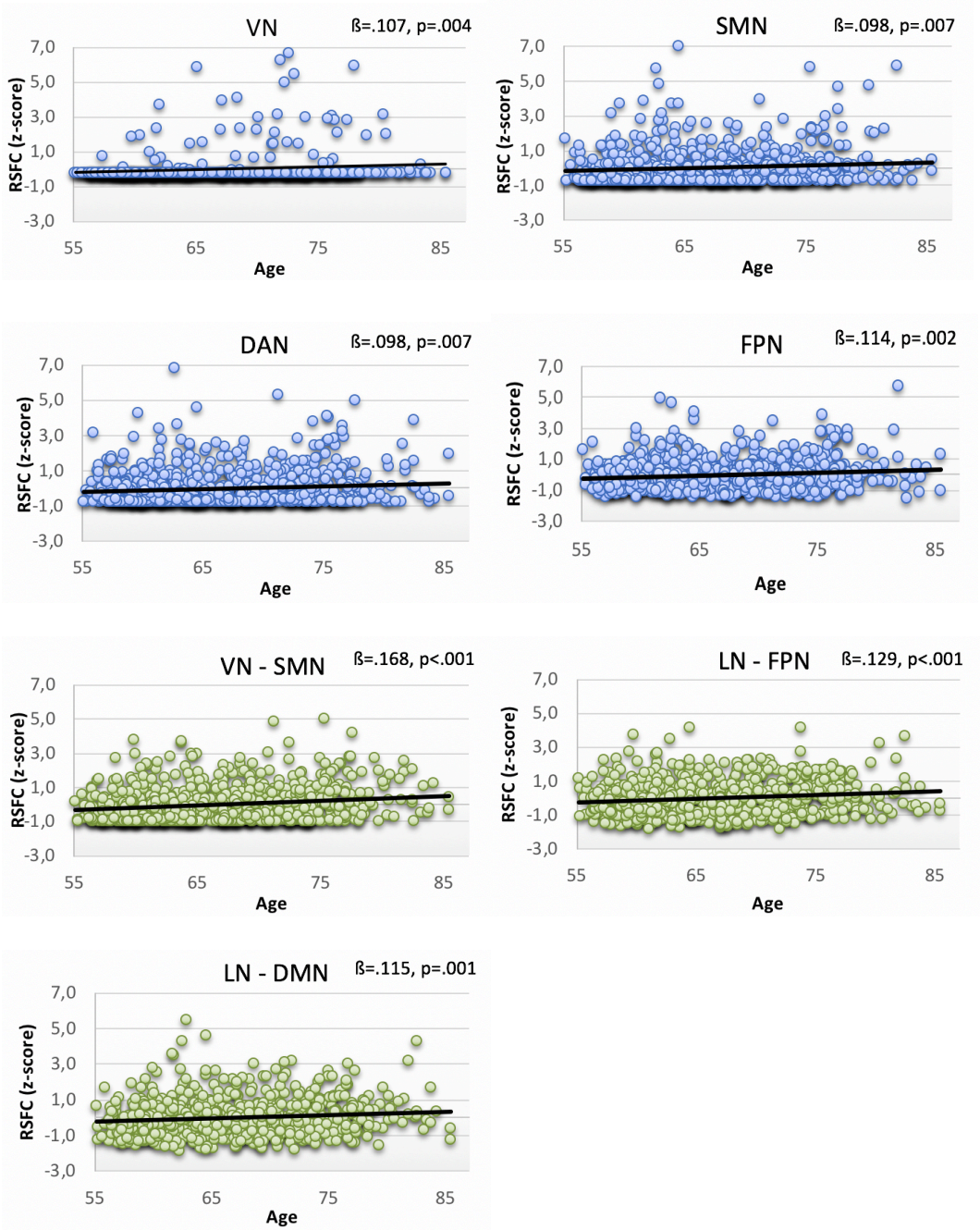
P-values (F-stats) from MANCOVAs with intra-, inter-, the ratio-scores and between-network $RSFC_{pos}$ as dependent variables and education as independent predictors.

	Education						
	VN	SMN	DAN	VAN	LN	FPN	DMN
Within	.123 (2.39)	.954 (0.003)	.413 (0.67)	.823 (0.05)	.677 (0.173)	.295 (1.1)	.122 (2.398)
Inter	.743 (0.108)	.28 (1.169)	.36 (4.435)	.590 (0.291)	.449 (0.573)	.505 (0.445)	.12 (6.411)
Ratio	.344 (0.897)	.766 (0.088)	.599 (0.277)	.817 (0.054)	.935 (0.007)	.747 (0.105)	.642 (0.216)
Between							
VN	*1*						
SMN	.362 (0.831)	*1*					
DAN	.382 (0.765)	.626 (0.238)	*1*				
VAN	.868 (0.028)	.166 (1.926)	.162 (1.961)	*1*			
LN	.394 (0.728)	.119 (2.431)	.658 (0.197)	.961 (0.002)	*1*		
FPN	.129 (2.306)	.426 (0.634)	.133 (2.267)	.744 (0.107)	.945 (0.005)	*1*	
DMN	.335 (0.929)	.937 (0.006)	.140 (2.183)	.830 (0.046)	.551 (0.355)	.460 (4.006)	*1*

Supplementary Table 5: Results of all relations between network-wise $RSFC_{neg}$ estimates and age and sex.

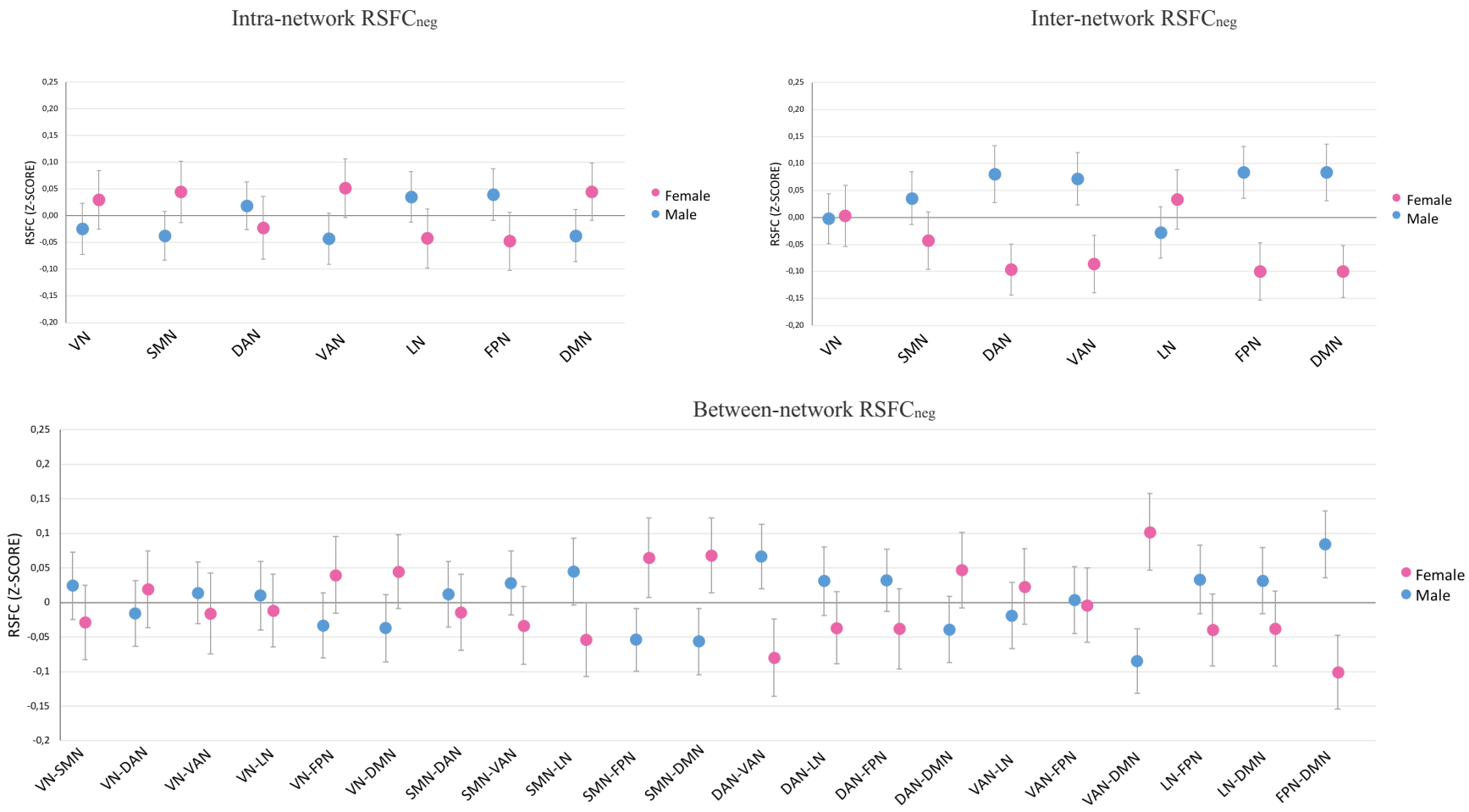
P-values (F-stats) from MANCOVAs with intra-, inter- and between-network $RSFC_{neg}$ as dependent variables and age and sex as independent predictors (covariate: education). Significant values (intra-, inter-network $RSFC_{neg} < 0.007$ and between-network $RSFC_{neg} < 0.002$ after Bonferroni-correction), that additionally survived post-hoc bootstrap validation, are indicated by an *asterisk* and highlighted in grey.

	Age							**Sex**						
	VN	SMN	DAN	VAN	LN	FPN	DMN	VN	SMN	DAN	VAN	LN	FPN	DMN
Within	.004 * (8.294)	.007 * (7.38)	.007 * (7.317)	.019 (5.516)	.602 (0.272)	.002 * (10.074)	.185 (1.76)	.774 (0.083)	.198 (1.662)	.021 (5.309)	.028 (4.86)	.599 (0.276)	.017 (5.685)	.008 (6.982)
Inter	.525 (0.404)	.989 (0)	.326 (0.965)	.089 (2.897)	.068 (3.33)	.03 (4.725)	.035 (4.458)	.327 (0.961)	.617 (0.25)	.486 (0.485)	.606 (0.266)	.138 (2.207)	.094 (2.807)	.534 (0.387)
Between														
VN	1							1						
SMN	<.001* (22.09)	1						.521 (0.412)	1					
DAN	.237 (1.4)	.005 (7.82)	1					.658 (0.196)	.481 (0.497)	1				
VAN	.201 (1.64)	.212 (1.561)	.705 (0.143)	1				.842 (0.04)	.344 (0.896)	.076 (3.153)	1			
LN	.139 (2.191)	.005 (7.966)	.077 (3.128)	.787 (0.073)	1			.932 (0.007)	.174 (1.854)	.268 (1.227)	.893 (0.018)	1		
FPN	.288 (1.129)	.369 (0.808)	.663 (0.19)	.019 (5.503)	<.001 * (12.839)	1		.289 (1.126)	.321 (0.986)	.305 (1.052)	.484 (0.49)	.192 (1.705)	1	
DMN	.637 (0.223)	.599 (0.276)	.288 (1.131)	.127 (2.335)	.001 * (10.18)	.085 (2.974)	1	.181 (1.792)	.225 (1.472)	.323 (0.976)	.064 (3.451)	.231 (1.436)	.014 (6.079)	1



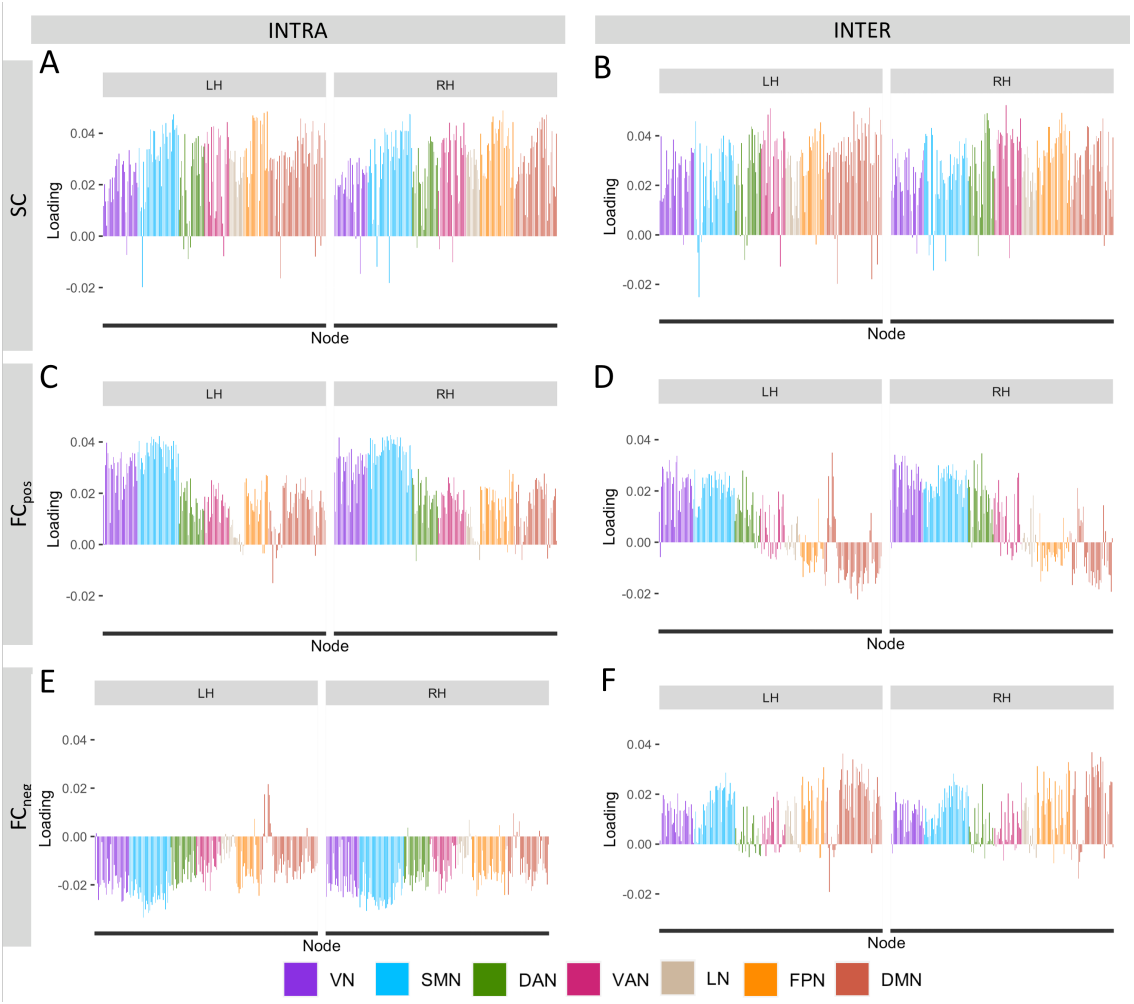
Supplementary Figure 1: Scatterplots of the relation between age and network-wise $RSFC_{neg}$ estimates.

The visualized results (z-scores) all showed a significant age effect and additionally survived post-hoc bootstrap validation: intra-network $RSFC_{neg}$ (blue) of the VN, SMN, DAN and FPN, between-network $RSFC_{neg}$ (green) between the VN and SMN, the LN and FPN as well as DMN. Age-related increasing RSFC indicate higher $RSFC_{neg}$ estimates in higher age.



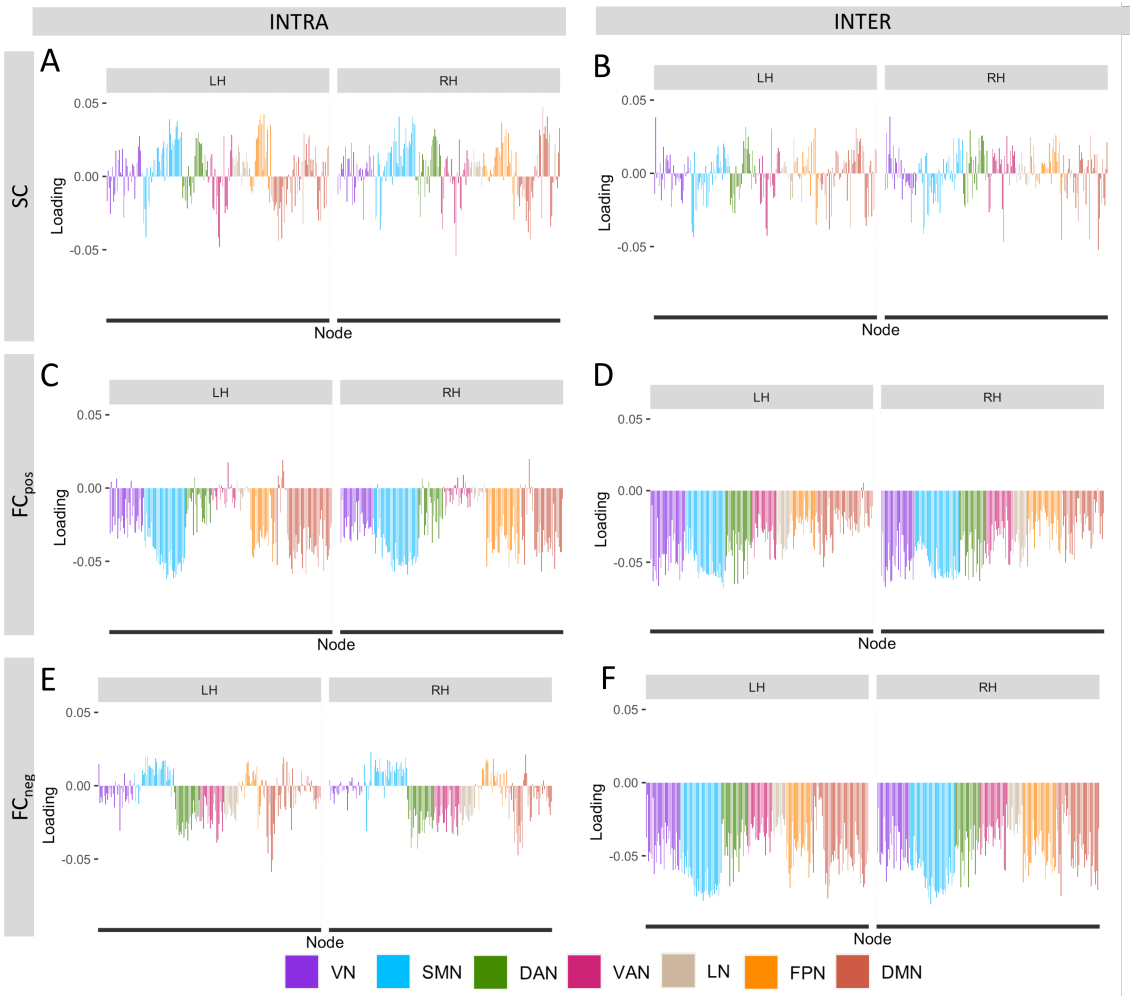
Supplementary Figure 2: Network-wise sex-related $RSFC_{neg}$ differences.

Visualized intra-network $RSFC_{neg}$, inter-network $RSFC_{neg}$ and between-network $RSFC_{neg}$ differences (z-scores, including error bars) between male (blue dots) and female (pink dots). No significant sex-related $RSFC_{neg}$ differences were found (intra-, inter-network $RSFC_{neg} < 0.007$ and between-network $RSFC_{neg} < 0.002$ after Bonferroni-correction).



Supplementary Figure 3: Node-wise loading values of component one.

Intra- (A, C, E) and inter-network (B, D, F) connectivity of SC (A, B), $RSFC_{pos}$ (C, D) and $RSFC_{neg}$ (E, F) visualized as bar plots (colored according to their respective network).



Supplementary Figure 4: Node-wise loading values of component two.
Intra- (A, C, E) and inter-network (B, D, F) connectivity of SC (A, B), $RSFC_{pos}$ (C, D) and $RSFC_{neg}$ (E, F) visualized as bar plots (colored according to their respective network).

List of Publications

Paper

In revision Glaubitz, L., **Stumme, J.**, Lucht, S., Moebus, S., Schramm, S., Jockwitz, C, Hoffmann, B. & Caspers, S. *Association between Long-Term Air Pollution, Chronic Traffic Noise, and Resting-State Functional Connectivity in the 1000BRAINS Study.* Environmental Health Perspectives.

Hild, K., **Stumme, J**., Jockwitz, C, Caspers, S. & Heim, S. *The influence of bilingualism on gray matter volume in the course of aging: A longitudinal study.* Neurobiology of Aging.

Jockwitz, C., Krämer, C., **Stumme, J.**, Dellani, P., Moebus, S., Bittner, N. & Caspers, S. *Characterization of the angular gyrus in an older adult population: A multimodal multilevel approach.* Brain Structure and Function.

Stumme, J., Krämer, C., Schreiber, J., Caspers, S. & Jockwitz, C. *Interrelating differences of structural and functional connectivity in the older adult's brain*. Human Brain Mapping.

2022 Bittner, N., Korf, H.W., **Stumme, J.**, Jockwitz, C., Moebus, S., Schmidt, B., Dragano, N. & Caspers, S. *Multimodal investigation of the association between shift work and the brain in a population-based sample of older adults.* Scientific Reports, 12(1), 1-19.

Lavanga, M., **Stumme, J.**, Yalcinkaya, B. H., Fousek, J., Jockwitz, C., Sheheitli, H., ... & Jirsa, V. (2022). *The virtual aging brain: a model-driven explanation for cognitive decline in older subjects.* bioRxiv.

2021 Jockwitz, C., Wiersch, L., **Stumme, J.**, & Caspers, S. (2021). *Cognitive profiles in older males and females.* Scientific reports, 11(1), 1-13.

2020 **Stumme, J**., Jockwitz, C., Hoffstaedter, F., Amunts, K., & Caspers, S. (2020). *Functional network reorganization in older adults: Graph-theoretical analyses of age, cognition and sex.* NeuroImage, 116756.

2019 Heim, S., **Stumme, J**., Bittner, N., Jockwitz, C., Amunts, K., & Caspers, S. (2019). *Bilingualism and "brain reserve": A matter of age.* Neurobiology of aging, 81, 157-165.

Poster

2021 Bittner, N., Korf, H.W., **Stumme, J.**, Jockwitz, C., Moebus, S., Schmidt, B., Dragano, N., Caspers, S. (2021). *Multimodal investigation of the association between shift work and the brain in a population-based sample of older adults.* 46. Jahrestagung Psychologie und Gehirn (PuG) & 6th international Conference of Aging & Cognition by EUCAS.

Glaubitz, L.1, **Stumme, J.**, Lucht, S., Moebus, S., Sara Schramm, S., Jockwitz, C, Hoffmann, B., Caspers, S. (2021). *Association between long-term air pollution, traffic noise and resting-state brain connectivity.* 26th Annual Meeting of the Organization for Human Brain Mapping, Seoul, Korea.

Haddad, L., **Stumme, J.**, Caspers, S., Jockwitz, C. (2021). *Do personality traits explain differences in resting state functional connectivity in older adults?* 26th Annual Meeting of the Organization for Human Brain Mapping, Seoul, Korea.

Hild, K., **Stumme, J.**, Jockwitz, C., Caspers, S., Heim, S. (2021). *The influence of bilingualism on gray matter volume in the course of aging.* 26th Annual Meeting of the Organization for Human Brain Mapping, Seoul, Korea.

Krämer, C., Jockwitz, C., **Stumme, J**., Campos, L., Rubbert, C., Caspers, J., Caspers, S. (2021). *Classification and prediction of cognitive performance differences in older age.* 46. Jahrestagung Psychologie und Gehirn (PuG) & 26th Annual Meeting of the Organization for Human Brain Mapping, Seoul, Korea.

Jockwitz, C., Wiersch, L., **Stumme, J.**, & Caspers, S. (2021). *Cognitive Profiles in Older Males and Females.* 6th international Conference of Aging & Cognition by EUCAS.

Stumme, J., Caspers, S., Jockwitz, C. (2021). *Vulnerability of inter-hemispheric functional connectivity in the aging sensorimotor network*. 46. Jahrestagung Psychologie und Gehirn (PuG) & 26th Annual Meeting of the Organization for Human Brain Mapping, Seoul, Korea.

Stumme, J., Caspers, S., Jockwitz, C. (2021). Cognitive decline: Which performances reveal our chronological age? 6th international Conference of Aging & Cognition by EUCAS.

2020 Bittner, N., Korf, H.-W, **Stumme, J**., Caspers, S. (2020). *Does shift work affect brain and cognitive health? Multimodal results from a population-based sample.* 25th Annual Meeting of the Organization for Human Brain Mapping, Montreal, Canada.

Glaubitz, L., **Stumme, J**., Jockwitz, C., Lucht, S. A., Moebus, S., Jöckel, K., Hoffmann, B., Caspers, S. (2020). *Association between long-term exposure to air pollution and ambient noise with altered resting-state brain connectivity in the 1000BRAINS study.* Annual Meeting of the International Society for Environmental Epidemiology.

Jockwitz, C., Wiersch, L., **Stumme, J**., Caspers, S. (2020). *Sex-specific cognitive profiles relate to resting state functional connectivity in males and females.* 25th Annual Meeting of the Organization for Human Brain Mapping, Montreal, Canada.

Stumme, J., Jockwitz, C., Schreiber, J., Hoffstaedter, F., Caspers, S. (2020). *Age prediction by functional and structural connectivity: a multivariate pattern analysis.* 25th Annual Meeting of the Organization for Human Brain Mapping, Montreal, Canada.

2019 Bittner, N., Korf, H.-W, **Stumme, J.**, Caspers, S. (2019). *Does shiftwork affect connectivity of the default mode network in the human brain?* A pilot study. 33. Arbeitstagung der Anatomischen Gesellschaft, Würzburg, Germany.

Stumme, J., Jockwitz, C. Schreiber, J., Hoffstaedter, F., Caspers, S. (2019). *Disentangling the relation of structural and functional connectivity reorganization in older adults.* 24th Annual Meeting of the Organization for Human Brain Mapping, Rom, Italy.

2018 **Stumme, J.**, Jockwitz, C. Amunts, K., Caspers, S. (2018). *Functional network reorganization in older adults: graph-theoretical analyses of age, sex and cognition.* 23rd Annual Meeting of the Organization for Human Brain Mapping, Singapore.

2017 Heim, S., **Stumme, J.**, Bittner, N., Jockwitz, C., Amunts, K., & Caspers, S. (2017). *Bilingualism, Age, and the "Brain Reserve"*. SNL Annual Meeting, Baltimore, Maryland.

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Erklärung zur Datenaufbewahrung

Erklärung § 5 Abs. 1 zur Datenaufbewahrung

Hiermit erkläre ich, dass die dieser Dissertation zu Grunde liegenden Originaldaten

in dem **Institut für Neurowissenschaft und Medizin -1 des Forschungszentrums Jülich**

hinterlegt sind.

Johanna Stumme

Eidesstattliche Erklärung

Eidesstattliche Erklärung gemäß § 5 Abs. (1) und § 11 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, **Johanna Stumme** an Eides statt, dass ich folgende in der von mir selbstständig erstellten Dissertation „**Functional Network Reorganization in older Adults: Structural relations and its impact on sex and cognitive performance**“ dargestellten Ergebnisse erhoben habe:

Bei der Durchführung der Arbeit hatte ich folgende Hilfestellungen, die in der Danksagung angegeben sind:

	Johanna Stumme	Christiane Jockwitz	Felix Hoffstaedter	Jan Schreiber	Svenja Caspers	Katrin Amunts	Summe (%)
Studienüberwachung					70	30	100
Studiendesign / Konzeption					70	30	100
Datenaufbereitung der Resting State Daten	60		40				100
Datenaufbereitung der Diffusion Daten	60			40			100
Statistische Auswertung Studie 1	80	20					100
Statistische Auswertung Studie 2	80	20					100
Interpretation der Datenauswertung	60	20			10	10	100
Interpretation und Zusammenbringung beider Studien im gesamtheitlichen Kontext	100						100
Verfassung des Manuskripts	100						100
Korrektur des Manuskripts		50			50		100

_____

Unterschrift der Doktorandin/des Doktoranden
Johanna Stumme

Als Betreuer der obigen Dissertation bestätige ich die Angaben von Johanna Stumme.

_____

Unterschrift des Doktorvaters
Univ.-Prof. Dr. Dr. Klaus Mathiak

Lebenslauf

Johanna Stumme

24.07.1989 in Hamburg, Germany
Graeffstraße 12, 50823 Cologne, Germany
☎ +49 (157) 35245953
✉ j.stumme@fz-juelich.de

Education

04/2014 – 09/2016	**Master of Science** Teaching and Research Logopedics RWTH Aachen University, Aachen, Germany
09/2009 – 07/2013	**Bachelor of Health** Logopedics HAN - University of Applied Sciences, Nijmegen, Netherlands
06/2009	**School diploma – A-level**
2006 – 2009	Gymnasium Willhöden, Hamburg, Germany
2005 – 2006	Western Heights High School, New Zealand
2000 – 2005	Gymnasium Rissen, Hamburg
1996 – 2000	Grundschule Marschweg, Hamburg

Experience

Since 10/2020	**Research Assistant** at Institute for Anatomy I, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany (Prof. Dr. Dr. Svenja Caspers)
Since 10/2016	**PhD Program** at Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, RWTH Aachen University, Aachen, Germany Title: „Functional Network Reorganization in older Adults: Structural relations and its impact on sex and cognitive performance“ (Prof. Dr. Dr. Klaus Mathiak, Prof. Dr. Dr. Svenja Caspers)
Since 10/2016	**Guest Scientist** at Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany (Prof. Dr. Dr. Svenja Caspers)
10/2016 – 09/2020	**Research Assistant** at Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, RWTH Aachen University, Aachen, Germany (Prof. Dr. Dr. Klaus Mathiak)
01/2016 – 09/2016	**Masterthesis** at Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany Title: „Structural differences of monolinguals and bilinguals during the course of aging“ (Prof. Dr. Stefan Heim, Prof. Dr. Dr. Svenja Caspers)
11/2014 – 09/2016	Part-time Speech Therapist, St. Katharinen-Hospital Frechen, Stroke-Unit
05/2015 – 12/2015	Part-time Speech Therapist, Praxis für Logopädie Agnes Molnar

Teaching and Supervisory Work

Since 2021	Teaching at HeiCAD, Heinrich Heine University, Düsseldorf, Germany Elective Subject: Neuroimaging and Precision Medicine
Since 2019	Teaching at Medical Faculty, Heinrich Heine University, Düsseldorf, Germany Elective Subjects: NeuroRevolutions Master's Programme: Translational Neuroscience

Kreutz (2019). Interaction between the networks for language and executive functions – a cross-sectional analysis in the framework of the 1000BRAINS study. Master Thesis, RWTH Aachen.
Moser (2019). The impact of bilingualism on functional connectivity in the brain over the life span: A cross-sectional analysis within the 1000BRAINS study. Master Thesis, RWTH Aachen.
Peters (2019). Interaction between the networks for language and executive functions – a longitudinal analysis in the framework of the 1000BRAINS study. Master Thesis, RWTH Aachen.
Philippek (2020). The impact of bilingualism on cognition and functional connectivity in the brain during aging: A longitudinal analysis within the 1000BRAINS study. Master Thesis, RWTH Aachen.
Zimmermann (2020). Quantitative and qualitative analysis of verbal fluency performance: individual differences in cluster and switching strategies in the framework of the 1000BRAINS study. Master Thesis, RWTH Aachen.

Skills

Languages	German (native language)
	English (fluent)
	Dutch (NT2 level)
	Latin (Latinum)
EDV	Textprocessing in MS-Office, Open-Office
	Dataprocessing SPSS, Excel und R
	Basic skills in structural brain image processing using FreeSurfer
	Basic skills in preprocessing and analysis of functional brain images using SPM12, FSL
IT-Kenntnisse	Basic skills in MATLAB, Bash, Python und R

Cologne, 30.03.2022

Johanna Stumme