UNIVERSITÄTSKLINIKUM HAMBURG-EPPENDORF

Klinik und Poliklinik für Neurologie

Direktor: Prof. Dr. med. Christian Gerloff

Age-related association of functional brain networks with white matter lesions and cortical thinning

Dissertation

zur Erlangung des Grades eines Doktors des PhD an der Medizinischen Fakultät der Universität Hamburg.

vorgelegt von:

Maximilian Schulz
aus Bergen auf Rügen

Hamburg 2022

Angenommen von der
Medizinischen Fakultät der Universität Hamburg am:
19.01.2023

Veröffentlicht mit Genehmigung der
Medizinischen Fakultät der Universität Hamburg

Prüfungsausschuss, der/die Vorsitzende:

Prof. Dr. Götz Thomalla

Prüfungsausschuss, zweite/r Gutachter:

Prof. Dr. Renate Bonin-Schnabel

Table of Contents

1 Introduction

1.1 General Overview

The significant progress of modern medicine in recent decades has led to a sharp increase in life expectancy, especially in the western world, leading in combination with declining birth rates to a progressive aging of the population and a shift in the age distribution towards an elderly population. This development is accompanied by an increasing incidence of neurodegenerative and other age-related diseases such as Alzheimer's disease[1], Parkinson's disease[2] or Cerebral Small Vessel Disease (CSVD)[33] and has implications not only for health but also for the economic aspects of our society. Even in the absence of overt neurodegenerative disease, age-related brain changes are associated with cognitive alterations that have been replicated in multiple studies, including degradation of processing speed, perception, memory, and executive function[4,5,6,7]. This cognitive decline erodes the benefits of increased longevity and is one of the most troubling effects of ageing for individuals. Higher cognitive brain functions rely on multi-site communication in large-scale distributed networks of different brain regions[8]. In this regard, an increasing number of studies suggest that cognitive deficits in normal aging arise from subtle anatomical disruptions between these brain regions that normally function together, possibly due to loss of white matter integrity or demyelination causing alterations in functional properties of coordinated brain systems[9,10,11]. These functional brain properties are determined by the anatomical backbone of white-matter pathways that coordinate synchronized neural activity and cognition[12,13]. Accordingly, age-related functional brain alterations are thought to occur in response to a general reduction in the structural integrity of white matter, focal brain lesions and loss of grey matter volume[14,15], even after consideration for age-related changes in health of cerebral vessels[16]. Studies in recent years have already yielded useful insights into disrupted functional networks and their associations with cognitive function in pathologies such as multiple sclerosis[17] or diabetes[18] all of which involve white matter damage.

However, the nature of this interaction between functional and structural integrity in context of cerebral small vessel disease, vascular brain lesions and aging with vascular risk factors but without overt pathology remains insufficiently understood. Therefore, relating structural brain changes and physical connections to patterns of functional interactions in the brain is

still a key research area in neuroscience. In recent decades, neuroimaging has emerged as a powerful tool to investigate the structural and functional changes in the ageing brain, and to characterize how these changes relate to accompanying alterations in cognitive function. By using modern tools of MRI analyses, the studies of the present thesis aim to shed light on the interaction between structural brain changes and functional brain connectivity in relation to cerebral small vessel disease and to vascular risk factors in healthy elderly.

This thesis is based on two publications, namely "Functional connectivity changes in cerebral small vessel disease - a systematic review of the resting-state MRI literature"[19] and "Association of age and structural brain changes with functional connectivity and executive function in a middle-aged to older population-based cohort"[20]. In addition, a further study entitled "Topological differences in functional networks between patients with small vessel disease and healthy controls" is reported, which was not published but has substantially contributed to the knowledge gained in this thesis. The basis for this unpublished analysis was the sample cohort of the CONNECT study. Prior analyses from this study with a different focus have been published in two publications "Higher white matter hyperintensity lesion load is associated with reduced long-range functional connectivity"[21] and "Intrinsic functional brain connectivity is resilient to chronic hypoperfusion caused by unilateral carotid artery stenosis"[22] in which I was contributing as co-author. Further I participated as a co-author in the systemic review "Characterization of white matter hyperintensities in large-scale MRI-studies"[23].

In the following section **(1.2)** of this synopsis, I first summarize the methodologies of the three studies and define the research questions of these analyses. The second part of this synopsis, section **(2)**, reports the results of the studies, starting with a description of the background and the key concepts. In this regard, section **(2.1)** provides a content introduction to our systematic review of resting state MRI literature and the small sample study with CSVD patients by describing the pathological sources, the development, and consequences of CSVD as well as the association with altered imaging parameters. Section **(2.2)** summarizes the results of our systematic literature analysis and the ensuing trends and methodological difficulties in small vessel disease research. Section **(2.3)** outlines in brief our results of the topological difference in functional networks between patients with small vessel disease and healthy controls. Section **(2.4)** introduces the second study by providing information on

structural and functional change with increasing age outside clinically present CSVD. In addition, the section highlights the pathological link between white matter lesions and decreasing cortical thickness and refers to the importance and function of large-scale resting state networks. Finally, section **(2.5)** summarizes our results on the association between structural damage in the form of white matter integrity and cortical thickness with Functional Connectivity (FC) in 976 cognitive normal participants at cardiovascular risk. Section **(3)** discusses the key results of this thesis and gives an outlook on potential further research approaches.

1.2 Experimental Approach and Objectives of the Dissertation

The analytical approaches to assess the impact of structural brain alterations on functional properties included state-of-the-art techniques of brain network analysis based on structural and functional Magnetic Resonance Imaging (MRI) and different samples of patients and healthy subjects. More specifically, these samples included 17 patients with small vessel disease and 20 controls enrolled at the Department of Neurology, University Medical Centre Hamburg-Eppendorf as well as 976 healthy elderly people with an increased vascular risk profile from the Hamburg City Health Study (HCHS). In addition, a systematic meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[24], which ultimately identified 44 articles, published in the previous 10 years reporting on MRI-derived functional connectivity alterations at rest in patients with white matter hyperintensities of presumed vascular origin as a marker of CSVD.

The meta-analysis aimed to survey the current literature, review methodological advances made in recent years, and update our understanding of the neural mechanisms underlying ischemic white matter damage, functional changes, and cognitive deficits in patients facing CSVD. For this purpose, the PubMed online database was queried for studies that were published since January 2010, following the PRISMA protocol. Articles reporting on MRI-derived resting-state functional brain connectivity in patients with white matter hyperintensities of presumed vascular origin were extracted. Further, based on patient characteristics and research objective the articles were grouped and evaluated according to different criteria. Finally, the risk of methodological bias in the individual studies was assessed using the Appraisal Tool for Cross-Sectional Studies (AXIS tool)[25], which was modified in such

a way that items related to presentation of results, discussion of results, or study funding were not considered[26].

The objective of the first study, was to analyse the difference in brain network topology between 17 patients with cerebral small-vessel disease and 20 healthy control participants. Patients were characterized by an age over 50 years with a high load of white matter lesions (Fazekas > 2) as a neuroimaging feature for cerebral small-vessel disease and no history of stroke, dementia, or depression nor any severe neuropsychiatric disease or significant neurological symptoms. Control participants were defined by low to no white matte lesion load no history of any neurological or psychiatric disorders, no cognitive impairment, and no abnormalities in their conventional brain MRI images. The extent and localization of white matter brain lesions was measured on Fluid-attenuated Inversion Recovery sequence (FLAIR) and evaluated independently by two radiologists. Functional brain connectivity was measured by functional MRI at rest and were based on the parcellation of the cerebral cortex into 264 regions of interest according to the group-wise graph theory-based parcellation atlas of Shen et al[27]. Graph theory-based analyses were employed to analyse quantitative differences of global and local network organization i.e., global, and local efficiency. Finally, a Mann-Whitney-U-Test was used as a non-parametric statistical hypothesis test to reveal functional differences present in patients with CSVD.

The second study addressed the question of whether functional connectivity is affected by structural brain damage in a healthy population of 976 participants between 45 and 74 years of age with altogether low load of white matter lesions but at cardiovascular risk from the Hamburg City Health Study (HCHS). Cardiovascular risk factors were represented in varying proportions in the form of smoking status, diabetes, Body-Mass-Index (BMI), or hypertension. Functional connectomes were constructed from resting-state functional magnetic resonance imaging, based on the a priori parcellation of the cortex into 200 regions and 7 resting-state networks by the local-global parcellation of Schaefer atlas et al[28]. In addition, cortical thickness was measured across the entire cortex by T1-weighted imaging data along with the Peak Width of Skeletonized Mean Diffusivity (PSMD) as a novel biomarker for white matter damage from diffusion tensor imaging. Multivariate analysis was applied to assess the influence of age, microstructural white matter damage and cortical thickness on functional connectivity measures of the entire cortex as well as on the connectivity four hypothesis-based pre-defined

resting state networks. Furthermore, Network-Based Statistics (NBS) was employed to investigate whether age-related network changes are driven by specific functional domains in the form of functionally disconnected subnetworks. Finally, possible mediating effects of structural damage on the relationship between age and functional connectivity of these subnetworks were analysed as well as a possible role of the subnetworks themselves as mediators between age and executive cognitive function.

In conclusion, this thesis analyses the interaction between age-related structural brain damage, particularly in form of white matter lesions, and functional brain connectivity in three sequential steps.

In an effort to provide a substantive foundation for our research the systematic meta-analysis addressed the following research question:

- *What state of knowledge has research reached over the past 10 years about the impact of CSVD on functional connectivity and what are the methodological concerns that accompany these findings?*

The subsequent studies address the following research questions:

- *Is structural damage in the form of cerebral small vessel disease associated with a relevant disruption in the topological architecture of the functional brain connectome?*

  Hypothesis 1:
  We hypothesized that the decreasing structural integrity due to advanced cerebral microangiopathy is associated with altered network properties of functional brain networks.

- *What is the nature of the relationship between age-related structural brain damage and functional change outside of severe pathological developments?*

Hypothesis 2:

We hypothesized that even in healthy aging, white matter damage and cortical thinning are associated with an alteration in resting-state functional connectivity. Further, we predicted that part of the effect of age on functional connectivity is mediated by structural parameters.

2 Key concepts and summary of the individual studies

2.1 Altered measures of structural and functional MRI in context of small vessel disease

Age-related diseases will increasingly challenge society and healthcare systems. More than 40 million people worldwide currently suffer from dementia, and the number is expected to almost double every 20 years[29]. Cerebral small vessel disease, commonly observed on neuroimaging among elderly individuals, is now recognized to be the leading cause of vascular cognitive impairment and dementia[30,31,32,33]. Cerebral Small vessel disease is additionally estimated to be the main etiological factor in up to 23% of all ischaemic strokes[34] and is associated with gait impairment and mood disturbances[35,36]. Its prevalence is highly age-dependent in individuals older than 60 years[37], in particular in the presence of vascular risk factors such as hypertension or diabetes[38,39]. The disease itself is defined by pathological changes in arteries, arterioles, capillaries, venules, and small veins due to atherosclerotic, genetic, idiopathic, infectious, immune-mediated, or other secondary etiologies[40]. This development leads to a state of impaired blood circulation in the arterioles of the brain[41] resulting into lesions in the white matter[42]. Magnetic resonance imaging has become increasingly important in the study of the mechanisms underlying CSVD and the discovery of surrogate markers of CSVD progression[43]. White matter lesions are identified by magnetic resonance imaging scanning as diffuse White Matter Hyperintensities (WMH) in periventricular and deep white matter regions and as subcortical and lacunar infarcts[44,42]. These WMHs are defined by thickening of the vessel walls, enlarged perivascular spaces, decreased vessel density, increased vessel tortuosity, and the presence of plasma proteins[45]. As such WMH have become a biomarker for long-term cerebrovascular disease[46] and are associated with clinical manifestations of cognitive impairment[47,48] including memory[49], executive functions[50], attention[51] and motor impairments[52].

However, clinical symptoms of patients with CSVD are often highly inconsistent in nature and severity, despite identical appearance of WMH on imaging[53]. In addition, MRI techniques, such as fluid-attenuated inversion recovery (FLAIR), coarsely subdivide tissue into abnormal and normal tissue and reveal only the tip of the iceberg in terms of the tissue changes associated with CSVD. Furthermore, white matter lesions affect the whole brain despite being localized in subcortical areas so that CSVD must be considered as a global rather than a focal disease[53]. Therefore, the simple evaluation of lesion volume seems to fall short for measuring the progression of brain damage and neuronal impairment caused by CSVD.

In contrast, quantitative imaging techniques, including magnetization transfer imaging and Diffusion Tensor Imaging (DTI) can provide a detailed assessment of underlying tissue changes at the voxel level[54]. These diffusion-weighted images allow the extraction of white matter fibre tracings, which then can be used to construct a structural network. Previous literature has emphasized the importance of viewing the brain as a network or set of networks and applying network-based methods rather than relying on focal analysis[55]. Cognitive brain functions depend on the efficient functioning of distributed brain networks connected by white matter pathways[56]. Graph theory enables the analysis of these networks and describes brain connections as a collection of brain regions (nodes) that communicate with each other via white matter tracts (connecting edges), defined by diffusion tensor tractography. Previous studies report disrupted organizational characteristics of structural brain networks and their associations with cognitive abilities in different pathologies[57,58,59]. Disrupted network measures in relation to compromised white matter integrity were observed in CSVD as well[56,60] and have been termed as “disconnection syndrome”[11,61]. This hypothesis states that if compromised integrity of white matter tracts leads to disconnection of brain regions, a deficit in function will follow[62,11]. Previous structural network analysis consolidated the hypothesis of CSVD being a disconnection syndrome and structural neuroimaging measures of CSVD-related changes correspond with cognitive impairment[63,64]. Yet, structural brain analysis explains only partially the heterogeneity of behavioural outcomes[45]. Therefore, there is an acute need to better understand how CSVD affects the aging brain and leads to clinical symptoms.

The integrity of brain networks can also be assessed using functional connectivity, which measures Blood Oxygen Level Dependent (BOLD) contrast with MRI and is defined as the

temporal dependency of neuronal activation patterns[65]. Resting State Functional MRI (rs-fMRI) has the unique advantage of not requiring continuous activity[66], making it a potentially powerful approach for studying functional changes in the brain, especially for older participants and children. In addition, rs-fMRI is able to provide an up to three times higher Signal-To-Noise Ratio (SNR) compared to task-fMRI[67], which facilitates the detection of group differences or subtle abnormalities, and measures of rs-fMRI are reported to be reliable within and across sessions, both within and between participants[68]. Functional neuroimaging enables the analysis of the functional neuroanatomy of spatially distributed but functionally linked regions that continuously share information with each other[53] and elucidates changes inaccessible to structural imaging techniques. Thereby, this technique reveals the degree of covariation in the neural activity of a network of brain regions, which is a measure of how well information processing is shared between different regions, and therefore allows an assessment of the efficiency of cognitive processes[69]. And Indeed, resting-state fMRI connectivity has been proven useful in identifying neural correlates of cognitive function and mood disorders[70,71]. WMH could result in impaired speed of this signal transmission or even disconnect functionally connected cortical regions entirely, resulting in reduced functional connectivity and cognitive impairment. Rs-fMRI is increasingly used for the assessment of global brain networks as well as description of disrupted networks in several pathological conditions, including Alzheimer's disease, multiple sclerosis, and epilepsy[72]. Past studies of CSVD pathology, however, were diverse in their methodologies and have mainly relied on seed-based approaches or single networks to assess FC changes in key region of the cortex[73,74] while few studies used whole brain network connectivity or graph theory to analyse global network properties. This diversity of analytical approaches and the need to classify the resulting findings requires a systematic survey of the past literature as a foundation of content for further research.

2.2 Summary Review "Functional connectivity changes in cerebral small vessel disease - a systematic review of the resting-state MRI literature"

Question of the meta-analysis: What is the state of knowledge that research has reached in the last 10 years about the impact of CSVD on functional connectivity?

A large number of studies that have already assessed rs-fMRI changes in small cerebral vessel disease highlight an ongoing interest in understanding the interplay between structural brain damage, associated changes in the spatiotemporal organization of neuronal activity, and cognitive outcomes. However, the breadth of the field makes it difficult to identify specific patterns of altered functional connectivity associated with CSVD. Therefore, we used the systematic review, considered as the strongest form of evidence, to provide an exhaustive summary of the current hints for functional resting-state changes associated with CSVD.

The analysis was performed according to the PRISMA protocol. Of 493 potentially relevant papers, 417 were excluded based on their title or abstract, and the remaining 76 studies were read in full. Finally, this meta-analysis included 44 articles published after 2010 reporting resting-state functional brain connectivity in association with white matter hyperintensities of presumed vascular origin (see **Figure 1A**[19]). Half of these 44 studies primarily examined changes in functional connectivity patterns in the presence of cerebral small vessel disease and their association with cognitive abilities. Of these CSVD-focused studies, six reports concentrated exclusively on patients affected by CSVD, and the remaining studies additionally included a comparison to healthy controls or patients with nonvascular cognitive impairment or both. 12 studies with populations of healthy participants without clinically manifest vascular pathology or cognitive impairment reported measures of white matter damage associated with a more comprehensive assessment of structural brain parameters and functional connectivity. The remaining eight articles examined functional connectivity and white matter damage in the context of other clinical conditions not directly related to vascular pathology. The number of subjects, including both patients with small vessel disease and control subjects, varied from 11 to 1584, depending on the study, with a mean average age ranging from 50.0 to 76.4 years.

Different procedures were used to evaluate white matter damage among the various study groups (see **Figure 1B**). Of the 24 studies with altered functional connectivity and CSVD as the primary research objective, 17 assessed the presence of white matter hyperintensities on T2-

weighted cerebral MR imaging using validated rating scales such as the Fazekas[75] or Wahlnud[76] scales. The majority of studies which examined a healthy population, quantified white matter lesion burden volumetrically, and some articles did not provide a precise definition of imaging criteria at all. Beyond the presence of white matter lesions, 13 studies considered evidence of lacunes or recent lacunar infarcts, although the distinction between these two forms was rather imprecise. Complementary to the imaging findings, clinical characteristics were used to better characterize patient cohorts and categorize them according to cognitive impairment and vascular and nonvascular pathology. Scales such as the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment Battery (MoCA), or the Clinical Dementia Rating Scale (CDR) were used to measure these characteristics, in addition to specific diagnostic criteria for different dementias. However, only three studies used Positron Emission Tomography (PET) to differentiate tau and/or amyloid pathology from pure vascular disease.

Magnetic resonance imaging was performed with scanners from different manufacturers, and the description of functional MRI acquisition parameters was incomplete in 26 of the 44 studies analysed. The number of BOLD volumes recorded ranged from 100 to 700, and the strategies for regression of confounding factors and motion scrubbing were highly variable. Global Signal Regression (GSR) was performed in 27 studies, whereas subject-based censoring was used in 25 studies, and volume censoring was performed according to Framewise Displacement (FD) or framewise translation/rotation cut-off in 10 studies. A variety of methods were used to analyse functional connectivity (see **Figure 1C**). The majority of studies examined large-scale functional connectivity between distant brain areas and, in particular, the changes in functional connectivity associated with a small number of large-scale Resting-State brain Networks (RSN). A significant proportion of study used Seed-based Correlation Analysis (SCA) to explore functional connectivity within the brain. Eight reports used graph theoretical approaches to summarize connectivity patterns between multiple regions to reflect global organizing principles of brain networks. Three studies examined short-range connectivity using Regional Homogeneity (ReHo) to quantify similarity between BOLD signals as a marker of local connectivity.

To define regions of interest for further analysis, external a priori brain parcelling was used in 16 cases, while a data-driven approach was used to define regions of interest in 27 studies.

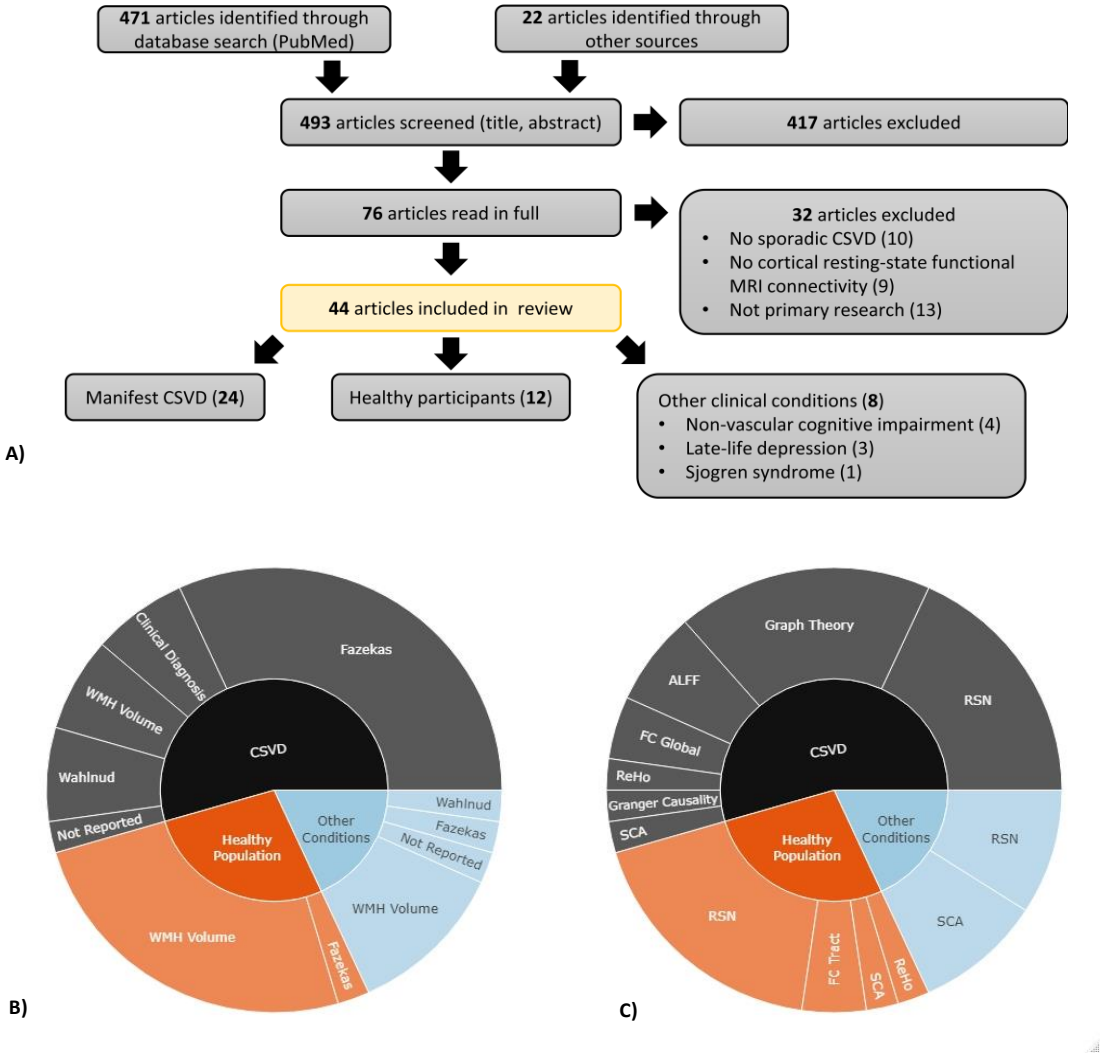

Figure 1: **A)** Systematic literature search and article screening results. The PubMed electronic database was searched on 1 December 2019, on 28 June 2020, and again on 22 November 2020. Together with articles obtained through other sources (personal communication, cited articles), 493 papers were identified, screened by M. S., and assessed based on inclusion and exclusion criteria. Full texts were obtained for 76 articles; these were assessed against the stated criteria by M. S. and E. S. The included 44 articles were classified on the basis of characteristics of the study population **B)** Overview of the distribution of methods for evaluation of white matter damage according to the characteristics of the study population **C)** Overview of the distribution of methods for connectivity analysis according to the characteristics of the study population. ALFF, amplitude of low frequency fluctuations; FC Global, functional connectivity throughout the whole cortex; FC Tract, functional connectivity within white matter tract´; ReHo, regional homogeneity; RSN, resting state network; SCA, seed-based correlation analysis; WMH, white matter hyperintensities

For all 24 studies that recruited patients with clinical cognitive impairment, the risk of bias was assessed using the AXIS tool showing that all studies had an at least moderate risk of bias (see **Figure 2**[19]). At the same time, we did not formally assess the risk of bias in studies that reported outcomes on FC and WMH in the context of conditions other than vascular cognitive impairment or in longitudinal studies.

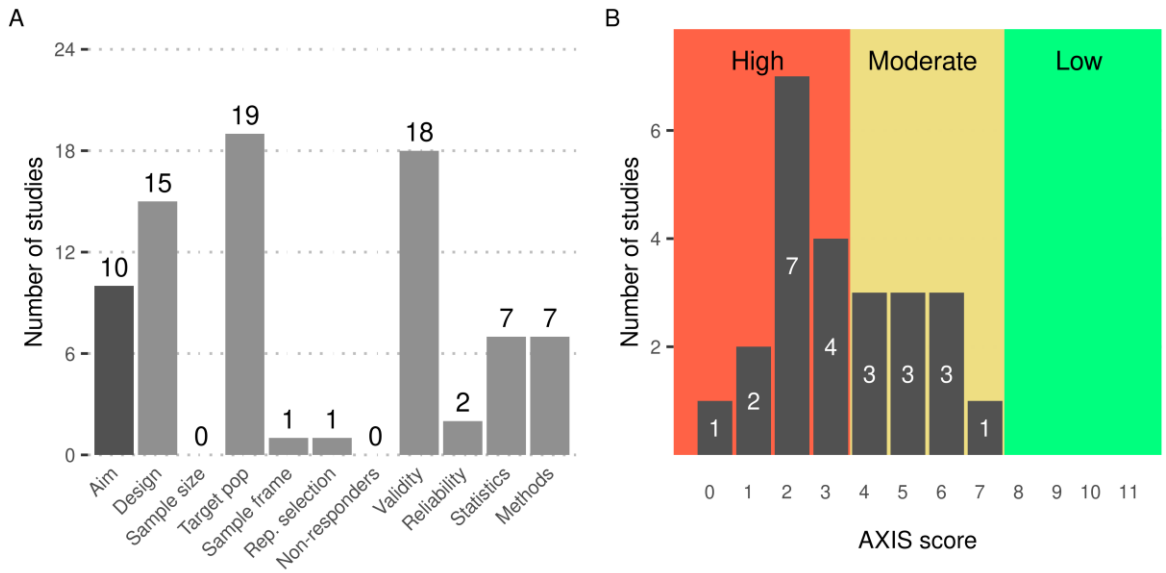

Figure 1: Assessment of risk of bias of 24 reviewed articles using the Appraisal tool for Cross-Sectional Studies (AXIS). **A)** Distribution of per-item scores, indicating, for each item, the number of articles satisfying its definition. A detailed description of AXIS items and shortcomings of individual articles is presented in Stabs 1 and 2 in the Supplement. **B)** Distribution of aggregate AXIS scores computed as the number of Items satisfied by any given reviewed article. Trichotomization of the theoretical range 0—11 leads to risk of bias being judged as high (0—3), moderate (4—7) or low (8—11).

The reported studies demonstrate increasing evidence for a model of network dysfunction underlying cognitive impairment in CSVD. These dysfunctions are characterised by disordered connectivity especially in large scale resting state brain networks defined as discernible functional communities like the Default Mode Network (DMN)[77]. Patterns of coordinated activity within and between these large-scale networks have been emerged as particular relevant in normal physiological circumstances[8]. The default mode network characterised by self-referential thought and is in anticorrelation with the activation of the Dorsal Attention Network (DAN) which is related to focused attention on external stimuli[78]. Moreover, the Frontoparietal Control Network (FPCN) exerts a modulatory role with increased connectivity to the DMN as a correlate of working memory performance[79,80] .

Consistent with the functional disconnection hypothesis[81], CSVD appears to impair cognition by disrupted connectivity patterns within and between the DMN and FPCN. This pattern is accompanied by increases and decreases of functional connectivity in the DAN and along with the FPCN, a change in coupling with the DMN. In addition, connectivity alterations in the Salience Network (SN) could be identified as a novel neural correlate of the cognitive deficits associated with CSVD. These changes include increased coupling with the DMN and FPCN, as

well as an increase in functional connectivity within the network. However, the heterogeneity of these results combined with limited correlation with cognitive test scores complicate the distinction between primary effects of disruption by CSVD from compensatory changes or sampling variability without physiological relevance. In addition, CSVD appears to alter functional connectivity tract-specific in a spatially-topologically inconsistent manner and, at the same time, exert an indirect effect by decoupling structural and functional connectivity with increasing WMH burden like in the cingulum bundle.

Thereby, the large-scale network changes are accompanied by uncoupling of neuronal activity along the anterior-posterior axis mediated by structural damage to long association pathways and cortical-subcortical connections which seems to be particularly momentous for impaired cognition. Apart from this impact of ischemic lesions on specific fibre tracts and functional connections, several studies also investigated how CSVD disrupts global organization of synchronous neural activity. Some of these graph-theoretic approaches indicate that the global topology of functional brain networks in the presence of CSVD exhibits increased path length and modularity and decreased small-worldness in functional networks, which correlates with cognition[82,83]. Finally, population-based studies in healthy participants with low disease burden in white matter suggest a pattern of increased functional connectivity in several frontal and temporal brain areas consistent with compensatory upregulation in low disease burden white matter in early CSVD[84,73,85].

Question of the meta-analysis: What are the methodological concerns?

While a large body of literature indicates some physiologically relevant patterns of altered FC associated with CSVD and cognitive impairment, the validity of individual outcomes is overshadowed by a strong heterogeneity, leading to a somewhat fragmented account of functional alterations. This heterogeneity is linked to a high degree of volatility in pre-processing and analytical approaches, the operationalisation of CSVD, and the investigated clinical population itself. Starting with the latter, the methodological variance already manifests with the sample size. Studies that examined patients with symptomatic CSVD had, on average, a significantly lower sample size than studies with clinically healthy participants. The lack of standardization continues in quantifying the severity of CSVD comprising patients at very different stages of the disease. While clinically focused reports tend to rely on validated rating scales, studies with clinically healthy patients, determine the severity of white matter

damage with the cumulative WMH volume. This quantification discrepancy is part of an ongoing debate about the extent to which vascular lesions must be present to be responsible for functional and clinical abnormalities. Nevertheless, systematic approaches to unify the assessment of CSVD progress, such as STandards for Reporting Vascular changes on Neuroimaging (STRIVE)[86], are employed very rarely. Moreover, although resting-state fMRI connectivity has been found to be a reliable analysis method, differences in pre-processing approaches contribute to the heterogeneity of findings. In this context, controversial decisions like the removal of the global signal or different motion adjustment strategies, in particular, have shown that not all results are robust with respect to such choices. Similarly, in reports of this review, the analysis of the BOLD signal has been performed by employing many different coupling measures and dimensionality reduction techniques. The use of a wide variety of different brain atlases, sometimes with structural and sometimes with functional origins, further hinders a consistent assessment of the literature results. In addition, while all the studies reviewed herein use the Pearson's correlations coefficient to quantify synchrony between the BOLD time series, crucial information are often missing, such as the consideration of negative correlations or whether full or partial correlation measurements were performed.

Indeed, apart from obvious differences in methodology, the assessment of risk of bias by the AXIS tool highlighted that MRI acquisition parameters and statistical procedures are often inadequately reported. Besides, several studies show a lack of clarity about the exact goals of the study and whether they represent an exploratory or confirmatory approach. The quality of results is further hampered by the absence of pre-registered reports and qualitative so-called multi centre studies. That is, together with a rather small sample size especially for reports with clinically symptomatic patients, these shortcomings cause a high risk of bias in individual cases and subsequently may have led to a considerable number of false-positive findings. One advantage of fMRI-BOLD data acquired at rest is that it removes confounding effects of performance differences between age groups that often exist in task-based fMRI studies of age. Yet, very few of the reviewed reports dealt with possibility of confounding by age-related pathologies such as Alzheimer's disease. Worryingly, age-related pathologies and age itself are suspected to be responsible for reduced reliability of estimates of functional connectivity[87,88]. Confounding may also arise from a number of physiological non-neural factors, such as changes in vasculature with age. Neurovascular coupling is known to be

altered in both normal aging and ischemic disease[89,90,91]. In particular, white matter lesions could affect the reliability of functional connectivity estimates by subcortical hypoperfusion and diminished cerebrovascular response. Therefore, disentangling the origin of functional connectivity change to either vascular or neuronal factors of CSVD remains challenging.

In view of these considerations there is an urgent need to avoid factors that contribute to poor reproducibility such as methodological variability and the reliance on relatively small sample sizes. Apart from replication failures, small sample size is associated with statistically underpowered analysis and inflated effect sizes. Even though, small-sample neuroimaging will always be critical for studying the human brain and probably no one-size-fits-all solution for neuroimaging studies exist, recent research reports that neural MRI analyses should operate with a sample size of around thousand participants to robustly characterize especially small effects[92]. In addition, the poor reliability of functional measurements with severe CSVD stands in contrast with the high reproducibility in rather healthy participants[93,94,95]. In order to gain as much insight as possible into this contrast of results between small studies with manifest CSVD and large studies with relatively healthy participants that emerged in the review, our following two studies rested on both, a small sample of patients with CSVD in group comparison to healthy controls and a large number of relatively healthy participants analysed with modern methodological approaches with multilevel analysis.

2.3 Summary Study I "Topological differences in functional networks between patients with small vessel disease and healthy controls"

Research question: Does structural damage in the form of cerebral small vessel disease disrupt the topological architecture of the functional brain connectome?

In an attempt to address this question, patients with cerebral microangiopathy without signs of vascular dementia and healthy control subjects of similar age were compared in a cross-sectional study. Resting-state functional MRI was employed to investigate topological difference of the functional connectomes between patients and healthy controls. The human neural network is able to maximize its information processing performance due to topological properties such as a large cluster coefficient, or short characteristic path lengths[96,97]. In our group comparison, global graph parameters such as path length or global efficiency were investigated. Path length is considered a measure of global capacity for parallel information integration between different cortical regions while global efficiency is an index of overall capacity or efficiency of parallel information transmission and integrated processing in the brain network[98,96]. Further, measures of local specialization such as the clustering coefficient and local efficiency were analysed[99,100]. In addition, we compared the degree of modularity, a measure which quantifies the extent to which a network can be decomposed into internally integrated, yet globally segregated communities[101]. Severe cognitive impairment is generally presumed to correlate with a variety of factors, including lower global and local efficiency, as well as greater absolute path length and higher cluster coefficients[102,103]. Even though there are indications for impairment of functional topology by white matter damage in the reviewed literature[82] none of the aforementioned alterations of graph parameters in patients with CSVD compared with healthy controls could be observed in our study. In contrast to our hypothesis, neither global network properties such as global efficiency nor local network parameters in the form of local efficiency or clustering coefficient were significantly different between patients and healthy controls (see **Figure 3**).

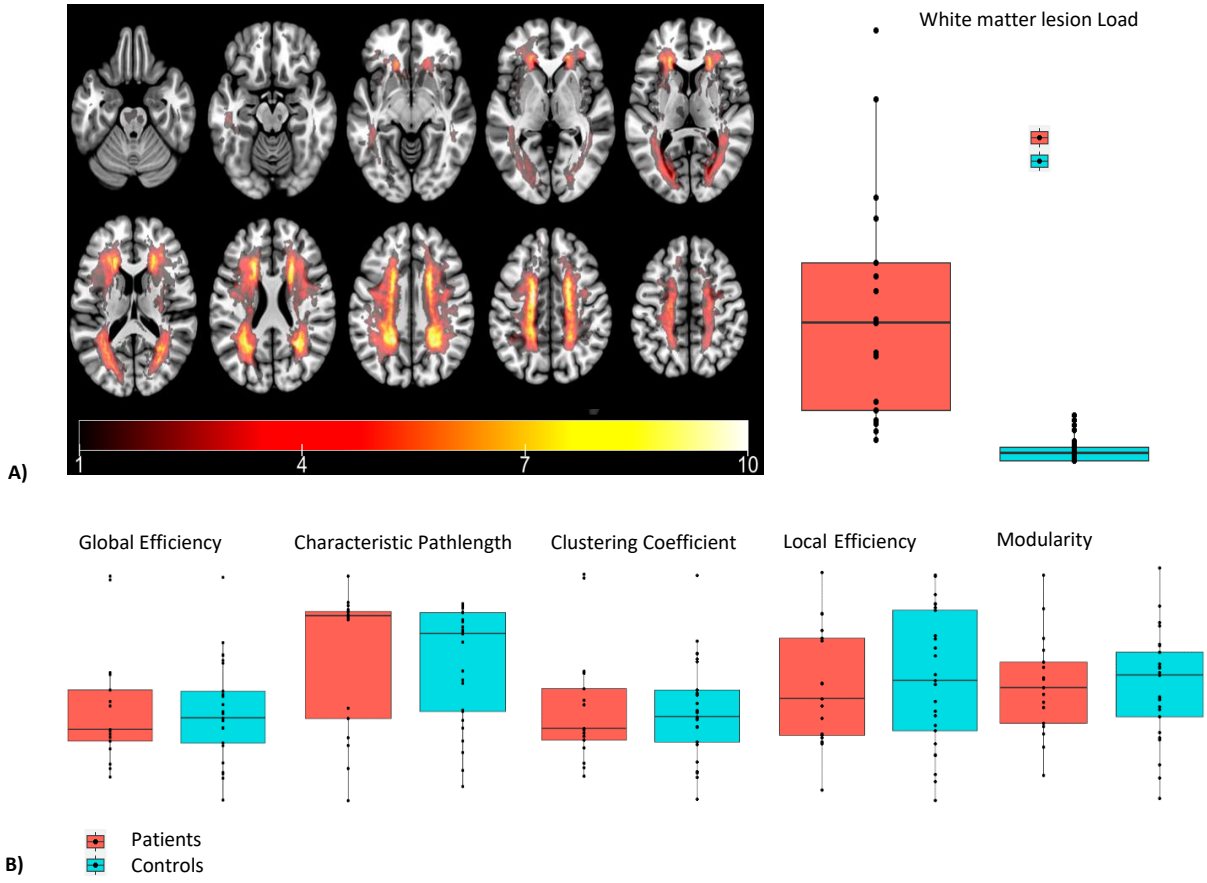

Figure 3: **A)** Distribution of white matter hyperintensities (in all participants, projected on a brain template in MNI-space. Frequency of WMH is illustrated as indicated by the colour bar and group difference for white matter lesion volume, normalised for intercranial volume. **B)** Boxplots showing the group difference in global efficiency, characteristic pathlength, clustering coefficient, local efficiency and modularity between patients with CSVD and healthy control participants.

At this point, we cannot rule out the possibility that white matter damage due to brain reserve does not affect network topology in these CSVD patients. This concept describes that those individuals with greater brain reserve tolerate a greater burden of pathology before clinical symptoms occur than individuals with less brain reserve[104]. Indeed, patients with WMHs who did not exhibit cortical atrophy were reported to have a lower risk of dementia than patients with cortical atrophy[105]. However, another consideration concerns graph theory itself. Its network parameters have been defined for structural brain networks and are not validated for networks derived from functional connectivity[106]. Several studies further suggest that the test-retest reliability of graph-based functional network metrics is low in older adults and especially in CSVD patients[87,88,107]. More importantly, since subtle effects with small effect sizes may remain hidden due to the small sample size these data were not published. Subsequently, the endeavour to overcome the shortcomings of small sample size and

potentially low reliability of functional measurements in patients with advanced CSVD set the premises for the second study.

2.4 Altered structural and functional measures in "healthy aging"

In the young brain with intact white matter network and without grey matter damage, information is effectively transferred between brain regions via the most efficient routes. The biology of "normal" brain aging is associated with a variety of physical, biological, chemical, and cognitive changes across the lifespan[108]. Neuropathophysiological processes thought to cause age-related changes, ranging from proteinopathies[109] to vascular pathologies[110]. In the face of these adverse events associated with ageing, white matter damage is accumulating relatively frequent among healthy adults even in the absence of overt disease[111]. These less dramatic white matter damages can equally lead to interruptions in circuits connecting different brain regions and to degeneration of brain tissue. Indeed, age-related structural changes have been documented in grey matter volume[112,113] and cortical atrophy has been observed in multiple studies[114,115]. Recent reports have been linked this decreasing cortical thickness directly with white matter lesions, showing that cortical atrophy in different regions is shaped by the underlying white matter integrity[116]. That way, cortical degeneration is suspected to be caused by damage to white matter tracts[117] and since dendrites are essential in neuron-to-neuron communication, changes in functional interareal connectivity are thought to follow this phenomenon[118]. Thus, together with white matter lesions, atrophy leads to a reduction in healthy neural tissue available for the computations needed to maintain cognitive function[119].

However, although recent research on patients with severe white matter damage in form of CSVD increasingly suggests an association between structural brain damage and functional connectivity, this association appears to be less clear in large community studies with cognitive normal and relatively healthy participants. Some of these studies not only showed an increase in functional connectivity with increasing lesion volume[73,120] others even failed to observe any association between structural damage and FC[121,122].

Therefore, disentangling the heterogeneity of multiple co-occurring pathological structural brain damage and subsequent functional alterations in cognitively normal older adults remains challenging. The effects of age itself on functional connectivity is emerging as complex by showing progressive decrease of mean global functional connectivity throughout the entire

cortex[123] but also increases and decreases of mean FC across different cortical regions[124,125,126].

Yet, functional imaging techniques demonstrate that age-related impairment in cognition is associated with changing functional connectivity[127,124,11] and especially changes in resting state networks appear to be a key toward understanding the cognitive trajectory of aging. Brain activity at rest in adults is organized into predominantly segregated functional networks, and regions within these distinct networks show spontaneous but correlated fluctuations in functional activity[128,129,130]. The existence of these networks is believed to bring several organizational benefits, such as adaptability and robustness in response to changing environment, minimization of the wiring costs, and facilitation of functional specialization[131,132,133,134].

Healthy cognitive function depends on the speed and efficiency of communication between these large-scale neural networks like the default or salience network, and impairments are thought to result from white matter disruptions that lead to declines in cognitive performance[135,136,137]. Recent research increasingly focuses on changes in connectivity within and between these networks separately and reports that FC between networks remains stable or even increases with age, while FC within networks tends to decrease[138], resulting in a lower functional segregation and altered topology[139,140]. As a result, clarifying the susceptibility of global connectivity and these resting state networks to aging and structural damage may reveal a functional basis for age-related changes in cognitive functions, leading to the question we addressed in the following study.

2.5 Summary Study II "Association of age and structural brain changes with functional connectivity and executive function in a middle-aged to older population-based cohort"

Research question: What is the nature of the relationship between age-related structural brain damage and functional change outside of severe pathological developments?

To elucidate the relationship between structural brain damage and functional connectivity in "normal" brain aging, we used a multi-scale approach to explore associations between white matter damage, and cortical thinning on functional connectivity in a cognitive healthy population of 976 participants at increased cardiovascular risk. In this regard, the influence of age and the two markers of structural damage on FC was examined in Multiple Linear Regressions (MLR). Quantification of white matter damage was performed by calculating the peak-width of skeletonized mean diffusivity. The measurement of PSMD excludes contamination from Cerebrospinal Fluid (CSF) and the histogram-based approach improves the ability to characterize subtle, diffuse disease in the brain[141]. In addition, the PSMD is also closely related to global cognition and has been shown to be associated with higher WMH lesion burden[142]. Since intrinsic whole-brain functional connectivity patterns measured at rest have been associated with general intelligence[143,144], working memory capacity[79,145] and other cognitive abilities. Measures of functional connectivity included mean connectivity across the entire cortex, and additionally separated into connectivity within and between resting state networks.

Further, we focused on a parsimonious set of four associative resting state networks that are theoretically linked to the cognitive domain of executive function. These networks serve integrative tasks and appear to be more vulnerable to aging than sensory systems in the brain[139] which predisposes them to the study of arguably more subtle pathologies. Age-related changes in many resting-state networks remain debatable and, in an attempt, to better characterize the picture of functional decline, we extracted disconnected subnetworks from the associative networks. These subnetworks represent the age affected part of the original network that drives the loss of functional efficiency and cognitive decline.

Finally, we examined a possible mediating effect of PSMD and cortical thickness on the relationship between age and the disconnected portion of the associative networks. Given the age-sensitive nature of the associative system, along with its role for cognitive operations, in particular executive function, we set out to explore whether the disconnected subnetworks

mediate the relationship between age and executive cognition measured by the Trail Making Test (TMT).

Previous findings describing the relationship between structural brain damage and functional connectivity shifts have been quite inconsistent. This is especially true for studies analysing a small number of patients with severe small vessel disease and diminished cerebrovascular response, leading to reduced reliability of functional estimates and statistically underpowered results. By using a large, relatively healthy well-characterized sample and modern methods, we aimed to obtain more precise results and contribute to a more complete picture of age-related structural brain damage and functional consequences.

In conclusion, we discovered an age-related linear increase in markers of structural brain damage and a linear decrease in functional connectivity with age, although the latter association was rather weak. This trend of decreasing functional connectivity with increasing age was visible globally and in individual networks and, in contrast to other studies, did not differ between intra- and inter-network connectivity. Further, older age was associated with poorer psychomotor speed and executive function as measured by the parts A and B of the trail making test (see **Figure 4**[20]).

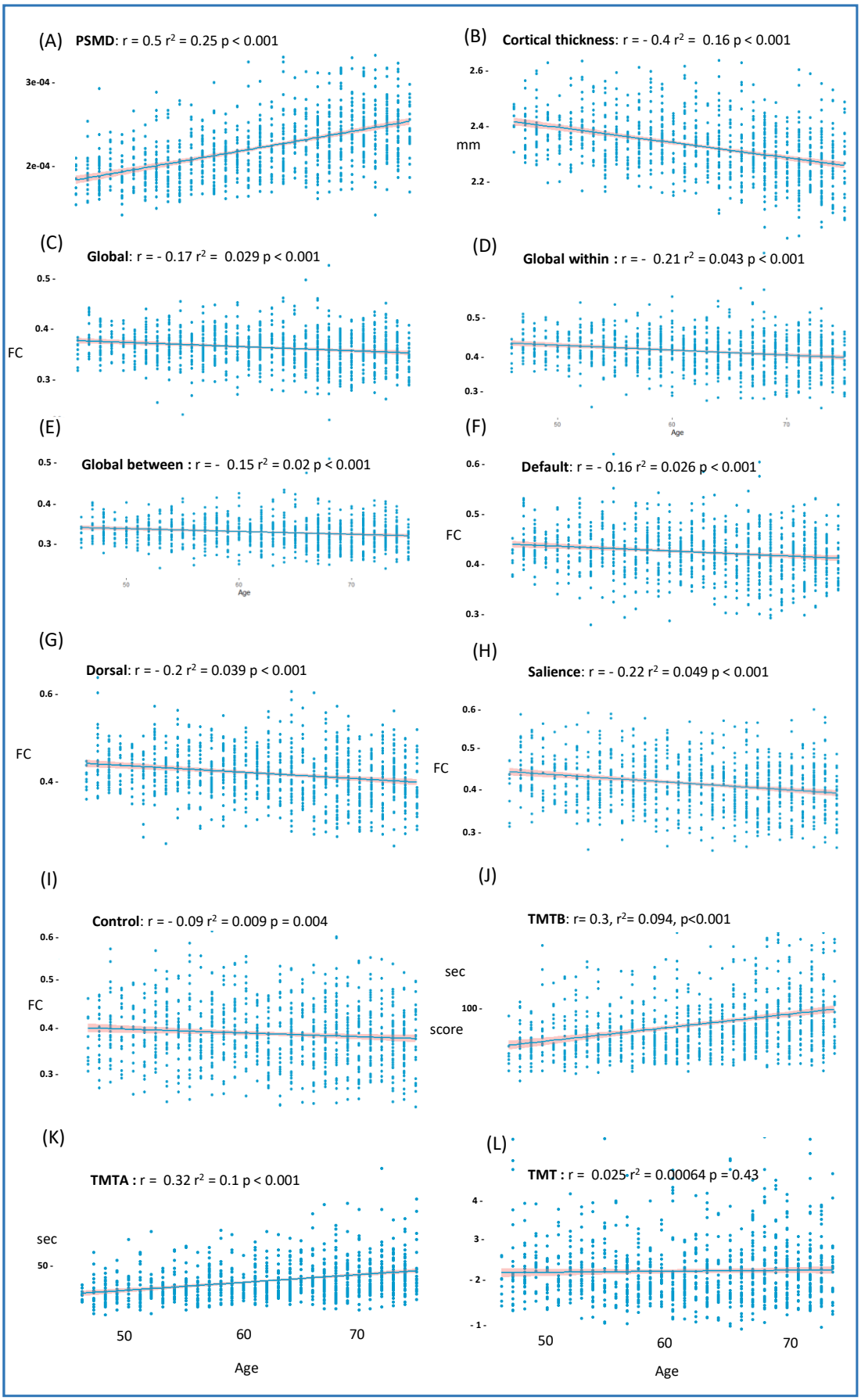

FIGURE 4: Effects of age on the PSMD **A)** cortical thickness, **B)** on global functional connectivity, **C)** global intranetwork connectivity, **D)** global between network connectivity, **E)** within default, **F)** dorsal, **G)** salience, **H)** control network, **I)** the Trail Making Test B (TMTB), **J)** TMTA, **K)** and TMT ratio score **L)**. Above r and r2 corresponds to the linear model before covariate inclusion. Shade around the regression line shows the 95% CI.

In contrast to our original hypothesis, in our multiple regression model, neither the PSMD nor cortical thinning revealed any association with functional connectivity on global scale or in any of the resting-state networks when corrected for age. Age itself, on the other hand, continued to exert a significant negative influence on functional connectivity on global scale and in three of the four associative networks, with the exception of the control network (see **Table 1A**[20]). Additionally, out of these three associative networks affected by age, we were able to extract subnetworks consisting only of connection that decline with age. These subnetworks consisted of between 10% and 36% of the associative network connections, involved both hemispheres equally, and included both inter- and intrahemispheric connections (see **Figure 5**[20]).

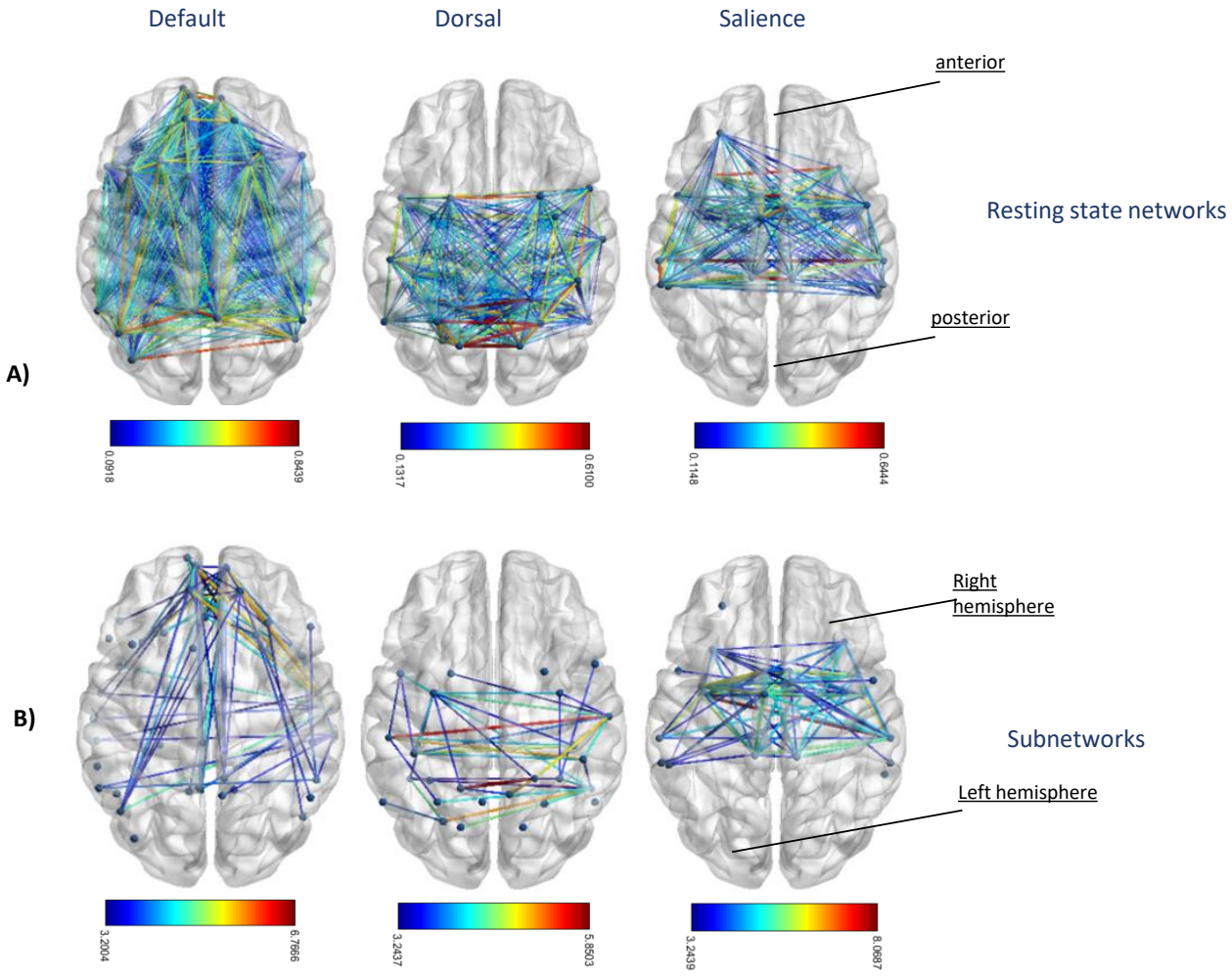

FIGURE 5: A) Original resting-state networks of default, dorsal, and salience network from left to right. The colours of the edges represent different correlation strength of the mean connectivity matrix. **B)** The corresponding extracted subnetworks network-based statistic (NBS) identified age-related disconnected functional subnetworks in default, dorsal, and salience network. The disconnections comprising this subnetwork correspond to pairs of nodes between which the resting-state times series was less correlated with increasing age. The colours of the edges represent test statistic results of the suprathresholded links, which exceed the threshold of t-value = 3.2

Our mediation analysis further discovered a weak mediation effect of decreasing cortical thickness between age and functional connectivity of the default subnetwork. The Default-subnetwork itself, mediated part of the relationship between age and executive cognitive function as measured by the TMT part B (see **Table 1B**[20]). In contrast, the PSMD, as a marker of white matter microstructural damage, showed no mediating effect between age and FC changes.

Significant Results

Variables	Beta	Std. Error	Std. Beta	p-Value	R^2
A) Alteration of functional connectivity with age					
Global mean connectivity	- 0.0007	0.0002	- 0.14	p < 0.001	0.034
Global mean within network connectivity	- 0.0009	0.0002	- 0.17	p < 0.001	0.049
Global mean between network connectivity	- 0.0006	0.0002	- 0.14	p < 0.001	0.027
Mean Default connectivity	- 0.0006	0.0002	- 0.11	p = 0.005	0.029
Mean Dorsal connectivity	- 0.001	0.0003	- 0.17	p < 0.001	0.039
Mean Salience connectivity	- 0.002	0.0003	- 0.2	p < 0.001	0.055
B) Mediation Model one					
Total Effect	- 0.004	< 0.0001	- 0.29	p < 0.001	-
Direct Effect	- 0.003	< 0.0001	- 0.24	p < 0.001	-
Indirect Effect	- 0.001	< 0.0001	- 0.04	p = 0.002	-
Mediation Model two					
Total Effect	1.365	0.138	0.31	p < 0.001	-
Direct Effect	1.234	0.142	0.28	p < 0.001	-
Indirect Effect	0.101	0.045	0.02	p = 0.025	-

Table 1. Significant results after multiple testing correction for **A)** the multiple regression as well as **B)** the mediation analysis, representing unstandardized coefficient estimate (Beta), the standard error, standardized estimate (std. Beta) the p-value and the r^2 value.

The linear age-related pattern of structural damage, functional connectivity, and cognitive performance in our analysis accords with previously suggested trajectories in other studies[125,146]. The negative trend of the inter-network connectivity seems to be contradictory at first, but it can be explained by the use of absolute correlation values. Increasing positive correlation and decreasing negative correlation between networks cannot be distinguished by

the calculation with the absolute value. In fact, when calculating with anti-correlations, we found a positive trend in connectivity between networks with increasing age.

The decline of connectivity within default, dorsal and salience network observed in our study is indicative for diminishing functional specialization and confirms the vulnerability of associative systems. Further, the composition of the subnetworks implies that the impact of age affects a limited number of widely distributed connections within these associative networks and does not show any specific pattern. We did not detect any effect of age on the control network in the multiple regression, possibly due to its role as a servant of cognitive reserve. The control network is highly connected to other networks and can orchestrate the activation of other networks[147]. Stable connectivity in this network might enable more flexible management of local damage to other neural networks such as the DMN[148,149].

Taken together, the nonuniform and relatively weak decrease in functional connectivity throughout the cortex and within the associative networks might indicate a certain resilience of neuronal communication to brain aging.

Functional resilience might also explain that no direct effect of structural damage on functional connectivity was observed. Based on our results, we could conclude that the lack of a direct effect of PSMD and cortical thickness on functional connectivity suggests that low white matter lesion volume load and mild brain atrophy do not significantly interfere with inter-neuronal processing.

On the other hand, structural damage emerging in less strategic areas may be compensated easily by bypassing the information around the damaged area via alternative or redundant paths. Structural damage in strategic areas, more relevant for transmitting specific information is likely to result in significant functional distortions. Our quantification of structural parameters by total normalized values throughout the whole brain was probably insufficient to model this subtle and non-homogeneous relationship between structure and function in the brain. In this regard, the indirect mediation effect of cortical thinning between older age and connectivity of the default subnetwork, also tends to indicate a localized relationship between structural decline and functional consequences. Reduced cortical thickness due to decreased blood flow, neuron and myelin loss consequently weakens brain function of the default network. This weakening functional connectivity within the default network mediates, at least in part, the age-related decline of executive function. Although

linking complex cognitive functions to connectivity of brain regions within a single network is likely to be too short-sighted, this observation fits into the concept of insufficient task deactivation of the default mode network in elders[81]. According to this theory, insufficient deactivation of the default-mode network disrupts communication of other networks relevant for directed tasks, such as the control and dorsal networks, resulting in ruptures of focused attention[81].

Although the limited number of structural, functional, and cognitive variables, as well as the cross-sectional design and limited age range, necessitate cautious interpretation of these results. In particular, the narrow age range of 29 years and the maximum age of 75 years may have prevented the observation of stronger associations between age and functional connectivity. This study adds to a growing body of evidence suggesting that in the absence of severe disease, structural and functional parameters are at least on large-scale independent measures and representing different aspects of the underlying influence of age on the central nervous system. Further, our results indicate that existing links between structural damage and functional connectivity are topographically specific.

3 Discussion

Understanding how age-related structural brain damage affects functional properties is vital for furthering our scientific knowledge of the ageing process. The present thesis intended to fill this research gap by pursuing three different approaches:

First, a comprehensive and systematic analysis of current research on small vessel disease and functional connectivity, and methodological evaluation of the corresponding literature. Second, the investigation of topological differences in global functional networks between small vessel disease patients and healthy controls. Third, a multilevel analysis to examine the relationships between white matter damage and cortical thinning on whole cortex functional connectivity and within connectivity of four associative networks in a cognitively healthy population

Even though theory draws a straight line from aging affecting the cerebral vasculature, leading to deterioration of brain structure, which in turn affects the functional integrity of the brain and eventually leads to decreased cognitive performance. The dynamics between structural pathology and functional parameters remains complex. Functional connectivity appeared to be independent of white matter burden, both in our study of small vessel disease and in the analysis of a relatively healthy cohort. At first glance this might seem contradictory to the literature from our review, which analysed mainly patients with clinically manifested small vessel disease. However, our initial approach joins a series of small sample studies whose power is limited and often suffers from low test-retest reliability. An emerging possibility is also that macroscopic graph representations of functional networks, do not contain the necessary biological details that can be used to characterize these networks. At the same time, we consider our results to be well compatible with existing studies with large numbers of cognitively healthy participants, which also did not observe any association between structural damage and functional changes[150,151,121,152,153]. What these studies, like ours, have in common is that their participants may still possess cognitive reserves and functional brain changes may most likely become apparent at a later stage of emerging brain pathology.

Still, the challenge of linking structural change and functional connectivity might be rooted in other sources as well. We were able to confirm a global change in functional connectivity that

is not limited to specific networks but seems to be present in almost all identified resting-state networks, although not to the same extent. The mediation effect of cortical thickness in our cohort and a series of studies on small vessel disease from the review suggest there is a link between structural damage on functional connectivity. But focusing on white matter damage in general isolates one factor that may or may not be causative for the progressive change in neuronal properties of the brain, while in all likelihood multiple interacting factors, both deleterious and protective, shape the dynamics of functional networks across aging. These interweaving of mechanisms underlying network dynamics are probably a continuum only partially revealed by existing techniques[154]. In this context, methodologically specific thresholds for a particular marker such as STRIVE are essential for future studies. In addition, in most studies, nodes in structural or functional analysis are considered to be the same. However, brain regions differ in several local attributes, including gene transcription, cytoarchitecture, receptor profiles, and temporal dynamics[155]. Variations in local microscale attributes may influence how neuronal populations transmit and integrate signalling[155]. These microscale properties could lead to regional differences in the macroscale relationship between structural and functional properties, so that different levels of analysis lead to different models of neurocognitive disconnection. Thus, for future approaches that seek to connect age-related change in structure and function, it will be essential to use more than one or two structural biomarkers to capture the heterogeneity and subtypes of brain aging.

Within this context, it must be recognized that the functional connectivity does not simply match structural connectivity. In other words, tight functional connections can exist between regions not directly connected by major white matter tracts[156]. In fact, due to the sparse nature of structural connectivity, most functional connections are not supported by direct underlying structural connection. Studies in which whole-brain structural connectivity was used to predict whole-brain functional connectivity found moderate agreement with empirical patterns of functional connectivity, ranging from 25% to 50% of the variance explained[157]. This dependency is very heterogeneous across the brain with structure and function tightly coupled in sensory networks, while higher hierarchy associative networks exhibiting weak structure–function coupling[158,159]. Optimistically, this implies that direct structural connectivity does not explain more than 50% of the variance in functional connectivity. Hence, the possibility to explain functional changes by biomarkers of white matter damage or cortical thickness might be also limited, especially in associative networks.

In an attempt, to relate the organization of physical connections to patterns of functional interactions, new functional biomarkers must be considered as well.

There is strong evidence that structural integrity is important not solely for functional integration within networks but also for functional connectivity between networks and both features are necessary for optimal cognitive processing[160,161,162]. Recent reports increasingly focus on an overall age-related rise in synchrony and the loss of anti-correlation between resting state networks[162,163]. This phenomenon, described as decreasing segregation between networks, is consistent with the idea that the aging brain loses functional diversity and complexity[162]. The ability to "stay selectively connected ", however is thought to be essential for successful brain aging[164]. This de-differentiation, or loss of functional specialization of brain activity, probably leads to a loss of the ability to suppress irrelevant information[165] and is thus critical to cognitive decline in old age. The segregation index has been shown to be more sensitive than other graph-theoretic metrics to age-related changes in functional organization[139] and therefore, may also be more strongly related to structural damage than functional connectivity within individual networks or across the cortex.

The strength of the presented thesis lies in the application of a modern and reproducible image processing pipeline, as well as the combination of a systematic comprehensive literature analysis and a large and high-quality data set with multi-level analysis. In conclusion, this work suggests an independent age-related development of declining structural integrity and functional measures on large scale. This independence is contrasted by a heterogeneous relationship between brain structure and functional properties at meso- and micro scales. At the same time, the literature on CSVD suggests that beyond a certain level of damage, the impact on functional connectivity increases precipitously.

We close by highlighting again the need for future studies with well-documented, modern and, above all, standardized methods. Ideally, future studies using a multicentre or multidata base approach with a large sample size of patients with severe CSVD could resolve the controversy results between current small sample studies of CSVD and large cohort studies with healthy participants. Considering our findings, future research may be more successful by attempting to characterize the impact of structural damage on functional connectivity at multiple scales simultaneously. Further we posit that accounting for regional heterogeneity of

microscale features such as qualitative and topographic details of lesions or transcriptomic or cytoarchitectural background information could help to better differentiate the extent of structural damage. In a similar vein, the influence of systemic factors like life stressors or the degree of neurovascular coupling on functional properties must be further analysed, to better isolate the relationship between structural integrity and neural communication. In order to draw a cause-and-effect relationship from the pattern of statistical associations, a prospective longitudinal study could provide this missing interpretive link. Finally, emerging functional approaches such as the analysis of network hubs, dynamic functional connectivity, or further investigation of the functional segregation described here may provide more sensitive insights into the functional consequences of age-related structural change.

Summary

The sharp increase of life expectancy in the last decades has led to a progressive aging of the population and an increasing incidence of age-related diseases, like cerebral small vessel disease. These pathological developments are accompanied by a decline in cognitive abilities that contrasts with the benefits of increased life expectancy. Despite some efforts in the past, the relationship between structural damage in the brain, altered communication between neurons and cognitive consequences remains complex. This dissertation addresses the question of the extent to which age-related structural damage, in particular in the form of cerebral vascular lesions, influences the functional properties of the brain. To pursue this research question, a systematic literature review was conducted and supplemented with a small study of severely affected CSVD patients and a large cohort study of relatively healthy participants. A variety of study results from systematic review show evidence for a model of network dysfunction, particularly in the resting state networks, that underlies the cognitive impairment caused by white matter damage. However, the association between structural damage and altered functional connectivity showed a discrepancy between the results of small studies with severely affected patients and large cohort studies with relatively healthy participants. This contradiction is accompanied by a great heterogeneity of individual results, as well as analytical approaches and study populations, which, combined with a lack of standardisation of methods, suggest a cautious interpretation of the results. In the two subsequent studies, the functional topology of 17 CSVD patients was compared with 20 healthy controls and the influence of decreasing white matter integrity and cortical thickness on the functional connectomes of 976 relatively healthy participants was investigated. However, both the functional topology of CSVD patients and the functional connectivity of the cohort study participants were found to be independent of structural brain impairment at a global scale. Solely the part of the default mode network affected by age showed an indirect relationship with decreasing cortical thickness. These results indicate a certain resilience of neural communication to structural degeneration, whose direct influence on functional connectivity is more locally observable at the meso or micro level.

Zusammenfassung

Der starke Anstieg der Lebenserwartung in den letzten Jahrzehnten hat zu einer fortschreitenden Alterung der Bevölkerung und einer zunehmenden Inzidenz altersbedingter Krankheiten wie der zerebralen Mikroangiopathie geführt. Diese pathologischen Entwicklungen gehen mit einem Abbau der kognitiven Fähigkeiten einher, die im Kontrast zu den Vorteilen einer erhöhten Lebenserwartung stehen. Trotz einiger zurückliegender wissenschaftlicher Anstrengungen in der Vergangenheit, gestaltet sich dabei die Beziehung zwischen strukturellen Schäden des Gehirns, veränderter Kommunikation zwischen Neuronen und kognitiven Folgen weiterhin als Komplex. Die vorliegende Dissertation beschäftigt sich mit der Frage, inwieweit altersbedingte strukturelle Schädigungen in Form von zerebralen vaskulären Läsionen Einfluss auf die funktionalen Eigenschaften des Gehirns nehmen. Um dieser Fragestellung nachzugehen, wurde zunächst eine systematische Literaturanalyse durchgeführt und diese mit einer kleinen Studie schwer betroffener CSVD Patienten, sowie mit einer großen Kohortenstudie mit relativ gesunden Teilnehmern ergänzt. Eine Reihe von Studienergebnissen der systematischen Literaturanalyse zeigen Belege für ein Modell der Netzwerkdysfunktion, insbesondere in den Resting-State Netzwerken, die der kognitiven Beeinträchtigung durch Schädigung der weißen Substanz zugrunde liegt. Allerdings zeichnete sich bei der Assoziation zwischen struktureller Schädigung und veränderter funktionaler Konnektivität eine Diskrepanz zwischen den Resultaten von Studien mit geringer Anzahl an schwer betroffenen Patienten und großen Kohortenstudien mit relativ gesunden Teilnehmern ab. Dieser Widerspruch wird von einer großen Heterogenität der einzelnen Ergebnisse, sowie der analytischen Ansätze und Studienpopulationen begleitet, die in Verbindung mit fehlender Standardisierung der Methoden, die zu einer vorsichtigen Interpretation der Ergebnisse anraten. In den beiden nachfolgenden Studien wurde die funktionale Topologie von 17 CSVD Patienten mit 20 gesunden Kontrollen verglichen und der Einfluss von abnehmender Integrität der weißen Substanz und kortikaler Dicke auf die funktionalen Konnektome von 976 relativ gesunden Teilnehmern untersucht. Dabei stellte sich, sowohl die funktionale Topologie von CSVD Patienten als auch die funktionale Konnektivität der Teilnehmer der Kohortenstudie auf globaler Ebene als unabhängig von strukturellen Beeinträchtigungen des Gehirns da. Lediglich zu dem vom Alter betroffenen Teil des Default Mode Netzwerks ließ sich eine indirekte Beziehung zu abnehmender Kortikaler Dicke nachweisen. Diese Ergebnisse weisen auf eine gewisse Resilienz der neuronalen Kommunikation gegenüber struktureller Degeneration hin,

dessen direkter Einfluss auf die funktionale Konnektivität eher lokal auf Meso- bzw. Mikroebene zu beobachten ist.

Description of Own Contribution

As first author of the systematic review, I researched the literature, screened the articles, extracted metadata and key findings. In addition, I summarized the relevant patterns of functional connectivity that became apparent and wrote a first version of the manuscript. As a potential first author of the CONNECT study, I performed the structural as well as functional pre-processing, conducted the statistical analysis, researched the literature, and wrote an initial manuscript. As first author of the second study, my work included conceptualization of the study, the formal analysis of the data, the statistical analysis, the visualization and writing of the paper.

Commonly used acronyms

CSVD	Cerebral Small Vessel Disease
FC	Functional Connectivity
MRI	Magnetic Resonance Imaging
HCHS	Hamburg City Health Study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
AXIS	Appraisal Tool for Cross-Sectional Studies
FLAIR	Fluid-attenuated Inversion Recovery sequence
BMI	Body-Mass-Index
PSMD	Peak Width of Skeletonized Mean Diffusivity
NBS	Network-Based Statistics
WMH	White Matter Hyperintensities
DTI	Diffusion Tensor Imaging
BOLD	Blood Oxygen Level Dependent
rs-fMRI	Resting-state Functional MRI
SNR	Signal-To-Noise Ratio
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment Battery
CDR	Clinical Dementia Rating Scale
GSR	Global Signal Regression
RSN	Resting-State brain Networks
SCA	Seed-based Correlation Analysis
ReHo	Regional Homogeneity
DMN	Default Mode Network
DAN	Dorsal Attention Network
FPCN	Frontoparietal Control Network
SN	Salience Network
STRIVE	Standards for Reporting Vascular changes on Neuroimaging

MLR	Multiple Linear Regressions
CSF	Cerebrospinal Fluid
TMT	Trail making test

References

1. Guerreiro, R. & Bras, J. The age factor in Alzheimer's disease. *Genome Med.* **7**, 1–3 (2015).
2. Reeve, A., Simcox, E. & Turnbull, D. Ageing and Parkinson's disease: Why is advancing age the biggest risk factor? *Ageing Res. Rev.* **14**, 19 (2014).
3. Li, T. *et al.* Age-related cerebral small vessel disease and inflammaging. *Cell Death Dis. 2020 1110* **11**, 1–12 (2020).
4. Park, D. C. & Reuter-Lorenz, P. The Adaptive Brain: Aging and Neurocognitive Scaffolding. *Annu. Rev. Psychol.* **60**, 173 (2009).
5. The Handbook of Aging and Cognition. *Handb. Aging Cogn.* (2011) doi:10.4324/9780203837665/HANDBOOK-AGING-COGNITION-FERGUS-CRAIK-TIMOTHY-SALTHOUSE.
6. Cognitive neuroscience of aging: Linking cognitive and cerebral aging. - PsycNET. https://psycnet.apa.org/record/2004-21799-000.
7. Lindenberger, U. & Baltes, P. B. Sensory functioning and intelligence in old age: A strong connection. *Psychol. Aging* **9**, 339–355 (1994).
8. Bressler, S. L. & Menon, V. Large-scale brain networks in cognition: emerging methods and principles. *Trends Cogn. Sci.* **14**, 277–290 (2010).
9. Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging - PubMed. https://pubmed.ncbi.nlm.nih.gov/10918325/.
10. Salat, D. H. *et al.* Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiol. Aging* **26**, 1215–1227 (2005).
11. O'Sullivan, M. *et al.* Evidence for cortical 'disconnection' as a mechanism of age-related cognitive decline. *Neurology* **57**, 632–638 (2001).
12. Suárez, L. E., Markello, R. D., Betzel, R. F. & Misic, B. Linking Structure and Function in Macroscale Brain Networks. *Trends Cogn. Sci.* **24**, 302–315 (2020).
13. Bettinardi, R. G. *et al.* How structure sculpts function: Unveiling the contribution of anatomical connectivity to the brain's spontaneous correlation structure. *Chaos* **27**, (2017).
14. Greenwood, P. M. Functional plasticity in cognitive aging: review and hypothesis. *Neuropsychology* **21**, 657–673 (2007).
15. Goh, J. O. & Park, D. C. Neuroplasticity and cognitive aging: The scaffolding theory of aging and cognition. *Restor. Neurol. Neurosci.* **27**, 391 (2009).
16. Raz, N. *et al.* Neuroanatomical correlates of fluid intelligence in healthy adults and persons with vascular risk factors. *Cereb. Cortex* **18**, 718–726 (2008).
17. Soares, J. M. *et al.* Alterations in functional connectivity are associated with white matter lesions and information processing efficiency in multiple sclerosis. *Brain Imaging Behav.* **15**, 375–388 (2021).
18. Van Duinkerken, E. *et al.* Resting-state brain networks in type 1 diabetic patients with and without microangiopathy and their relation to cognitive functions and disease variables. *Diabetes* **61**, 1814–1821 (2012).
19. Schulz, M., Malherbe, C., Cheng, B., Thomalla, G. & Schlemm, E. Functional connectivity changes in cerebral small vessel disease - a systematic review of the resting-state MRI literature. *BMC Med.* **19**, 1–29 (2021).
20. Schulz, M. *et al.* Association of Age and Structural Brain Changes With Functional Connectivity and Executive Function in a Middle-Aged to Older Population-Based Cohort. *Front. Aging Neurosci.* **14**, 18 (2022).
21. Quandt, F. *et al.* Higher white matter hyperintensity lesion load is associated

with reduced long-range functional connectivity. *Brain Commun.* **2**, (2020).
22. Fischer, F. *et al.* Intrinsic functional brain connectivity is resilient to chronic hypoperfusion caused by unilateral carotid artery stenosis. *NeuroImage. Clin.* **34**, 103014 (2022).
23. Frey, B. M. *et al.* Characterization of White Matter Hyperintensities in Large-Scale MRI-Studies. *Front. Neurol.* **10**, (2019).
24. Liberati, A. *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* **339**, (2009).
25. Downes, M. J., Brennan, M. L., Williams, H. C. & Dean, R. S. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). *BMJ Open* **6**, 1–7 (2016).
26. Ma, L. L. *et al.* Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: What are they and which is better? *Mil. Med. Res.* **7**, 1–11 (2020).
27. Shen, X., Tokoglu, F., Papademetris, X. & Constable, R. T. Groupwise whole-brain parcellation from resting-state fMRI data for network node identification. *Neuroimage* **82**, 403–415 (2013).
28. Schaefer, A. *et al.* Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cereb. Cortex* **28**, 3095–3114 (2018).
29. Martin Prince, A. *et al.* World Alzheimer Report 2015 The Global Impact of Dementia An AnAlysIs of prevAlence, IncIDence, cosT AnD TrenDs.
30. Dichgans, M. & Leys, D. Vascular Cognitive Impairment. *Circ. Res.* **120**, 573–591 (2017).
31. Pantoni, L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet. Neurol.* **9**, 689–701 (2010).
32. Wardlaw, J. M., Smith, C. & Dichgans, M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol.* **18**, 684–696 (2019).
33. Dichgans, M. *et al.* METACOHORTS for the study of vascular disease and its contribution to cognitive decline and neurodegeneration: An initiative of the Joint Programme for Neurodegenerative Disease Research. *Alzheimers. Dement.* **12**, 1235–1249 (2016).
34. Feigin, V. L., Lawes, C. M. M., Bennett, D. A. & Anderson, C. S. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *Lancet. Neurol.* **2**, 43–53 (2003).
35. De Laat, K. F. *et al.* Gait in elderly with cerebral small vessel disease. *Stroke* **41**, 1652–1658 (2010).
36. Van Agtmaal, M. J. M., Houben, A. J. H. M., Pouwer, F., Stehouwer, C. D. A. & Schram, M. T. Association of Microvascular Dysfunction With Late-Life Depression: A Systematic Review and Meta-analysis. *JAMA psychiatry* **74**, 729–739 (2017).
37. Vermeer, S. E., Longstreth, W. T. & Koudstaal, P. J. Silent brain infarcts: a systematic review. *Lancet. Neurol.* **6**, 611–619 (2007).
38. Liao, D. *et al.* Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control. The ARIC Study. Atherosclerosis Risk in Communities Study. *Stroke* **27**, 2262–2270 (1996).
39. Reijmer, Y. D. *et al.* Microstructural white matter abnormalities and cognitive functioning in type 2 diabetes: a diffusion tensor imaging study. *Diabetes Care* **36**, 137–144 (2013).
40. Cannistraro, R. J. *et al.* CNS small vessel disease: A clinical review. *Neurology*

92, 1146–1156 (2019).
41. Schroeter, M. L., Cutini, S., Wahl, M. M., Scheid, R. & Yves von Cramon, D. Neurovascular coupling is impaired in cerebral microangiopathy--An event-related Stroop study. *Neuroimage* **34**, 26–34 (2007).
42. Wardlaw, J. M., Smith, C. & Dichgans, M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet. Neurol.* **12**, 483–497 (2013).
43. Liu, R. *et al.* Distinctive and pervasive alterations of functional brain networks in cerebral small vessel disease with and without cognitive impairment. *Dement. Geriatr. Cogn. Disord.* **47**, 55–67 (2019).
44. Black, S., Gao, F. & Bilbao, J. Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment. *Stroke* **40**, (2009).
45. Gouw, A. A. *et al.* Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. *J. Neurol. Neurosurg. Psychiatry* **82**, 126–135 (2011).
46. Chutinet, A. & Rost, N. S. White matter disease as a biomarker for long-term cerebrovascular disease and dementia. *Curr. Treat. Options Cardiovasc. Med.* **16**, 292 (2014).
47. Pantoni, L., Poggesi, A. & Inzitari, D. The relation between white-matter lesions and cognition. *Curr. Opin. Neurol.* **20**, 390–397 (2007).
48. Schmidt, R. *et al.* Heterogeneity in age-related white matter changes. *Acta Neuropathol.* **122**, 171–185 (2011).
49. Nordahl, C. W. *et al.* White Matter Changes Compromise Prefrontal Cortex Function in Healthy Elderly Individuals. *J. Cogn. Neurosci.* **18**, 418 (2006).
50. Kramer, J. H., Reed, B. R., Mungas, D., Weiner, M. W. & Chui, H. C. Executive dysfunction in subcortical ischaemic vascular disease. *J. Neurol. Neurosurg. Psychiatry* **72**, 217 (2002).
51. Viana-Baptista, M. *et al.* Cognitive function correlates with frontal white matter apparent diffusion coefficients in patients with leukoaraiosis. *J. Neurol.* **255**, 360–366 (2008).
52. Silbert, L. C., Nelson, C., Howieson, D. B., Moore, M. M. & Kaye, J. A. Impact of white matter hyperintensity volume progression on rate of cognitive and motor decline. *Neurology* **71**, 108 (2008).
53. Ter Telgte, A. *et al.* Cerebral small vessel disease: From a focal to a global perspective. *Nature Reviews Neurology* vol. 14 387–398 (2018).
54. Wardlaw, J. M., Valdés Hernández, M. C. & Muñoz-Maniega, S. What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. *J. Am. Heart Assoc.* **4**, 001140 (2015).
55. Sporns, O. Contributions and challenges for network models in cognitive neuroscience. *Nat. Neurosci.* **17**, 652–660 (2014).
56. Lawrence, A. J., Chung, A. W., Morris, R. G., Markus, H. S. & Barrick, T. R. Structural network efficiency is associated with cognitive impairment in small-vessel disease. *Neurology* **83**, 304 (2014).
57. Lo, C. Y. *et al.* Diffusion tensor tractography reveals abnormal topological organization in structural cortical networks in Alzheimer's disease. *J. Neurosci.* **30**, 16876–16885 (2010).
58. Griffa, A., Baumann, P. S., Thiran, J. P. & Hagmann, P. Structural connectomics in brain diseases. *Neuroimage* **80**, 515–526 (2013).
59. Reijmer, Y. D. *et al.* Disruption of cerebral networks and cognitive impairment in Alzheimer disease. *Neurology* **80**, 1370–1377 (2013).
60. Heinen, R. *et al.* The cumulative effect of small vessel disease lesions is

reflected in structural brain networks of memory clinic patients. *NeuroImage. Clin.* **19**, 963–969 (2018).
61. Yuan, J. L. *et al.* Disconnections of Cortico-Subcortical Pathways Related to Cognitive Impairment in Patients with Leukoaraiosis: A Preliminary Diffusion Tensor Imaging Study. *Eur. Neurol.* **78**, 41–47 (2017).
62. Friston, K. J. The disconnection hypothesis. in *Schizophrenia Research* vol. 30 115–125 (Elsevier, 1998).
63. van Norden, A. G. W., van Uden, I. W. M., de Laat, K. F., van Dijk, E. J. & de Leeuw, F.-E. Cognitive function in small vessel disease: the additional value of diffusion tensor imaging to conventional magnetic resonance imaging: the RUN DMC study. *J. Alzheimers. Dis.* **32**, 667–676 (2012).
64. Kim, S. H. *et al.* Voxel-based analysis of diffusion tensor imaging in patients with subcortical vascular cognitive impairment: correlates with cognitive and motor deficits. *J. Neuroimaging* **21**, 317–324 (2011).
65. van den Heuvel, M. P. & Hulshoff Pol, H. E. Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur. Neuropsychopharmacol.* **20**, 519–534 (2010).
66. Fox, M. D. & Raichle, M. E. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat. Rev. Neurosci. 2007 89* **8**, 700–711 (2007).
67. Fox, M. D. & Greicius, M. Clinical applications of resting state functional connectivity. *Front. Syst. Neurosci.* **4**, 19 (2010).
68. Choe, A. S. *et al.* Reproducibility and Temporal Structure in Weekly Resting-State fMRI over a Period of 3.5 Years. *PLoS One* **10**, (2015).
69. Goh, J. O., Suzuki, A. & Park, D. C. Reduced neural selectivity increases fMRI adaptation with age during face discrimination. *Neuroimage* **51**, 336–344 (2010).
70. Farràs-Permanyer, L., Guàrdia-Olmos, J. & Peró-Cebollero, M. Mild cognitive impairment and fMRI studies of brain functional connectivity: the state of the art. *Front. Psychol.* **6**, 1095 (2015).
71. Takamura, T. & Hanakawa, T. Clinical utility of resting-state functional connectivity magnetic resonance imaging for mood and cognitive disorders. *J. Neural Transm.* **124**, 821–839 (2017).
72. Stam, C. J. Modern network science of neurological disorders. *Nat. Rev. Neurosci. 2014 1510* **15**, 683–695 (2014).
73. De Marco, M., Manca, R., Mitolo, M. & Venneri, A. White matter hyperintensity load modulates brain morphometry and brain connectivity in healthy adults: A neuroplastic mechanism? *Neural Plast.* **2017**, (2017).
74. Vipin, A. *et al.* Cerebrovascular disease influences functional and structural network connectivity in patients with amnestic mild cognitive impairment and Alzheimer's disease. *Alzheimer's Res. Ther.* **10**, (2018).
75. Fazekas, F. *et al.* CT and MRI rating of white matter lesions. *Cerebrovasc. Dis.* **13 Suppl 2**, 31–36 (2002).
76. Wahlund, L. O. *et al.* A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke* **32**, 1318–1322 (2001).
77. van den Heuvel, M. P. & Sporns, O. An Anatomical Substrate for Integration among Functional Networks in Human Cortex. *J. Neurosci.* **33**, 14489–14500 (2013).
78. Anticevic, A. *et al.* The role of default network deactivation in cognition and disease. *Trends Cogn. Sci.* **16**, 584–592 (2012).
79. Hampson, M., Driesen, N. R., Skudlarski, P., Gore, J. C. & Constable, R. T.

Brain connectivity related to working memory performance. *J. Neurosci.* **26**, 13338–13343 (2006).
80. Silton, R. L. *et al.* The time course of activity in dorsolateral prefrontal cortex and anterior cingulate cortex during top-down attentional control. *Neuroimage* **50**, 1292–1302 (2010).
81. Dey, A. K., Stamenova, V., Turner, G., Black, S. E. & Levine, B. Pathoconnectomics of cognitive impairment in small vessel disease: A systematic review. *Alzheimer's Dement.* **12**, 831–845 (2016).
82. Yi, L. Y. *et al.* Disrupted Topological Organization of Resting-State Functional Brain Network in Subcortical Vascular Mild Cognitive Impairment. *CNS Neurosci. Ther.* **21**, 846–854 (2015).
83. Wang, J. *et al.* The Role of Disturbed Small-World Networks in Patients with White Matter Lesions and Cognitive Impairment Revealed by Resting State Function Magnetic Resonance Images (rs-fMRI). *Med. Sci. Monit.* **25**, 341–356 (2019).
84. Zhang, X. D. *et al.* Altered hippocampal functional connectivity in primary Sjögren syndrome: a resting-state fMRI study. *Lupus* **29**, 446–454 (2020).
85. Park, B. yong, Byeon, K., Lee, M. J., Kim, S. H. & Park, H. The orbitofrontal cortex functionally links obesity and white matter hyperintensities. *Sci. Rep.* **10**, 1–11 (2020).
86. Wardlaw, J. M. *et al.* Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet. Neurol.* **12**, 822–838 (2013).
87. Guo, C. C. *et al.* One-year test-retest reliability of intrinsic connectivity network fMRI in older adults. *Neuroimage* **61**, 1471 (2012).
88. Song, J. *et al.* Age-related differences in test-retest reliability in resting-state brain functional connectivity. *PLoS One* **7**, (2012).
89. D'Esposito, M., Deouell, L. Y. & Gazzaley, A. Alterations in the BOLD fMRI signal with ageing and disease: A challenge for neuroimaging. *Nat. Rev. Neurosci.* **4**, 863–872 (2003).
90. Shabir, O., Berwick, J. & Francis, S. E. Neurovascular dysfunction in vascular dementia, Alzheimer's and atherosclerosis. *BMC Neurosci.* **19**, (2018).
91. Fabiani, M. *et al.* Neurovascular coupling in normal aging: a combined optical, ERP and fMRI study. *Neuroimage* **85 Pt 1**, 592–607 (2014).
92. Marek, S. *et al.* Reproducible brain-wide association studies require thousands of individuals. *Nature* **603**, 654–660 (2022).
93. Telesford, Q. K. *et al.* Reproducibility of graph metrics in fMRI networks. *Front. Neuroinform.* **4**, 117 (2010).
94. Braun, U. *et al.* Test-retest reliability of resting-state connectivity network characteristics using fMRI and graph theoretical measures. *Neuroimage* **59**, 1404–1412 (2012).
95. Wang, J. H. *et al.* Graph theoretical analysis of functional brain networks: test-retest evaluation on short- and long-term resting-state functional MRI data. *PLoS One* **6**, (2011).
96. Sporns, O. & Zwi, J. D. The small world of the cerebral cortex. *Neuroinformatics* **2**, 145–162 (2004).
97. Kaiser, M. & Hilgetag, C. C. Nonoptimal component placement, but short processing paths, due to long-distance projections in neural systems. *PLoS Comput. Biol.* **2**, 0805–0815 (2006).
98. Achard, S. & Bullmore, E. Efficiency and cost of economical brain functional networks. *PLoS Comput. Biol.* **3**, 0174–0183 (2007).

99. Qin, Y., Zhu, W., Liu, C., Wang, Z. & Zhu, W. Functional brain connectome and its relation to mild cognitive impairment in cerebral small vessel disease patients with thalamus lacunes: A cross-sectional study. *Med. (United States)* **98**, (2019).
100. Watts, D. J. & Strogatz, S. H. Collective dynamics of 'small-world' networks. *Nat. 1998 3936684* **393**, 440–442 (1998).
101. Newman, M. E. J. Modularity and community structure in networks. *Proc. Natl. Acad. Sci. U. S. A.* **103**, 8577–8582 (2006).
102. Liu, Y. *et al.* Disrupted small-world networks in schizophrenia. *Brain* **131**, 945–961 (2008).
103. Lin, H. *et al.* Brain connectivity markers in advanced Parkinson's disease for predicting mild cognitive impairment. *Eur. Radiol.* (2021) doi:10.1007/s00330-021-08086-3.
104. Brickman, A. M. *et al.* White matter hyperintensities and cognition: testing the reserve hypothesis. *Neurobiol. Aging* **32**, 1588–1598 (2011).
105. Smith, E. E. *et al.* Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. *Arch. Neurol.* **65**, 94–100 (2008).
106. Sporns, O. Graph theory methods: applications in brain networks. *Dialogues Clin. Neurosci.* **20**, 111 (2018).
107. Lawrence, A. J., Tozer, D. J., Stamatakis, E. A. & Markus, H. S. A comparison of functional and tractography based networks in cerebral small vessel disease. *NeuroImage Clin.* **18**, 425–432 (2018).
108. Huang, C. C. *et al.* Age-Related Changes in Resting-State Networks of A Large Sample Size of Healthy Elderly. *CNS Neurosci. Ther.* **21**, 817–825 (2015).
109. Noor, A., Zafar, S. & Zerr, I. Neurodegenerative proteinopathies in the proteoform spectrum—tools and challenges. *International Journal of Molecular Sciences* vol. 22 1–15 (2021).
110. Brown, W. R. & Thore, C. R. Review: Cerebral microvascular pathology in ageing and neurodegeneration. *Neuropathol. Appl. Neurobiol.* **37**, 56–74 (2011).
111. De Marco, M., Manca, R., Mitolo, M. & Venneri, A. White Matter Hyperintensity Load Modulates Brain Morphometry and Brain Connectivity in Healthy Adults: A Neuroplastic Mechanism? *Neural Plast.* **2017**, 1–10 (2017).
112. Sowell, E. R. *et al.* Mapping cortical change across the human life span. *Nat. Neurosci.* **6**, 309–315 (2003).
113. Ziegler, G. *et al.* Brain structural trajectories over the adult lifespan. *Hum. Brain Mapp.* **33**, 2377–2389 (2012).
114. Fjell, A. M. & Walhovd, K. B. Structural brain changes in aging: courses, causes and cognitive consequences. *Rev. Neurosci.* **21**, 187–221 (2010).
115. Azevedo, C. J. *et al.* Contribution of normal aging to brain atrophy in MS. *Neurol. Neuroimmunol. neuroinflammation* **6**, (2019).
116. Mayer, C. *et al.* Linking cortical atrophy to white matter hyperintensities of presumed vascular origin. *J. Cereb. Blood Flow Metab.* (2020) doi:10.1177/0271678X20974170.
117. Thong, J. Y. J. *et al.* Association of silent lacunar infarct with brain atrophy and cognitive impairment. *J. Neurol. Neurosurg. Psychiatry* **84**, 1219–1225 (2013).
118. Vieira, B. H., Rondinoni, C. & Garrido Salmon, C. E. Evidence of regional associations between age-related inter-individual differences in resting-state functional connectivity and cortical thinning revealed through a multi-level analysis. *Neuroimage* **211**, (2020).

119. De Marco, M., Manca, R., Mitolo, M. & Venneri, A. White Matter Hyperintensity Load Modulates Brain Morphometry and Brain Connectivity in Healthy Adults: A Neuroplastic Mechanism? *Neural Plast.* **2017**, (2017).
120. Shi, L. *et al.* The spatial associations of cerebral blood flow and spontaneous brain activities with white matter hyperintensities-An exploratory study using multimodal magnetic resonance imaging. *Front. Neurol.* **8**, 1–8 (2017).
121. Hedden, T. *et al.* Multiple Brain Markers are Linked to Age-Related Variation in Cognition. *Cereb. Cortex* **26**, 1388–1400 (2016).
122. Madden, D. J. *et al.* Sources of disconnection in neurocognitive aging: cerebral white-matter integrity, resting-state functional connectivity, and white-matter hyperintensity volume. *Neurobiol. Aging* **54**, 199–213 (2017).
123. Farras-Permanyer, L. *et al.* Age-related changes in resting-state functional connectivity in older adults. *Neural Regen. Res.* **14**, 1544–1555 (2019).
124. Onoda, K., Ishihara, M. & Yamaguchi, S. Decreased functional connectivity by aging is associated with cognitive decline. *J. Cogn. Neurosci.* **24**, 2186–2198 (2012).
125. Vidal-PiÃ±eiro, D. *et al.* Decreased Default Mode Network connectivity correlates with age-associated structural and cognitive changes. *Front. Aging Neurosci.* **6**, 1–17 (2014).
126. Zonneveld, H. I. *et al.* Patterns of functional connectivity in an aging population: The Rotterdam Study. *Neuroimage* **189**, 432–444 (2019).
127. Hausman, H. K. *et al.* The Role of Resting-State Network Functional Connectivity in Cognitive Aging. *Front. Aging Neurosci.* **12**, 177 (2020).
128. Biswal, B., Yetkin, F. Z., Haughton, V. M. & Hyde, J. S. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn. Reson. Med.* **34**, 537–541 (1995).
129. Damoiseaux, J. S. *et al.* Reduced resting-state brain activity in the 'default network' in normal aging. *Cereb. Cortex* **18**, 1856–1864 (2008).
130. Fox, M. D. *et al.* The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc. Natl. Acad. Sci. U. S. A.* **102**, 9673–9678 (2005).
131. Kashtan, N. & Alon, U. Spontaneous evolution of modularity and network motifs. *Proc. Natl. Acad. Sci. U. S. A.* **102**, 13773–13778 (2005).
132. Bullmore, E. & Sporns, O. The economy of brain network organization. *Nat. Rev. Neurosci. 2012 135* **13**, 336–349 (2012).
133. Sporns, O. & Betzel, R. F. Modular Brain Networks. *Annu. Rev. Psychol.* **67**, 613–640 (2016).
134. Meunier, D., Lambiotte, R. & Bullmore, E. T. Modular and hierarchically modular organization of brain networks. *Front. Neurosci.* **4**, (2010).
135. Damoiseaux, J. S. & Greicius, M. D. Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. *Brain Struct. Funct.* **213**, 525–533 (2009).
136. Johansen-Berg, H. Imaging the relationship between structure, function and behaviour in the human brain. *Brain Struct. Funct. 2009 2136* **213**, 499–500 (2009).
137. Sang, L. *et al.* Progressively disrupted brain functional connectivity network in subcortical ischemic vascular cognitive impairment patients. *Front. Neurol.* **9**, 94 (2018).
138. Betzel, R. F. *et al.* Changes in structural and functional connectivity among resting-state networks across the human lifespan. *Neuroimage* **102**, 345–357 (2014).

139. Chan, M. Y., Park, D. C., Savalia, N. K., Petersen, S. E. & Wig, G. S. Decreased segregation of brain systems across the healthy adult lifespan. *Proc. Natl. Acad. Sci. U. S. A.* **111**, E4997–E5006 (2014).
140. Ng, K. K., Lo, J. C., Lim, J. K. W., Chee, M. W. L. & Zhou, J. Reduced functional segregation between the default mode network and the executive control network in healthy older adults: A longitudinal study. *Neuroimage* **133**, 321–330 (2016).
141. Low, A. *et al.* Peak Width of Skeletonized Mean Diffusivity as a Marker of Diffuse Cerebrovascular Damage. *Front. Neurosci.* **14**, (2020).
142. Wei, N. *et al.* A neuroimaging marker based on diffusion tensor imaging and cognitive impairment due to cerebral white matter lesions. *Front. Neurol.* **10**, (2019).
143. Van Den Heuvel, M. P., Stam, C. J., Kahn, R. S. & Hulshoff Pol, H. E. Efficiency of functional brain networks and intellectual performance. *J. Neurosci.* **29**, 7619–7624 (2009).
144. Santarnecchi, E., Galli, G., Polizzotto, N. R., Rossi, A. & Rossi, S. Efficiency of weak brain connections support general cognitive functioning. *Hum. Brain Mapp.* **35**, 4566–4582 (2014).
145. Alavash, M., Doebler, P., Holling, H., Thiel, C. M. & Gießing, C. Is functional integration of resting state brain networks an unspecific biomarker for working memory performance? *Neuroimage* **108**, 182–193 (2015).
146. Onoda, K., Ishihara, M. & Yamaguchi, S. *Decreased Functional Connectivity by Aging Is Associated with Cognitive Decline*. (2012).
147. Cole, M. W. *et al.* Multi-task connectivity reveals flexible hubs for adaptive task control. *Nat. Neurosci.* **16**, 1348–1355 (2013).
148. Greicius, M. D., Srivastava, G., Reiss, A. L. & Menon, V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc. Natl. Acad. Sci. U. S. A.* **101**, 4637–4642 (2004).
149. Desgranges, B., Mevel, K., Chételat, G. & Eustache, F. The default mode network in healthy aging and Alzheimer's disease. *Int. J. Alzheimers. Dis.* **2011**, (2011).
150. Staffaroni, A. M. *et al.* The longitudinal trajectory of default mode network connectivity in healthy older adults varies as a function of age and is associated with changes in episodic memory and processing speed. *J. Neurosci.* **38**, 2809–2817 (2018).
151. He, J. *et al.* Influence of functional connectivity and structural MRI measures on episodic memory. *Neurobiol. Aging* **33**, 2612–2620 (2012).
152. Madden, D. J. *et al.* Sources of disconnection in neurocognitive aging: cerebral white-matter integrity, resting-state functional connectivity, and white-matter hyperintensity volume. *Neurobiol. Aging* **54**, 199–213 (2017).
153. Tsapanou, A. *et al.* Brain biomarkers and cognition across adulthood. *Hum. Brain Mapp.* **40**, 3832–3842 (2019).
154. Jagust, W. Vulnerable Neural Systems and the Borderland of Brain Aging and Neurodegeneration. *Neuron* **77**, 219 (2013).
155. Suárez, L. E., Markello, R. D., Betzel, R. F. & Misic, B. Linking Structure and Function in Macroscale Brain Networks. *Trends Cogn. Sci.* **24**, 302–315 (2020).
156. Fjell, A. M. *et al.* Relationship between structural and functional connectivity change across the adult lifespan: A longitudinal investigation. *Hum. Brain Mapp.* **38**, 561 (2017).
157. Messé, A., Rudrauf, D., Giron, A. & Marrelec, G. Predicting functional

connectivity from structural connectivity via computational models using MRI: an extensive comparison study. *Neuroimage* **111**, 65–75 (2015).
158. ´ Azquez-Rodríguez, B. V *et al.* Gradients of structure-function tethering across neocortex. **15**, 21219–21227 (2019).
159. Paquola, C. *et al.* Microstructural and functional gradients are increasingly dissociated in transmodal cortices. *PLoS Biol.* **17**, (2019).
160. Stam, C. J. Characterization of anatomical and functional connectivity in the brain: a complex networks perspective. *Int. J. Psychophysiol.* **77**, 186–194 (2010).
161. Bonnelle, V. *et al.* Salience network integrity predicts default mode network function after traumatic brain injury. *Proc. Natl. Acad. Sci. U. S. A.* **109**, 4690–4695 (2012).
162. Ferreira, L. K. *et al.* Aging Effects on Whole-Brain Functional Connectivity in Adults Free of Cognitive and Psychiatric Disorders. *Cereb. Cortex* **26**, 3851–3865 (2016).
163. Tsvetanov, K. A. *et al.* Extrinsic and Intrinsic Brain Network Connectivity Maintains Cognition across the Lifespan Despite Accelerated Decay of Regional Brain Activation. *J. Neurosci.* **36**, 3115–3126 (2016).
164. Antonenko, D. & Flöel, A. Healthy aging by staying selectively connected: a mini-review. *Gerontology* **60**, 3–9 (2014).
165. Geerligs, L., Saliasi, E., Maurits, N. M., Renken, R. J. & Lorist, M. M. Brain mechanisms underlying the effects of aging on different aspects of selective attention. *Neuroimage* **91**, 52–62 (2014).

Danksagung

Im Zuge meiner Promotion bin ich Teil der wirklich großartigen CSI Arbeitsgruppe geworden. Die Atmosphäre und der Zusammenhalt dieses Teams habe ich immer als etwas Besonderes empfunden und möchte mich an dieser Stelle ausdrücklich für die Unterstützung, den Zusammenhalt und fachliche Kompetenz bedanken.

Insbesondere mochte ich mich bei meinem Doktorvater Prof. Dr. med. Götz Thomalla bedanken, für die Möglichkeit bei ihm bzw. mit seiner Hilfe zu promovieren, für die umfassende Unterstützung, die zielführende, sowie konstruktive Betreuung als auch wertvollen Anregungen und Diskussionen.

Weiterhin gilt mein besonderer Dank Felix Fischer für die zuverlässige, kompetente Betretung und kontinuierlicher Hilfsbereitschaft zu Beginn meiner Arbeit, sowie Eckhard Schlemm für die Zusammenarbeit bei der Literaturanalyse, von dessen Fachwissen und Kompetenz ich sehr viel lernen konnte und der stets eine offene Tür hatte für wissenschaftlichen Fragen und forschungsbezogenen Gespräche.

Ich möchte auch ausdrücklich Caroline Malherbe, Carola Meyer und Marvin Petersen danken, für dich fachliche Unterstützung und die vielen anregende Diskussionen, sowie allen weiteren Mitgliedern der Arbeitsgruppe mit welchen ich zusammenarbeiten durfte.

Und schließlich gilt ein großer Dank meinen Eltern für die moralische Unterstützung und den anhaltenden, liebevollen Zuspruch, sowie Simeon Kuhnert und Francy Köllner und allen Freunden, die an meiner Seite standen und immer wieder ermutigende Worte gefunden haben.

Lebenslauf

Curriculum Vitae

Contact Information

Name	Maximilian Schulz
Address	Ohnhorststraße 66, 20097 Hamburg
Country	Germany
Mobile	+49 15202781606
E-Mail	mschulz3731@gmail.com

Education

08/2018 – 06/2022	
12/2017 – 10/2015	Molecular Medicine (M.Sc.) at Eberhard Karls University of Tübingen Master Thesis at the Bernhard-Nocht-Institut, Hamburg
10/2011 – 12/2015	Molecular Medicine (B.Sc.) at Eberhard Karls University of Tübingen Bachelor Thesis at the at Tropical Institute of Tübingen
09/2013 – 08/204	Year abroad at the Medicine School of Zagreb in Croatia
08/2003 - 07/2010	Jenisch all-day High School, Hamburg General Certificate of A-level General Certificate of Secondary Education
08/2002 - 07/2003	Gelehrtenschule des Johanneums, Hamburg

Work experience

09/2010 – 08/2011	Civil service in UK at the University of Warwick (caring for a student with muscle dystrophy)
07/2007 – 08/2007	Nursing-internship at the Dr. Guth Hospital, Hamburg
04/2015 – 06/2015	Resaerch assisstant at the Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE)
04/2015 – 05/2015	Internship at Tropical Institute of Tübingen
12/2017 – 04/2028	Research Assistant at the Center for Molecular Neuroscience Hamburg (ZMNH)

Skill

Language	German	Native
	English	Proficient
	Latin	School Certificate
IT	Bash, MatLab, R Programming, MS-Office, Image preprocessing	
Interests	Swimming, Surfing, Chess	

10. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.
Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: .....

Schulz et al. BMC Medicine (2021) 19:103
https://doi.org/10.1186/s12916-021-01962-1

BMC Medicine

RESEARCH ARTICLE Open Access

Functional connectivity changes in cerebral small vessel disease - a systematic review of the resting-state MRI literature

Maximilian Schulz[1], Caroline Malherbe[1,2], Bastian Cheng[1], Götz Thomalla[1] and Eckhard Schlemm[1*]

Abstract

Background: Cerebral small vessel disease (CSVD) is a common neurological disease present in the ageing population that is associated with an increased risk of dementia and stroke. Damage to white matter tracts compromises the substrate for interneuronal connectivity. Analysing resting-state functional magnetic resonance imaging (fMRI) can reveal dysfunctional patterns of brain connectivity and contribute to explaining the pathophysiology of clinical phenotypes in CSVD.

Materials and methods: This systematic review provides an overview of methods and results of recent resting-state functional MRI studies in patients with CSVD. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol, a systematic search of the literature was performed.

Results: Of 493 studies that were screened, 44 reports were identified that investigated resting-state fMRI connectivity in the context of cerebral small vessel disease. The risk of bias and heterogeneity of results were moderate to high. Patterns associated with CSVD included disturbed connectivity within and between intrinsic brain networks, in particular the default mode, dorsal attention, frontoparietal control, and salience networks; decoupling of neuronal activity along an anterior–posterior axis; and increases in functional connectivity in the early stage of the disease.

Conclusion: The recent literature provides further evidence for a functional disconnection model of cognitive impairment in CSVD. We suggest that the salience network might play a hitherto underappreciated role in this model. Low quality of evidence and the lack of preregistered multi-centre studies remain challenges to be overcome in the future.

Keywords: Brain network, Cerebral small vessel disease, Cognition, Functional connectivity, Magnetic resonance imaging, Resting state, Risk of bias, Patho-connectomics, Systematic review

* Correspondence: e.schlemm@uke.de
[1]Department of Neurology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany
Full list of author information is available at the end of the article

Background

Cerebral small vessel disease (CSVD) is a term that describes clinical, neuroimaging, and pathological features assumed to arise from compromised blood flow in the intrinsic cerebral arteriolar system [1]. In its later stages, CSVD is associated with neurological symptoms, in particular lacunar ischaemic stroke, and cognitive impairment ranging from mild deficits to vascular dementia [2, 3]. Small vessel disease is estimated to be the main etiological factor in up to 23% of all ischaemic strokes [4] and to be the second most common contributing factor to dementia after Alzheimer's pathology [5] and is thus responsible for a growing disease burden in ageing societies.

Even in its pre-symptomatic stage, CSVD is associated with structural brain changes on neuroimaging, in particular white matter hyperintensities (WMH) of presumed vascular origin, lacunes, cerebral microbleeds, enlarged perivascular spaces, and brain atrophy [6]. Cardiovascular risk factors, such as hypertension, diabetes, smoking, or dyslipidaemia, are associated with both WMH and the clinical sequelae associated with CSVD [7, 8].

In recent years, the network perspective on the human brain has revolutionised neuroscience and advanced our understanding of neurological and psychiatric disorders [9–12]. The network paradigm posits that different brain regions, while spatially remote, are structurally and functionally linked and interact to facilitate brain functions. Analysis of structural brain networks by magnetic resonance diffusion tensor imaging revealed that WMH disrupts the topological organisation of the brain connectome and that the associated loss of network efficiency links vascular risk burden and cognitive impairment [13–16]. Nevertheless, there remains considerable variability in clinical phenotypes, such as cognitive impairment or affective functions, that is not explained by structural markers alone [17–19].

Functional connectivity (FC), on the other hand, is defined as the pattern of synchronous neuronal activation [20], which, in turn, can be probed in vivo using the blood-oxygen level-dependent (BOLD) signal in magnetic resonance imaging (MRI) [21]. Functional connectivity can be analysed either in response to tasks and external stimuli or in the resting-state which minimises the cognitive and behavioural demand on subjects [21]. The latter provides a description of the spatiotemporal organisation of brain activity, from which discrete modes can be extracted as intrinsic resting-state networks that correspond to specific cognitive domains [22].

Recently, the benefits of such a shift of perspective toward a more global understanding of brain function have also been recognised for cerebral small vessel disease [23]. While the clinical benefits of understanding patterns of disrupted FC associated with CSVD might seem, at the moment, very limited, our vision is that, ultimately, it might contribute to designing and implementing patient-specific interventions in the form of neuropsychological training or electromagnetic stimulation to help ameliorate cognitive impairment. Evidence for the relevance of disturbed connectivity especially in the default mode, dorsal attention, and frontoparietal control networks to cognitive impairment in CSVD has been reviewed previously, covering the literature up to 2014 [24]. In the present article, we provide an overview over the rapidly expanding recent literature on altered resting-state connectivity patterns associated with CSVD. In contrast to previous work, we include studies of both clinically healthy individuals and patients with manifest CSVD and consider both distributed networks and point-to-point connectivity. In order to keep the review focused, we restrict attention to resting-state functional MRI studies and do not review studies using a task-based design or different imaging modalities, such as electro- or magnetoencephalography. The goal is to take stock of the current literature, review methodological advances in recent years, and update our understanding of the neural mechanisms underlying the cognitive deficits that patients with CSVD face.

Methods

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [25]; the protocol for the review was not preregistered.

Literature search and study selection

Inclusion criteria for articles considered in this review were as follows: (1) written in English, (2) analysing exclusively human study participants, (3) published after January 2010, (4) radiological evidence of sporadic cerebral small vessel disease with structural brain imaging showing manifestations of CSVD in the form of white matter hyperintensities in at least a subset of the study population, and (5) analysis of resting-state functional connectivity using functional MRI. We excluded review articles; descriptions of ongoing studies; functional imaging studies using only electroencephalography, magnetoencephalography, or positron emission tomography; and reports concentrating exclusively on patients with non-sporadic CSVD, e.g. of genetic origin, or non-vascular dementias, e.g. Alzheimer's disease.

Following a prespecified search strategy, the PubMed online database was queried for studies published between January 2010 and November 2020 using the conjunction of keywords specific for pathology ('small

vessel disease', 'white matter lesion', 'leukoaraiosis', 'microangiopathy'), network science ('connectivity', 'network', 'graph', 'module'), and imaging modality ('MRI', 'BOLD', 'resting state') as search criteria (see Additional file 1 for the exact search strategy). In addition, references of search results were screened for further eligible articles. Studies were discarded if the title or abstract indicated failure to meet all the specified inclusion or satisfaction of at least one exclusion criterion. The remaining articles were read in full and evaluated according to the stated criteria.

The risk of methodological bias in individual studies (PRISMA items 12 and 19) was assessed using the Appraisal tool for Cross-Sectional Studies (AXIS tool) [26], modified to not contain items related to presentation of the Results, the Discussion of findings, or the Funding of the study [27]. Detailed descriptions of individual items are presented in Additional file 1: Table S1. Based on the number of quality criteria satisfied, each study was assigned an integer score from 0 (no criteria satisfied) to 11 (all criteria satisfied). Trichotomising this ordinal scale, we classified the risk of bias as high (score 0–3), moderate (4–7), or low (8–11). We strived to cover the literature comprehensively, and even a high risk of basis was therefore not defined as an exclusion criterion for this review.

Data extraction and analysis

After screening, the following data were extracted from the articles: year of publication; sample size; average age and clinical characteristics of study populations including measures undertaken to minimise confounding by comorbidities; the employed operationalisation of cerebral small vessel disease and severity grading of WMH; details of the scanning parameters and pre-processing steps including the controversial topics of motion scrubbing and global signal regression; the analytical approach to functional connectivity; and key results regarding patterns of altered connectivity in patients with CSVD and, if reported, their relation to cognitive performance.

For ease of presentation, studies were classified according to clinical characteristics of the study population—manifest CSVD, healthy participants, or others, not primarily vascular clinical conditions—and their main approach to quantifying and analysing connectivity. These predefined analytical categories included short-range connectivity within a part of the brain, long-range connectivity between pairs of remote brain areas defined either a priori or using a data-driven approach, and global analyses of topological properties of the functional connectome. We also reviewed the cognitive tests applied in these studies and associations of cognitive ability with functional connectivity measurements.

Results

Study characteristics

The results of the search and selection process are summarised in Fig. 1. We identified a total of 493 potentially relevant papers, 471 of which were obtained by searching PubMed and 22 through personal communication or as references cited in other works. Four hundred seventeen papers were excluded based on their title or abstract. Of the remaining 76 studies, which were read in full by both MS and ES, 44 were included in this review. Details of individual studies are summarised in Table 1.

The number of subjects, including both patients with small vessel disease and controls depending on study design, varied between 11 and 1584 with a median sample size of 72.5 (interquartile range [IQR] 50.8–106.8). Mean age across studies ranged from 50.0 to 76.4 years, with a median of 66.0 years (IQR 62.4–69.8 years).

Regarding the underlying research questions, roughly half of the included studies (24/44) reported the investigation of altered functional connectivity patterns in the presence of cerebral small vessel disease and its relation to cognitive ability as their primary research objective. Of these, six reports focused on patients with CSVD exclusively, whereas the study designs of the remaining reports involved comparing groups of healthy controls, patients with non-vascular cognitive impairment, or both. Twelve studies reported measures of cerebral small vessel disease, often as part of a more comprehensive assessment of structural brain parameters, and functional connectivity in populations of healthy participants without clinically manifest vascular pathology or cognitive impairment. Eight articles addressed functional connectivity in the context of other clinical conditions not directly related to vascular pathology, such as tau pathology-associated cognitive impairment or depression, but included markers of small vessel disease as covariates.

Operationalisation of CSVD and associated cognitive impairment

All of the 24 MRI studies reporting on resting-state functional connectivity in the context of clinically overt CSVD defined the presence of white matter hyperintensities on T2-weighted cerebral MR imaging as one of their inclusion criteria. In more than half of the studies (14/24), these were evaluated according to the ordinal Fazekas scale [55, 56]; in three studies, authors chose the Wahlund scale to assess age-related white matter changes [32]; white matter lesion load was also quantified volumetrically in eight studies; no precise definition of imaging criteria was reported in five articles.

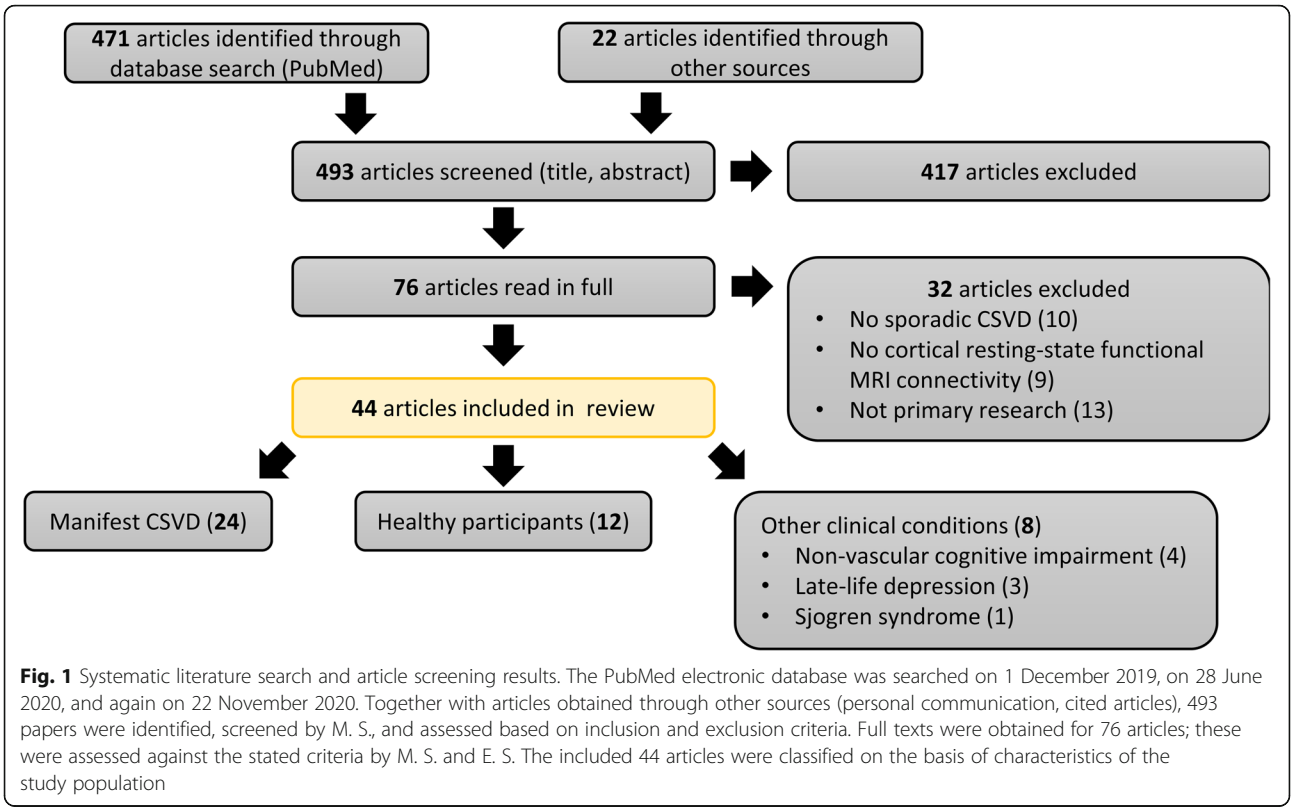

Fig. 1 Systematic literature search and article screening results. The PubMed electronic database was searched on 1 December 2019, on 28 June 2020, and again on 22 November 2020. Together with articles obtained through other sources (personal communication, cited articles), 493 papers were identified, screened by M. S., and assessed based on inclusion and exclusion criteria. Full texts were obtained for 76 articles; these were assessed against the stated criteria by M. S. and E. S. The included 44 articles were classified on the basis of characteristics of the study population

When white matter disease was reported as a structural covariate in the investigation of functional connectivity, the extent of structural changes was quantified using either absolute or relative white matter hyperintensity volumes. Techniques for segmenting WMH on either T2 or FLAIR sequences included manual, semi-manual, and fully automated approaches; in one case, the algorithm was not described [57].

Beyond the presence of white matter lesions, evidence of lacunes or recent lacunar infarcts was considered in 13/24 studies; the distinction between the two entities was often imprecise, with only three articles referring to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE, [6]) consensus statement in this context [31, 50, 51]. Reflecting their conceptualisation as fluid-filled cavities, lacunes were defined as hypointense ovoid regions on T2- or FLAIR-weighted imaging with a diameter ranging from [2–3] to [15–20] mm. Three studies required patients with CSVD to have evidence of at least one lacuna or recent lacunar infarct [28, 42, 52], while one report excluded such patients [36]. Information on the number of lacunes contributed to the definition of a compositive CSVD score in one study [49]; in the remaining cases, it was either reported descriptively or used as a covariate in statistical analyses [50]. While most studies specified cortical or large subcortical infarcts as an exclusion criterion, one article included such patients specifically [43].

In addition to imaging findings, clinical characteristics were used to define patient cohorts. This was done to either separate patients and participants with and without cognitive impairment; to differentiate patients with CSVD from patients with non-vascular cognitive impairment, especially Alzheimer's disease; or to grade the severity of vascular cognitive impairment, ranging from cognitively normal (CN) over mildly affected (variably called *subcortical vascular mild cognitive impairment* [svMCI], or *vascular cognitive impairment no dementia* [VICND]) to subcortical vascular dementia (SVaD). In addition to dedicated diagnostic criteria for different dementias [58, 59], cognitive assessment was based predominantly on scales such as the Mini Mental State Examination (MMSE), Montreal Cognitive Assessment battery (MoCA), or Clinical Dementia Rating scale (CDR). A minority of studies used the Petersen criteria and included functional activities and temporal evolution of cognitive abilities in their definition of mild cognitive impairment [60, 61]. Only three studies employed positron emission tomography (PET) to distinguish tau and/or amyloid pathology from purely vascular disease [49, 62, 63], and the risk of confounding by mixed disease seems therefore high in the majority of reported studies.

Table 1 Summary of included articles analysing resting-state functional connectivity in patients with manifest cerebral small vessel disease (CSVD). We report imaging and clinical characteristics of patients included in each study, key steps in the acquisition and pre-processing of BOLD data, analysis of functional connectivity, and FC patterns found to be associated with CSVD. Descriptive statistics as extracted from articles are reported as mean ± standard deviation. Missing information is indicted by empty brackets ([]). Arrows indicate increased (↑) or reduced (↓) values, as well as positive (↗) and negative (↘) associations

Reference	Participants	Characteristics of patients with CSVD		MRI acquisition params	BOLD pre-processing	FC analysis	FC patterns associated with CSVD	Risk of bias (AXIS)
		Neuroimaging	Cognition					
[28]	18 CSVD-CN 16 CSVD-MCI	WMH and lacunes (clinical diagnosis)	*MMSE* CN 28.9 ± 1.3 MCI 28.1 ± 1.4	Philips Achieva, 3 T TR 2000 ms, TE 30 ms 64 × 64 × [] 3.6 × 3.6 × 4 mm^3 220 volumes eyes open	DPARSF v2.0, SPM 5, REST [Confound regression] Motion scrubbing - Max motion > 1 mm/1°	PCC from external template SCA to define DMN Pearson correlation	↓ FC in DMN in the left middle temporal gyrus, left ant. cingulate/left middle frontal gyrus, right caudate, right middle frontal gyrus, and left medial frontal gyrus/paracentral lobule ↑ FC in DMN in the right inf. temporal gyrus, left middle temporal gyrus, left precentral gyrus, and left sup. parietal lobule	High (2)
[29]	29 CSVD	WMH (clinical diagnosis) *WMH volume* VRF 0, 20.4 ± 19.3 VRF 1, 27.3 ± 21.5 VRF 3, 17.4 ± 19.5	*MoCA* VRF 0, 25.8 ± 3.5 VRF 1, 22.0 ± 6.2 VRF 3, 21.0 ± 5.4	Philips Achieva, 3 T TR 2000 ms, TE 30 ms 64 × 64 × 40 3.6 × 2.9 × 3 mm^3 184–259 volumes, [eyes]	FSL v4.1 Confound regression - ICA Motion scrubbing - 'relative motion' > 1.5 mm	ICA to define DMN, SMN, medial-visual RSN Pearson correlation	FC in DMN ↗ cardiovascular reactivity	Moderate (4)
[30]	21 CSVD-CN 16 CSVD-MCI 13 SVaD	WMH (clinical diagnosis)	*MMSE* CN 28.9 ± 0.7 MCI 26.3 ± 1.0 SVaD 20.5 ± 2.3 *MoCA* CN 24.6 ± 2.9 MCI 20.6 ± 2.8 SVaD 15.1 ± 3.6	Siemens, 3 T TR 2480 ms, TE 30 ms 64 × 64 × 36, 3 × 3 × 4 mm^3 240 volumes eyes closed	SPM 8 [Confound regression] Motion scrubbing - Head motion > 2 mm/2°	AAL atlas Pearson correlation, (extended) maximal information coefficient SVM classification	None	High (3)
[31]	46 CSVD 41 CADASIL	*WMH volume* 0.3% [0.03, 3.1]% of intracranial volume *Lacunes* 0 (0) [0–20]	MMSE median 29, IQR [26, 32]	Siemens Skyra/Prisma, 3 T, 64-/32-channel head coils, multi-band × 8 TR 700 ms, TE 39 ms [matrix] 3 × 3 × 3 mm^3 2.4 × 2.4 × 2.4 mm^3 675–700 volumes eyes closed	FSL, ANTs, BRAMILA v2.0 Confound regression - ICA-AROMA non-aggressive - Linear trend, 6 motion params - GSR: CSF, WM Motion scrubbing - Volume censoring (FD > 0.5 mm, total time < 5 min)	Power atlas to define DMN, FPCN, hand-SMN, VN Pearson correlation graph theory	No association between WMH and FC Poor reproducibility of network measures in CSVD	Moderate (6)

Table 1 Summary of included articles analysing resting-state functional connectivity in patients with manifest cerebral small vessel disease (CSVD). We report imaging and clinical characteristics of patients included in each study, key steps in the acquisition and pre-processing of BOLD data, analysis of functional connectivity, and FC patterns found to be associated with CSVD. Descriptive statistics as extracted from articles are reported as mean ± standard deviation. Missing information is indicted by empty brackets ([]). Arrows indicate increased (↑) or reduced (↓) values, as well as positive (↗) and negative (↘) associations *(Continued)*

Reference	Participants	Characteristics of patients with CSVD		MRI acquisition params	BOLD pre-processing	FC analysis	FC patterns associated with CSVD	Risk of bias (AXIS)
		Neuroimaging	Cognition					
[33]	33 MCI with confluent (C) WMH 30 MCI with non-confluent (NC) WMH	*Fazekas* C-WMH 8.0 ± 2.4 NC-WMH 3.2 ± 1.2 *WMH volume* C-WMH 8.7 ± 9.2 ml NC-WMH 1.9 ± 1.5 ml	*MMSE* C-WMH 27.6 ± 1.5 NC-WMH 27.8 ± 1.7	Siemens Trio, 3 T TR 2000 ms, TE 30 ms [] × []× 36, 3 × 3 × 3 mm^3 240 volumes [eyes]	CONN 18b Confound regression - GSR: WM, CSF - Motion parameters Motion correction - Artefact Detection Tools - Spike regression (FD > 0.5 mm)	CONN atlas with 138 ROIs to define DMN, SMN, VN, DAN, FPCN language, and cerebellar networks Bivariate correlation coefficients	↑ Interregional FC (C-WMH > NC-WMH) ↑ Intra-regional FC (C-WMH > NC-WMH) Few ↓ interregional FC (C-WMH < NC-WMH)	High (2)
[34]	29 CSVD with gait disorder (GD+) 29 CSVD without gait disorder (GD–)	Fazekas ≥2 *WMH volume* GD+, 6.12 mm^3 GD–, 3.53 mm^3 *Lacunes* GD+, 7.45 ± 4.01 GD–, 5.62 ± 3.35	*MMSE* GD+, 25.14 ± 3.24 GD–, 25.69 ± 3.32	GE Signa, 3 T, 8-channel head coil TR 2000 ms, TE 30 ms 64 × 64 × [] 3.75 × 3.75 × 4.6 mm^3 240 volumes eyes closed	DPABI, SPM 8 Confound regression - Linear trend, 24p - GSR: CSF, WM Motion scrubbing - 'displacement' > 2.5 mm /2.5°	fALFF Pearson correlation VBM	↓ FC between left SMA and temporal lobe (GC+ < GD–) ↗ gait speed fALFF in left SMA ↗ cadence	Moderate (4)
Healthy controls and patients with CSVD without mandatory cognitive impairment								
[35]	12 CSVD 21 HC	Wahlund 8.3 ± 4.0 Lacunes 1.9 ± 2.4	MMSE 27.6 ± 1.5	[Scanner, field str.] TR 2300 ms, [TE] [matrix], 3 × 3 × 4 mm^3 300 volumes [eyes]	FSL, AFNI, SPM B_0 field map correction Confound regression - Linear/quadratic trend - 6 motion parameters - GSR: WM, CSF signal [Motion scrubbing]	Eigenvector centrality	↓ FC in ventromedial PFC, MCC, and sup. parietal lobe ↑ FC in the cerebellar regions I–VI FC ↗ WMH in the middle temporal sulcus, inf. temporal gyrus, cerebellar lobules Crus II, VIIb, VIII FC ↘ WMH in ventromedial PFC, SMA, PCC, and sup. parietal lobe	High (1)
[36]	30 CSVD 26 HC	Fazekas 1–3 Lacunes excluded	MoCA 22.9 ± 3.4 (pooled)	Siemens, 3 T TR 2480 ms, TE 30 ms 64 × 64 × 36, 3 × 3 × 4 mm^3 240 volumes, eyes closed	SPM 8 [Confound regression] Motion scrubbing - Head movement > 2 mm/2°	ICA to define SMN voxel-wise two-sample *t* test	↓ FC in the right cingulate motor area, left posterior insula, and left ventral premotor area	High (2)
[37]	28 CSVD 30 HC	Fazekas 2.9 ± 1.2	MMSE 27.9 ± 1.6 MoCA 25.7 ± 2.0	Siemens Trio, 3 T TR 2000 ms, TE 30 ms 64 × 64 × [] 3.5 × 3.5 × 3 mm^3 240 volumes [eyes]	SPM 8, DPABI, REST [Confound regression] Motion scrubbing - Head movement > 2 mm/2°	ALFF, SCA	↓ ALFF in the left parahippocampus ↑ ALFF in the left inf. semi-lunar lobule and right frontal sup. orbital gyrus ↑ FC between right insula–right sup. orbitofrontal gyrus and right calcarine–left parahippoca. gyrus	High (2)

Table 1 Summary of included articles analysing resting-state functional connectivity in patients with manifest cerebral small vessel disease (CSVD). We report imaging and clinical characteristics of patients included in each study, key steps in the acquisition and pre-processing of BOLD data, analysis of functional connectivity, and FC patterns found to be associated with CSVD. Descriptive statistics as extracted from articles are reported as mean ± standard deviation. Missing information is indicted by empty brackets ([]). Arrows indicate increased (↑) or reduced (↓) values, as well as positive (↗) and negative (↘) associations *(Continued)*

Reference	Participants	Characteristics of patients with CSVD		MRI acquisition params	BOLD pre-processing	FC analysis	FC patterns associated with CSVD	Risk of bias (AXIS)
		Neuroimaging	Cognition					
[38]	16 CSVD 13 HC	WMH (clinical diagnosis, Fazekas)	MMSE 23.7 ± 3.9 MoCA 18.3 ± 4.1	Siemens, 3 T TR 2000 ms, TE 30 ms 64 × 64 × 35 3 × 3 × 3 mm^3 230 volumes eyes closed	SPM 8 Confound regression - Linear trend Motion scrubbing - Head movement > 2 mm/2°	Regional homogeneity	↓ ReHo in the left insula, right sup. temporal gyrus, Rolandic operculum, precentral gyrus, and cerebellum; bilateral ant. cingulate gyrus, ant. MCC, PFC, and SMA ↑ ReHo values in the left middle temporal gyrus, cuneus and sup. occipital gyrus, and the bilateral angular gyrus, precuneus, postcentral gyrus, inf. and sup. parietal gyrus	Moderate (5)
[39]	15 CSVD 15 HC	WMH (clinical diagnosis, Fazekas)	MMSE 23.7 ± 4.0 MoCA 18.6 ± 4.1	Siemens, 3 T TR 2000 ms, TE 30 ms 64 × 64 × [] 3 × 3 × 4 mm^3 230 volumes eyes closed	DPABI v2.1 Confound regression - Linear trend - 24p [40] - GSR: WM, CSF - Spike regressor (FD > 0.2 mm) Motion scrubbing - Mean FD > group mean + 2*SD	36 ROIs representing DMN, DAN, FPCN, SMN, VN Pearson correlation Network-based statistics (NBS) [41]	↓ AN-SMN network FC ↑ DAN-FPCN network FC ↓ Edge FC SMN-AN, SMN-VN, FPCN-AN and DAN-VN pairs, and within AN and VN ↑ Edge FC in DMN-AN, DMN-FPCN, and DAN-FPCN pairs	High (3)
[42]	26 lacunar stroke patients 19 HC	Fazekas ≥2 Lacunes 1–17 (6) WMH 33 ± 34 ml	History of lacunar stroke syndrome	Siemens Verio, 3 T, 32-channel head coil TR 2430 ms TE 1/2/3 13/31/48 ms 64 × 64 × 34 3.75 × 3.75 × 4.18 mm^3 269 volumes, eyes open	SPM, CONN Confound regression - Motion parameters [details] - GSR: WM, CSF [Motion scrubbing]	Desikan–Killiany parcellation Pearson correlation Probab. tractography Graph theory	No difference in FC or brain network topology	Moderate (6)
[43]	36 CSVD 31 HC	Fazekas ≥2	*MMSE* HC 28.4 ± 1.8 CSVD 26.4 ± 3.7	Siemens Verio, 3 T, 12-channel head coil TR 2000 ms, TE 25 ms 64 × 64 × [z] 3.75 × 3.75 × 4 mm^3 [volumes], [eyes]	DPARSF, SPM 8 Confound regression - 6 head motions params - GSR: global, WM, CSF Motion scrubbing - Head movement > 2 mm/2°	AAL 90 Pearson correlation Graph theory NBS	↓ Global FC ↑ Characteristic path length ↓ Global efficiency	High (0)

Table 1 Summary of included articles analysing resting-state functional connectivity in patients with manifest cerebral small vessel disease (CSVD). We report imaging and clinical characteristics of patients included in each study, key steps in the acquisition and pre-processing of BOLD data, analysis of functional connectivity, and FC patterns found to be associated with CSVD. Descriptive statistics as extracted from articles are reported as mean ± standard deviation. Missing information is indicted by empty brackets ([]). Arrows indicate increased (↑) or reduced (↓) values, as well as positive (↗) and negative (↘) associations *(Continued)*

Reference	Participants	Characteristics of patients with CSVD		MRI acquisition params	BOLD pre-processing	FC analysis	FC patterns associated with CSVD	Risk of bias (AXIS)
		Neuroimaging	Cognition					
Healthy controls and patients with CSVD with mandatory cognitive impairment								
[44]	26 svMCI 28 HC	Wahlund ≥ 2 ± lacunes	Subjective complaints MMSE 25.7 ± 2.7	Siemens, 3 T TR 2000 ms, TE 40 ms 64 × 64 × 28 4 × 4 × 5 mm^3 239 volumes eyes closed	SPM 5 Confound regression - Linear trend - 6 motion profiles - GSR: WM, CSF Motion scrubbing - Head movement > 3 mm/3°	ALFF, SCA, FC density Pearson correlation (only positive)	↓ ALFF in bilateral medial PFC ↑ ALFF in right PCC, precuneus, right hippocampus, right thalamus ↓ FC in DMN (PCC/precuneus, medial PFC, sup. frontal gyrus, inf. parietal lobule and hippocampus) and inferior/middle frontal gyrus	High (2)
[45]	21 svMCI 26 HC	Wahlund ≥ 2 ± lacunes	Subjective complaints MMSE 25.5 ± 2.7	Siemens, 3 T TR 2000 ms, TE 40 ms 64 × 64 × 28 4 × 4 × 5 mm^3 239 volumes eyes closed	SPM 5 and 8, REST, DARTEL Confound regression - Linear trend - 6 motion profiles - GSR: WM, CSF Motion scrubbing - Head movement > 3 mm/3° - Volume censoring (FD > 0.3 mm, < 3 min)	H-1024 parcellation Pearson correlation Graph theory	↑ Characteristic path length, ↑ modularity ↑ Within-module degree in the medial PFC, left insula, and cuneus ↓ Within-module degree in the middle cingulate gyrus ↑ Participation coefficient in the left inferior/superior parietal cortex	High (1)
[46]	37 PiB+ AD 37 PiB− SVaD 13 mixed dementia 65 HC	Fazekas (severe)	*MMSE* PiB+ AD, 18.1 ± 4.2 PiB− SVaD, 21.5 ± 4.3 MD, 17.9 ± 4.9 HC, 28.9 ± 1.2	Philips Achieva, 3 T, 8-channel head coil TR 3000 ms, TE 35 ms [matrix], 1.7 × 1.7 × 4 mm^3 100 volumes, eyes open	AFNI Despiking [Confound regression] Motion scrubbing - Max FD > 0.3 mm - Head movement > 2 mm/2°	ICA to define DMN and FPCN W-score maps	↓ FC in DMN in the left superior frontal gyrus ↓ FC in FPCN in the left insula	Moderate (5)
[47]	32 CSVD-CI 23 HC	Fazekas 2–3 ± lacunes	MMSE 23.8 ± 2.7	GE Signa, 3 T TR 2000 ms, TE 30 ms 64 × 64 × [] 3.75 × 3.75 × 4.6 mm^3 240 volumes eyes closed	SPM 8, DPARSF, CONN Confound regression - compCor - GSR: global signal [Motion scrubbing]	Medial PFC and thalamus from ext. template SCA Pearson correlation	↓ FC between the left thalamus and right sup. temporal gyrus, left sup. frontal gyrus, left and putamen ↓ FC between the right thalamus and left inferior temporal gyrus ↑ FC between the bilateral thalamus and right inferior/middle frontal gyri ↓ FC between the med. PFC and bilateral SMA, thalamus, left sup. frontal gyrus, ACC, sup. parietal lobe, and hippocampus	High (2)

Table 1 Summary of included articles analysing resting-state functional connectivity in patients with manifest cerebral small vessel disease (CSVD). We report imaging and clinical characteristics of patients included in each study, key steps in the acquisition and pre-processing of BOLD data, analysis of functional connectivity, and FC patterns found to be associated with CSVD. Descriptive statistics as extracted from articles are reported as mean ± standard deviation. Missing information is indicted by empty brackets ([]). Arrows indicate increased (↑) or reduced (↓) values, as well as positive (↗) and negative (↘) associations *(Continued)*

Reference	Participants	Characteristics of patients with CSVD		MRI acquisition params	BOLD pre-processing	FC analysis	FC patterns associated with CSVD	Risk of bias (AXIS)
		Neuroimaging	Cognition					
[48]	14 CSVD-CN 27 CSVD-MCI 12 SVaD 30 HC	Fazekas (cut-off not specified)	*MMSE* CSVD-CN 29.1 ± 1.0 CSVD-MCI 27.2 ± 2.4 SVaD 23.3 ± 3.4	Siemens, 3 T TR 2000 ms, TE 30 ms 64 × 64 × 32, 4 × 4 × 3.7 mm^3 [volumes], eyes closed	SPM 8 [Confound regression] Motion scrubbing - Head movement > 2 mm/2°	ICA to define DMN, SN, FPCN SCA from the right fronto-insular cortex	↓ FC between SN-DMN ↑ FC between SN-FPCN and within SN	High (3)
[49]	36 CSVD 50 AD 55 HC	*WMH volume* svMCI 22.6 ± 6.1 ml SVaD 44.8 ± 10.1 ml *Lacunes* svMCI 6.5 ± 7.5 SVaD 7.4 ± 7.2 *Microbleeds* svMCI 13.4 ± 18.7 SVaD 26.0 ± 49.2	*MMSE* svMCI 25.4 ± 3.7 SVaD 17.4 ± 4.2	Siemens, 3 T TR 3000 ms, TE 35 ms [matrix] 3.4 × 3.4 × 3.4 mm^3 200 volumes [eyes]	SPM 12 No smoothing Confound regression - Motion parameters - Linear trend - GSR: WM, CSF Motion scrubbing - Volume censoring (FD > 1 mm, > 30%)	Schaefer 400 atlas Pearson correlation AV1451 tau-PET	FC ↗ tau covariance, no associations with WMH	Moderate (7)
[50]	25 CSVD-CN 24 CSVD-MCI 36 HC	Fazekas ≥2 ± lacunes WMH CN 3.0 (0.76, 4.0) ml MCI 4.8 (0.76, 5.6) ml	*MMSE* CN 28.4 ± 1.3 MCI 27.8 ± 2.1 *MoCA* CN 26.1 ± 0.5 MCI 21.4 ± 0.5	Philips, 3 T TR 2000 ms, TE 30 ms 64 × 64 × 35 3.75 × 3.75 × 4 mm^3 230 volumes eyes closed	GRETNA v2.0, SPM 8 Confound regression - Linear trend, 24p - GSR: GS, WM, CSF Motion scrubbing - Head movement > 2 mm/2°	H-1024 parcellation Pearson correlation Graph theory to define DMN, FPCN, SMN, and VN	No robust associations	Moderate (4)
[51]	21 CSVD-CN 20 CSVD-MCI 25 HC	WMH volume CN 3.2 ± 3.0 ml CI 3.4 ± 4.1 ml ± lacunes	*MMSE* CN 28.5 ± 1.3 MCI 28.1 ± 1.3 *MoCA* CN 25.6 ± 1.9 MCI 22.2 ± 2.9	Philips, 3 T, 32-channel head coil TR 2000 ms, TE 30 ms 64 × 64 × 35 3.75 × 3.75 × 4 mm^3 230 volumes Eyes closed	DPABI Confound regression - 24p - GSR: GS, WM, CSF Motion scrubbing - Head movement > 3 mm/3°	PCC, dlPFC, IPS from external template SCA to define DMN, FPCN, and DAN	↓ FC in DMN in the right thalamus, hippocampus, and precuneus ↑ FC in FPCN in the right inf. parietal lobule ↓ FC between PCC-FPCN in the left precentral gyrus and bilateral middle cingulate gyri ↓ FC between PCC-DAN in the bilateral paracentral lobule and precuneus ↓ FC between PCC-DAN in the bilateral PCC and right precuneus	Moderate (6)

Table 1 Summary of included articles analysing resting-state functional connectivity in patients with manifest cerebral small vessel disease (CSVD). We report imaging and clinical characteristics of patients included in each study, key steps in the acquisition and pre-processing of BOLD data, analysis of functional connectivity, and FC patterns found to be associated with CSVD. Descriptive statistics as extracted from articles are reported as mean ± standard deviation. Missing information is indicted by empty brackets ([]). Arrows indicate increased (↑) or reduced (↓) values, as well as positive (↗) and negative (↘) associations *(Continued)*

Reference	Participants	Characteristics of patients with CSVD		MRI acquisition params	BOLD pre-processing	FC analysis	FC patterns associated with CSVD	Risk of bias (AXIS)
		Neuroimaging	Cognition					
[52]	14 CSVD + THA LAC 27 CSVD − THA LAC 34 HC	Fazekas 3–6 *Lacunes* LAC+, 5.6 ± 3.9 LAC−, 2.0 ± 1.4	*MMSE* LAC+, 26.3 ± 2.8 LAC−, 28.1 ± 2.0	GE Discovery, 3 T TR 2000 ms, TE 35 ms 64 × 64 × 36 3.4 × 3.4 × 4 mm^3 210 volumes eyes closed	SPM 8 Confound regression - 6 motion parameters - GSR: WM, CSF Motion scrubbing - Head movement > 2 mm/2°	AAL 90 Pearson correlation Graph theory, Network-based statistics	↓ FC in para-/limbic and subcortical regions	Moderate (5)
[53]	32 CSVD-MCI 20 SVaD 35 HC	Fazekas ≥1	*MMSE* MCI 25.5 ± 1.8 SVaD 22.0 ± 2.0 *MoCA* MCI 22.2 ± 1. SVaD 17.4 ± 2.9	Siemens Verio, 3 T TR 2000 ms, TE 30 ms 64 × 64 × 32 4 × 4 × 4.2 mm^3 240 volumes eyes closed	DPARSF Confound regression - Linear/quadratic, 24p - GSR: WM, CSF Motion scrubbing - Head movement > 3 mm/3°	AAL atlas Pearson correlation Graph theory	↓ Global FC ↓ Small-worldness	Moderate (4)
[54]	20 LA-VAD 32 LA-VCIND 35 HC	Not reported	*MMSE* HC 29.4 ± 1.1 LA-VCIND 27.9 ± 1.8 LA-VaD 23.0 ± 3.8 *MoCA* HC 26.0 ± 2.5 LA-VCIND 25.8 ± 2.0 LA-VaD 23.2 ± 2.8	Siemens, 3 T TR 2000 ms, TE 30 ms 64 × 64 × 20 4 × 4 × 6 mm 250 volumes eyes closed	DPARSF Confound regression - 24p - GSR: WM, CSF Motion scrubbing - Head movement > 3 mm/3°	Group ICA (GIFT) Granger causality	Unclear; text and figures not consistent	High (2)

Functional MRI acquisition and pre-processing

Magnetic resonance imaging was performed on scanners from a variety of vendors (Siemens, Philips, GE), usually at 3 Tesla. The use of specialised receiver head coils, multi-band, or multi-echo techniques was rarely reported. Repetition time (TR) and echo time (TE) were predominantly set at 2000 ms and 30 ms, respectively, with exceptional values ranging from 700 to 4500 ms and 13 to 84 ms, respectively. Reconstructed voxel sizes in the BOLD scans varied in the range [1.7–4] × [1.7–4] × [2–6] mm^3, arranged in a three-dimensional matrix of dimensions varying in the range [64–128] × [64–128] × [20–64]. The number of acquired BOLD volumes varied between 100 and 700 (median 230, IQR 180–240). Participants were asked to keep their eyes open in 12 and closed in 20 of the reviewed studies; 12 articles provided no information. Description of functional MRI acquisition parameters was incomplete in 26 of the 44 analysed studies (61%); methods were judged as not-repeatable in these cases (AXIS item 11). Hemodynamic lags were not considered.

Pre-processing steps common to most studies included slice-time correction; realignment to a reference volume to correct for head motion; normalisation to a template space (usually MNI EPI [64]) including resampling; temporal band-pass filtering (lower end 0.005–0.01 Hz; upper end 0.08–0.15 Hz); and smoothing with a Gaussian filter of full-width at half maximum (FWHM) between 4 and 8 mm.

Confound regression and motion scrubbing were performed and reported less uniformly, as detailed in Tables 1 and 2. Specifically, global signal regression (GSR), that is orthogonalisation of voxel-wise timeseries with respect to the average BOLD signals from the white and grey matter, or the whole brain, was undertaken in 27/44 studies. Twenty-five studies employed subject-wise censoring in which participants were excluded from further analysis if the maximum or average head translation or rotation during the scan exceeded a certain threshold ranging from 0.5 to 3 mm translation and 0.5 to 3° rotation. Ten studies performed volume censoring according to a framewise displacement (FD) or framewise translation/rotation cut-off, excluding participants with too few remaining uncontaminated volumes [31, 49]. Two studies used spike regression [39, 65].

Connectivity analysis

The majority of studies investigated large-scale functional connectivity between remote brain areas, choosing full or partial temporal correlations between the BOLD time courses as a measure of connectivity. Regions of interest were defined a priori using external brain parcellations in 16 cases. Twenty-seven studies used a data-driven approach such as independent component analysis (ICA), seed-based connectivity analysis (SCA), or local BOLD activity (amplitudes of low-frequency fluctuations [ALFF]) to define regions of interest for further analysis. Many authors interpreted alterations in functional connectivity in the context of a small number of large-scale resting-state brain networks (RSNs), in particular the default mode (DMN) and frontoparietal control (FPCN) networks, but also the dorsal attention (DAN) and salience (SN) networks [22]. Eight reports used graph theoretical approaches, including global network parameters such as efficiency and clustering coefficient [31, 42, 43, 52, 53]; analysis of modularity structures [45, 50]; and self-referential quantification of region-specific centrality [35] to summarise the patterns of connectivity between multiple regions and to thus reflect global organisational principles of the brain networks.

Three studies investigated short-range connectivity [38, 66, 67], using regional homogeneity (ReHo) to quantify the similarity between BOLD signals as a marker of local connectivity [68].

The main findings of individual studies with respect to alterations in resting-state functional connectivity in the context of cerebral small vessel disease are summarised in Table 1. Patterns of altered connectivity were expressed either in comparison to healthy controls or along a gradient of increasing severity of CSVD imaging markers. For clinically or radiologically manifest CSVD, reduced functional connectivity dominated the findings on a global scale [43, 45, 53]. Within resting-state networks, lower functional coupling was repeatedly reported between components of the default mode network [28, 35, 44, 46, 47, 51], which is further supported by the co-occurrence of reduced DMN connectivity and increased WMH burden in patients with non-vascular cognitive impairment [62]. Within the FPCN, reduced connectivity was found in the left insula [46], whereas the right inferior parietal cortex appeared to be more strongly coupled to the rest of this network [51]. The average coupling between the DMN and FPCN was found to be reduced in patients with CSVD [51], even though a small number of inter-network edges showed increased connectivity [39]. The connectivity of the DAN was altered in relation to other networks with increased coupling to the FPCN and reduced coupling to the posterior DMN [39, 51]. The same pattern of altered inter-network connectivity was reported for the salience network [48]; intrinsic connectivity in the SN was increased in patients with CSVD and in association with the extent of white matter disease [83]. In healthy individuals or patients without symptomatic CSVD (Table 2), most studies did not report significant associations between FC and WMH burden [66, 79, 82, 86, 92]. Two studies found an association between higher FC,

Table 2 Summary of included articles analysing resting-state functional connectivity in healthy participants or patients without vascular cognitive impairment. We report imaging and clinical characteristics of patients included in each study, key steps in the acquisition and pre-processing of BOLD data, analysis of functional connectivity, and FC patterns found to be associated with CSVD. Descriptive statistics as extracted from articles are reported as range (min–max) and/or mean ± standard deviation. Missing information is indicted by empty brackets ([]). Reported are clinical characteristics of patients included in each study, details about the quantification of white matter hyperintensities, key steps in the analysis of functional connectivity, and FC patterns found to be associated with CSVD. Arrows indicate increased (↑) or reduced (↓) values, as well as positive (↗) and negative (↘) associations

Reference	Participants	Quantification of WMH load	rs-fMRI acquisition parameters	BOLD pre-processing	FC analysis	FC patterns associated with CSVD
[69]	12 depression 12 HC	Fuzzy connected algorithm [70]	GE Signa, 1.5 T TR 2000 ms, TE 35 ms 64 × 64 × 26, 3.75 × 3.75 × 3.8 mm^3 [volumes], eyes open	AFNI [Confound regression] [Motion scrubbing]	PCC from ext. template SCA to define DMN Pearson correlation	FC in DMN ↘ WMH in medial PFC
[71]	47 depression 46 HC	Not reported	Siemens Trio, 3 T TR 2000 ms, TE 32 ms 128 × 128 × 28, 2 × 2 × 2 mm^3 150 volumes, eyes open	SPM 5 [Confound regression] [Motion scrubbing]	PCC from ext. template SCA to define DMN Pearson correlation	↓ Association between DMN-FC and treatment response after controlling for WMH load
[62]	13 early AD 17 MCI 14 HC	Semi-automatic using FireVoxel [72]	[Scanner] TR 3000 ms, TE 30 ms [matrix], 3.3 × 3.3 × 3.3 mm^3 140 volumes, [eyes]	[Confound regression] [Motion scrubbing]	Medial PFC and PCC from ext. atlas SCA to define DMN fALFF	Both increased WMH load and reduced DMN-FC in AD and MCI compared to HC
[73]	100 MCI	In-house automatic pipeline [74]	Philips Achieva, 3 T TR 2000 ms, TE 30 ms [matrix], [resolution] 200 volumes eyes closed	DPARSF Confound regression - 6 motion parameters - GSR: CSF, WM, global [Motion scrubbing]	SCA from the hippocampus and PCC	No association between WMH load and FC
[63]	43 MCI 24 HC	Histogram segmentation [75]	*Training* Philips, 3 T, 8-channel head coil TR 3000 ms, [TE] [matrix], 3.3 × 3.3 × 3.3 mm^3 140 volumes eyes open *Testing* Siemens Verio, 3 T, 32-channel head coil TR 2580 ms, [TE] [matrix], 3.5 × 3.5 × 3.5 mm^3	DARTEL Confound regression - 6 motion parameters - GSR: CSF, WM [Motion scrubbing]	Whole-brain SCA Pearson correlation	No association between WMH and FC

Table 2 Summary of included articles analysing resting-state functional connectivity in healthy participants or patients without vascular cognitive impairment. We report imaging and clinical characteristics of patients included in each study, key steps in the acquisition and pre-processing of BOLD data, analysis of functional connectivity, and FC patterns found to be associated with CSVD. Descriptive statistics as extracted from articles are reported as range (min–max) and/or mean ± standard deviation. Missing information is indicted by empty brackets ([]). Reported are clinical characteristics of patients included in each study, details about the quantification of white matter hyperintensities, key steps in the analysis of functional connectivity, and FC patterns found to be associated with CSVD. Arrows indicate increased (↑) or reduced (↓) values, as well as positive (↗) and negative (↘) associations *(Continued)*

Reference	Participants	Quantification of WMH load	rs-fMRI acquisition parameters	BOLD pre-processing	FC analysis	FC patterns associated with CSVD
			180 volumes eyes closed			
[65]	90 MCI 140 HC	SPM Lesion Segmentation Tool [76]	Siemens Trio, 3 T TR 2300 ms, TE 30 ms [] × [] × 34, 3 × 3 × 4 mm^3 [volumes] eyes closed	CONN, SPM 12 Confound regression - compCor - GSR: CSF, WM Motion scrubbing - Artefact Detection Tools - Spike regression (FD > 0.5 mm)	Preselected cognitive control networks (FPCN, SN) + DMN Pearson correlation Structural equation modelling	Weaker negative association between executive function/memory and WMH load in patients with high global FC
[77]	18 svMCI + depression 17 svMCI − depression 23 HC	Fazekas scale	GE MR750, 3 T TR 2000 ms, TE 35 ms 64 × 64 × 26, 4 × 4 × 4 mm^3 240 volumes [eyes]	DPABI Confound regression - Linear and quadratic trends, 24p - GSR: CSF, WM, global Motion scrubbing - Head motion > 3 mm/3° - Volume censoring (FD > 0.5 mm)	VBM SCA from altered regions Pearson correlation	↑ FC between right middle cingulate cortex and right parahippocampal gyrus
[78]	38 P w Sjogren syndrome 40 HC	Wahlund score	Siemens Trio, 3 T TR 2500 ms, TE 30 ms 96 × 96 × 40, 2.3 × 2.3 × 3 mm^3 204 volumes eyes closed	Matlab, DPABI Confound regression - Linear trend - GSR: CSF, WM, global Motion scrubbing - Mean FD > 0.2 mm	SCA from hippocampi Pearson correlation	FC ↗ WMH left hippocampus and right inf. orbital and inf. temporal gyrus
Healthy participants						
[79]	76 healthy participants	Mixture model [80]	GE Signa, 1.5 T TR 2000 ms, TE 40 ms [] × [] × 24, [] × [] × 5 mm^3 240 volumes [eyes]	REST Confound regression - Head motion parameters - GSR: CSF,WM, global Motion scrubbing - > 58 outlier volumes (> 1.5 mm/1.5°)	PCC from ext. template SCA to define DMN Pearson correlation	No association between WMH load and FC Episodic memory ↗ medial PFC–left inferior parietal cortex FC in patients with low grey matter volume

Table 2 Summary of included articles analysing resting-state functional connectivity in healthy participants or patients without vascular cognitive impairment. We report imaging and clinical characteristics of patients included in each study, key steps in the acquisition and pre-processing of BOLD data, analysis of functional connectivity, and FC patterns found to be associated with CSVD. Descriptive statistics as extracted from articles are reported as range (min–max) and/or mean ± standard deviation. Missing information is indicted by empty brackets ([]). Reported are clinical characteristics of patients included in each study, details about the quantification of white matter hyperintensities, key steps in the analysis of functional connectivity, and FC patterns found to be associated with CSVD. Arrows indicate increased (↑) or reduced (↓) values, as well as positive (↗) and negative (↘) associations *(Continued)*

Reference	Participants	Quantification of WMH load	rs-fMRI acquisition parameters	BOLD pre-processing	FC analysis	FC patterns associated with CSVD
[81]	127 healthy (Harvard Ageing Brain Study)	Fazekas 0–1 vs. 2–3	Siemens Trio, 3 T, 12-channel head coil TR 3000 ms, TE 30 ms 72 × 72 × [], 3 × 3 × 3 mm^3 124 volumes eyes open	SPM 8 Confound regression - Realignment params + derivatives - GSR: WM, CSF, global Motion scrubbing - Mean FD > 0.15 mm - ≥ 20 outlier volumes (> 0.75 mm/1.5°)	PCC and medial PFC from external DMN template Partial Pearson correlation Probabilistic tractography	↓ Association between PCC-medial PFC FC and mean diffusivity in cingulum bundle
[82]	186 clinically healthy (Harvard Ageing Brain Study)	Automated fuzzy-connected algorithm [70]	Simens Trio, 3 T, 12-channel head coil TR 3000 ms, TE 30 ms 72 × 72 × 47, 3 × 3 × 3 mm^3 2 × 124 volumes eyes open	SPM 8 Confound regression - 12 motion parameters Motion scrubbing - 'mean movement' > 0.2 mm - > 20 outlier volumes (> 0.75 mm/1.5°)	Template-based rotation to define DMN and FPCN Pearson correlation	No association between WMH load and FC
[83]	51 healthy participants	SPM Lesion Segmentation Tool [76]	Phillips Ingenia, 3 T TR 2600 ms, TE 35 ms 128 × 128 × 35, 1.8 × 1.8 × 4 mm^3 125 volumes, [eyes]	REST, GIFT [Confound regression] [Motion scrubbing]	ICA to define DMN, SN, FPN, VN	FC in DMN ↗ WMH in the mediotemporal complex FC in SN ↗ WMH in the right S1 and sup./inf. parietal cortex
[84]	1584 healthy participants (Rotterdam Study)	Tract-specific WMH load [85]	GE Signa, 1.5 T TR 2900 ms, TE 60 ms 64 × 64 × 31, 3.3 × 3.3 × 3.3 mm^3 160 volumes, eyes open	FSL Confound regression - Low-frequency drifts - Motion components - ICA Motion scrubbing - Max FD > 0.5 mm, abs. motion > 3 mm	Desikan–Killiany parcellation Pearson correlation Probabilistic tractography	FC ↘ WMH both tract-specific and global
[86]	145 healthy participants	SPM Lesion Segmentation Tool [76]	GE MR750, 3 T TR 1500 ms, TE 27 ms 64 × 64 × 29, 3.75 × 3.75 × 4 mm^3 162 volumes eyes open	FSL Confound regression - GSR: CSF, WM Motion scrubbing - FD > 0.5 mm	ICA to define DMN, SMN, FPCN Pearson correlation	No association between WMH load and FC

Table 2 Summary of included articles analysing resting-state functional connectivity in healthy participants or patients without vascular cognitive impairment. We report imaging and clinical characteristics of patients included in each study, key steps in the acquisition and pre-processing of BOLD data, analysis of functional connectivity, and FC patterns found to be associated with CSVD. Descriptive statistics as extracted from articles are reported as range (min–max) and/or mean ± standard deviation. Missing information is indicted by empty brackets ([]). Reported are clinical characteristics of patients included in each study, details about the quantification of white matter hyperintensities, key steps in the analysis of functional connectivity, and FC patterns found to be associated with CSVD. Arrows indicate increased (↑) or reduced (↓) values, as well as positive (↗) and negative (↘) associations *(Continued)*

Reference	Participants	Quantification of WMH load	rs-fMRI acquisition parameters	BOLD pre-processing	FC analysis	FC patterns associated with CSVD
[87]	69 healthy participants	Coarse-to-fine in-house developed mathematical morphology method [88]	Phillips Achieva, 3 T TR 2050 ms, TE 25 ms 64 × 64 × 47, 3.2 × 3.2 × 3.2 mm^3 210 volumes eyes open	CONN Confound regression - 6 motion parameters - GSR: WM, CSF [Motion scrubbing]	AAL atlas, DTI atlas Whole-brain SCA Intrinsic connectivity contrast	FC in the left cuneus and right sup. occipital cortex ↗ WMH in the right ant. corona radiata FC in the left superior occipital cortex ↗ WMH in the right superior corona radiata
[67]	400 healthy participants (Baltimore Longitudinal Study of Aging)	Multimodal supervised classification algorithm [89]	Philips Achieva, 3 T TR 2000 ms, TE 30 ms [matrix], 3 × 3 × 3 mm^3 180 volumes [eyes]	Confound regression - 24 motion parameters - GSR: global, WM, CSF Motion scrubbing - 'summary motion value' > 0.2 mm - Volume censoring (FD > 0.5 mm, < 5 min)	Geodesic graph-based segmentation Regional homogeneity Sparse connectivity patterns	Pattern of advanced brain ageing characterised by both increased WMH burden and reduced FC compared to resilient agers
[66]	11 healthy participants	Automated regression algorithm [90] using a Hidden Markov Random Field with Expectation Maximization [91]	Siemens Trio, 3 T TR 2000 ms, TE 27 ms 92 × 92 × 43, 2.5 × 2.5 × 3 mm^3 240 volumes eyes closed	SPM12 Confound regression - Linear/quadratic, 18 motion parameters - GSR: CSF, WM Motion scrubbing -> 3 mm max, > 3° max -> 24 spikes (FD > 1 mm)	Brainnetome atlas (228) Graph theory to define DMN Pearson correlation	No association between WMH load and DMN FC trajectories
[92]	562 healthy participants	SPM Lesion Segmentation Tool [76]	Phillips Achieva, 3 T TR 2000 ms, TE 20 ms 112 × 112 × 37, 2 × 2 × 3 mm^3 [volumes], [eyes]	[Confound regression] [Motion scrubbing] Mean FD as covariate in analysis	Desikan–Killiany parcellation FC measure not specified	No association between WMH load and FC
[93]	182 participants (UK Biobank)	BIANCA with manual correction [94]	Siemens Skyra, 3 T TR 735 ms, TE 39 ms 88 × 88 × 64, 2.4 × 2.4 × 2.4 mm^3 490 volumes, [eyes]	FMRIB (FSL), ICA-FIX Confound regression - ICA [Motion scrubbing]	ICA, AAL atlas Pearson correlation Degree centrality	FC ↗ WMH in right orbitofrontal cortex

Table 2 Summary of included articles analysing resting-state functional connectivity in healthy participants or patients without vascular cognitive impairment. We report imaging and clinical characteristics of patients included in each study, key steps in the acquisition and pre-processing of BOLD data, analysis of functional connectivity, and FC patterns found to be associated with CSVD. Descriptive statistics as extracted from articles are reported as range (min–max) and/or mean ± standard deviation. Missing information is indicted by empty brackets ([]). Reported are clinical characteristics of patients included in each study, details about the quantification of white matter hyperintensities, key steps in the analysis of functional connectivity, and FC patterns found to be associated with CSVD. Arrows indicate increased (↑) or reduced (↓) values, as well as positive (↗) and negative (↘) associations *(Continued)*

Reference	Participants	Quantification of WMH load	rs-fMRI acquisition parameters	BOLD pre-processing	FC analysis	FC patterns associated with CSVD
[95]	250 healthy (Harvard Aging Brain Study)	Automated fuzzy-connected algorithm [70]	Siemens Trio, 3 T TR 3000 ms, TE 30 ms [matrix], $3 \times 3 \times 3$ mm^3 2×124 volumes, eyes open	SPM 8 Template-based rotation method [Confound regression] [Motion scrubbing]	Template-based rotation to define DMN, SMN, DMN, and FPCN Pearson correlation	Association between WMH load and FC not investigated FC in DMN ↘ risk of progression to MCI

especially in occipital and frontal areas, and WMH burden [87, 93], whereas in patients with late-life depression the pattern was more similar to the one seen in patients with CSVD [69, 71].

Assessment of cognitive impairment

In the majority of studies, cognitive testing on participants was performed and investigated in association with the extent of white matter disease and functional connectivity. In addition to scales covering the global level of cognitive functions and deficits (MMSE, MoCA, and CDR), impairments in specific cognitive domains were quantified by sub-scores of these global scales or specialised neuropsychological test batteries, operationalising, in particular, executive function, processing speed, and memory. Table 3 summarises key findings of individual studies in these different domains. Most studies were able to confirm known associations between CSVD and cognitive impairment on the one hand, and, albeit less robustly, between functional connectivity and cognitive impairment on the other hand. Only few articles, however, addressed the question of how structural white matter damage and functional connectivity interact to affect cognition. In one analysis of 127 clinically healthy participants of the Harvard Ageing Brain Study, it was shown that the extent of WMH-associated decoupling of structural and functional connectivity in the default mode network correlated with both executive function and memory [81]. Moreover, in a combined analysis of 140 healthy participants and 90 patients with both vascular and non-vascular cognitive impairment, the authors demonstrated that the association of higher WMH load with poorer executive function and memory scores was moderated by global functional connectivity in the FPCN and by local FC in the salience network [65].

Risk of bias and confounding

Risk of bias was assessed using the AXIS tool for all 24 studies recruiting patients with clinical CSVD. We did not formally assess the risk of bias in studies reporting results on FC and WMH in the context of conditions different from vascular cognitive impairment or in longitudinal studies. According to the AXIS tool, all studies thus assessed had an at least moderate risk of bias (10/24 moderate, 14/24 high). The distribution of assessments of individual quality items of the tool is depicted in Fig. 2 a. The overall aim or objective of the study (Item 1) was deemed unclear in 14 studies, often because of a lack of distinctions between exploratory and confirmatory, and causal and correlational approaches. In 9 cases, where aims included the inference of causal effects or were too broad to be assessed, a cross-sectional design was judged as inappropriate (Item 2). The sample size was not satisfactorily justified in any study. The reference population (Item 4) was mostly adequately specified as patients with CSVD, qualified by lists of inclusion and exclusion criteria. In five studies, the definition of the target population was unclear or contradictory. All but one article reported results from single-centre studies that recruited a convenience sample from a clinical setting; in these cases, the sample frame (Item 5) was judged as inappropriate and the selection process (Item 6) as non-representative. The exceptions were an analysis of a formal clinical register [84, 99]. No article addressed non-responders. Risk factors and outcomes (Item 7) were mostly valid (see above); exceptions included one unvalidated method to quantify WMH load [87] and the use of global graph parameters such as efficiency and path length. Reliability of outcome measures (Item 9) was generally judged to be low given the poor reproducibility of FC estimates in the context of CSVD, except for studies who explicitly estimated reliability as part of the study design [31, 42]. There were two main problems with the statistical methods used: firstly, confusion of exploratory and confirmatory approaches (cf. Item 1) led to a lack of clearly specified hypotheses and thus to inappropriately controlled type-I error rates in the case of multiple testing; secondly, many papers employed multi-scale approaches, in which results from the first, often global, analyses informed hypotheses tested in later, often more local, analyses. It is known that this method can inflate the rate of false-positive findings if the entire analysis pipeline is not accounted for properly, for example in a bootstrap loop [100]. The quality of the description of methods varied considerably. No article provided links to the program code used in the analysis, but this was not required to satisfy Item 12. Specific shortcoming included incomplete reporting of MRI acquisition parameters, lack of description of structural image pre-processing, and lack of detail in the description of statistical methods, such as choice of covariates, method to determine of p-values, or correction for multiple testing. The distribution of aggregate AXIS scores is shown in Fig. 2b. Given that none of the included studies had a low risk of bias or was preregistered, the overall risk of bias in the reviewed literature seems high.

Cardiovascular risk factors such as age, hypertension, diabetes mellitus, and dyslipidaemia are known to be associated with imaging markers of CSVD [101]. They also affect cerebrovascular reactivity and the circulatory autoregulation in response to neuronal activity (*neurovascular coupling*) [29] and are thus potential confounders of the relation between WMH and BOLD-derived functional connectivity. Similarly, vasoactive medications, in particular antihypertensives, which are commonly prescribed to patients with CSVD as well as substances like nicotine or caffeine may alter neurovascular coupling

Table 3 Summary of reported associations between altered FC patterns in CSVD and cognitive ability. Arrows indicate positive (↗) and negative (↘) associations

Cognitive domain	Reference	Instruments	
General	[47]	–	MMSE ↗ FC between the left thalamus–left orbitofrontal lobe
	[38]	–	MMSE ↗ ReHo in the right angular gyrus and precuneus MoCA ↗ ReHo in the bilateral angular gyrus, the right precuneus, medial/dorsolateral PFC, and supplementary motor area
	[39]	–	MMSE ↗ FC right precentral–right calcarine fissure, left posterior inferior parietal lobe–left Heschl, right posterior inferior parietal lobe–right dorsolateral PFC MMSE ↘ FC right posterior inferior parietal lobe–left Heschl, left intraparietal sulcus–right superior temporal gyrus MoCA ↗ FC right posterior inferior parietal lobe–right anterior PFC, right posterior inferior parietal lobe–right dorsolateral PFC MoCA ↘ FC right posterior inferior parietal lobe–left Heschl, left intraparietal sulcus–right superior temporal gyrus
	[53]	–	MoCA ↗ small-worldness
	[33]	–	MMSE ↘ parieto-occipital FC in patients with confluent WMH
Executive function	[35]	CERAD battery [96]	Phonemic fluency ↗ FC in bilateral sup. parietal lobe, SMA, premotor cortex, MCC, and posterior superior frontal sulcus $RT_{Stroop,\ neutral}$ ↘ FC in the bilateral premotor cortex, superior frontal sulcus, left inferior frontal sulcus, left SMA, left middle temporal sulcus, and right MCC $RT_{Stroop,\ neutral}$ ↗ FC in the inferior parietal lobe and cerebellar lobules Crus II, VIIb, and VIII $RT_{TMT\text{-}A}$ ↘ FC in the bilateral premotor cortex, left posterior middle frontal gyrus, left inferior frontal sulcus, right superior parietal lobe, and left SMA $RT_{Stroop,\ incongruent}$ ↘ FC in the left premotor cortex/posterior middle frontal gyrus $RT_{Stroop,\ incongruent}$ ↗ FC in the cerebellar regions VI, Crus I, and Crus II
	[81]	Letter/category fluency, letter-number sequencing of the WAIS-III, Digit Span Backward of the WAIS revised (WAIS-R), Self-Ordered Pointing task, mod. Flanker task, and TMT A/B Confirmatory factor analysis [97]	Executive function ↗ FC-SC decoupling in DMN
	[36]	Visuospatial/executive sub-score of MoCA	Executive function ↗ FC in the right cingulate motor area
	[83]	Stroop test	Time interference index ↗ FC in anterior DMN and SN
	[65]	TMT A/B, Stroop test Latent variables	Association (executive function ↘ WMH) attenuated in patients with high global FC in FPCN Associations (executive function ↘ WMH) and (memory ↘ WMH attenuated) in patients with high local FC in SN
	[51]	TMT-A/B, Stroop test	$RT_{TMT\text{-}A}$ ↘ FC in FPCN in the right inferior parietal lobule $RT_{TMT\text{-}A}$ ↘ FC between the dorsolateral PFC and DMN between bilateral PCC and right precuneus
	[43]	Semantic similarity test Stroop test	Mean FC ↗ similarity index Stroop C score ↗ path length, ↘ global efficiency
Memory	[45]	Auditory Verbal Learning Test [AVLT] [98]	Delayed recall ↘ participation coefficient left superior parietal lobule Recognition ↘ characteristic path length
	[65]	AVLT, structural equation modelling	Memory ↗ WML*global FC
	[52]	AVLT	FC ↘ long recall between right olfactory–right rectus; ↘ short recall between right olfactory–left pallidum FC ↗ $RT_{TMT\text{-}A}$ between right olfactory–left pallidum

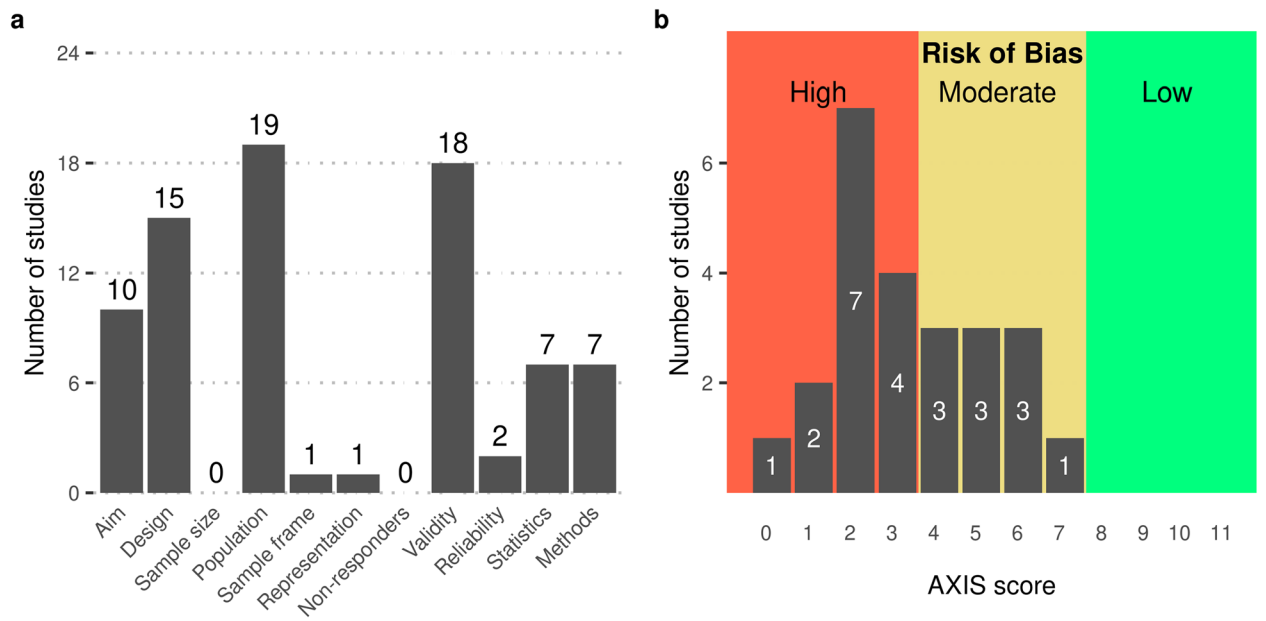

Fig. 2 Assessment of risk of bias of 24 reviewed articles using the Appraisal tool for Cross-Sectional Studies (AXIS). **a** Distribution of per-item scores, indicating, for each item, the number of articles satisfying its definition. A detailed description of AXIS items and shortcomings of individual articles is presented in Additional file 1: Tables S1 and S2. **b** Distribution of aggregate AXIS scores computed as the number of items satisfied by any given reviewed article. Trichotomisation of the theoretical range 0–11 leads to the risk of bias being judged as high (0–3), moderate (4–7), or low (8–11)

[102]. Despite this, reporting of and adjustment for co-morbidities and medication was poor in the reviewed studies. While information on the demographic variables age and sex was provided in all reviewed articles, only about half reported results of analyses adjusted for these factors. Nine articles gave details on cardiovascular risk factors, yet none attempted to control for their potential confounding effect. Effects of prescribed medication or caffeine intake were not considered.

Discussion

For this systematic review, we identified 44 articles published in the previous 10 years reporting on MRI-derived resting-state functional brain connectivity in patients with white matter hyperintensities of presumed vascular origin as a marker of cerebral small vessel disease. Based on patient characteristics and research objective, studies could be divided into three groups: (1) group comparisons of patients with clinically and/or radiologically manifest CSVD, often involving a control group of healthy participants or patients with CSVD at different levels of cognitive impairment; (2) cohort studies of clinically healthy individuals in which white matter hyperintensities are reported as one of several parameters, often with the aim of characterising structure–function relationships or patterns of brain ageing; (3) investigations of resting-state connectivity in clinical conditions not primarily related to vascular pathology, in which measures of white matter disease were reported as covariates.

The overall median sample size of included studies was 68. There was a stark contrast in sample size between studies of patients with symptomatic CSVD (median 58, IQR 46–84, $n = 24$) and studies of clinically healthy participants (median 145, IQR 73–293, $n = 12$). Samples in studies focusing on non-vascular clinical conditions were of intermediate size (median 73, IQR 55–95, $n = 8$). These differences might be due to increased complexities associated with recruiting patients in a clinical context or the fact that some of the larger studies used data from comprehensive population-based research efforts, such as the Rotterdam Study [84, 103], the Harvard Brain Ageing Study [81, 82, 104], or the UK Biobank [93, 105].

Operationalisation of CSVD is study-context dependent

In addition to sample size, groups of studies also differed in their approaches to quantifying the severity of white matter disease. Clinically focused studies tended to rely on validated rating scales, such as the Fazekas or Wahlund scale, which assign an ordinal score based on the extent and distribution of white matter hyperintensities on T2-weighted MR imaging. A minority of studies considered the presence of lacunar infarcts as an additional marker for CSVD. The population-based studies of healthy participants, on the other hand, employed the

cumulative volume of WMH as a continuous measure of disease burden. Numerical lesion load has the advantage of providing better resolution of inter-individual differences in groups of mildly affected participants; in addition, it can be determined reasonably reliably using automatic or semi-automatic image processing methods, although some degree of manual post-processing was usually done in the studies reviewed here [106]. Brain atrophy as a structural marker of both CSVD and neurodegenerative disease is known to be associated with changes in intrinsic brain connectivity [107]; it was included in many of the population-based studies using either the total intracranial volume to normalise observed WMH loads or region-specific grey matter volume, such as can be obtained from voxel-based morphometry (VBM) or cortical thickness measurements. Although methods have been developed to segment perivascular spaces (PVS) and cerebral microbleeds in an automated fashion [108–114], none of the reviewed articles utilised enlarged PVS, and only one used microbleeds [49] as a marker of CSVD.

The variety of qualitative and quantitative analysis methods reflects the clinical heterogeneity of study populations comprising patients with CSVD at different stages of the disease. An attempt at standardising the assessment and reporting of imaging markers of CSVD was made in the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) position paper [6]. However, despite being published in 2013, the definitions and recommendations outlined in the STRIVE were referenced in only six of the 33 reviewed papers published after 2013 [31, 50–52, 62, 108].

Functional connectivity methods reflect clinical heterogeneity

The analysis of recorded BOLD signals has not been standardised, with a broad variety of coupling measures and dimensionality reduction techniques being at the disposal of the researcher [20]. All reviewed studies used Pearson's correlation coefficient to quantify the synchrony between BOLD time series in different parts of the brain. No clear distinction between full and partial correlations was often made, thus making the interpretation of direct or indirect connectivities difficult [115]. Similarly, the handling and interpretation of negative correlations was rarely reported or discussed [116–118]. None of the included articles attempted to estimate directed [119–121] or time-varying functional connectivities [122–124], or to quantify patterns of synchronous activity involving more than two regions [125, 126]. Analytical approaches included whole-brain analyses (eigenvector centrality, connectivity density); the investigation of functional connectivities between region of interests, often components of well-defined intrinsic resting-state networks, which were either derived from the data themselves (independent component analysis) or specified a priori by an external brain parcellation; and combinations of the two (seed-based correlation analysis).

Brain parcellations for the region-of-interest-based analyses were mostly based on anatomically defined atlases, such as the automatic anatomical labelling (AAL) atlas [127], the Desikan–Killiany parcellation [128], or the H-1024 random parcellation [129], which do not take into account the functional architecture of the brain. Only three very recent articles [31, 49, 66] used the multimodal brain parcellations of Power [130] or Schaefer [131], or the Brainnetome atlas [132], which have been shown to better respect the functional organisation of the brain [22]. In addition to interpreting changes in functional connectivity directly, a few studies attempted to summarise patterns of FC by measures of global network organisation using graph theory. These approaches have been instrumental in the study of complex brain networks and include parameters to reflect the notions of integration, such as efficiency or characteristic path length; segregation, such as clustering coefficients; or community structure, quantified by modularity scores and participation coefficients [9, 133, 134]. With the exception of community detection, however, these network parameters have been defined only for structural brain networks and lack validation for networks derived from functional connectivity [135].

Structure–function coupling shapes the impact of CSVD

The large-scale temporospatial organisation of neuronal activity in the brain is known to be supported and constrained by the anatomy of axonal projections that form structural connections between both adjacent and remote brain areas [136, 137]. This coupling between structure and function is particularly pronounced in the default mode network [138], possibly reflecting the long periods of time that the brain is engaged in inward-directed thought, memory formation and retrieval, or social estimation [139]. While the structural connectome thus contributes to maintaining stable neural activity patterns, it also means that normal functional connectivity is vulnerable to damage to white matter pathways as occurring in CSVD [140]. Most articles included in this review quantified the extent of white matter damage by using either neuroradiological rating scales or total lesion volume, as detailed above. Such global approaches are, however, not able to differentiate between lesions in functionally silent brain areas that can more easily be compensated by rerouting information through alternative redundant pathways, and lesions in functionally critical, strategic locations, where even spatially limited damage can be associated with substantial behavioural

sequelae. In the context of cognition, damage to subcortical nuclei and tracts with a high density of neuromodulatory projections such as the dorsomedial and anterior thalamic nuclei or the anterior limb of the internal capsule appears to be particularly consequential [24, 52, 87, 141]. Advanced diffusion-weighted structural imaging modalities allow the spatial mapping of fibre tracts and the quantification of tract-specific white matter lesion loads [142, 143]. In combination with resting-state BOLD imaging, this approach has been used to show that leukoaraiosis disrupts functional connectivity in a spatio-topological non-uniform way that is shaped by the anatomy of the brain's white matter scaffold [84]. The strongest association between tract-specific ischaemic damage and reduced FC was observed in the fronto-occipital fasciculus, which supports connectivity between the salience and frontoparietal control networks [144]. In addition to affecting functional connectivity directly, ischaemic white matter disease also seems to exert an indirect effect by modulating the coupling between structural and functional connectivity. Specifically, the association between mean diffusivity in the cingulum bundle and functional connectivity between the medial prefrontal and posterior cingulate cortices was significantly attenuated in patients with higher WMH burden, thus contributing to decoupling the anterior and posterior parts of the default mode network [81].

Both structural and functional connectomes share properties of complex networks, such as the presence of network communities, high-clustering with short path length (small-worldness), and hierarchical organisation [11, 145]. With cognition considered an emergent property of distributed neuronal activity in the brain [146, 147], understanding the behavioural sequelae of CSVD requires an understanding of how ischaemic lesions disturb not only specific fibre tracts and functional connections but also the global organisation of synchronous activity. Graph theoretical analyses have suggested that the global topology of functional brain networks in the presence of CSVD exhibits increased path length and modularity and reduced small-worldness that correlated with cognition [45, 53]. A similar effect was also observed in the structural networks of patients with CSVD and ischaemic stroke [13, 15, 148–150].

An intriguing open question is the differentiation between altered functional connectivity as a direct consequence of damage to the supporting fibre tracts, and compensatory changes. The latter are thought to contribute to maintaining normal cognitive function in the early stages of the disease [83]. Indeed, increased coupling between brain areas has repeatedly been reported in cognitively normal individual with white matter hyperintensities [78, 87, 93].

Resting-state FC informs an updated disconnection hypothesis

The association of white matter hyperintensities of presumed vascular origin with cognition has been extensively described [151–153], and indeed, cognitive impairment is one of the clinical hallmarks of manifest cerebral small vessel disease [154]. On the other hand, resting-state fMRI connectivity has been found useful in extracting neural correlates of cognitive function and mood disorders [155, 156]. Under normal physiological circumstances, patterns of coordinated activity within and between a small number of large-scale intrinsic brain networks have emerged as particularly relevant [146], including activation of the default mode network in brain states characterised by self-referential thought or rest that is anti-correlated with activation of the dorsal attention network; deactivation of the default mode network during focused attention on external stimuli [157]; and a modulating role of a frontoparietal control network with increased connectivity to the DMN as a correlate of working memory performance [158, 159]. Building upon these 'cornerstones' of functional connectivity under normal physiological circumstances, a disconnection hypothesis has been developed that postulates reduced DMN and FPCN connectivity, decoupling of neuronal activity along the anterior–posterior axis, and functional disconnection of the prefrontal cortex as neuronal correlates of cognitive impairment in CSVD [24]. This model is supported by several recent studies that reported decreased functional connectivity between the medial PFC and posterior components of the DMN in patients with CSVD [28, 44, 47], and observed an association with reaction times in the Stroop test [35]. A behaviorally relevant dissociation in functional resting-state fMRI activity and local connectivity was found between the anterior and posterior parts of the DMN with lower ReHo and ALFF values in the medial PFC and higher values in the precuneus and posterior cingulate cortex in patients with CSVD compared to healthy controls [38, 44]. Both increases and decreases of FC within the FPCN and DAN as well as their coupling with the DMN have been reported to be associated with CSVD [39, 46, 51], but the heterogeneity of these results and limited correlation with cognitive test scores makes it difficult to distinguish primary effects of disconnection from compensatory changes or sampling variability without physiological relevance.

In addition to these established networks, connectivity patterns of the salience network (SN) have recently been investigated, with increased SN-FPCN and SN-DMN couplings associated with small vessel disease [51]; additionally, increased connectivity within the SN in patients with CSVD was associated with worse performance in the Stroop interference test [83]. In patients with mild

cognitive impairment, the association between white matter disease and executive function was attenuated in the presence of increased local connectivity of the salience network [65]. The salience network includes the anterior insula, the dorsal anterior cingulate cortex, and subcortical components. Similar to the FPCN, it has a critical role in switching activity between different brain networks and has been implicated as a key component in network models of neuropsychiatric disorders [160–162]. Specifically, increased connectivity within the SN and altered SN-DMN and SN-FPCN coupling have been described in patients with Alzheimer's disease and mild cognitive impairment [163–165].

Community-dwelling adults with early CSVD often perform normally on neuropsychological tests and only report mild subjective cognitive deficits [166]. This preclinical stage has been linked to compensatory mechanisms especially in patients who benefit from a larger cognitive reserve [167, 168]. Three recent studies provide further evidence for this hypothesis, linking increased functional connectivity to frontal and temporal areas to ischaemic white matter lesion load in cognitively normal subjects [78, 83, 93].

Current knowledge is limited by the risk of bias, confounding, and methodological constraints

While it is possible to extract consistent themes from the reviewed articles that point toward physiologically relevant patterns of altered FC in the context of CSVD and cognitive impairment, the current literature is characterised by a high degree of heterogeneity of individual results. As discussed above, this may partly reflect variability in pre-processing and analytical approaches as well as heterogeneity in the clinical populations under investigation. However, given the absence of preregistered reports or high-quality multi-centre studies and the predominantly moderate-to-high risk of bias in individual studies, it must be assumed that selective reporting allowed the literature to be contaminated by a substantial number of false-positive findings, reflecting spurious associations and group differences. In addition, it is possible that reported results are confounded by the presence of other age-related pathology or neurodegenerative comorbidities, such as Alzheimer's disease [169], which were considered specifically in only a small minority of studies.

Comparison and synthesis of individual study findings is further hampered by differences in data cleaning techniques, which are known to influence functional connectivity estimates [170]. Two important dimensions of BOLD pre-processing relate to removal of the global signal from the whole brain or tissue type compartments, and handling of subjects or frames with high motion. Global signal regression is known to be effective at mitigating the widespread inflation of connectivity estimates induced by subject motion, resulting in an elevated distance-dependence of residual motion artefacts [171]. Despite this theoretical prediction and the observation that GSR might improve associations between FC and behavioural measures [172], the use of GSR was not associated with specific patterns of altered connectivity or stronger relations with cognitive measures in the reviewed papers. Similarly, no clear effect of different motion scrubbing strategies, i.e. the censoring of subjects or individual volumes due to excessive average or frame-wise displacement, could be recognised. It seems likely that the myriad of unstandardised pre-processing choices is contributing to the heterogeneity of published results and that findings which have not been shown to be robust with respect to such choices should therefore be interpreted with great care.

Even ignoring potential biases inherent in study design and publication practice, the study of FC in the context of CSVD may be limited by more fundamental obstructions. One concern is that the reliability of estimating functional connectivity may be negatively affected by the presence of white matter lesions itself. Two of the reviewed studies reported results from repeated measurements on participants in longitudinal designs [31, 42]. Worryingly, in both cases, resting-state fMRI measures were found to be poorly reproducible, indicating a further need to evaluate their robustness as an imaging biomarker. In one case, this might have been a consequence, in part, of using a brain parcellation that does not respect the functional boundaries between brain areas, which is known to be damaging to network estimation [119]. However, the persistence of low reliability measures for a range of network characteristics across network densities and atlas resolutions, as well as the particularly poor reproducibility of functional network measures in patients with CSVD compared to controls, suggests more fundamental problems beyond the choice of parcellation. The finding of poor reproducibility of RSNs and graph metrics in CSVD contrasts with high reproducibility reported in healthy participants [173–176] and patients with stable multiple sclerosis [177–179]. It has been suggested that age and confounding age-related pathologies could be responsible for reduced reliability of functional connectivity estimates [180, 181]; however, specific methodological challenges arise in patients with cerebral small vessel disease as a consequence of microvascular pathology, that are absent in other conditions.

As a measure of synchronous brain activity, the interpretation of BOLD-derived functional connectivity is contingent upon an understanding of the relation between neuronal activity and local blood flow. This neurovascular coupling, however, is known to be altered in

normal ageing as well as the presence of ischaemic disease [102, 182, 183], and attributing differences in BOLD-derived measures of connectivity to either vascular or neuronal factors is therefore challenging [184]. More specifically, white matter lesions of presumed vascular origin are known to be associated with subcortical hypoperfusion [185], possibly reflecting observed rarefaction of the microcirculation in a mouse genetic model of CSVD [186]. The later stages of neurovascular coupling involve dynamic upregulation of regional blood flow mediated by increased CO_2 concentration in areas of increased neuronal activity [102]. This mechanism appears to be affected in the presence of CSVD as demonstrated by a diminished cerebrovascular response to hypercapnia in an early study involving 24 patients with leukoaraiosis [187], and an association between WMH load and sonographically assessed measures of pulsatility and dynamic autoregulation in a cohort of elderly patient with cardiovascular risk factors [188]. These findings are further complicated by differences in age-related changes in cerebrovascular reactivity between grey and white matter [189]. BOLD-derived functional connectivity is a function of BOLD activity in remote brain areas, and spatial variations in age- or disease-related changes in neurovascular coupling might therefore affect FC estimates in unpredictable ways [190]. A small study of 25 subjects with WMH found that while cardiovascular risk factors are associated with cerebrovascular reactivity, no such association was observed for resting-state functional connectivity in the default mode network [29]. One potentially testable hypothesis about the effects of impaired neurovascular coupling on functional connectivity estimates derives from the observation that BOLD-derived measures of synchronous brain activity are a composite of true coincident neuronal activation ('signal') and shared noise, where the latter tends to be more dominant for short-range connections [171]. Reduced 'signal' strength as a consequence of a lower vascular response would therefore be expected to result in weaker and less precise FC estimates, especially in long-range connections.

Limitations

While being comprehensive in our inclusion of primary research articles from electronic databases and other sources, we cannot exclude the possibility that additional findings from the grey literature, such as blogs or unpublished conference abstracts, have not been covered by this review. In order to keep the scope of the work focused, we have not included reports of task-based connectivity or resting-state connectivity derived from electrophysiological recordings. Findings obtained using these alternative paradigms and modalities might lend further support to the themes of disturbed connectivity patterns outlined above. This review attempted a qualitative synthesis of the recent literature; the heterogeneity of study designs and populations did not permit the extraction and quantitative analysis of numerical effect estimates beyond sample size and age of participants. From a meta-analytical perspective, it can be noted, however, that all studies of patients with clinically manifest CSVD report significant FC alterations, while that is the case for only 30% of the population-based studies despite larger sample sizes. This discrepancy could reflect larger effect sizes in clinically preselected patients or indicate selective reporting in the sense of publication bias [191].

For conciseness, we have concentrated our attention on cognitive impairment as one of the main clinical sequelae of CSVD. Associations of altered patterns of functional connectivity with depressive symptoms, apathy, or gait imbalance were rarely reported and have not systemically been explored here. As an entry point to the recent literature, we note that abnormal functional coupling has been observed as a correlate of late-life depression in the context of the vascular depression hypothesis [192–195]; while apathy has been investigated using resting-state fMRI in various clinical contexts [196–198], results on gait disorders are scarce [34, 199]. Functional connectivity does not seem to interact with race or socio-economic status as possible contributing factors to neurodegeneration [200].

Conclusion

The large number of recent studies investigating resting-state fMRI connectivity in the presence of cerebral small vessel disease reflects an active ongoing interest to understand the interplay between structural brain damage, associated changes in the spatiotemporal organisation of neural activity, and clinical sequelae. The literature documents accumulating evidence for a network disruption model underlying cognitive impairment in CSVD that is characterised by disordered connectivity patterns in the DMN and FPCN and a decoupling of neuronal activity along the anterior–posterior axis, mediated by structural damage to long association tracts and cortico-subcortical connections. In addition, evidence is emerging that altered connectivity of the salience network might be a novel neuronal correlate of cognitive deficits in patients with CSVD.

The synthesis of population-based studies involving healthy participants with low white matter disease burden and clinical studies recruiting patients with manifest CSVD suggests a pattern of increased functional connectivity in various frontal and temporal brain areas consistent with compensatory upregulation at low white matter disease burden in the early stages of the disease, and dysfunctional patterns of functional connectivity

among distributed brain networks in more severely affected patients, possibly reflecting a break-down of compensatory mechanisms as the disease progresses and cognitive symptoms develop.

Further research is needed to address the problem of poor reproducibility of resting-state functional brain networks in patients with CSVD and to establish interacting effects of white matter damage of presumed vascular origin and functional reorganisation on cognition in preregistered, sufficiently powered, longitudinal studies. We expect particularly useful insights from multimodal investigations that combine resting-state and task functional MRI with electrophysiological recordings or metabolic imaging to improve temporal resolution and infer cellular processes relating to pathology.

Abbreviations

AAL: Automatic anatomical labelling; ACC: Anterior cingulate cortex; AD: Alzheimer's disease; AFNI: Analysis of Functional NeuroImages; ALFF: Amplitude of low-frequency fluctuations; AN: Auditory network; ANTs: Advanced Normalisation Tools; AROMA: Automatic Removal of Motion Artifacts; AVLT: Auditory verbal learning test; AXIS: Appraisal tool for Cross-Sectional Studies; BRAMILA: BRAin and MInd LAb; CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CDR: Clinical Dementia Rating scale; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CN: Cognitively normal; compCor: Component-based noise correction; CONN: Functional connectivity toolbox; CSF: Cerebrospinal fluid; CSVD: Cerebral small vessel disease; DAN: Dorsal attention network; DARTEL: Diffeomorphic Anatomical Registration using Exponentiated Lie algebra; DMN: Default mode network; DPABI: Data Processing & Analysis for Brain Imaging; DPARSF: Data Processing Assistant for Resting-State fMRI; DTI: Diffusion tensor imaging; EEG: Electroencephalography; fALFF: Fractional ALFF; FC: Functional connectivity; FD: Framewise displacement; FLAIR: Fluid-attenuated inversion recovery; FPCN: Frontoparietal control network; FSL: Functional Magnetic Resonance Imaging of the Brain Software Library; GIFT: Group ICA Of fMRI Toolbox; GRETNA: GRaph thEoreTical Network Analysis; GSR: Global Signal Regression; HC: Healthy control; ICA: Independent component analysis; MCC: Middle cingulate cortex; MCI: Mild cognitive impairment; MMSE: Mini Mental State Exam; MoCA: Montreal Cognitive Assessment; MRI: Magnetic resonance imaging; NBS: Network-based statistics; PET: Positron emission tomography; PCC: Posterior cingulate cortex; PFC: Prefrontal cortex; PiB: Pittsburgh compound B; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; ReHo: Regional homogeneity; REST: REsting State fMRI data analysis Toolkit; ROI: Region of interest; RSN: Resting-state network; RT: Reaction time; SC: Structural connectivity; SCA: Seed-based connectivity analysis; SMA: Supplementary motor area; SMN: Somatomotor network; SN: Salience network; SPM: Statistical Parametric Mapping; STRIVE: STandards for ReportIng Vascular changes on nEuroimaging; SVaD: Subcortical vascular dementia; svMCI: Subcortical vascular MCI; T: Tesla; TE: Echo time; THA LAC: Thalamus lacune; TMT: Trail making test; TR: Repetition time; VBM: Voxel-based morphometry; VN: Visual network; WAIS: Wechsler Adult Intelligence Scale; WM: White matter; WMH: White matter hyperintensity

Supplementary Information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12916-021-01962-1.

Additional file 1: Search strategy. Detailed description of search parameters to identify relevant literature. Risk of bias assessment. Supplementary methods and results relating to the assessment of bias in individual studies. **Table S1.** Description of items used to score risk of bias. **Table S2.** Results of risk-of-bias assessments using the AXIS tool.

Acknowledgements

Not applicable

Authors' contributions

MS searched the literature, screened articles, extracted metadata and key results, and wrote a first version of the manuscript. CM revised the manuscript for critical intellectual content. BC secured funding and revised the manuscript for critical intellectual content. GT conceptualised the study, secured funding, and revised the manuscript for critical intellectual content. ES conceptualised the study, validated the inclusion and exclusion of articles, extracted metadata and key results, performed risk-of-bias assessment, synthesised findings, wrote the manuscript, and created tables and visualisations. The authors read and approved the final manuscript.

Funding

This work was supported by a grant from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), Sonderforschungsbereich (SFB) 936, Project C2 (MS, GT, BC, ES). Open Access funding enabled and organized by Projekt DEAL.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate

No ethical approval or consent to participate was necessary for the presented study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Neurology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany. [2]Department of Computational Neuroscience, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany.

Received: 9 March 2021 Accepted: 17 March 2021
Published online: 05 May 2021

References

1. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. Lancet Neurol. 2013;12:483–97. https://doi.org/10.1016/S1474-4422(13)70060-7.
2. Rensma SP, van Sloten TT, Launer LJ, Stehouwer CDA. Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2018;90:164–73.
3. Hu HY, Ou YN, Shen XN, Qu Y, Ma YH, Wang ZT, et al. White matter hyperintensities and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 36 prospective studies. Neurosci Biobehav Rev. 2021;120:16–27.
4. Feigin VL, Lawes CMM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol. 2003;2:43–53.
5. Fitzpatrick AL, Kuller LH, Ives DG, Lopez OL, Jagust W, Breitner JCS, et al. Incidence and prevalence of dementia in the cardiovascular health study. J Am Geriatr Soc. 2004;52:195–204. https://doi.org/10.1111/j.1532-5415.2004.52058.x.
6. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 2013;12:822–38. https://doi.org/10.1016/S1474-4422(13)70124-8.
7. Veldsman M, Kindalova P, Husain M, Kosmidis I, Nichols TE, Nichols E, et al. Spatial distribution and cognitive impact of cerebrovascular risk-related white matter hyperintensities. BioRxiv. 2020;28:2020.06.12.147934. https://doi.org/10.1101/2020.06.12.147934.

8. Cox SR, Lyall DM, Ritchie SJ, Bastin ME, Harris MA, Buchanan CR, et al. Associations between vascular risk factors and brain MRI indices in UK Biobank. Eur Heart J. 2019;40:2290–9. https://doi.org/10.1093/eurheartj/ehz100.
9. van den Heuvel MP, Sporns O. A cross-disorder connectome landscape of brain dysconnectivity. Nat Rev Neurosci. 2019;20:435–46. https://doi.org/10.1038/s41583-019-0177-6.
10. Fornito A, Zalesky A, Breakspear M. The connectomics of brain disorders. Nat Rev Neurosci. 2015;16:159–72. https://doi.org/10.1038/nrn3901.
11. Bassett DS, Sporns O. Network neuroscience. Nat Neurosci. 2017;20:353–64.
12. Rubinov M, Bullmore E. Fledgling pathoconnectomics of psychiatric disorders. Trends Cogn Sci. 2013;17:641–7. https://doi.org/10.1016/j.tics.2013.10.007.
13. Lawrence AJ, Chung AW, Morris RG, Markus HS, Barrick TR. Structural network efficiency is associated with cognitive impairment in small-vessel disease. Neurology. 2014;83:304–11. https://doi.org/10.1212/WNL.0000000000000612.
14. Tuladhar AM, Van Uden IWM, Rutten-Jacobs LCA, Lawrence A, Van Der Holst H, Van Norden A, et al. Structural network efficiency predicts conversion to dementia. Neurology. 2016;86:1112–9. https://doi.org/10.1212/WNL.0000000000002502.
15. Shen J, Tozer DJ, Markus HS, Tay J. Network efficiency mediates the relationship between vascular burden and cognitive impairment: a diffusion tensor imaging study in UK Biobank. Stroke. 2020:1682–9. https://doi.org/10.1161/STROKEAHA.119.028587.
16. Frey BM, Petersen M, Schlemm E, Mayer C, Hanning U, Engelke K, et al. White matter integrity and structural brain network topology in cerebral small vessel disease: the Hamburg city health study. Hum Brain Mapp. 2020: hbm.25301. doi:https://doi.org/10.1002/hbm.25301.
17. Gouw AA, Seewann A, Van Der Flier WM, Barkhof F, Rozemuller AM, Scheltens P, et al. Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. J Neurol Neurosurg Psychiatry. 2011;82:126–35. https://doi.org/10.1136/jnnp.2009.204685.
18. Stephan BC, Matthews FE, Khaw K-T, Dufouil C, Brayne C. Beyond mild cognitive impairment: vascular cognitive impairment, no dementia (VCIND). Alzheimers Res Ther. 2009;1:4. https://doi.org/10.1186/alzrt4.
19. Hermann P, Romero C, Schmidt C, Reis C, Zerr I. CSF biomarkers and neuropsychological profiles in patients with cerebral small-vessel disease. PLoS One. 2014;9:e105000. https://doi.org/10.1371/journal.pone.0105000.
20. Wang HE, Bénar CG, Quilichini PP, Friston KJ, Jirsa VK, Bernard C. A systematic framework for functional connectivity measures. Front Neurosci. 2014;405 https://doi.org/10.3389/fnins.2014.00405.
21. van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol. 2010;20:519–34. https://doi.org/10.1016/j.euroneuro.2010.03.008.
22. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol. 2011;106:1125–65.
23. Ter Telgte A, Van Leijsen EMC, Wiegertjes K, Klijn CJM, Tuladhar AM, De Leeuw FE. Cerebral small vessel disease: from a focal to a global perspective. Nat Rev Neurol. 2018;14:387–98. https://doi.org/10.1038/s41582-018-0014-y.
24. Dey AK, Stamenova V, Turner G, Black SE, Levine B. Pathoconnectomics of cognitive impairment in small vessel disease: a systematic review. Alzheimers Dement. 2016;12:831–45. https://doi.org/10.1016/j.jalz.2016.01.007.
25. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62:e1–34. https://doi.org/10.1016/j.jclinepi.2009.06.006.
26. Downes MJ, Brennan ML, Williams HC, Dean RS. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). BMJ Open. 2016;6:e011458. https://doi.org/10.1136/bmjopen-2016-011458.
27. Ma LL, Wang YY, Yang ZH, Huang D, Weng H, Zeng XT. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? Military Med Res. 2020;7:1–11. https://doi.org/10.1186/s40779-020-00238-8.
28. Sun Y, Qin L, Zhou Y, Xu Q, Qian L, Tao J, et al. Abnormal functional connectivity in patients with vascular cognitive impairment, no dementia: a resting-state functional magnetic resonance imaging study. Behav Brain Res. 2011;223:388–94.
29. Tchistiakova E, Crane DE, Mikulis DJ, Anderson ND, Greenwood CE, Black SE, et al. Vascular risk factor burden correlates with cerebrovascular reactivity but not resting state coactivation in the default mode network. J Magn Reson Imaging. 2015;42(5):1369–76.
30. Li R, Lai Y, Zhang Y, Yao L, Wu X. Classification of cognitive level of patients with leukoaraiosis on the basis of linear and non-linear functional connectivity. Front Neurol. 2017;8(2):12.
31. Gesierich B, Tuladhar AM, ter Telgte A, Wiegertjes K, Konieczny MJ, Finsterwalder S, et al. Alterations and test–retest reliability of functional connectivity network measures in cerebral small vessel disease. Hum Brain Mapp. 2020;41:2629–41. https://doi.org/10.1002/hbm.24967.
32. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke. 2001;32:1318–22.
33. Kumar D, Vipin A, Wong B, Ng KP, Kandiah N. Differential effects of confluent and nonconfluent white matter hyperintensities on functional connectivity in mild cognitive impairment. Brain Connect. 2020;10:547–54. https://doi.org/10.1089/brain.2020.0784.
34. Zhou X, Zhang C, Li L, Zhang Y, Zhang W, Yin W, et al. Altered brain function in cerebral small vessel disease patients with gait disorders: a resting-state functional MRI study. Front Aging Neurosci. 2020;12 https://doi.org/10.3389/fnagi.2020.00234.
35. Schaefer A, Quinque EM, Kipping JA, Arélin K, Roggenhofer E, Frisch S, et al. Early small vessel disease affects frontoparietal and cerebellar hubs in close correlation with clinical symptoms - a resting-state fMRI study. J Cereb Blood Flow Metab. 2014;(7):1091–5.
36. Wu X, Lai Y, Zhang Y, Yao L, Wen X. Breakdown of sensorimotor network communication in leukoaraiosis. Neurodegener Dis. 2015;15:322–30.
37. Cheng R, Qi H, Liu Y, Zhao S, Li C, Liu C, et al. Abnormal amplitude of low-frequency fluctuations and functional connectivity of resting-state functional magnetic resonance imaging in patients with leukoaraiosis. Brain Behav. 2017;7(6):e00714.
38. Ding X, Ding J, Hua B, Xiong X, Xiao L, Peng F, et al. Abnormal cortical functional activity in patients with ischemic white matter lesions: a resting-state functional magnetic resonance imaging study. Neurosci Lett. 2017;644:10–17.
39. Ding J-RR, Ding X, Hua B, Xiong X, Wen Y, Ding Z, et al. Altered connectivity patterns among resting state networks in patients with ischemic white matter lesions. Brain Imaging Behav. 2018;12:1239–50.
40. Friston KJ, Williams S, Howard R, Frackowiak RSJ, Turner R. Movement-related effects in fMRI time-series. Magn Reson Med. 1996;35:346–55.
41. Zalesky A, Fornito A, Bullmore ET. Network-based statistic: identifying differences in brain networks. Neuroimage. 2010;53:1197–207.
42. Lawrence AJ, Tozer DJ, Stamatakis EA, Markus HS. A comparison of functional and tractography based networks in cerebral small vessel disease. NeuroImage Clin. 2018;18:425–32. https://doi.org/10.1016/j.nicl.2018.02.013.
43. Zhu Y, Lu T, Xie C, Wang Q, Wang Y, Cao X, et al. Functional disorganization of small-world brain networks in patients with ischemic leukoaraiosis. Front Aging Neurosci. 2020;12 https://doi.org/10.3389/fnagi.2020.00203.
44. Yi L, Wang J, Jia L, Zhao Z, Lu J, Li K, et al. Structural and functional changes in subcortical vascular mild cognitive impairment: a combined voxel-based morphometry and resting-state fMRI study. PLoS One. 2012;7:e44758. https://doi.org/10.1371/journal.pone.0044758.
45. Yi LY, Liang X, Liu DM, Sun B, Ying S, Yang DB, et al. Disrupted topological organization of resting-state functional brain network in subcortical vascular mild cognitive impairment. CNS Neurosci Ther. 2015;21:846–54.
46. Kim HJ, Cha J, Lee JM, Shin JS, Jung NY, Kim YJ, et al. Distinctive resting state network disruptions among Alzheimer's disease, subcortical vascular dementia, and mixed dementia patients. J Alzheimers Dis. 2016;50:709–18.
47. Zhou X, Hu X, Zhang C, Wang H, Zhu X, Xu L, et al. Aberrant functional connectivity and structural atrophy in subcortical vascular cognitive impairment: relationship with cognitive impairments. Front Aging Neurosci. 2016;8(14):8.
48. Chen H, Li Y, Liu Q, Shi Q, Wang J, Shen H, et al. Abnormal interactions of the salience network, central executive network, and default-mode network in patients with different cognitive impairment loads caused by leukoaraiosis. Front Neural Circuits. 2019;13 https://doi.org/10.3389/fncir.2019.00042.
49. Franzmeier N, Rubinski A, Neitzel J, Kim Y, Damm A, Na DL, et al. Functional connectivity associated with tau levels in ageing, Alzheimer's, and small vessel disease. Brain. 2019;142:1093–107. https://doi.org/10.1093/brain/awz026.

50. Liu R, Chen H, Qin R, Gu Y, Chen X, Zou J, et al. The altered reconfiguration pattern of brain modular architecture regulates cognitive function in cerebral small vessel disease. Front Neurol. 2019;324 https://doi.org/10.3389/fneur.2019.00324.
51. Liu R, Wu W, Ye Q, Gu Y, Zou J, Chen X, et al. Distinctive and pervasive alterations of functional brain networks in cerebral small vessel disease with and without cognitive impairment. Dement Geriatr Cogn Disord. 2019;47:55–67. https://doi.org/10.1159/000496455.
52. Qin Y, Zhu W, Liu C, Wang Z, Zhu W. Functional brain connectome and its relation to mild cognitive impairment in cerebral small vessel disease patients with thalamus lacunes: a cross-sectional study. Med (United States). 2019;98 https://doi.org/10.1097/MD.0000000000017127.
53. Wang J, Chen Y, Liang H, Niedermayer G, Chen H, Li Y, et al. The role of disturbed small-world networks in patients with white matter lesions and cognitive impairment revealed by resting state function magnetic resonance images (rs-fMRI). Med Sci Monit. 2019;25:341–56.
54. Shi Q, Chen H, Jia Q, Yuan Z, Wang J, Li Y, et al. Altered granger causal connectivity of resting-state neural networks in patients with leukoaraiosis-associated cognitive impairment—a cross-sectional study. Front Neurol. 2020;11 https://doi.org/10.3389/fneur.2020.00457.
55. Fazekas F, Barkhof F, Wahlund LO, Pantoni L, Erkinjuntti T, Scheltens P, et al. CT and MRI rating of white matter lesions. Cerebrovasc Dis. 2002;13(SUPPL. 2):31–6. https://doi.org/10.1159/000049147.
56. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. Am J Roentgenol. 1987;149:351–6. https://doi.org/10.2214/ajr.149.2.351.
57. Andreescu C, Tudorascu DL, Butters MA, Tamburo E, Patel M, Price J, et al. Resting state functional connectivity and treatment response in late-life depression. Psychiatry Res. 2011;194:39–46. https://doi.org/10.1016/j.pscychresns.2011.04.003.
58. Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology. 1993;43:250–60. https://doi.org/10.1212/WNL.43.2.250.
59. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group⋆ under the auspices of department of health and human services task force on Alzheimer's disease. Neurology. 1984;34:939–44. https://doi.org/10.1212/wnl.34.7.939.
60. Knopman DS, Boeve BF, Petersen RC. Essentials of the proper diagnoses of mild cognitive impairment, dementia, and major subtypes of dementia. In: Mayo Clinic Proceedings. Elsevier Ltd; 2003. p. 1290–1308. doi:https://doi.org/10.4065/78.10.1290.
61. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. J Intern Med. 2014;275:214–28. https://doi.org/10.1111/joim.12190.
62. Zhou Y, Yu F, Duong TQ. White matter lesion load is associated with resting state functional MRI activity and amyloid PET but not FDG in mild cognitive impairment and early Alzheimer's disease patients. J Magn Reson Imaging. 2015;41:102–9.
63. Franzmeier N, Caballero MAA, Taylor ANW, Simon-Vermot L, Buerger K, Ertl-Wagner B, et al. Resting-state global functional connectivity as a biomarker of cognitive reserve in mild cognitive impairment. Brain Imaging Behav. 2017;11:368–82.
64. Evans AC, Janke AL, Collins DL, Baillet S. Brain templates and atlases. Neuroimage. 2012;62:911–22.
65. Benson G, Hildebrandt A, Lange C, Schwarz C, Kobe T, Sommer W, et al. Functional connectivity in cognitive control networks mitigates the impact of white matter lesions in the elderly. Alzheimers Res Ther. 2018;10:109. https://doi.org/10.1186/s13195-018-0434-3.
66. Staffaroni AM, Brown JA, Casaletto KB, Elahi FM, Deng J, Neuhaus J, et al. The longitudinal trajectory of default mode network connectivity in healthy older adults varies as a function of age and is associated with changes in episodic memory and processing speed. J Neurosci. 2018;38:2809–17.
67. Eavani H, Habes M, Satterthwaite TD, An Y, Hsieh M-KK, Honnorat N, et al. Heterogeneity of structural and functional imaging patterns of advanced brain aging revealed via machine learning methods. Neurobiol Aging. 2018;71:41–50. https://doi.org/10.1016/j.neurobiolaging.2018.06.013.
68. Jiang L, Zuo XN. Regional homogeneity: a multimodal, multiscale neuroimaging marker of the human connectome. Neuroscientist. 2016;22:486–505.
69. Wu M, Andreescu C, Butters MA, Tamburo R, Reynolds CF, Aizenstein H. Default-mode network connectivity and white matter burden in late-life depression. Psychiatry Res - Neuroimaging. 2011;194:39–46. https://doi.org/10.1016/j.pscychresns.2011.04.003.
70. Wu M, Rosano C, Butters M, Whyte E, Nable M, Crooks R, et al. A fully automated method for quantifying and localizing white matter hyperintensities on MR images. Psychiatry Res - Neuroimaging. 2006;148:133–42. https://doi.org/10.1016/j.pscychresns.2006.09.003.
71. Andreescu C, Tudorascu DL, Butters MA, Tamburo E, Patel M, Price J, et al. Resting state functional connectivity and treatment response in late-life depression. Psychiatry Res - Neuroimaging. 2013;214:313–21. https://doi.org/10.1016/j.pscychresns.2013.08.007.
72. Mikheev A, Nevsky G, Govindan S, Grossman R, Rusinek H. Fully automatic segmentation of the brain from T1-weighted MRI using Bridge Burner algorithm. J Magn Reson Imaging. 2008;27:1235–41. https://doi.org/10.1002/jmri.21372.
73. Suo C, Singh MF, Gates N, Wen W, Sachdev P, Brodaty H, et al. Therapeutically relevant structural and functional mechanisms triggered by physical and cognitive exercise. Mol Psychiatry. 2016;21:1633–42. https://doi.org/10.1038/mp.2016.19.
74. Wen W, Sachdev P. The topography of white matter hyperintensities on brain MRI in healthy 60- to 64-year-old individuals. Neuroimage. 2004;22:144–54. https://doi.org/10.1016/j.neuroimage.2003.12.027.
75. Otsu N. Threshold selection method from gray-level histograms. IEEE Trans Syst Man Cybern. 1979;SMC-9:62–6.
76. Schmidt P, Gaser C, Arsic M, Buck D, Förschler A, Berthele A, et al. An automated tool for detection of FLAIR-hyperintense white-matter lesions in multiple sclerosis. Neuroimage. 2012;59:3774–83. https://doi.org/10.1016/j.neuroimage.2011.11.032.
77. Lyu H, Wang J, Xu J, Zheng H, Yang X, Lin S, et al. Structural and functional disruptions in subcortical vascular mild cognitive impairment with and without depressive symptoms. Frontiers Media S.A.; 2019. doi:https://doi.org/10.3389/fnagi.2019.00241.
78. Zhang XD, Zhao LR, Zhou JM, Su YY, Ke J, Cheng Y, et al. Altered hippocampal functional connectivity in primary Sjögren syndrome: a resting-state fMRI study. Lupus. 2020;29:446–54. https://doi.org/10.1177/0961203320908936.
79. He J, Carmichael O, Fletcher E, Singh B, Iosif A-MM, Martinez O, et al. Influence of functional connectivity and structural MRI measures on episodic memory. Neurobiol Aging. 2012;33:2612–20. https://doi.org/10.1016/j.neurobiolaging.2011.12.029.
80. DeCarli C, Massaro J, Harvey D, Hald J, Tullberg M, Au R, et al. Measures of brain morphology and infarction in the Framingham heart study: establishing what is normal. Neurobiol Aging. 2005;26:491–510. https://doi.org/10.1016/j.neurobiolaging.2004.05.004.
81. Reijmer YD, Schultz AP, Leemans A, O'Sullivan MJ, Gurol ME, Sperling R, et al. Decoupling of structural and functional brain connectivity in older adults with white matter hyperintensities. Neuroimage. 2015;117:222–9. https://doi.org/10.1016/j.neuroimage.2015.05.054.
82. Hedden T, Schultz AP, Rieckmann A, Mormino EC, Johnson KA, Sperling RA, et al. Multiple brain markers are linked to age-related variation in cognition. Cereb Cortex. 2016;26:1388–400. https://doi.org/10.1093/cercor/bhu238.
83. De Marco M, Manca R, Mitolo M, Venneri A. White matter hyperintensity load modulates brain morphometry and brain connectivity in healthy adults: a neuroplastic mechanism? Neural Plast. 2017;2017:10.
84. Langen CD, Zonneveld HI, White T, Huizinga W, Cremers LGM, de Groot M, et al. White matter lesions relate to tract-specific reductions in functional connectivity. Neurobiol Aging. 2017;51:97–103. https://doi.org/10.1016/j.neurobiolaging.2016.12.004.
85. de Boer R, Vrooman HA, van der Lijn F, Vernooij MW, Ikram MA, van der Lugt A, et al. White matter lesion extension to automatic brain tissue segmentation on MRI. Neuroimage. 2009;45:1151–61.
86. Madden DJ, Parks EL, Tallman CW, Boylan MA, Hoagey DA, Cocjin SB, et al. Sources of disconnection in neurocognitive aging: cerebral white-matter integrity, resting-state functional connectivity, and white-matter hyperintensity volume. Neurobiol Aging. 2017;54:199–213.
87. Shi L, Miao X, Lou W, Liu K, Abrigo J, Wong A, et al. The spatial associations of cerebral blood flow and spontaneous brain activities with white matter hyperintensities-an exploratory study using multimodal magnetic resonance imaging. Front Neurol. 2017. doi:https://doi.org/10.3389/fneur.2017.00593.

88. Shi L, Wang D, Liu S, Pu Y, Wang Y, Chu WCW, et al. Automated quantification of white matter lesion in magnetic resonance imaging of patients with acute infarction. J Neurosci Methods. 2013;213:138–46. https://doi.org/10.1016/j.jneumeth.2012.12.014.
89. Lao Z, Shen D, Liu D, Jawad AF, Melhem ER, Launer LJ, et al. Computer-assisted segmentation of white matter lesions in 3D MR images using support vector machine. Acad Radiol. 2008;15:300–13.
90. Dadar M, Pascoal TA, Manitsirikul S, Misquitta K, Fonov VS, Tartaglia MC, et al. Validation of a regression technique for segmentation of white matter hyperintensities in Alzheimer's disease. IEEE Trans Med Imaging. 2017;36:1758–68. https://doi.org/10.1109/TMI.2017.2693978.
91. Avants BB, Tustison NJ, Wu J, Cook PA, Gee JC. An open source multivariate framework for N-tissue segmentation with evaluation on public data. Neuroinformatics. 2011;9:381–400. https://doi.org/10.1007/s12021-011-9109-y.
92. Tsapanou A, Habeck C, Gazes Y, Razlighi Q, Sakhardande J, Stern Y, et al. Brain biomarkers and cognition across adulthood. Hum Brain Mapp. 2019;40:3832–42. https://doi.org/10.1002/hbm.24634.
93. Park BY, Byeon K, Lee MJ, Kim SH, Park H. The orbitofrontal cortex functionally links obesity and white matter hyperintensities. Sci Rep. 2020;10 https://doi.org/10.1038/s41598-020-60054-x.
94. Griffanti L, Zamboni G, Khan A, Li L, Bonifacio G, Sundaresan V, et al. BIANCA (Brain Intensity AbNormality Classification Algorithm): a new tool for automated segmentation of white matter hyperintensities. Neuroimage. 2016;141:191–205. https://doi.org/10.1016/j.neuroimage.2016.07.018.
95. Rabin JS, Neal TE, Nierle HE, Sikkes SAM, Buckley RF, Amariglio RE, et al. Multiple markers contribute to risk of progression from normal to mild cognitive impairment. NeuroImage Clin. 2020;28 https://doi.org/10.1016/j.nicl.2020.102400.
96. Fillenbaum GG, van Belle G, Morris JC, Mohs RC, Mirra SS, Davis PC, et al. Consortium to establish a registry for Alzheimer's disease (CERAD): the first twenty years. Alzheimer's and Dementia. 2008;4:96–109. https://doi.org/10.1016/j.jalz.2007.08.005.
97. Hedden T, Van Dijk KRA, Shire EH, Sperling RA, Johnson KA, Buckner RL. Failure to modulate attentional control in advanced aging linked to white matter pathology. Cereb Cortex. 2012;22:1038–51. https://doi.org/10.1093/cercor/bhr172.
98. Rey A. L'examen psychologique dans les cas d'encéphalopathie traumatique. Arch Psychol. 1941;28:215–285. doi:1943–03814-001.
99. Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. Neurology. 2010;74:201–9. https://doi.org/10.1212/WNL.0b013e3181cb3e25.
100. Kriegeskorte N, Simmons WK, Bellgowan PS, Baker CI. Circular analysis in systems neuroscience: the dangers of double dipping. Nat Neurosci. 2009;12:535–40. https://doi.org/10.1038/nn.2303.
101. Van Dijk EJ, Breteler MMB, Schmidt R, Berger K, Nilsson LG, Oudkerk M, et al. The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study. Hypertension. 2004;44(5):625–30.
102. D'Esposito M, Deouell LY, Gazzaley A. Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. Nat Rev Neurosci. 2003;4:863–72. https://doi.org/10.1038/nrn1246.
103. Hofman A, Breteler MMB, Van Duijn CM, Krestin GP, Pols HA, Stricker BHC, et al. The Rotterdam study: objectives and design update. Eur J Epidemiol. 2007;22:819–29. https://doi.org/10.1007/s10654-007-9199-x.
104. Dagley A, LaPoint M, Huijbers W, Hedden T, McLaren DG, Chatwal JP, et al. Harvard aging brain study: dataset and accessibility. Neuroimage. 2017;144 Pt B:255–8. doi:https://doi.org/10.1016/j.neuroimage.2015.03.069.
105. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12:e1001779. https://doi.org/10.1371/journal.pmed.1001779.
106. Frey BM, Petersen M, Mayer C, Schulz M, Cheng B, Thomalla G. Characterization of white matter hyperintensities in large-scale MRI-studies. Front Neurol. 2019;238:16.
107. Lehmann M, Madison CM, Ghosh PM, Seeley WW, Mormino E, Greicius MD, et al. Intrinsic connectivity networks in healthy subjects explain clinical variability in Alzheimer's disease. Proc Natl Acad Sci U S A. 2013;110:11606–11. https://doi.org/10.1073/pnas.1221536110.
108. Park SH, Zong X, Gao Y, Lin W, Shen D. Segmentation of perivascular spaces in 7 T MR image using auto-context model with orientation-normalized features. Neuroimage. 2016;134:223–35.
109. Ballerini L, Booth T, Valdés Hernández M del C, Wiseman S, Lovreglio R, Muñoz Maniega S, et al. Computational quantification of brain perivascular space morphologies: associations with vascular risk factors and white matter hyperintensities. A study in the Lothian Birth Cohort 1936. NeuroImage Clin. 2020;25:102120. doi:https://doi.org/10.1016/j.nicl.2019.102120.
110. Dubost F, Yilmaz P, Adams H, Bortsova G, Ikram MA, Niessen W, et al. Enlarged perivascular spaces in brain MRI: automated quantification in four regions. Neuroimage. 2019;185:534–44.
111. Boespflug EL, Schwartz DL, Lahna D, Pollock J, Iliff JJ, Kaye JA, et al. MR imaging-based multimodal autoidentification of perivascular spaces (mMAPS): automated morphologic segmentation of enlarged perivascular spaces at clinical field strength. Radiology. 2018;286:632–42. https://doi.org/10.1148/radiol.2017170205.
112. Chen H, Yu L, Dou Q, Shi L, Mok VCT, Heng PA. Automatic detection of cerebral microbleeds via deep learning based 3D feature representation. In: Proceedings - International Symposium on Biomedical Imaging. New York: IEEE Computer Society; 2015. p. 764–7.
113. Seghier ML, Kolanko MA, Leff AP, Jäger HR, Gregoire SM, Werring DJ. Microbleed detection using automated segmentation (MIDAS): a new method applicable to standard clinical MR images. PLoS One. 2011;6 https://doi.org/10.1371/journal.pone.0017547.
114. Morrison MA, Payabvash S, Chen Y, Avadiappan S, Shah M, Zou X, et al. A user-guided tool for semi-automated cerebral microbleed detection and volume segmentation: evaluating vascular injury and data labelling for machine learning. NeuroImage Clin. 2018;20:498–505. https://doi.org/10.1016/j.nicl.2018.08.002.
115. Marrelec G, Krainik A, Duffau H, Pélégrini-Issac M, Lehéricy S, Doyon J, et al. Partial correlation for functional brain interactivity investigation in functional MRI. Neuroimage. 2006;32:228–37. https://doi.org/10.1016/j.neuroimage.2005.12.057.
116. Cole DM, Smith SM, Beckmann CF. Advances and pitfalls in the analysis and interpretation of resting-state FMRI data. Front Syst Neurosci. 2010;4 https://doi.org/10.3389/fnsys.2010.00008.
117. Fox MD, Zhang D, Snyder AZ, Raichle ME. The global signal and observed anticorrelated resting state brain networks. J Neurophysiol. 2009;101:3270–83. https://doi.org/10.1152/jn.90777.2008.
118. Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? Neuroimage. 2009;44:893–905. https://doi.org/10.1016/j.neuroimage.2008.09.036.
119. Smith SM, Miller KL, Salimi-Khorshidi G, Webster M, Beckmann CF, Nichols TE, et al. Network modelling methods for FMRI. Neuroimage. 2011;54:875–91. https://doi.org/10.1016/j.neuroimage.2010.08.063.
120. Ramsey JD, Hanson SJ, Hanson C, Halchenko YO, Poldrack RA, Glymour C. Six problems for causal inference from fMRI. Neuroimage. 2010;49:1545–58. https://doi.org/10.1016/j.neuroimage.2009.08.065.
121. Patel RS, Bowman FDB, Rilling JK. A Bayesian approach to determining connectivity of the human brain. Hum Brain Mapp. 2006;27:267–76. https://doi.org/10.1002/hbm.20182.
122. Preti MG, Bolton TA, Van De Ville D. The dynamic functional connectome: state-of-the-art and perspectives. Neuroimage. 2017;160:41–54.
123. Calhoun VD, Miller R, Pearlson G, Adali T. The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron. 2014;84:262–74.
124. Lindquist MA, Xu Y, Nebel MB, Caffo BS. Evaluating dynamic bivariate correlations in resting-state fMRI: a comparison study and a new approach. Neuroimage. 2014;101:531–46.
125. Nolte M, Gal E, Markram H, Reimann MW. Impact of higher order network structure on emergent cortical activity. Netw Neurosci. 2019;4:292–314. https://doi.org/10.1162/netn_a_00124.
126. Battiston F, Cencetti G, Iacopini I, Latora V, Lucas M, Patania A, et al. Networks beyond pairwise interactions: structure and dynamics. Phys Rep. 2020; https://doi.org/10.1016/j.physrep.2020.05.004.
127. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. 2002;15:273–89. https://doi.org/10.1006/nimg.2001.0978.
128. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006;31:968–80.

129. Zalesky A, Fornito A, Harding IH, Cocchi L, Yücel M, Pantelis C, et al. Whole-brain anatomical networks: does the choice of nodes matter? Neuroimage. 2010;50:970–83. https://doi.org/10.1016/j.neuroimage.2009.12.027.
130. Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, et al. Functional network organization of the human brain. Neuron. 2011;72:665–78. https://doi.org/10.1016/j.neuron.2011.09.006.
131. Schaefer A, Kong R, Gordon EM, Laumann TO, Zuo X-N, Holmes AJ, et al. Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. Cereb Cortex. 2018;28:3095–114. https://doi.org/10.1093/cercor/bhx179.
132. Fan L, Li H, Zhuo J, Zhang Y, Wang J, Chen L, et al. The human brainnetome atlas: a new brain atlas based on connectional architecture. Cereb Cortex. 2016;26:3508–26. https://doi.org/10.1093/cercor/bhw157.
133. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci. 2009;10:186–98.
134. Rubinov M, Sporns O. Weight-conserving characterization of complex functional brain networks. Neuroimage. 2011;56:2068–79. https://doi.org/10.1016/j.neuroimage.2011.03.069.
135. Sporns O. Graph theory methods: applications in brain networks. Dialogues Clin Neurosci. 2018;20:111–21. http://www.ncbi.nlm.nih.gov/pubmed/30250388. Accessed 19 May 2019
136. Suárez LE, Markello RD, Betzel RF, Misic B. Linking structure and function in macroscale brain networks. Trends Cogn Sci. 2020;24:302–15. https://doi.org/10.1016/j.tics.2020.01.008.
137. Van Den Heuvel MP, Mandl RCW, Kahn RS, Hulshoff Pol HE. Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. Hum Brain Mapp. 2009;30:3127–41. https://doi.org/10.1002/hbm.20737.
138. Khalsa S, Mayhew SD, Chechlacz M, Bagary M, Bagshaw AP. The structural and functional connectivity of the posterior cingulate cortex: comparison between deterministic and probabilistic tractography for the investigation of structure-function relationships. Neuroimage. 2014;102:118–27. https://doi.org/10.1016/j.neuroimage.2013.12.022.
139. Horn A, Ostwald D, Reisert M, Blankenburg F. The structural-functional connectome and the default mode network of the human brain. Neuroimage. 2014;102:142–51.
140. Ye Q, Bai F. Contribution of diffusion, perfusion and functional MRI to the disconnection hypothesis in subcortical vascular cognitive impairment. Neurology. 2018;3:e000080, 131–9.
141. Bohnen NI, Bogan CW, Müller MLTM. Frontal and periventricular brain white matter lesions and cortical deafferentation of cholinergic and other neuromodulatory axonal projections. Eur Neurol J 2009;1:33–50. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC338799. Accessed 1 July 2020.
142. Egorova N, Dhollander T, Khlif MS, Khan W, Werden E, Brodtmann A. Pervasive white matter fiber degeneration in ischemic stroke. Stroke. 2020;51:1507–13. https://doi.org/10.1161/STROKEAHA.119.028143.
143. Smith RE, Tournier JD, Calamante F, Connelly A. Anatomically-constrained tractography: improved diffusion MRI streamlines tractography through effective use of anatomical information. Neuroimage. 2012;62:1924–38. https://doi.org/10.1016/j.neuroimage.2012.06.005.
144. Waller R, Dotterer HL, Murray L, Maxwell AM, Hyde LW. White-matter tract abnormalities and antisocial behavior: a systematic review of diffusion tensor imaging studies across development. NeuroImage: Clinical. 2017;14:201–15. https://doi.org/10.1016/j.nicl.2017.01.014.
145. Bassett DS, Bullmore ET. Small-world brain networks revisited. Neuroscientist. 2017;23:499–516.
146. Bressler SL, Menon V. Large-scale brain networks in cognition: emerging methods and principles. Trends Cogn Sci. 2010;14:277–90.
147. Postle BR. Working memory as an emergent property of the mind and brain. Neuroscience. 2006;139:23–38.
148. Petersen M, Frey BM, Schlemm E, Mayer C, Hanning U, Engelke K, et al. Network localisation of white matter damage in cerebral small vessel disease. Sci Rep. 2020;10:1–9. https://doi.org/10.1038/s41598-020-66013-w.
149. Cheng B, Schlemm E, Schulz R, Boenstrup M, Messé A, Hilgetag C, et al. Altered topology of large-scale structural brain networks in chronic stroke. Brain Commun. 2019;1 https://doi.org/10.1093/braincomms/fcz020.
150. Schlemm E, Schulz R, Bönstrup M, Krawinkel L, Fiehler J, Gerloff C, et al. Structural brain networks and functional motor outcome after stroke—a prospective cohort study. Brain Commun. 2020;2:fcaa001. https://doi.org/10.1093/braincomms/fcaa001.
151. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9:689–701.
152. Van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MMB. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam scan study. Stroke. 2008;39:2712–9. https://doi.org/10.1161/STROKEAHA.107.513176.
153. Østergaard L, Engedal TS, Moreton F, Hansen MB, Wardlaw JM, Dalkara T, et al. Cerebral small vessel disease: capillary pathways to stroke and cognitive decline. J Cerebral Blood Flow Metab. 2016;36:302–25. https://doi.org/10.1177/0271678X15606723.
154. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. Lancet Neurol. 2019;18:684–96. https://doi.org/10.1016/S1474-4422(19)30079-1.
155. Takamura T, Hanakawa T. Clinical utility of resting-state functional connectivity magnetic resonance imaging for mood and cognitive disorders. J Neural Transm. 2017;124:821–39. https://doi.org/10.1007/s00702-017-1710-2.
156. Farràs-Permanyer L, Guàrdia-Olmos J, Peró-Cebollero M. Mild cognitive impairment and fMRI studies of brain functional connectivity: the state of the art. Front Psychol. 2015;6:1095. https://doi.org/10.3389/fpsyg.2015.01095.
157. Anticevic A, Cole MW, Murray JD, Corlett PR, Wang XJ, Krystal JH. The role of default network deactivation in cognition and disease. Trends Cogn Sci. 2012;16:584–92.
158. Hampson M, Driesen NR, Skudlarski P, Gore JC, Constable RT. Brain connectivity related to working memory performance. J Neurosci. 2006;26:13338–43. https://doi.org/10.1523/JNEUROSCI.3408-06.2006.
159. Silton RL, Heller W, Towers DN, Engels AS, Spielberg JM, Edgar JC, et al. The time course of activity in dorsolateral prefrontal cortex and anterior cingulate cortex during top-down attentional control. Neuroimage. 2010;50:1292–302.
160. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci. 2011;15:483–506.
161. Nekovarova T, Fajnerova I, Horacek J, Spaniel F. Bridging disparate symptoms of schizophrenia: a triple network dysfunction theory. Front Behav Neurosci. 2014:171. doi:https://doi.org/10.3389/fnbeh.2014.00171.
162. Sridharan D, Levitin DJ, Menon V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci U S A. 2008;105:12569–74. https://doi.org/10.1073/pnas.0800005105.
163. Balthazar MLF, Pereira FRS, Lopes TM, da Silva EL, Coan AC, Campos BM, et al. Neuropsychiatric symptoms in Alzheimer's disease are related to functional connectivity alterations in the salience network. Hum Brain Mapp. 2014;35:1237–46. https://doi.org/10.1002/hbm.22248.
164. He X, Qin W, Liu Y, Zhang X, Duan Y, Song J, et al. Abnormal salience network in normal aging and in amnestic mild cognitive impairment and Alzheimer's disease. Hum Brain Mapp. 2014;35:3446–64. https://doi.org/10.1002/hbm.22414.
165. Badhwar AP, Tam A, Dansereau C, Orban P, Hoffstaedter F, Bellec P. Resting-state network dysfunction in Alzheimer's disease: a systematic review and meta-analysis. Alzheimer's Dement Diagnosis Assess Dis Monit. 2017;8:73–85.
166. Dey AK, Stamenova V, Bacopulos A, Jeyakumar N, Turner GR, Black SE, et al. Cognitive heterogeneity among community-dwelling older adults with cerebral small vessel disease. Neurobiol Aging. 2019;77:183–93.
167. Pinter D, Enzinger C, Fazekas F. Cerebral small vessel disease, cognitive reserve and cognitive dysfunction. J Neurol. 2015;262:2411–9. https://doi.org/10.1007/s00415-015-7776-6.
168. Barulli D, Stern Y. Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. Trends Cogn Sci. 2013;17:502–9.
169. Kim HW, Hong J, Jeon JC. Cerebral small vessel disease and Alzheimer's disease: a review. Front Neurol. 2020;11:927. https://doi.org/10.3389/fneur.2020.00927.
170. Ciric R, Wolf DH, Power JD, Roalf DR, Baum GL, Ruparel K, et al. Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity. Neuroimage. 2017;154:174–87.
171. Ciric R, Rosen AFG, Erus G, Cieslak M, Adebimpe A, Cook PA, et al. Mitigating head motion artifact in functional connectivity MRI. Nat Protoc. 2018;13:2801–26. https://doi.org/10.1038/s41596-018-0065-y.
172. Li J, Kong R, Liégeois R, Orban C, Tan Y, Sun N, et al. Global signal regression strengthens association between resting-state functional

connectivity and behavior. Neuroimage. 2019;196:126–41. https://doi.org/10.1016/j.neuroimage.2019.04.016.
173. Telesford QK, Morgan AR, Hayasaka S, Simpson SL, Barret W, Kraft RA, et al. Reproducibility of graph metrics in fMRI networks. Front Neuroinform. 2010:117. doi:https://doi.org/10.3389/fninf.2010.00117.
174. Braun U, Plichta MM, Esslinger C, Sauer C, Haddad L, Grimm O, et al. Test-retest reliability of resting-state connectivity network characteristics using fMRI and graph theoretical measures. Neuroimage. 2012;59:1404–12.
175. Wang JH, Zuo XN, Gohel S, Milham MP, Biswal BB, He Y. Graph theoretical analysis of functional brain networks: test-retest evaluation on short- and long-term resting-state functional MRI data. PLoS One. 2011;6:e21976. https://doi.org/10.1371/journal.pone.0021976.
176. Zuo XN, Kelly C, Adelstein JS, Klein DF, Castellanos FX, Milham MP. Reliable intrinsic connectivity networks: test-retest evaluation using ICA and dual regression approach. Neuroimage. 2010;49:2163–77.
177. Choe AS, Jones CK, Joel SE, Muschelli J, Belegu V, Caffo BS, et al. Reproducibility and temporal structure in weekly resting-state fMRI over a period of 3.5 years. PLoS One. 2015;10:e0140134. https://doi.org/10.1371/journal.pone.0140134.
178. Pinter D, Beckmann C, Koini M, Pirker E, Filippini N, Pichler A, et al. Reproducibility of resting state connectivity in patients with stable multiple sclerosis. PLoS One. 2016;11:e0152158. https://doi.org/10.1371/journal.pone.0152158.
179. Abrol A, Damaraju E, Miller RL, Stephen JM, Claus ED, Mayer AR, et al. Replicability of time-varying connectivity patterns in large resting state fMRI samples. Neuroimage. 2017;163:160–76.
180. Song J, Desphande AS, Meier TB, Tudorascu DL, Vergun S, Nair VA, et al. Age-related differences in test-retest reliability in resting-state brain functional connectivity. PLoS One. 2012;7 https://doi.org/10.1371/journal.pone.0049847.
181. Guo CC, Kurth F, Zhou J, Mayer EA, Eickhoff SB, Kramer JH, et al. One-year test-retest reliability of intrinsic connectivity network fMRI in older adults. Neuroimage. 2012;61:1471–83. https://doi.org/10.1016/j.neuroimage.2012.03.027.
182. Shabir O, Berwick J, Francis SE. Neurovascular dysfunction in vascular dementia, Alzheimer's and atherosclerosis. BMC Neurosci. 2018;19:62. https://doi.org/10.1186/s12868-018-0465-5.
183. Fabiani M, Gordon BA, Maclin EL, Pearson MA, Brumback-Peltz CR, Low KA, et al. Neurovascular coupling in normal aging: a combined optical, ERP and fMRI study. Neuroimage. 2014;85 0 1:592–607. doi:https://doi.org/10.1016/j.neuroimage.2013.04.113.
184. Tsvetanov KA, Henson RNA, Rowe JB. Separating vascular and neuronal effects of age on fMRI BOLD signals. Philos Trans R Soc B Biol Sci. 2019;376:20190631. https://doi.org/10.1098/rstb.2019.0631.
185. Hatazawa J, Shimosegawa E, Satoh T, Toyoshima H, Okudera T. Subcortical hypoperfusion associated with asymptomatic white matter lesions on magnetic resonance imaging. Stroke. 1997;28(10):1944–7.
186. Joutel A, Monet-Leprêtre M, Gosele C, Baron-Menguy C, Hammes A, Schmidt S, et al. Cerebrovascular dysfunction and microcirculation rarefaction precede white matter lesions in a mouse genetic model of cerebral ischemic small vessel disease. J Clin Invest. 2010;120(2):433–45.
187. Kuwabara Y, Ichiya Y, Sasaki M, Yoshida T, Fukumura T, Masuda K, et al. Cerebral blood flow and vascular response to hypercapnia in hypertensive patients with leukoaraiosis. Ann Nucl Med. 1996;10:293–8.
188. Purkayastha S, Fadar O, Mehregan A, Salat DH, Moscufo N, Meier DS, et al. Impaired cerebrovascular hemodynamics are associated with cerebral white matter damage. J Cereb Blood Flow Metab. 2014;34(2):228–34.
189. Thomas BP, Liu P, Park DC, Van Osch MJP, Lu H. Cerebrovascular reactivity in the brain white matter: magnitude, temporal characteristics, and age effects. J Cereb Blood Flow Metab. 2014;34(2):242–7.
190. Golestani AM, Kwinta JB, Strother SC, Khatamian YB, Chen JJ. The association between cerebrovascular reactivity and resting-state fMRI functional connectivity in healthy adults: the influence of basal carbon dioxide. Neuroimage. 2016;132:301–13.
191. Song F, Khan KS, Dinnes J, Sutton AJ. Asymmetric funnel plots and publication bias in meta-analyses of diagnostic accuracy. Int J Epidemiol. 2002;31:88–95. https://doi.org/10.1093/ije/31.1.88.
192. Karim HT, Andreescu C, Tudorascu D, Smagula SF, Butters MA, Karp JF, et al. Intrinsic functional connectivity in late-life depression: trajectories over the course of pharmacotherapy in remitters and non-remitters. Mol Psychiatry. 2017;22:450–7. https://doi.org/10.1038/mp.2016.55.
193. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. Mol Psychiatry. 2013;18:963–74. https://doi.org/10.1038/mp.2013.20.
194. Kenny ER, O'Brien JT, Cousins DA, Richardson J, Thomas AJ, Firbank MJ, et al. Functional connectivity in late-life depression using resting-state functional magnetic resonance imaging. Am J Geriatr Psychiatry. 2010;18:643–51.
195. Bohr IJ, Kenny E, Blamire A, O'Brien JT, Thomas AJ, Richardson J, et al. Resting-state functional connectivity in late-life depression: higher global connectivity and more long distance connections. Front Psychiatry. 2013;116 https://doi.org/10.3389/fpsyt.2012.00116.
196. Alexopoulos GS, Hoptman MJ, Yuen G, Kanellopoulos D, K. Seirup J, Lim KO, et al. Functional connectivity in apathy of late-life depression: a preliminary study. J Affect Disord 2013;149:398–405. doi:https://doi.org/10.1016/j.jad.2012.11.023.
197. Joo SH, Lee CU, Lim HK. Apathy and intrinsic functional connectivity networks in amnestic mild cognitive impairment. Neuropsychiatr Dis Treat. 2017;13:61–7. https://doi.org/10.2147/NDT.S123338.
198. Moretti R, Signori R. Neural correlates for apathy: frontal-prefrontal and parietal cortical-subcortical circuits. Front Aging Neurosci. 2016;289 https://doi.org/10.3389/fnagi.2016.00289.
199. Karim HT, Rosso A, Aizenstein HJ, Bohnen NI, Studenski S, Rosano C. Resting state connectivity within the basal ganglia and gait speed in older adults with cerebral small vessel disease and locomotor risk factors. NeuroImage Clin. 2020;28 https://doi.org/10.1016/j.nicl.2020.102401.
200. Meeker KL, Wisch JK, Hudson D, Coble D, Xiong C, Babulal GM, et al. Socioeconomic status mediates racial differences seen using the AT(N) framework. Ann Neurol. 2021;89:254–65. https://doi.org/10.1002/ana.25948.

Publisher's Note

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 25 February 2022
doi: 10.3389/fnagi.2022.782738

Association of Age and Structural Brain Changes With Functional Connectivity and Executive Function in a Middle-Aged to Older Population-Based Cohort

Maximilian Schulz[1], Carola Mayer[1], Eckhard Schlemm[1], Benedikt M. Frey[1], Caroline Malherbe[1,2], Marvin Petersen[1], Jürgen Gallinat[3], Simone Kühn[3], Jens Fiehler[4], Uta Hanning[4], Raphael Twerenbold[5,6], Christian Gerloff[1], Bastian Cheng[1] and Götz Thomalla[1]*

[1] Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [2] Institute of Computational Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [3] Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [4] Department of Neuroradiological Diagnostics and Intervention, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [5] Department of Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [6] University Center of Cardiovascular Science, Department of Cardiology, University Heart and Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

OPEN ACCESS

Edited by:
Adrian W. Gilmore, National Institutes of Health (NIH), United States

Reviewed by:
Peter Millar, Washington University School of Medicine in St. Louis, United States
Brigitta Malagurski, University of Zurich, Switzerland
Adriana L. Ruiz-Rizzo, Ludwig Maximilian University of Munich, Germany

***Correspondence:**
Maximilian Schulz
m.schulz1@uke.de

Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *24 September 2021*
Accepted: *06 January 2022*
Published: *25 February 2022*

Citation:
Schulz M, Mayer C, Schlemm E, Frey BM, Malherbe C, Petersen M, Gallinat J, Kühn S, Fiehler J, Hanning U, Twerenbold R, Gerloff C, Cheng B and Thomalla G (2022) Association of Age and Structural Brain Changes With Functional Connectivity and Executive Function in a Middle-Aged to Older Population-Based Cohort. Front. Aging Neurosci. 14:782738. doi: 10.3389/fnagi.2022.782738

Aging is accompanied by structural brain changes that are thought to underlie cognitive decline and dementia. Yet little is known regarding the association between increasing age, structural brain damage, and alterations of functional brain connectivity. The aim of this study was to evaluate whether cortical thickness and white matter damage as markers of age-related structural brain changes are associated with alterations in functional connectivity in non-demented healthy middle-aged to older adults. Therefore, we reconstructed functional connectomes from resting-state functional magnetic resonance imaging (MRI) (rsfMRI) data of 976 subjects from the Hamburg City Health Study, a prospective population-based study including participants aged 45–74 years from the metropolitan region Hamburg, Germany. We performed multiple linear regressions to examine the association of age, cortical thickness, and white matter damage quantified by the peak width of skeletonized mean diffusivity (PSMD) from diffusion tensor imaging on whole-brain network connectivity and four predefined resting state networks (default mode, dorsal, salience, and control network). In a second step, we extracted subnetworks with age-related decreased functional connectivity from these networks and conducted a mediation analysis to test whether the effect of age on these networks is mediated by decreased cortical thickness or PSMD. We observed an independent association of higher age with decreased functional connectivity, while there was no significant association of functional connectivity with cortical thickness or PSMD. Mediation analysis identified cortical thickness as a partial mediator between age and default subnetwork connectivity and functional connectivity within the default subnetwork as a partial mediator between age and executive cognitive function. These

results indicate that, on a global scale, functional connectivity is not determined by structural damage in healthy middle-aged to older adults. There is a weak association of higher age with decreased functional connectivity which, for specific subnetworks, appears to be mediated by cortical thickness.

Keywords: age, resting state functional MR imaging, functional connectivity, cortical atrophy, peak width of skeletonized mean diffusivity

INTRODUCTION

Higher age is accompanied by structural brain alterations, which are thought to give rise to functional abnormalities and decline in cognitive function, even in individuals free of neurodegenerative disease. Pathophysiological processes suspected to cause age-related neurodegeneration are heterogeneous and not well understood, ranging from proteinopathies (Noor et al., 2021) to vascular pathology (Brown and Thore, 2011). Modern brain magnetic resonance imaging (MRI) studies provide an opportunity to probe *in vivo* for changes in structural and functional imaging biomarkers during the aging process. Indeed, researchers observed many neuroimaging measures of brain structure and function that indicate deterioration during adult aging (Hedden and Gabrieli, 2004; Walhovd et al., 2011; Grady, 2012; Chen et al., 2016) with cortical thickness, white matter hyperintensity (WMH) load, and functional connectivity (FC) being the most prominent parameters.

White matter damage visible by hyperintensities (WMH) on T2-weighted MR images represents microvascular ischemic and demyelinating alterations (Chui, 2006; Launer et al., 2006). In the elderly population, white matter damage is considered a risk factor for cognitive impairment (Geppert et al., 2007), impairment in gait (Starr et al., 2003), depression (Dalby et al., 2012), and an increased risk for stroke and dementia (Debette and Markus, 2010). Beyond age, primary contributors to the development of microvascular damage include arteriolosclerosis as well as cardiovascular risk factors such as arterial hypertension, diabetes, and smoking (Stephan et al., 2009; Power et al., 2015; Frey et al., 2019).

Whole-brain decline of cortical thickness with increasing age has been consistently observed in previous research (Fjell and Walhovd, 2010; Hogstrom et al., 2013) and several studies have observed a relationship between cortical volume, cognition, and age (Head et al., 2008; Kirchhoff et al., 2014). Research about the inherent mechanisms describes an increase in glia and small-body neurons and decrease in large cell-body neurons populations throughout aging, contributing to a near constant cell density with diminishing brain volume (Terry et al., 1987; Martínez-Pinilla et al., 2016). Cortical thickness was also found to be associated with the extent of WMH in whole-brain- and region-specific analyses (Du et al., 2005; Seo et al., 2012; Tuladhar et al., 2015), which might be explained by secondary cortical degeneration through damaged white matter tracts (Alosco et al., 2013; Thong et al., 2013; Ter Telgte et al., 2018).

The effect of age on functional brain connectivity is more complex and studies reported heterogeneous effects captured by variety of different measuring methods during the last years. These effects report increase and decrease of mean FC across different cortical regions (Onoda et al., 2012; Vidal-Piñeiro et al., 2014; Zonneveld et al., 2019) as well as a progressive decrease in FC throughout the entire cortex (Farras-Permanyer et al., 2019). Recent studies that focused on alterations of intra- and internetwork connectivity separately report that FC between networks maintains stable or even increases with age, while FC within networks tends to decrease (Betzel et al., 2014; Chan et al., 2014). Looking at network characteristics, higher age was found to be associated with lower system segregation and altered network topology, both throughout the brain and in single-resting state networks (Geerligs et al., 2014).

Functional brain connectivity is considered to be determined by the structural connectome. An accumulating number of studies investigating resting-state fMRI connectivity in the presence of severe white matter damage in form of cerebral small vessel disease (CSVD) or stroke suggest that FC is negatively affected by white matter disconnection (Wu et al., 2015; Kim et al., 2016; Liu et al., 2019) and tract-specific reduction in FC in the context of WMH was reported (Langen et al., 2017). In addition, the hypothesis of secondary cortical degeneration through damaged white matter tracts indicates a direct pathophysiological link between WMH and cortical thickness (Alosco et al., 2013; Thong et al., 2013; Ter Telgte et al., 2018) and since dendrites are involved in interneural communication, it is suggested that alterations in functional interareal connectivity follow that phenomenon (Vieira et al., 2020).

Nevertheless, the question of whether there is an effect of age-related structural changes on FC in a healthy population with low-level white matter damage remains unanswered.

To gain a better insight into this relation, we investigated the association of age, white matter damage, and cortical thinning on FC in a healthy middle-aged to older population. Therefore, we first looked at the influence of age, microstructural white matter damage, and cortical thickness on FC in multiple linear regressions (MLRs). Instead of using WMH load as measure of microstructural alterations, we used the peak width of skeletonized mean diffusivity (PSMD) as a novel and fully automated MRI biomarker. Compared to white matter markers such as white hyperintensity volume, the PSMD eliminates contamination from cerebrospinal fluid (CSF) and the histogram-based approach enhances the ability to characterize subtle, diffuse diseases in the brain such as small vessel disease (Low et al., 2020). In addition, the PSMD is also strongly related to global cognition and has been shown to be closely associated with higher WMH lesion load (Wei et al., 2019). Measures of FC included mean connectivity of the entire cortex, additionally

separated in inter- vs. intranetwork connectivity as well as mean connectivity of the default, dorsal, salience, and control network. Since we expected to observe subtle effects in a relatively healthy cohort with a narrow range of age, we restricted our analysis to networks that perform associative, integrative tasks and, according to previous literature, exhibit greater changes with age than sensory systems in the brain (Chan et al., 2014). The default mode network is primarily composed of the medial prefrontal cortex, posterior cingulate cortex, precuneus, and the angular gyrus (Sormaz et al., 2018), while the dorsal attention network is primarily composed of the intraparietal sulcus and frontal eye fields (Fox et al., 2006; Farrant and Uddin, 2015). The default mode network shows greater activity in the task-free state and is mainly related to internally directed cognitions (Buckner et al., 2008); the dorsal attention network displays activation during performing tasks and supports external attention. Both the networks are anticorelated with each other in brain activity. The frontoparietal control network composes the dorsolateral prefrontal cortex and posterior parietal cortex and is considered to flexibly support both the default mode network and the dorsal attention network according to task demands, interpreted as a regulating role (Fornito et al., 2012; Elton and Gao, 2014). All the three functional networks are related to executive function (Niendam et al., 2012; Turner and Spreng, 2012; Dey et al., 2016). The major nodes of the salience network are in, particularly, the anterior insula and dorsal anterior cingulate cortex, which have been implicated as well in various features of executive function, including the orienting of attention (Corbetta and Shulman, 2002) and performance monitoring (Dosenbach et al., 2007). In a second step, we addressed the question if age-related network alterations are driven by specific functional areas and identified within default, dorsal, and salience network disconnected subnetworks that exhibited significant age-related decline in FC. With these subnetworks, representing only the portion of the functional network that is affected by the influence of age, we examined possible mediating effects of the PSMD and cortical thickness on the relationship between age and FC. Since among the different cognitive measurements, executive function seems to be the most vulnerable to age-related decline (Wecker et al., 2000; Verhaeghen and Cerella, 2002; Madden et al., 2017) and we investigated that if mean FC itself is a mediator of the relationship between age and executive cognitive function. We hypothesized that with an increasing age, white matter damage and cortical thickness are associated with an alterations in resting-state FC. Further, we predicted that part of the effect of age on FC is mediated by structural parameters Finally, we expected to observe that the effect of age on executive cognitive function is partially mediated by age-affected FC of the resting-state networks (subnetworks), due to their essential role in executive cognitive function, as described above.

MATERIALS AND METHODS

Study Population

For this study, we analyzed baseline data from the first 1,000 participants of the Hamburg City Health Study (HCHS) who were studied by brain MRI. The HCHS is a single center prospective, epidemiologic cohort study with an emphasis on imaging to improve the identification of individuals at risk for major chronic diseases and to improve early diagnosis and survival. A detailed description of the overall study design has been published separately (Jagodzinski et al., 2020). In brief, 45,000 citizens of the city of Hamburg, Germany, between 45 and 74 years were invited to an extensive baseline evaluation. A subgroup with present cardiovascular risk factors was invited to undergo standardized MRI brain imaging. For this analysis, we included the first 1,000 participants from this subgroup. Participants with brain MRI datasets imaging data of insufficient quality for white matter segmentation and construction of blood oxygenation level dependent (BOLD) signal were excluded from further analysis.

Baseline examinations in the HCHS comprise a set of standardized tests of cognitive function. To probe the association of age-related imaging correlates with executive function, we used data from the Trail Making Test part A and B (TMTA and TMTB) as well as the ratio score between both the tests. As an important covariate for cognitive function, we included information on the years of education. For descriptive purposes, we also included information on cardiovascular risk factors and comorbidities. This study was approved by the Local Ethics Committee of the Landesärztekammer Hamburg (State of Hamburg Chamber of Physicians, PV5131) and a written informed consent was obtained from all the participants.

Magnetic Resonance Imaging Acquisition

Images were acquired using the 3T Siemens Magnetom Skyra MRI Scanner (Siemens, Erlangen, Germany, United Kingdom). For three-dimensional (3D) T1-weighted anatomical images, rapid acquisition gradient-echo sequence [(Magnetization prepared rapid gradient echo-. sequence (MPRAGE)] was used with the following sequence parameters: repetition time (TR) = 2,500 ms, echo time (TE) = 2.12 ms, 256 axial slices, slice thickness (ST) = 0.94 mm, and in-plane resolution (IPR) = 0.83 mm^2 × 0.83 mm^2. 3D T2-weighted fluid-attenuated inversion recovery (FLAIR) images were measured with the following sequence parameters: TR = 4,700 ms, TE = 392 ms, 192 axial slices, ST = 0.9 mm, and IPR = 0.75 mm^2 × 0.75 mm^2. We used 5.2 min axial multi-echo echo-planar imaging (EPI) resting-state acquisition during which subjects were instructed to focus on a fixation cross. TR = 2,500 ms, TE = 25 ms, flip angle: 90°, Generalized Autocalibrating Partial Parallel Acquisition (GRAPPA): 2, acquisition matrix: 94 × 94, field of view (FOV): 250 mm^2 × 250 mm^2, 40 slices of 3 mm thickness, and 10% slice gap with a reconstructed voxel dimension of 2.7 mm^3 × 2.7 mm^3 × 3 mm^3. A total of 125 volumes were acquired. For the single-shell diffusion-weighted imaging (DWI), 75 axial slices were obtained covering the whole brain with gradients (b = 1,000 s/mm^2) applied along 64 non-collinear directions with the following sequence parameters: TR = 8,500 ms, TE = 75 ms, ST = 2 mm, IPR = 2 mm^2 × 2 mm^2, and anterior-posterior phase-encoding direction.

Peak Width of Skeletonized Mean Diffusivity and Cortical Thickness

The PSMD tool provided at http://www.psmd-marker.com was used to calculate the PSMD (Baykara et al., 2016). The process consists of two steps. First, DWI data including MD were skeletonized *via* tract-based spatial statistics (TBSS) procedure (Smith et al., 2006). Second, the PSMD is a diffusions tensor imaging (DTI)-derived measure based on skeletonization and histogram analysis and is calculated as the difference between the 95th and 5th percentile of MD values within the masked MD skeleton (Low et al., 2020). Mean cortical thickness across the entire cortex was measured on T1-weighted imaging data using the standardized FreeSurfer processing pipeline (version 6.0) (Fischl and Dale, 2000).

Preprocessing

All the data were preprocessed using fMRIPrep[1], a fully reproducible, preconfigured preprocessing pipeline for functional MRI, which works with several tools such as the Advanced Normalization Tools (ANTs)[2], and FreeSurfer version 6.0.[3] The preprocessing of the structural MR images included brain extraction, tissue segmentation, non-linear spatial normalization, surface preprocessing, and refinement of the brain mask. Functional preprocessing steps included BOLD reference image estimation, head-motion correction, susceptibility distortion correction (SDC), transformation of BOLD in native space, EPI to T1W registration, and resampling BOLD runs onto the Montreal National Institute (MNI) standard spaces.

Denoising

The denoising procedure was done with the XCP Imaging Pipeline (xcpEngine)[4] using independent component analysis (ICA)-based strategy for automatic removal of motion artifacts (ICA-Aroma) with the global signal regression to reduce the influence of motion on the data. ICA-AROMA uses four characteristics to determine whether each component corresponds to a signal or noise. The first two characteristics are spatial properties of the signal source: (1) the portion of the source that falls within a CSF compartment and (2) the portion of the source that falls along the edge or periphery of the brain. The other characteristics are derived from the time series of the source: (3) its maximum robust correlation with the time series, derived from realignment parameters and (4) its high-frequency spectral content. ICA-AROMA comprises two denoising steps. The first denoising step occurs immediately after classification. All the component time series (signal and noise) are included as predictors in the linear model and the residual BOLD time series is obtained *via* partial regression of only the noise time series. A second confound regression step occurs after temporal filtering (high-pass: 0.01, low-pass: 0.08), wherein mean signals from white matter and CSF and the global signal were regressed from the data (Ciric et al., 2017).

[1]http://fmriprep.org

[2]https://github.com/ANTsX/ANTs

[3]https://surfer.nmr.mgh.harvard.edu

[4]https://xcpengine.readthedocs.io

Network Construction and Measurement of Functional Connectivity

The reconstructed functional whole brain comprised nodes representing brain regions and edges as inter-regional resting-state FC. To define the network nodes, we divided the brain into 200 contiguous and uniform regions of interests (ROIs) based on local global parcelation of the human cerebral cortex by Schaefer et al. (2018). From these 200 ROIs, four resting-state networks were extracted, which contained the default mode network, dorsal attention network, salience network, and cognitive control network. All the regions of the resting-state networks were determined *a priori* by the Schaefer atlas and were, thus, unique in each resting-state network without overlapping between networks. The individual mean time series were then extracted for each ROI. Finally, absolute values of the Pearson's correlation coefficients were calculated between each pair of ROIs for each subject, which resulted in a square undirected correlation matrix representing the whole cortex and for each resting-state network. To further denoise spurious interregional correlations, the connectivity matrices were thresholded by preserving a proportion of 50% of the strongest weights. All the other weights and all the weights on the main diagonal (self-connections) were set to zero. Whole-brain and network FC was calculated by taking the mean of the edges between all the nodes in the matrix that were not excluded. In addition, as a measurement of control, we constructed connectivity matrices with absolute values as well as matrices with both the negative and positive correlations, which were unthresholded or preserving a portion of 70, 30, and 10% of the strongest weights (see **Supplementary Figures 2, 3**).

Trail Making Test

The Trail Making Test part A (TMTA) is a measure of psychomotor speed (Razzak, 2013). In this test, circles are numbered from 1 to 25 and subjects are required to draw a line connecting the circles in numerical sequence as quickly as possible. The Trail Making Test part B (TMTB) is a measure of executive cognitive control (Reitan, 1958). The TMT-B requires the subject to connect 25 encircled numbers and letters in numerical and alphabetical order, alternating between the numbers and letters, which are randomly distributed in space. The subject is also asked to connect the array of circles as quickly as possible without lifting the pencil. During the tests, the examiner corrects each error immediately (Terada et al., 2013). In both the parts of the trail making test, a shorter completion time is considered a gauge of better cognitive performance and is measured in seconds. In order to adjust for the influence of motor speed and visual search on executive function, we analyzed additionally the ratio score between both the tests (B/A).

Statistical Analysis

All the statistical analyses were conducted using R version 4.0.2. In an initial step, we used univariate analyses to examine the influence of age on all the imaging measurements and the cognitive TMTA, TMTB as well as the TMT ratio score. To assess the relationship between altered FC as the dependent variable and age, cortical thickness, and the PSMD as predictors, we applied several multiple linear regressions, adjusted for sex and

years of education. These linear models were calculated for the mean FC of the brain as a whole and separated for inter- vs. intranetwork connectivity as well as for all the four resting-state networks. To correct for multiple testing, the statistical threshold was set at $p \leq 0.007$ (0.05/7; based on four networks and three global measurements). All the networks that failed to show a correlation with age were excluded from further analysis. Within each resting-state network, we aimed to identify those edges or subnetworks that significantly correlate with an increasing age. Therefore, we used the network-based statistic (NBS) approach (Zalesky et al., 2010), which addresses multiple comparisons in network statistics. In summary, a *t*-test was performed on each pair of ROIs to test the significance of correlation between FC and an increasing age, based on the values stored in the connectivity matrix of each subject. The connections with a test statistic exceeding a threshold of $t = 3.2$ ($p = 0.0007$) were admitted to the set of suprathreshold links for which a path can be found between any two nodes, thereby forming an interconnected network and are referred to as connected components in graph theory. The assumption is that the topological configuration of a putative experimental effect is well represented by a component and is not confined to a single connection or distributed across multiple connections that are isolated from each other. To evaluate the significance for each component, a familywise error (FWE)-corrected *p*-value was then ascribed to each component based on its size using permutation testing. The NBS was then applied to the randomized data and the size of the largest component was recorded. A total of 5,000 permutations were generated to estimate the null distribution of the maximal component size. Subsequently, the corrected *p*-value for an observed component found in the original data was calculated as the proportion of permutations for which the maximal component size was greater than or equal to the observed component, ensuring control of the FWE rate. To better visualize the resting-state networks and their significant disconnected subnetworks correlated with age, we used the BrainNet Viewer (Xia et al., 2013). Finally, mediation analyses using the Lavaan package (Rosseel, 2012) were conducted to further interrogate first possible mediation effects of the PSMD and cortical thickness between age and FC in the studied subnetworks and second a possible mediation effect of FC between age and executive cognitive function. Therefore, we used non-parametric bootstrapping with 10,000 iterations to estimate direct and indirect effects between variables.

RESULTS

Sample Characteristics

The demographics for the entire HCHS cohort and the median values of the cognitive test are shown in **Table 1**. Of 1,000 study participants, 24 study participants had to be excluded. During the visual examination of FLAIR images, one subject was directly excluded for severe imaging artifacts ($n = 1$). In addition, we excluded 23 subjects after the preprocessing due to bad image quality resulting in missing data in the connectivity matrices ($n = 23$). The remaining 976 subjects showed good image quality metrics assessed with the MRI-QC toolbox (Esteban et al., 2017).[5] Median age was 63 years and 45.4% of participants were female. The median PSMD was 0.0002 [interquartile range (IQR) 0.0001], while global cortical thickness had a median of 2.319 (IQR 0.141). The distribution of the two structural parameters is shown in **Figure 1**; the cortical thickness for young as well as older participants of the cohort is additionally presented with a boxplot in **Figure 2C**. The mean FC throughout the whole cortex measured as the mean correlation between all the regions of all the participants was 0.362 (IQR = 0.04). The mean connectivity matrix of all the participants is shown in **Figure 2D** along with a difference map. **Figure 2E** shows the change in FC between younger and older participants of the cohort (see **Figure 2**). Within the resting-state networks, the default mode network showed a mean connectivity of 0.42 (IQR = 0.05), the dorsal network showed a mean connectivity of 0.42 (IQR = 0.08), the salience network showed a mean connectivity of 0.4 (IQR = 0.09), and the control network showed a mean connectivity of 0.38 (IQR = 0.09).

Effects of Age on Brain Structure, Functional Connectivity, and Executive Function

The univariate analyses revealed a significant effect of age on cortical thickness ($r^2 = 0.16$, $r = -0.4$, $p < 0.001$), the PSMD ($r^2 = 0.25$, $r = 0.5$, $p < 0.001$), global FC ($r^2 = 0.029$, $r = -0.17$, $p < 0.001$), global intranetwork connectivity ($r^2 = 0.043$, $r = -0.21$, $p < 0.001$), global between network connectivity ($r^2 = 0.02$, $r = -0.15$, $p < 0.001$) as well as on default ($r^2 = 0.026$, $r = -0.16$, $p < 0.001$), dorsal ($r^2 = 0.039$, $r = -0.2$, $p < 0.001$), salience ($r^2 = 0.049$, $r = -0.22$, $p < 0.001$), and control ($r^2 = 0.009$, $r = -0.09$, $p = 0.004$) network connectivity, and on the TMTA score ($r = 0.32$, $r^2 = 0.1$, $p < 0.001$) as well as on the TMTB score ($r^2 = 0.094$, $r = -0.3$, $p < 0.001$), as shown in **Figure 3**. The TMTB/TMTA ratio score failed to demonstrate any association with age and was, therefore, excluded from further analysis. The univariate analysis of age and FC was additionally performed with different thresholds for the connectivity matrices, showing robust results throughout different thresholding, as shown in **Supplementary Table 2**. Of particular importance, since we used absolute values, we might not have measured age-related increase in between network connectivity, which correspond to reductions in the magnitude of negative or anticorelation. Therefore as a measure of control, we investigated the relationship between age and whole-global FC as well as separated into intra- and internetwork connectivity without absolute values and instead with signed matrix values throughout different thresholds. **Supplementary Table 3** reports the results and **Supplementary Figure 3** shows the mean FC matrices with signed values of all the participants. If no links or 30% of the weakest connections were excluded, a weak increase in internetwork connectivity could be observed in contrast to the analysis with absolute values and, as a result, no significant

[5]https://mriqc.readthedocs.io/en/stable/

TABLE 1 | Sample characteristics and image analysis results—subjects used for MRI analysis of the Hamburg City Health Study.

	Sample characteristics (*N* = 976)	Sample characteristics young 45–63 years (*N* = 490)	Sample characteristics old 64–75 years (*N* = 486)
Female sex (*n*, %)	443 (45.4%)	240 (49%)	203 (42%)
Age (years), median (IQR)	63 (13)	56 (7.75)	69 (5)
Education (years), median (IQR)	13 (4)	14 (5)	13 (4)
TMT B Score (s), median (IQR)	79 (37)	70 (32.5)	86 (42)
TMT A Score (s), median (IQR)	36 (16)	33 (13)	41 (18)
Vascular risk factors			
Current smoking (*n*, %)	155 (17.4%)	98 (20%)	71 (15%)
Diabetes* (*n*, %)	82 (9%)	38 (7%)	53 (11%)
BMI (kg/m^2), median (IQR)	26.28 (5.6)	26.42 (5.8)	26.3 (5.5)
Hypertension** (*n*, %)	665 (72%)	283 (58%)	382 (79%)
Structural MRI measures			
PSMD, median (IQR)	0.000217 (0.00005)	0.0002 (0.00004)	0.00024 (0.00005)
Cortical thickness (mm) and median (IQR)	2.319 (0.141)	2.5 (0.12)	2.3 (0.14)

*BMI, body mass index; IQR, interquartile range; mm, millimeter; PSMD, peak width of skeletonized mean diffusivity; TMT, Trail Making test. *Presence of diabetes was defined as blood glucose level > 126 mg/dl or a self-reported prevalence of diabetes. **Presence of hypertension was defined as blood pressure > one-fourth 140/90 mm Hg, intake of antihypertensive medication, or a self-reported prevalence of hypertension.*

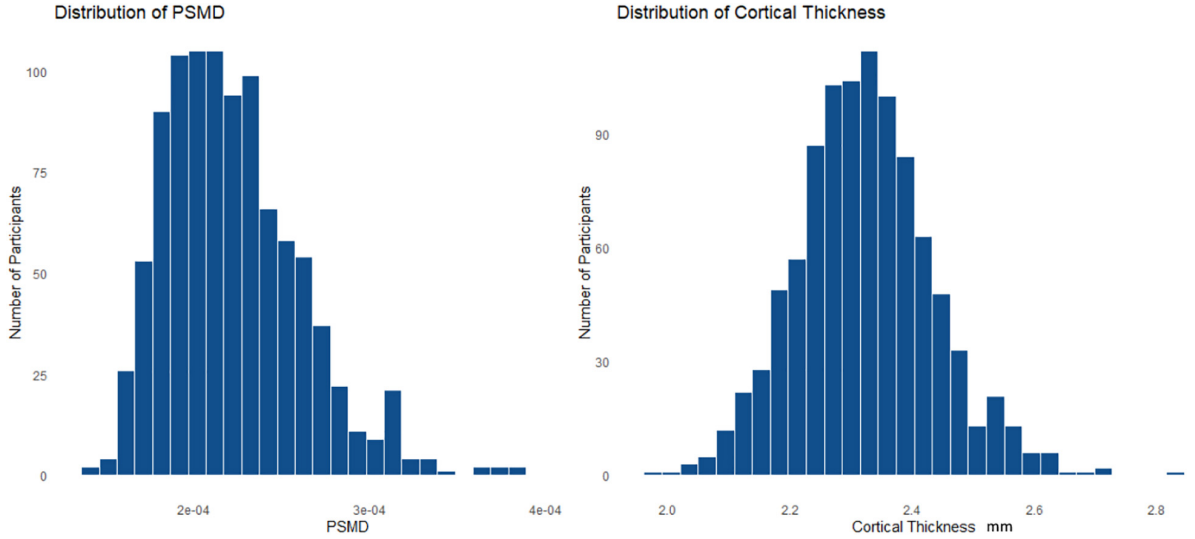

FIGURE 1 | Histogram **(A)** is showing the distribution of the peak width of skeletonized mean diffusivity (PSMD) and histogram **(B)** is representing the distribution of the cortical thickness throughout the whole cohort.

drop in whole global connectivity. This trend loses its significance when excluding 50% of the weakest connections and finally becomes negative when excluding 70% of the links.

Effects of Brain Structure on Functional Connectivity

To analyze the effect of age, cortical thinning, and the PSMD on FC, we performed multiple linear regression analyses, adjusted for sex, and years of education. Therefore, we iteratively tested the model on a global scale and for each resting state network (default, dorsal, salience, and control). After adjusting the threshold for multiple comparisons, neither cortical thinning nor the PSMD predicted FC. Instead, the results of the linear model indicated a negative, but weak association between age and FC. Decreasing FC with increasing age was continuously observed across the entire brain (r^2 = 0.034, r = −0.184, p < 0.001), for global intranetwork connectivity (r^2 = 0.055, r = −0.23, p < 0.001), global between network connectivity (r^2 = 0.036, r = −0.2, p < 0.001) as well as within the default (r^2 = 0.029, r = −0.17, p < 0.001), dorsal (r^2 = 0.039, r = −0.21, p < 0.001), and salience (r^2 = 0.055, r = −0.234, p < 0.001) network. The correlation between age and FC within the control network did not exceed our statistical threshold (r^2 = 0.014, r = −0.12, p = 0.04) and was, therefore, left out from further analysis. To investigate once again, if the results change using matrices with positive and negative values, the relationship between age,

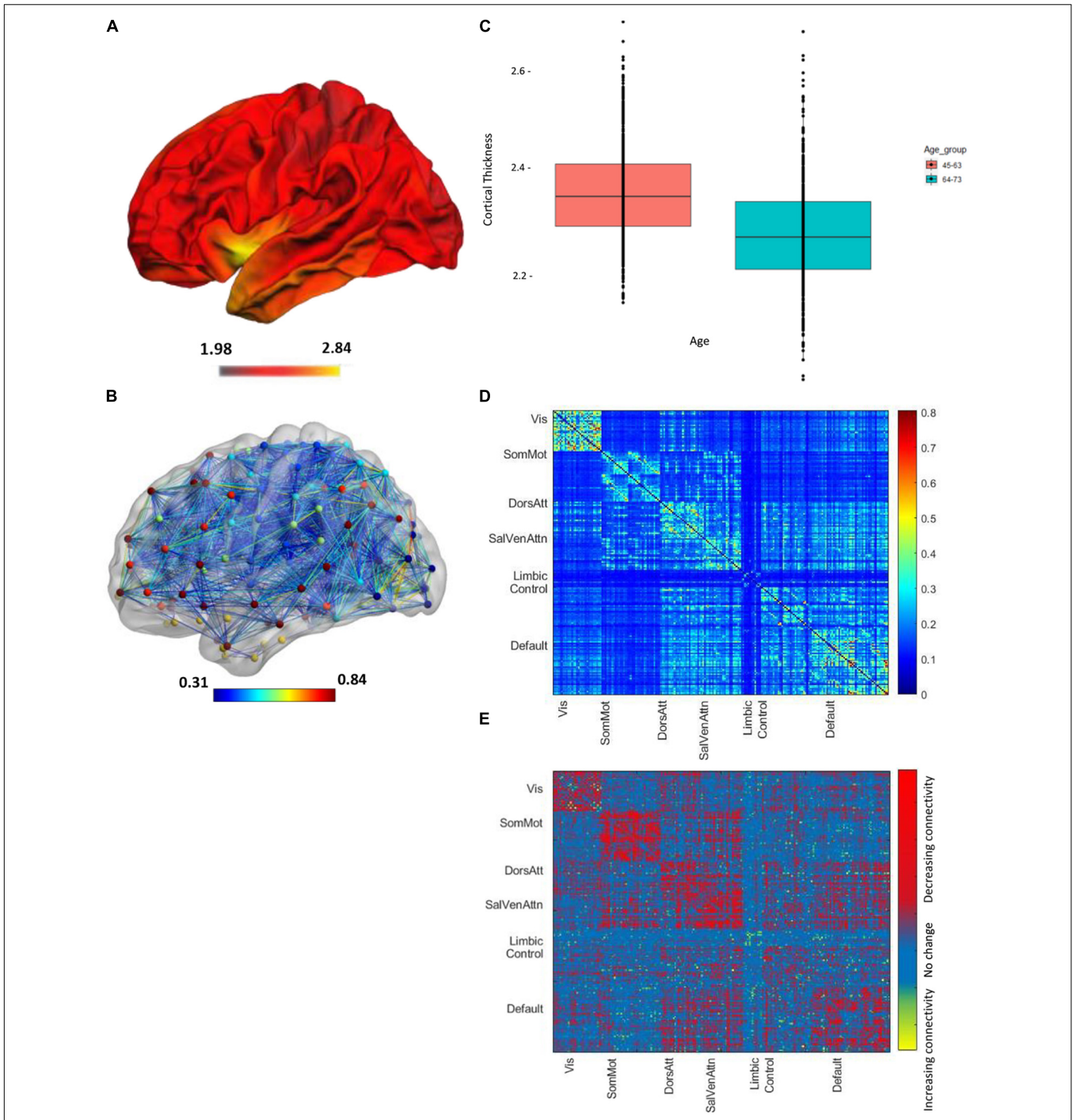

FIGURE 2 | Imaging parameters of all the n = 976 participants, projected on a brain template in the Montreal National Institute (MNI) space. The color bar shows the mean cortical thickness (in mm). **(A)** Visualization of cortical thickness. **(B)** The boxplot shows the mean cortical thickness of between 45 and 63 years of age (red box) and subjects between 45 and 75 years of age (blue box). **(C)** Global functional connectivity network, the colors of nodes represent different networks the nodes belong to. The edge colors represent the strength of the correlation values. **(D)** Mean node-to-node correlation matrix of the whole cohort. Names along axes represent network labels and the color bar shows the correlation strength. **(E)** The difference map regions with decreasing and increasing connectivity for the younger vs. older age brains.

structural parameters, and FC was additionally evaluated without absolute values at a threshold of 50%. With the exception of internetwork connectivity, which no longer demonstrated any change with age, no significant differences could be observed compared to the analysis with absolute values (see **Supplementary Table 4**).

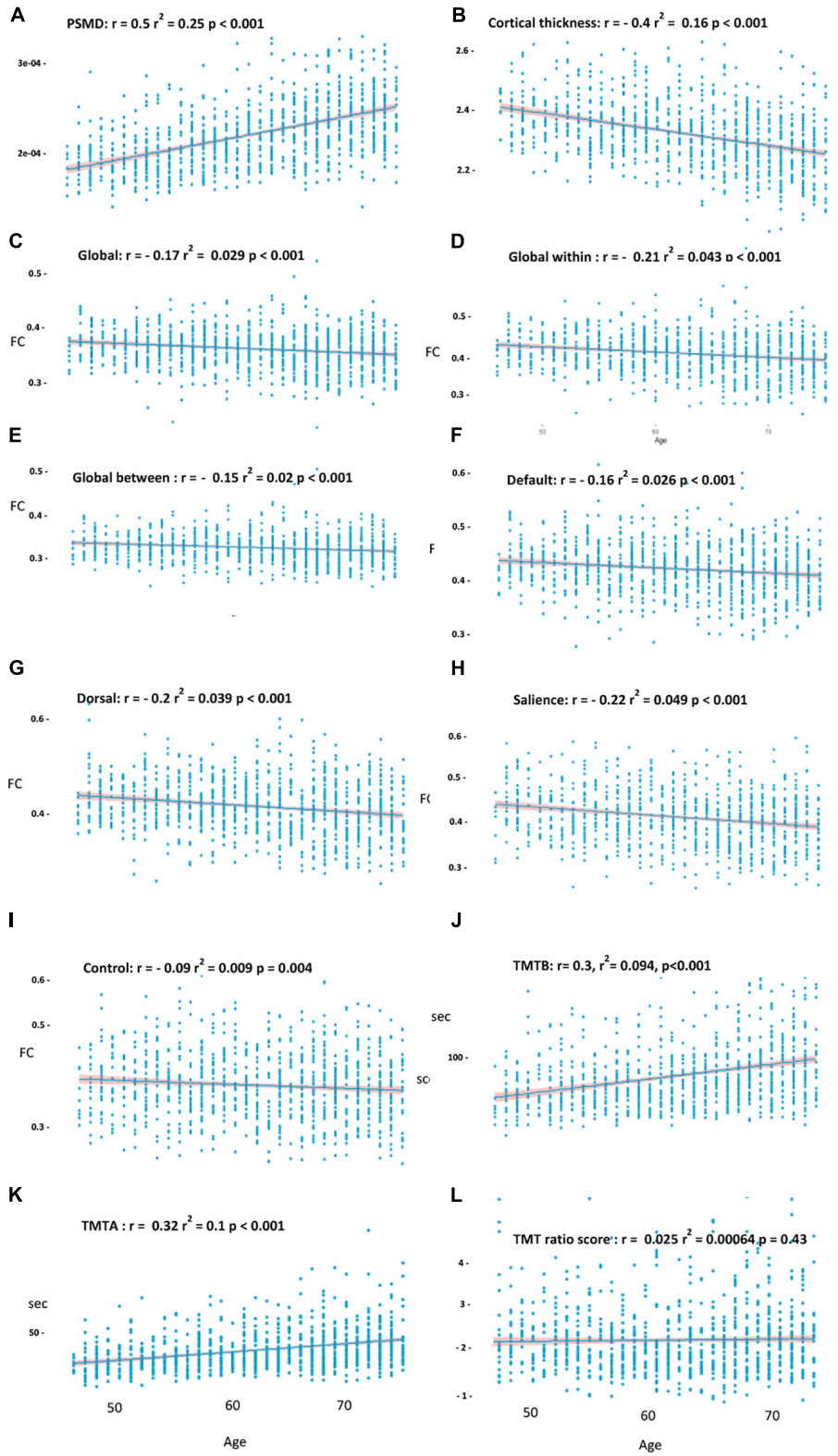

FIGURE 3 | Effects of age on the PSMD **(A)** cortical thickness, **(B)** on global functional connectivity, **(C)** global intranetwork connectivity, **(D)** global between network connectivity, **(E)** within default, **(F)** dorsal, **(G)** salience, **(H)** control network, **(I)** the Trail Making Test B (TMTB), **(J)** TMTA, **(K)** and TMT ratio score **(L)**. Above *r* and r^2 corresponds to the linear model before covariate inclusion. Shade around the regression line shows the 95% CI.

Disconnected Subnetwork With Reduced Functional Connectivity With Higher Age

The analysis using the NBS toolbox identified subnetworks significantly associated with age among the whole-brain network as well as within default, dorsal, and salience network, respectively (see **Figure 4**). **Supplementary Table 1** provides a list of nodes comprising the disconnected subnetwork as well as their degree in this subnetwork. Subnetworks showing a significant decrease in connectivity with increasing age among default, dorsal, and salience network comprised 10, 13, and 36% of the connections of the original networks. Overall, subnetworks of connections with age-related reduced FC appeared to include a similar amount of inter- and intrahemispheric connections with no specific pattern as compared to the whole resting-state networks. In addition, we investigated whether there are areas within the resting-state network that exhibits an increase in connectivity with aging. However, based on the statistical threshold for multicomparison, we did not find any connected graph components with the NBS toolbox that showed increasing connectivity with age. Since the threshold of 50% of the connectivity matrices we used for the NBS toolbox is arbitrary, we repeated our subnetwork extraction with non-thresholded matrices. Despite small variation in the total number of regions, subnetworks extracted from thresholded and unthresholded matrices were highly consistent in terms of the number of links and regions involved (data not shown).

Mediation Analysis

To assess whether structural parameters were mediators of the relation between age and FC, we performed mediation analyses of model one with age as a predictor of FC of our extracted subnetworks and the PSMD as well as cortical thickness as possible mediators between age and the outcome variables global, default, dorsal, and salience subnetworks mean connectivity (see **Figure 5A**). The mediators were modeled as operating

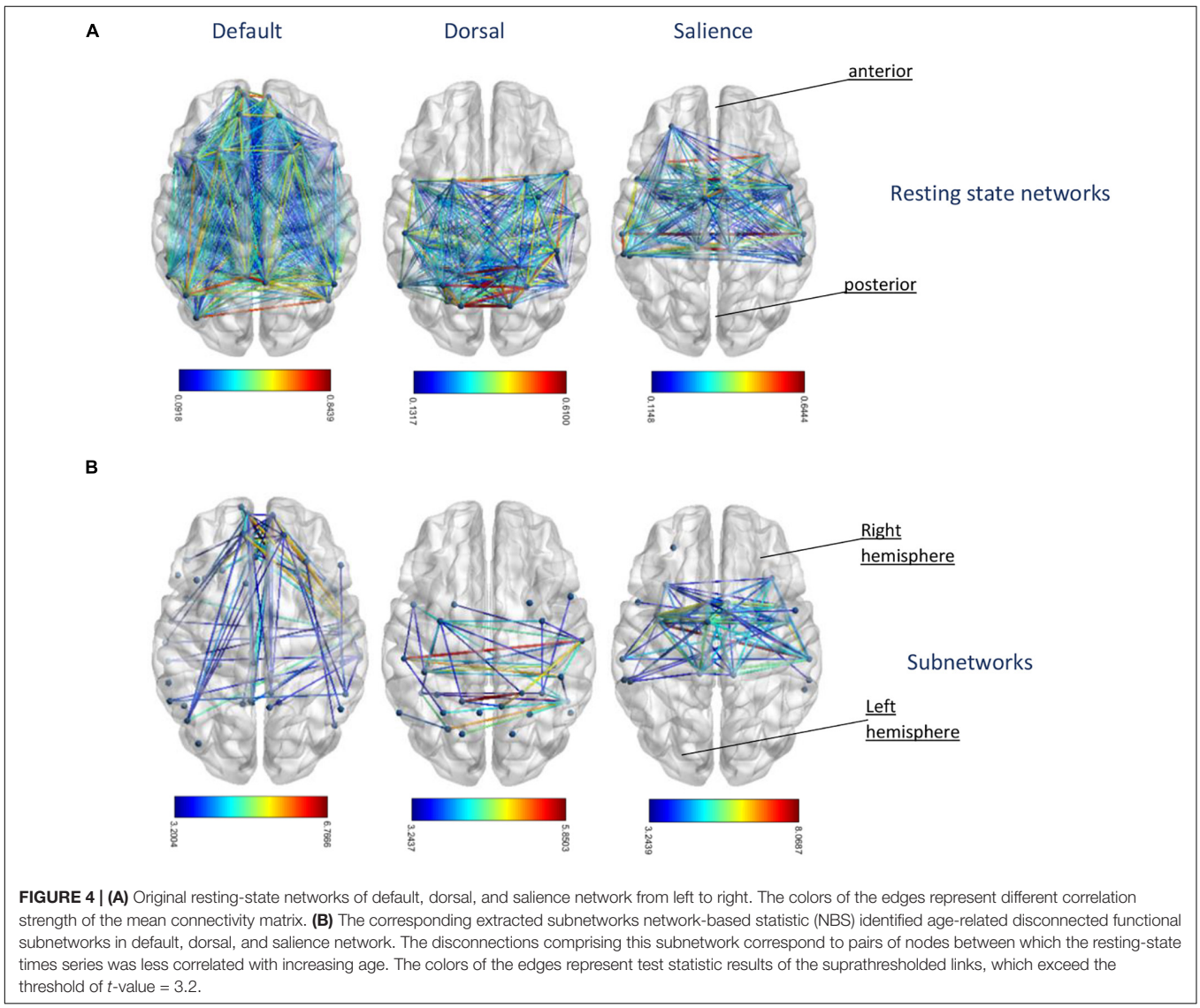

FIGURE 4 | (A) Original resting-state networks of default, dorsal, and salience network from left to right. The colors of the edges represent different correlation strength of the mean connectivity matrix. **(B)** The corresponding extracted subnetworks network-based statistic (NBS) identified age-related disconnected functional subnetworks in default, dorsal, and salience network. The disconnections comprising this subnetwork correspond to pairs of nodes between which the resting-state times series was less correlated with increasing age. The colors of the edges represent test statistic results of the suprathresholded links, which exceed the threshold of *t*-value = 3.2.

in parallel and, thus, each mediator was a covariate for the others. In model two, global network and default, dorsal, and salience subnetwork mean connectivity were examined as mediators operating in parallel as well between the predictor age and the TMTB or the TMT A score as outcome variables (see **Figure 5B**). Results of this analysis are given below (see **Table 2**).

In the first model, cortical thickness had a significant, but small ($\beta = -0.04$) partial mediating effect between age and FC in the default subnetwork, but not in other subnetworks (see **Figure 5A**). The PSMD had no significant mediating effect on the relationship between age and FC within the resting-state subnetworks.

Of all the subnetworks, only FC of the default subnetwork emerged as a significant, but weak partial mediator ($\beta = 0.02$) between age and the TMTB score (see **Figure 5B**), while FC in no other subnetwork had a significant mediating effect on the TMTB score. We did not observe any mediation effects of subnetworks between increasing age and the TMTA score outcomes. Even though not part of our hypothesis, we tested in an exploratory analysis the mediation effect of cortical thickness between age and the TMTB score in a separate model. Cortical thickness showed no significant mediation effects (see **Supplementary Figure 1**).

DISCUSSION

We studied the influence of age, microstructural white matter damage, and cortical thinning on FC and executive cognitive function in a healthy population at increased cardiovascular risk. We identified a significant association of age with all the structural and functional imaging parameters and cognition, although the association between age and FC was weak. However, neither the PSMD as a measure of diffuse white matter microstructural alteration nor cortical thinning revealed any association with FC when adjusted for age. After extracting subnetworks consisting exclusively of connections that showed a decreased connectivity with age, we discovered a small but significant mediation effect of global cortical thickness on the relation between age and FC in the default subnetwork. Finally, FC of the default subnetworks showing an age-associated decline had a weak but significant mediating effect on relation between age and executive cognitive function measured by the TMTB.

Age-related decline of brain function likely is the consequence of multiple biological factors, leading to structural and functional alterations, including cortical thinning, white matter injury, and loss of functional coordination between regions. In line with this assumption, with advancing age, we observed a linear pattern of increasing microstructural white matter damage (i.e., the

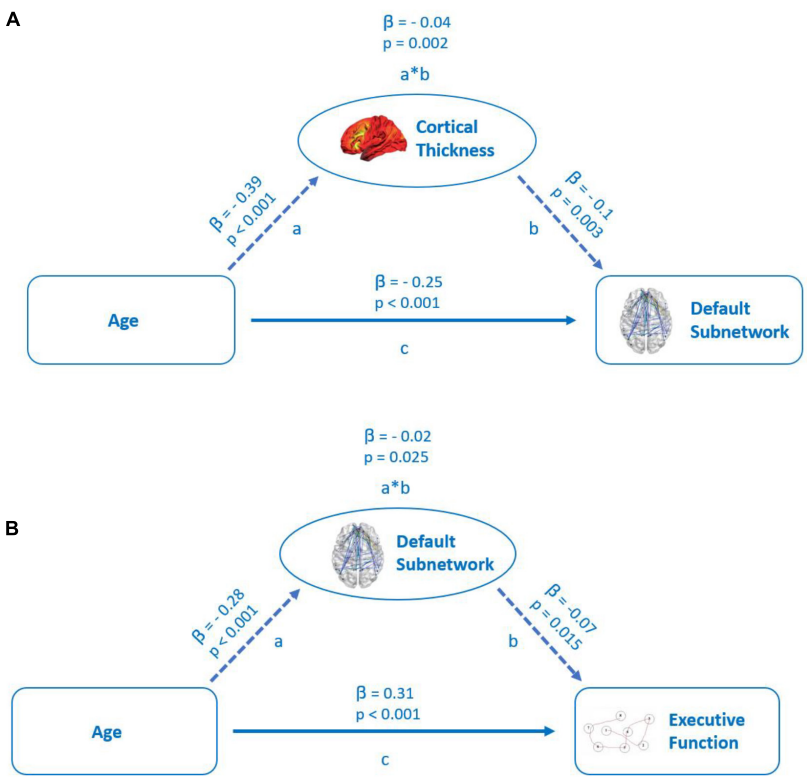

FIGURE 5 | (A) Mediation of the relation between age and functional connectivity in default subnetwork by cortical thickness. Path a: relationship between age and cortical thickness. Path b: relationship between cortical thickness and default subnetwork connectivity. Path c: direct relationship between age and default subnetwork connectivity. **(B)** Mediation of the relation between age and executive cognitive function (TMTB) by functional connectivity of the default subnetwork. Path a: relationship between age and default subnetwork connectivity. Path b: relationship between default subnetwork connectivity and executive cognitive function. Path c: direct relationship between age and executive cognitive function. Both the models represent standardized beta coefficients and the respective *p*-values.

TABLE 2 | Significant results after multiple testing corrections for the multiple regression as well as the mediation analysis, representing unstandardized coefficient estimate (beta), SE, standardized estimate (standard beta), the *p*-value, and the r^2 value.

Significant results					
Variables	**Beta**	**Std. error**	**Std. beta**	***p*-Value**	R^2
Alteration of functional connectivity with age					
Global mean connectivity	−0.0007	0.0002	−0.14	$p < 0.001$	0.034
Global mean within network connectivity	−0.0009	0.0002	−0.17	$p < 0.001$	0.049
Global mean between network connectivity	−0.0006	0.0002	−0.14	$p < 0.001$	0.027
Mean default connectivity	−0.0006	0.0002	−0.11	$p = 0.005$	0.029
Mean dorsal connectivity	−0.001	0.0003	−0.17	$p < 0.001$	0.039
Mean salience connectivity	−0.002	0.0003	−0.2	$p < 0.001$	0.055
Mediation model one					
Total effect	−0.004	<0.0001	−0.29	$p < 0.001$	–
Direct effect	−0.003	<0.0001	−0.24	$p < 0.001$	–
Indirect effect	−0.001	<0.0001	−0.04	$p = 0.002$	–
Mediation model two					
Total effect	1.365	0.138	0.31	$p < 0.001$	–
Direct effect	1.234	0.142	0.28	$p < 0.001$	–
Indirect effect	0.101	0.045	0.02	$p = 0.025$	–

increasing PSMD), increasing cortical thinning, and a weak decrease in FC. Moreover, older age was associated with worse psychomotor speed and executive function as measured by the TMTA and the TMTB. These findings confirm those previous studies showing age-dependent linear pattern of changes of resting-state FC, structural damage, and cognitive performance (Onoda et al., 2012; Veldsman et al., 2020). Some reports of non-linear age-related patterns demonstrate an accelerated decline in structural measurements (Fjell and Walhovd, 2010) and FC (Betzel et al., 2014) in old age or even a non-linear increase of FC in middle adulthood (Staffaroni et al., 2018) in particular concerning the global connectivity between networks (Betzel et al., 2014; Chan et al., 2014). We could only monitor an increase in connectivity between networks in the additional control analysis of matrices with negative and positive correlations that were subjected to a low threshold or no thresholding at all. The cross-sectional design and the limited range of age including only participants between 46 and 75 years of age may have reduced the possibility of detecting stronger or opposing age-related trends and, thus, further efforts are required to determine the shape of progression of imaging measurements over lifetime. Regarding FC in particular, we reproduced the overall findings in literature of age-related FC decrements, which seem to preferentially affect default (Damoiseaux et al., 2008; Dey et al., 2016), dorsal network (Tomasi and Volkow, 2012; Staffaroni et al., 2018), and salience network (Vidal-Piñeiro et al., 2014; Ng et al., 2016). However, the negative influence of age on FC identified in this study was only weak, which might indicate resilience of FC to aging across a wide age range. Other studies observed a somewhat stronger relationship between age and FC (Chan et al., 2014; Madden et al., 2017). This discrepancy can possibly be explained by the fact that their sample comprised a significantly higher age range and a higher age maximum. Stronger associations between age and FC are likely to be seen when comparing the brain of average 20-year-old and the brain of average 80-year-old (Betzel et al., 2014; Madden et al., 2017). Another possible explanation concerns the character of the studied cohort itself. Considering the expectation that cardiovascular risk factors are more prevalent in older adults, the selection may have a particular impact on younger middle-aged participants because they disproportionately represent individuals with poor cardiovascular health compared with age-matched individuals in other more healthier samples or the general population. Due to the sensitivity of FC to cardiovascular health, this may ultimately have reduced the age differences in FC in the current sample.

In our multiple regression model, we found no direct effect of the PSMD or cortical thinning on FC neither on global FC nor on the connectivity of the resting-state networks when corrected for age. Aging, on the other hand, was independent from the structural imaging measures associated with different degrees of lower average FC throughout the whole brain, global intra- as well as internetwork connectivity, and within three of the four resting-state networks, indicating a broadly distributed but not uniform age-related decline. In our multiple regression model, we did not detect an effect of age on the control network, even though a decrease of FC in this network has been reported (Betzel et al., 2014). The fact that no change could be observed in our sample can again probably be attributed to the lower median age and smaller age range as compared to other studies. A decrease of FC in the frontoparietal control network may only appear at a later point in time or only with more severe structural damage.

Nevertheless, our findings suggest an independent influence of age on structural brain changes and FC. While recent studies have found that FC tends to be reduced globally and within resting-state networks with increasing age, the relationship between structural white matter damage and FC seems to be less clear. According to current knowledge, temporospatial organization of neuronal activity in the brain is supported and constrained by the anatomy of axonal projections that form structural connections between both the adjacent and remote brain

areas (van den Heuvel and Sporns, 2019; Suárez et al., 2020). In this context, the "disconnection hypothesis" indicates that compromised integrity of these white matter pathways, e.g., WMH or altered MD, inflicts a deficit in FC. Yet, even though a variety of studies with clinically and/or radiologically manifest patients with CSVD report a relationship between white matter lesions and FC (Yi et al., 2012, 2015; Schaefer et al., 2014; Wang et al., 2019), several studies with cognitively normal and healthy individuals with low white matter lesion volume found no relationship between structural damage and FC (Madden et al., 2017; Staffaroni et al., 2018). At this point, we may conclude that a low lesion volume or small change in diffusion pattern does not affect the pattern of synchronous neuronal activation and that the measured decline in FC in our population is driven by other factors. However, in most articles, as also in this study, the extent of white matter damage has been quantified by total normalized values of the whole brain. If we assume that lesions in functionally silent brain areas can be compensated more easily by rerouting information through alternative redundant pathways, while even small lesions in functionally relevant hubs are likely to be associated with significant functional limitations. In this case, total lesion volume or the global PSMD may have insufficient explanatory value regarding the impairment of neuronal communication.

Given these considerations, the approach of measuring mean cortical thickness to reflect neurodegeneration can also be viewed critically, since the impact of cortical atrophy on FC may vary for different regions. Age-dependent cortical atrophy has been observed in several studies (Fjell et al., 2009; Azevedo et al., 2019) and could already be linked to FC (Kim and Lee, 2011; Van Tol et al., 2014). Cortical thickness has also been associated with white matter lesions (Mayer et al., 2020) and conceptualized as mechanism underlying this association, secondary cortical degeneration through white matter tracts damaged by WMH (Thong et al., 2013) was suggested. Indeed, several studies show that cortical atrophy in different regions is shaped by profiles and degree of underlying white matter connectivity and their corresponding lesions (Reijmer et al., 2017; Mayer et al., 2020). Thus, the impact on FC might differ according to the degree of atrophy in specific regions and the strategic importance of these affected regions.

We identified subnetworks of significant age-related decreased FC among the studied networks. These subnetworks comprised between 10 and 36% of the total network connections, affecting both the hemispheres equally and including both the inter- and intrahemispheric connections. These results suggest that the effect of age on FC does not show any specific regional pattern, but can be observed in a small fraction of functional connections across the entire brain. Overall, the relationship between cortical thickness and FC observed in this study was weak. This again might be related to the fact that broad structural measurements such as mean cortical thickness are too rough to detect subtle and more localized alterations in functional brain networks.

The association between age and executive function was in part mediated by FC among the network parts of the default subnetwork that were significantly altered with age. Executive function has been reported to be particularly sensitive to decline with increasing age (Wecker et al., 2000; Verhaeghen and Cerella, 2002) and associations of age-related decreased default mode activity and executive function have been observed in previous studies (Damoiseaux et al., 2008). In theory, the default mode network is deactivated when the person engages in a task and aging might impair this deactivation (Dey et al., 2016) and attenuate the function of the default mode network as a network-hub, leading to lower executive cognitive performance. Our results suggest that decline of executive cognitive performance with age might at least to some extent results from altered communication between brain regions representing nodes of the default mode network. Again, the association between disturbed FC and executive function was weak, which may relate to the fact that cognitive function is complex and the idea of relating specific cognitive functions to simple connectivity measures between specific brain regions within a single network is likely to fall short (Chan et al., 2014). In addition, our mediation analysis showed no significant mediator effect of FC on the TMTA, only a trend with the connectivity of the default subnetwork. However, because the TMTB/TMTA ratio score failed to demonstrate any alterations with an increasing age and was, therefore, not considered for the mediation model, we cannot exclude a potential influence of psychomotor speed on our measurement of executive cognitive function.

This study relies on a large number of participants and modern methodological approaches with multilevel analysis. Nevertheless, we included only a limited number of structural, functional, and cognitive variables. The total variance in FC shared with age; both the structural parameters and the covariates sex and education were ranging from ∼3 to 6% (by r^2) meaning that most of the person-specific variation in FC is explained by parameters not included in our model. Our ability to identify mediating influences of structural alterations on age-functional connectivity relationships may be compromised by the relatively small relationships between age and FC itself. Furthermore, it is likely that the observed functional decline in dorsal and salience networks is also reflected by changes in cognitive function, which, however, are not monitored by the TMTA or the TMTB. Finally, this is a cross-sectional study in which dynamic developments with age can only be captured to a limited extent and which does not allow inference about causality of observed association.

In summary, we report an age-accompanied linear increase in markers of structural brain damage and a weak linear decrease in FC and executive cognitive function in a large population-based cohort of middle-aged to older participants with vascular risk factors. Our results indicate that alterations in FC with increasing age are not uniform across all the networks and affected networks show a limited number of broadly distributed connections with age-related functional decrease. The PSMD, as a marker of microstructural white matter damage, had no mediating effect between age and FC changes, but decreased cortical thickness had such an effect, albeit weak. Finally, FC of the age-dependent parts of the default mode network showed a weak association with performance in a test of executive function.

Altogether, these findings suggest a potential although weak role of age-related cortical brain changes in mediating the effects of higher age on functional brain connectivity and weak role of age-related functional brain connectivity in selected brain networks on impaired cognitive function.

DATA AVAILABILITY STATEMENT

Anonymized data of the analysis not published within this article will be made available on reasonable request from any qualified investigator after evaluation of the request by the Steering Board of the HCHS. Requests to access these datasets should be directed to RT, r.twerenbold@uke.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Landesärztekammer Hamburg (State of Hamburg Chamber of Physicians, PV5131). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MS: conceptualization, formal analysis, visualization, and writing – original draft. MS, ES, MP, CMay, and BF: data curation. MS, ES, MP, CMal, BF, CMay, UH, RT, JF, SK, JG, CG, GT, and BC: investigation and writing – review and editing. MS, ES, and CMal: methodology and software. GT and BC: supervision. All authors described contributions to the manuscript using the CRediT contributor role taxonomy and approved the submitted version.

FUNDING

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The participating institutes and departments from the University Medical Center Hamburg-Eppendorf contribute all with individual and scaled budgets to the overall funding. The Hamburg City Health Study is also supported by Amgen, Astra Zeneca, Bayer, Badischen Anilin- & Sodafabrik (BASF), Deutsche Gesetzliche Unfallversicherung (DGUV), Deutsches Institut für Ernährungsforschung Potsdam-Rehbrücke (DIFE), the Innovative medicine initiative (IMI) under Grant Number 116074 and the Foundation Leducq under Grant Number 16 CVD 03., Novartis, Pfizer, Schiller, Siemens, Unilever and "Foerderverein zur Foerderung der HCHS e.V.". The funders were not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication. This work was supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)—178316478—Project C1 (CG) and Project C2 (BC,GT).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.782738/full#supplementary-material

REFERENCES

Alosco, M. L., Gunstad, J., Jerskey, B. A., Xu, X., Clark, U. S., Hassenstab, J., et al. (2013). The adverse effects of reduced cerebral perfusion on cognition and brain structure in older adults with cardiovascular disease. *Brain Behav.* 3, 626–636. doi: 10.1002/brb3.171

Azevedo, C. J., Cen, S. Y., Jaberzadeh, A., Zheng, L., Hauser, S. L., and Pelletier, D. (2019). Contribution of normal aging to brain atrophy in MS. *Neurol. Neuroimmunol. Neuroinflamm.*. 6:e616. doi: 10.1212/NXI.0000000000000616

Baykara, E., Gesierich, B., Adam, R., Tuladhar, A. M., Biesbroek, J. M., Koek, H. L., et al. (2016). A Novel Imaging Marker for Small Vessel Disease Based on Skeletonization of White Matter Tracts and Diffusion Histograms. *Ann. Neurol.* 80, 581–592. doi: 10.1002/ana.24758

Betzel, R. F., Byrge, L., He, Y., Goñi, J., Zuo, X. N., and Sporns, O. (2014). Changes in structural and functional connectivity among resting-state networks across the human lifespan. *Neuroimage* 102, 345–357. doi: 10.1016/j.neuroimage.2014.07.067

Brown, W. R., and Thore, C. R. (2011). Review: Cerebral microvascular pathology in ageing and neurodegeneration. *Neuropathol. Appl. Neurobiol.* 37, 56–74. doi: 10.1111/j.1365-2990.2010.01139.x

Buckner, R. L., Andrews-Hanna, J. R., and Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124, 1–38. doi: 10.1196/annals.1440.011

Chan, M. Y., Park, D. C., Savalia, N. K., Petersen, S. E., and Wig, G. S. (2014). Decreased segregation of brain systems across the healthy adult lifespan. *Proc. Natl. Acad. Sci. U. S. A.* 111, E4997–E5006. doi: 10.1073/pnas.1412122111

Chen, P.-Y., Chiou, J.-M., Yang, Y.-F., Chen, Y.-T., Hsieh, H.-L., Chang, Y.-L., et al. (2016). Heterogeneous Aging Effects on Functional Connectivity in Different Cortical Regions: a Resting-State Functional MRI Study Using Functional Data Analysis. *PLoS One* 11:e0162028. doi: 10.1371/journal.pone.0162028

Chui, H. C. (2006). Vascular cognitive impairment: today and tomorrow. *Alzheimers Dement.* 2, 185–194. doi: 10.1016/j.jalz.2006.03.003

Ciric, R., Wolf, D. H., Power, J. D., Roalf, D. R., Baum, G. L., Ruparel, K., et al. (2017). Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity. *Neuroimage* 154, 174–187. doi: 10.1016/j.neuroimage.2017.03.020

Corbetta, M., and Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nat. Rev. Neurosci.* 3, 201–215. doi: 10.1038/nrn755

Dalby, R. B., Frandsen, J., Chakravarty, M. M., Ahdidan, J., Sørensen, L., Rosenberg, R., et al. (2012). Correlations between Stroop task performance and white matter lesion measures in late-onset major depression. *Psychiatry Res. Neuroimaging* 202, 142–149. doi: 10.1016/j.pscychresns.2011.12.009

Damoiseaux, J. S., Beckmann, C. F., Arigita, E. J. S., Barkhof, F., Scheltens, P., Stam, C. J., et al. (2008). Reduced resting-state brain activity in the "default network" in normal aging. *Cereb. Cortex* 18, 1856–1864. doi: 10.1093/cercor/bhm207

Debette, S., and Markus, H. S. (2010). The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* 341:c3666. doi: 10.1136/bmj.c3666

Dey, A. K., Stamenova, V., Turner, G., Black, S. E., and Levine, B. (2016). Pathoconnectomics of cognitive impairment in small vessel disease: a systematic review. *Alzheimers Dement.* 12, 831–845. doi: 10.1016/j.jalz.2016.01.007

Dosenbach, N. U. F., Fair, D. A., Miezin, F. M., Cohen, A. L., Wenger, K. K., Dosenbach, R. A. T., et al. (2007). Distinct brain networks for adaptive and stable task control in humans. *Proc. Natl. Acad. Sci. U. S. A.* 104, 11073–11078. doi: 10.1073/pnas.0704320104

Du, A. T., Schuff, N., Chao, L. L., Kornak, J., Ezekiel, F., Jagust, W. J., et al. (2005). White matter lesions are associated with cortical atrophy more than entorhinal and hippocampal atrophy. *Neurobiol. Aging* 26, 553–559. doi: 10.1016/j.neurobiolaging.2004.05.002

Elton, A., and Gao, W. (2014). Divergent task-dependent functional connectivity of executive control and salience networks. *Cortex* 51, 56–66. doi: 10.1016/j.cortex.2013.10.012

Esteban, O., Birman, D., Schaer, M., Koyejo, O. O., Poldrack, R. A., and Gorgolewski, K. J. (2017). MRIQC: Advancing the automatic prediction of image quality in MRI from unseen sites. *PLoS One* 12:e0184661. doi: 10.1371/journal.pone.0184661

Farrant, K., and Uddin, L. Q. (2015). Asymmetric development of dorsal and ventral attention networks in the human brain. *Dev. Cogn. Neurosci* . 12, 165–174. doi: 10.1016/j.dcn.2015.02.001

Farras-Permanyer, L., Mancho-Fora, N., Montalà-Flaquer, M., Bartrés-Faz, D., Vaqué-Alcázar, L., Peró-Cebollero, M., et al. (2019). Age-related changes in resting-state functional connectivity in older adults. *Neural Regen. Res.* 14, 1544–1555. doi: 10.4103/1673-5374.255976

Fischl, B., and Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc. Natl. Acad. Sci. U. S. A.* 97, 11050–11055. doi: 10.1073/pnas.200033797

Fjell, A. M., and Walhovd, K. B. (2010). Structural brain changes in aging: courses, causes and cognitive consequences. *Rev. Neurosci.* 21, 187–221. doi: 10.1515/revneuro.2010.21.3.187

Fjell, A. M., Walhovd, K. B., Fennema-Notestine, C., McEvoy, L. K., Hagler, D. J., Holland, D., et al. (2009). One-year brain atrophy evident in healthy aging. *J. Neurosci.* 29, 15223–15231. doi: 10.1523/JNEUROSCI.3252-09.2009

Fornito, A., Harrison, B. J., Zalesky, A., and Simons, J. S. (2012). Competitive and cooperative dynamics of large-scale brain functional networks supporting recollection. *Proc. Natl. Acad. Sci. U. S. A.* 109, 12788–12793. doi: 10.1073/pnas.1204185109

Fox, M. D., Corbetta, M., Snyder, A. Z., Vincent, J. L., and Raichle, M. E. (2006). Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proc. Natl. Acad. Sci. U. S. A.* 103, 10046–10051. doi: 10.1073/pnas.0604187103

Frey, B. M., Petersen, M., Mayer, C., Schulz, M., Cheng, B., and Thomalla, G. (2019). Characterization of White Matter Hyperintensities in Large-Scale MRI-Studies. *Front. Neurol.* 10:238. doi: 10.3389/fneur.2019.00238

Geerligs, L., Renken, R. J., Saliasi, E., Maurits, N. M., and Lorist, M. M. (2014). A Brain-Wide Study of Age-Related Changes in Functional Connectivity. *Cereb. Cortex* 25, 1987–1999. doi: 10.1093/cercor/bhu012

Geppert, A. M., Wroblewska, K. A., and Przedpelska-Ober, E. M. (2007). Greater frequency of subcortical lesions in severely demented patients with early onset Alzheimer's disease. *Alzheimers Dement.* 3, 54–57. doi: 10.1016/j.jalz.2006.10.007

Grady, C. (2012). The cognitive neuroscience of ageing. *Nat. Rev. Neurosci.* 13, 491–505. doi: 10.1038/nrn3256

Head, D., Rodrigue, K. M., Kennedy, K. M., and Raz, N. (2008). Neuroanatomical and Cognitive Mediators of Age-Related Differences in Episodic Memory. *Neuropsychology* 22, 491–507. doi: 10.1037/0894-4105.22.4.491

Hedden, T., and Gabrieli, J. D. E. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nat. Rev. Neurosci.* 5, 87–96. doi: 10.1038/nrn1323

Hogstrom, L. J., Westlye, L. T., Walhovd, K. B., and Fjell, A. M. (2013). The structure of the cerebral cortex across adult life: age-related patterns of surface area, thickness, and gyrification. *Cereb. Cortex* 23, 2521–2530. doi: 10.1093/cercor/bhs231

Jagodzinski, A., Johansen, C., Koch-Gromus, U., Aarabi, G., Adam, G., Anders, S., et al. (2020). Rationale and Design of the Hamburg City Health Study. *Eur. J. Epidemiol.* 35, 169–181. doi: 10.1007/s10654-019-00577-4

Kim, H. J., Cha, J., Lee, J. M., Shin, J. S., Jung, N.-Y. Y., Kim, Y. J., et al. (2016). Distinctive Resting State Network Disruptions among Alzheimer's Disease, Subcortical Vascular Dementia, and Mixed Dementia Patients. *J. Alzheimers Dis.* 50, 709–718. doi: 10.3233/JAD-150637

Kim, J. H., and Lee, J. H. (2011). "Functional connectivity analysis with voxel-based morphometry for diagnosis of mild cognitive impairment," in *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, eds B. L. Lu, L. Zhang, and J. Kwok (Berlin: Springer), 306–313.

Kirchhoff, B. A., Gordon, B. A., and Head, D. (2014). Prefrontal gray matter volume mediates age effects on memory strategies. *Neuroimage* 90, 326–334. doi: 10.1016/j.neuroimage.2013.12.052

Langen, C. D., Zonneveld, H. I., White, T., Huizinga, W., Cremers, L. G. M., de Groot, M., et al. (2017). White matter lesions relate to tract-specific reductions in functional connectivity. *Neurobiol. Aging* 51, 97–103. doi: 10.1016/j.neurobiolaging.2016.12.004

Launer, L. J., Berger, K., Breteler, M. M. B., Dufouil, C., Fuhrer, R., Giampaoli, S., et al. (2006). Regional Variability in the Prevalence of Cerebral White Matter Lesions: an MRI Study in 9 European Countries (CASCADE). *Neuroepidemiology* 26, 23–29. doi: 10.1159/000089233

Liu, R., Wu, W., Ye, Q., Gu, Y., Zou, J., Chen, X., et al. (2019). Distinctive and pervasive alterations of functional brain networks in cerebral small vessel disease with and without cognitive impairment. *Dement. Geriatr. Cogn. Disord.* 47, 55–67. doi: 10.1159/000496455

Low, A., Mak, E., Stefaniak, J. D., Malpetti, M., Nicastro, N., Savulich, G., et al. (2020). Peak Width of Skeletonized Mean Diffusivity as a Marker of Diffuse Cerebrovascular Damage. *Front. Neurosci.* 14:238. doi: 10.3389/fnins.2020.00238

Madden, D. J., Parks, E. L., Tallman, C. W., Boylan, M. A., Hoagey, D. A., Cocjin, S. B., et al. (2017). Sources of disconnection in neurocognitive aging: cerebral white-matter integrity, resting-state functional connectivity, and white-matter hyperintensity volume. *Neurobiol. Aging* 54, 199–213. doi: 10.1016/j.neurobiolaging.2017.01.027

Martínez-Pinilla, E., Ordóñez, C., del Valle, E., Navarro, A., and Tolivia, J. (2016). Regional and gender study of neuronal density in brain during aging and in alzheimer's disease. *Front. Aging Neurosci.* 8:213. doi: 10.3389/fnagi.2016.00213

Mayer, C., Frey, B. M., Schlemm, E., Petersen, M., Engelke, K., Hanning, U., et al. (2020). Linking cortical atrophy to white matter hyperintensities of presumed vascular origin. *J. Cereb. Blood Flow Metab.* 41, 1682–1691. doi: 10.1177/0271678X20974170

Ng, K. K., Lo, J. C., Lim, J. K. W., Chee, M. W. L., and Zhou, J. (2016). Reduced functional segregation between the default mode network and the executive control network in healthy older adults: a longitudinal study. *Neuroimage* 133, 321–330. doi: 10.1016/j.neuroimage.2016.03.029

Niendam, T. A., Laird, A. R., Ray, K. L., Dean, Y. M., Glahn, D. C., and Carter, C. S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cogn. Affect. Behav. Neurosci.* 12, 241–268. doi: 10.3758/s13415-011-0083-5

Noor, A., Zafar, S., and Zerr, I. (2021). Neurodegenerative proteinopathies in the proteoform spectrum—tools and challenges. *Int. J. Mol. Sci.* 22:1085. doi: 10.3390/ijms22031085

Onoda, K., Ishihara, M., and Yamaguchi, S. (2012). Decreased functional connectivity by aging is associated with cognitive decline. *J. Cogn. Neurosci.* 24, 2186–2198. doi: 10.1162/jocn_a_00269

Power, M. C., Deal, J. A., Sharrett, A. R., Jack, C. R., Knopman, D., Mosley, T. H., et al. (2015). Smoking and white matter hyperintensity progression: the ARIC-MRI Study. *Neurology* 84, 841–848. doi: 10.1212/WNL.0000000000001283

Razzak, R. A. (2013). A preliminary study on the trail-making test in Arabic-English bilingual young adults. *Appl. Neuropsychol.* 20, 53–60. doi: 10.1080/09084282.2012.670163

Reijmer, Y. D., Fotiadis, P., Charidimou, A., Van Veluw, S. J., Xiong, L., Riley, G. A., et al. (2017). Relationship between white matter connectivity loss and cortical thinning in cerebral amyloid angiopathy. *Hum. Brain Mapp.* 38, 3723–3731. doi: 10.1002/hbm.23629

Reitan, R. M. (1958). Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Percept. Mot. Skills* 8, 271–276. doi: 10.2466/pms.1958.8.3.271

Rosseel, Y. (2012). Lavaan: an R package for structural equation modeling. *J. Stat. Softw.* 48, 1–36. doi: 10.3389/fpsyg.2014.01521

Schaefer, A., Kong, R., Gordon, E. M., Laumann, T. O., Zuo, X.-N., Holmes, A. J., et al. (2018). Local-Global Parcellation of the Human Cerebral Cortex

from Intrinsic Functional Connectivity MRI. *Cereb. Cortex* 28, 3095–3114. doi: 10.1093/cercor/bhx179

Schaefer, A., Quinque, E. M., Kipping, J. A., Arélin, K., Roggenhofer, E., Frisch, S., et al. (2014). Early small vessel disease affects frontoparietal and cerebellar hubs in close correlation with clinical symptoms -a resting-state fMRI study. *J. Cereb. Blood Flow Metab.* 34, 1091–1095. doi: 10.1038/jcbfm.2014.70

Seo, S. W., Lee, J. M., Im, K., Park, J. S., Kim, S. H., Kim, S. T., et al. (2012). Cortical thinning related to periventricular and deep white matter hyperintensities. *Neurobiol. Aging* 33, 1156–1167. doi: 10.1016/j.neurobiolaging.2010.12.003

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., et al. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31, 1487–1505. doi: 10.1016/j.neuroimage.2006.02.024

Sormaz, M., Murphy, C., Wang, H. T., Hymers, M., Karapanagiotidis, T., Poerio, G., et al. (2018). Default mode network can support the level of detail in experience during active task states. *Proc. Natl. Acad. Sci. U. S. A.* 115, 9318–9323. doi: 10.1073/pnas.1817966115

Staffaroni, A. M., Brown, J. A., Casaletto, K. B., Elahi, F. M., Deng, J., Neuhaus, J., et al. (2018). The longitudinal trajectory of default mode network connectivity in healthy older adults varies as a function of age and is associated with changes in episodic memory and processing speed. *J. Neurosci.* 38, 2809–2817. doi: 10.1523/JNEUROSCI.3067-17.2018

Starr, J. M., Leaper, S. A., Murray, A. D., Lemmon, H. A., Staff, R. T., Deary, I. J., et al. (2003). Brain white matter lesions detected by magnetic resosnance imaging are associated with balance and gait speed. *J. Neurol. Neurosurg. Psychiatry* 74, 94–98. doi: 10.1136/jnnp.74.1.94

Stephan, B. C. M., Matthews, F. E., Khaw, K.-T., Dufouil, C., and Brayne, C. (2009). Beyond mild cognitive impairment: vascular cognitive impairment, no dementia (VCIND). *Alzheimers Res. Ther.* 1:4. doi: 10.1186/alzrt4

Suárez, L. E., Markello, R. D., Betzel, R. F., and Misic, B. (2020). Linking Structure and Function in Macroscale Brain Networks. *Trends Cogn. Sci.* 24, 302–315. doi: 10.1016/j.tics.2020.01.008

Ter Telgte, A., Van Leijsen, E. M. C., Wiegertjes, K., Klijn, C. J. M., Tuladhar, A. M., and De Leeuw, F. E. (2018). Cerebral small vessel disease: from a focal to a global perspective. *Nat. Rev. Neurol.* 14, 387–398. doi: 10.1038/s41582-018-0014-y

Terada, S., Sato, S., Nagao, S., Ikeda, C., Shindo, A., Hayashi, S., et al. (2013). Trail Making Test B and brain perfusion imaging in mild cognitive impairment and mild Alzheimer's disease. *Psychiatry Res. Neuroimaging* 213, 249–255. doi: 10.1016/j.pscychresns.2013.03.006

Terry, R. D., DeTeresa, R., and Hansen, L. A. (1987). Neocortical cell counts in normal human adult aging. *Ann. Neurol.* 21, 530–539. doi: 10.1002/ana.410210603

Thong, J. Y. J., Hilal, S., Wang, Y., Soon, H. W., Dong, Y., Collinson, S. L., et al. (2013). Association of silent lacunar infarct with brain atrophy and cognitive impairment. *J. Neurol. Neurosurg. Psychiatry* 84, 1219–1225. doi: 10.1136/jnnp-2013-305310

Tomasi, D., and Volkow, N. D. (2012). Aging and functional brain networks. *Mol. Psychiatry* 17, 549–558. doi: 10.1038/mp.2011.81

Tuladhar, A. M., Reid, A. T., Shumskaya, E., De Laat, K. F., Van Norden, A. G. W., Van Dijk, E. J., et al. (2015). Relationship between white matter hyperintensities, cortical thickness, and cognition. *Stroke* 46, 425–432. doi: 10.1161/STROKEAHA.114.007146

Turner, G. R., and Spreng, R. N. (2012). Executive functions and neurocognitive aging: dissociable patterns of brain activity. *Neurobiol. Aging* 33, 826.e1–13. doi: 10.1016/j.neurobiolaging.2011.06.005

van den Heuvel, M. P., and Sporns, O. (2019). A cross-disorder connectome landscape of brain dysconnectivity. *Nat. Rev. Neurosci.* 20, 435–446. doi: 10.1038/s41583-019-0177-6

Van Tol, M. J., Li, M., Metzger, C. D., Hailla, N., Horn, D. I., Li, W., et al. (2014). Local cortical thinning links to resting-state disconnectivity in major depressive disorder. *Psychol. Med.* 44, 2053–2065. doi: 10.1017/S0033291713002742

Veldsman, M., Tai, X. Y., Nichols, T., Smith, S., Peixoto, J., Manohar, S., et al. (2020). Cerebrovascular risk factors impact frontoparietal network integrity and executive function in healthy ageing. *Nat. Commun.* 11:4340 . doi: 10.1038/s41467-020-18201-5

Verhaeghen, P., and Cerella, J. (2002). Aging, executive control, and attention: a review of meta-analyses. *Neurosci. Biobehav. Rev.* 26, 849–857. doi: 10.1016/s0149-7634(02)00071-4

Vidal-Piñeiro, D., Valls-Pedret, C., Fernández-Cabello, S., Arenaza-Urquijo, E. M., Sala-Llonch, R., Solana, E., et al. (2014). Decreased Default Mode Network connectivity correlates with age-associated structural and cognitive changes. *Front. Aging Neurosci.* 6:256. doi: 10.3389/fnagi.2014.00256

Vieira, B. H., Rondinoni, C., and Garrido Salmon, C. E. (2020). Evidence of regional associations between age-related inter-individual differences in resting-state functional connectivity and cortical thinning revealed through a multi-level analysis. *Neuroimage* 211:116662. doi: 10.1016/j.neuroimage.2020.116662

Walhovd, K. B., Westlye, L. T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., et al. (2011). Consistent neuroanatomical age-related volume differences across multiple samples. *Neurobiol. Aging* 32, 916–932. doi: 10.1016/j.neurobiolaging.2009.05.013

Wang, J., Chen, Y., Liang, H., Niedermayer, G., Chen, H., Li, Y., et al. (2019). The Role of Disturbed Small-World Networks in Patients with White Matter Lesions and Cognitive Impairment Revealed by Resting State Function Magnetic Resonance Images (rs-fMRI). *Med. Sci. Monit.* 25, 341–356. doi: 10.12659/MSM.913396

Wecker, N. S., Kramer, J. H., Wisniewski, A., Delis, D. C., and Kaplan, E. (2000). Age effects on executive ability. *Neuropsychology* 14, 409–414. doi: 10.1037//0894-4105.14.3.409

Wei, N., Deng, Y., Yao, L., Jia, W., Wang, J., Shi, Q., et al. (2019). A neuroimaging marker based on diffusion tensor imaging and cognitive impairment due to cerebral white matter lesions. *Front. Neurol.* 10:81. doi: 10.3389/fneur.2019.00081

Wu, X., Lai, Y., Zhang, Y., Yao, L., and Wen, X. (2015). Breakdown of Sensorimotor Network Communication in Leukoaraiosis. *Neurodegener. Dis.* 15, 322–330. doi: 10.1159/000435918

Xia, M., Wang, J., and He, Y. (2013). BrainNet Viewer: a Network Visualization Tool for Human Brain Connectomics. *PLoS One* 8:e68910. doi: 10.1371/journal.pone.0068910

Yi, L. Y., Liang, X., Liu, D. M., Sun, B., Ying, S., Yang, D. B., et al. (2015). Disrupted Topological Organization of Resting-State Functional Brain Network in Subcortical Vascular Mild Cognitive Impairment. *CNS Neurosci. Ther.* 21, 846–854. doi: 10.1111/cns.12424

Yi, L., Wang, J., Jia, L., Zhao, Z., Lu, J., Li, K., et al. (2012). Structural and functional changes in subcortical vascular mild cognitive impairment: a combined voxel-based morphometry and resting-state fMRI study. *PLoS One* 7:e44758. doi: 10.1371/journal.pone.0044758

Zalesky, A., Fornito, A., and Bullmore, E. T. (2010). Network-based statistic: identifying differences in brain networks. *Neuroimage* 53, 1197–1207. doi: 10.1016/j.neuroimage.2010.06.041

Zonneveld, H. I., Pruim, R. H., Bos, D., Vrooman, H. A., Muetzel, R. L., Hofman, A., et al. (2019). Patterns of functional connectivity in an aging population: the Rotterdam Study. *Neuroimage* 189, 432–444. doi: 10.1016/j.neuroimage.2019.01.041

Conflict of Interest: The authors declare that this study received funding from Amgen, Astra Zeneca, Bayer, Badischen Anilin & Sodafabrik (BASF), Novartis, Pfizer, Schiller, Siemens, and Unilever. The funders were not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication.