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Distinguishing older subjects with cognitive performance differences based on their brain network patterns: a machine learning approach

Dissertation

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Summary

The aging brain experiences changes in function and structure, which are accompanied by age-related cognitive decline. The degree to which healthy older adults encounter age-related cognitive decline, however, varies greatly. In consideration of the growing aging population and the relevance of cognition for quality of life, research has embarked on exploring possible bases for this high inter-individual variability in aging. One potential explanation for cognitive performance differences may be alterations in the brain's network architecture. Resting-state functional connectivity (RSFC) network estimates, which may centrally characterize this network architecture, already successfully distinguished between healthy older adults and patients with neurodegenerative diseases, e.g. Alzheimer's disease. It, however, remains unknown whether functional network information can be used to distinguish and predict cognitive performance differences in healthy older adults and whether prediction performance may be boosted by using multimodal data, i.e. grey matter volume (GMV) and structural connectivity (SC) estimates. In this context, machine learning (ML) methods may be particularly suited to address these questions due to their ability to deal with high dimensional data and uncover hidden patterns in data. Further insight in this regard may be highly relevant on the road to developing a prognostic marker for age-related cognitive decline and to designing early targeted interventions to combat cognitive decline. Thus, this dissertation was aimed at systematically examining (1) whether functional brain network information, i.e. RSFC estimates, may classify and predict cognitive performance differences, (2) whether age-characteristic interrelations between RSFC and SC patterns and cognitive performance may be derived in older adults and (3) whether the integration of information across modalities, i.e. region-wise GMV, RSFC and SC estimates, may improve prediction performance of cognitive targets in healthy older adults (N>500, age: 55-85) from the 1000BRAINS study using a set of ML approaches. In the first study, RSFC estimates led to low classifiability and predictability of global and domain-specific cognitive performance differences across different analytic choices. The second study revealed the existence of three prominent aging profiles based on connectivity data and cognition in older adults. In the third study, global and domain-specific cognitive targets could only be successfully predicted from multimodal data in absence of confounder control. Conclusively, this dissertation demonstrated that RSFC estimates may only serve to a limited degree as markers for age-related cognitive decline. Furthermore, it emphasized despite the possible benefits of using multimodal approaches in aging studies, the challenges that remain in developing a biomarker for age-related cognitive decline.

Zusammenfassung

Das alternde Gehirn verändert sich in Struktur und Funktion begleitet durch altersbedingten kognitiven Abbau. Das Ausmaß, mit dem gesunde ältere Menschen den kognitiven Abbau erleben, variiert jedoch stark zwischen Personen. Angesichts der zunehmend alternden Bevölkerung und der Wichtigkeit von Kognition für die Lebensqualität, wurde begonnen, nach möglichen Ursprüngen für die hohe inter-individuelle Variabilität zu suchen. Als eine mögliche Erklärung für die beträchtliche Varianz kommen Veränderungen in der Netzwerkarchitektur des Gehirns in Frage. Netzwerkparameter basierend auf funktioneller Konnektivität im Ruhezustand (RSFC), die diese Architektur genauer charakterisieren, wurden bereits erfolgreich genutzt, um zwischen normal alternden Personen und Patienten mit einer neurodegenerativen Erkrankung, z.B. Alzheimer Erkrankung, zu unterscheiden. Es bleibt jedoch unklar, ob funktionelle Netzwerkinformationen auch Kognitionsunterschiede in gesunden älteren Menschen erkennen und vorhersagen können und ob die Vorhersagekraft durch einen multimodalen Ansatz gesteigert werden kann. Methoden des maschinellen Lernens (ML) scheinen besonders geeignet diese Fragestellungen zu adressieren, da sie versteckte Muster in Daten aufdecken können. Die Gewinnung weiterer Einblicke erscheint vor allem für die mögliche Entwicklung eines prognostischen Markers für altersbedingten kognitiven Abbau und den Entwurf von frühzeitigen individuellen Interventionen relevant. Folglich zielte diese Dissertation auf die systematische Untersuchung (1) der Klassifizier- und Vorhersagbarkeit von Kognitionsunterschieden basierend auf funktionellen Netzwerkinformationen, (2) des Zusammenhanges zwischen RSFC, struktureller Konnektivität (SC) und Kognition und (3) des möglichen Vorteils eines multimodalen Ansatzes, i.e. Volumen der grauen Substanz, RSFC und SC, für die Vorhersage von kognitiven Fähigkeiten in gesunden älteren Menschen (1000BRAINS, N>500, Altersspanne: 55-85 Jahre) mit Hilfe eines ML Ansatzes ab. In der ersten Studie erreichten funktionelle Konnektivitätsparameter nur eine geringe Klassifizier- und Vorhersagbarkeit von globalen und domänen-spezifischen Kognitionsunterschieden. In der zweiten Studie konnten drei verschiedene Alterungsprofile basierend auf Konnektivitätsdaten und Kognition extrahiert werden. Die dritte Studie deutete darauf hin, dass Kognitionsunterschiede im Alter nur bei fehlender Kontrolle für Störfaktoren basierend auf multimodalen Daten vorhergesagt werden können. Insgesamt, hebt diese Dissertation das limitierte Potenzial von funktionellen Konnektivitätsparametern als alleinige Marker für kognitive Alterung hervor und unterstreicht trotz möglicher Vorteile eines multimodalen Ansatzes, die vielfältigen verbleibenden Herausforderungen bei der Entwicklung eines Markers für altersbedingten kognitiven Abbau.

List of abbreviations

ABCD Adolescent Brain Cognitive Development consortium

AD Alzheimer's disease

CV cross-validation

DAN dorsal attention network

dFC dynamic functional connectivity

DMN default mode network

dMRI diffusion-weighted magnetic resonance imaging

FPN frontoparietal network

GMV grey matter volume

GM grey matter

HC healthy controls

HCP Human Connectome Project

MCI mild cognitive impairment

ML machine learning

PLSR partial least squares regression

RSFC resting-state functional connectivity

rsfMRI resting-state functional magnetic resonance imaging

sMRI structural magnetic resonance imaging

SC structural connectivity

SMN somatomotor network

TVB The Virtual Brain

VAN ventral attention network

VN visual network

WM white matter

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1 Introduction

1.1 General introduction

Aging is typically accompanied by a decline in various cognitive functions (Salthouse, 2010, 2004). Nonetheless, healthy older individuals vary markedly in the severity to which they experience age-related cognitive decline (Habib et al., 2007; Hedden and Gabrieli, 2004). Understanding the sources for why some people experience cognitive decline earlier than others has become a pressing topic of our times as aging populations are increasing worldwide with accelerating pace (Cabeza et al., 2018). Numerically, this is expressed in a projected doubling of the number of people over the age of 60 to 2.1 billion individuals by 2050 (World Health Organization, 2020). In turn, this demographic shift has extensive societal and economic consequences with the number of people needing care in the next years augmenting drastically (United Nations et al., 2020).

Considering the steadily increasing number of older adults and the significance of cognition for the quality of life and functional independence of older adults, reliable and automated markers for individual cognitive ability in older age become more and more important (Beard et al., 2016; Dodge et al., 2006; Kwak et al., 2021b; Stites et al., 2018; Tomaszewski Farias et al., 2009; United Nations et al., 2020). With the many technological advances in neuroimaging and the upsurge of machine learning (ML) tools, a new era for biomarker development in the field of neuroscience has commenced. While many new insights have already been gained, the majority of successful prediction reports of cognitive functions from imaging data so far have been collected in healthy young adults. In normal aging, the search for a marker for cognitive performance has remained challenging. It is generally agreed upon that brain structure, function and network organization experience changes throughout the aging process (Cabeza, 2002; Cabeza et al., 2018; Ferreira and Busatto, 2013; Fjell et al., 2009; Grady, 2012; Kennedy and Raz, 2009; Madden et al., 2009; Raz et al., 2005). Further, these alterations have been linked to cognitive performance differences in healthy older adults (Andrews-Hanna et al., 2007; Chong et al., 2019; Fjell et al., 2016; Geerligs et al., 2015; Stumme et al., 2020). Nevertheless, it is still unclear what type of input feature may be best suited as a marker for age-related cognitive decline due to differences in samples, selected cognitive variables, input features and applied methods. The current dissertation, thus, aimed at contributing to the search for an imaging marker for age-related cognitive decline and providing a greater understanding of the structure-function relation in aging and its link to cognition. Particularly, it was directed at (1) investigating the biomarker potential of functional brain network information for cognitive functioning, (2) examining age-characteristic interrelations between resting-state functional

connectivity (RSFC) and structural connectivity (SC) patterns and cognitive performance as well as (3) providing further insight into the usefulness of a multimodal approach for cognition prediction in normal aging in a comprehensive analysis of different ML approaches in a population-based study consisting of older adults, the German 1000BRAINS study (Caspers et al., 2014).

1.2 Age-related cognitive decline

Cognition refers to mental processes of knowledge acquisition and comprehension through thinking, experiencing and perceiving that is fundamental to us in navigating and engaging with the world (Bayne et al., 2019). The overarching concept of cognition can be further divided into different domains that entail specialized forms of processing, e.g. memory, attention, executive and language functions (Harvey, 2019).

Across the aging process, declines in various cognitive functions have been reported with some cognitive domains being more strongly impacted by aging than others (Grady, 2012; Hedden and Gabrieli, 2004; Salthouse, 2010). Particularly, processing speed, executive and memory functions tend to decline strongly with advancing age (Grady, 2012; Hedden and Gabrieli, 2004; Park and Reuter-Lorenz, 2009). Age-related performance alterations in these functions may already be observed before the age of 50 with more rapid declines in performance beginning around the age of 60 (LaPlume et al., 2022; Salthouse, 2009, 2004). In contrast, some other cognitive abilities were found to increase up to the age of 60 and to remain rather stable during higher ages, e.g. verbal abilities and semantic knowledge (Hedden and Gabrieli, 2004; Mather, 2010; Salthouse, 2004). Thus, cognition per se is not a unitary concept, but includes distinct facets that may differ in their aging trajectories.

In addition to this cross-domain variability in cognitive decline, the older adult population is characterized by a high inter-individual variability, i.e. individuals vary substantially in the degree to which they experience age-related cognitive decline (Cabeza, 2001; Damoiseaux et al., 2008; Habib et al., 2007; Hedden and Gabrieli, 2004; LaPlume et al., 2022; Raz, 2000; Raz and Rodrigue, 2006). While some 80 year old individuals may perform cognitively like 60 year old individuals (e.g. show similar memory performance and capacity to learn new things, process information with a similar speed than younger older adults), others at the age of 60 may already display extensive cognitive performance declines. In this context, age-related deterioration of cognitive abilities may have far-reaching consequences for an individual's quality of life, everyday functioning and independence (Beard et al., 2016; Kwak et al., 2021b; Stites et al., 2018). As such, maintaining cognitive functions to the best possible degree until old age is central for older adults to actively and independently

participate and engage in all activities of everyday life, which may foster their quality of life. Along the lines, given the accelerating aging population, it, thus, prospectively becomes important to identify those individuals, who will be most strongly affected by age-related cognitive decline, and provide preventive interventions early on to ensure functional independence at higher ages. To lay the foundation for such an endeavour, it becomes necessary to examine potential sources for the high variance and to investigate whether information on the root causes can be used to predict cognitive functioning.

Thus, to understand the underlying mechanisms, research has turned to the brain, the examination of brain-behaviour relationships and the search for appropriate input features to act as markers for age-related cognitive decline in healthy older adults. With the help of new technological advances such as magnetic resonance imaging (MRI), it has been shown that brain structural and functional changes take place during aging accompanied by declines in cognition (Cabeza, 2002; Cabeza et al., 2018; Ferreira and Busatto, 2013; Fjell et al., 2009; Grady, 2012; Kennedy and Raz, 2009; Madden et al., 2009; Raz et al., 2005). Nevertheless, it still remains unclear what brain data may best explain the high inter-individual variability in aging. In this context, recent studies have turned away from solely looking at brain structure and function, but to focus on the brain network organization, especially on the communication between brain regions, to address changes in cognition during aging. This is due to the fact that cognitive functions are thought to strongly rely on the integration of information across the brain and the connection between distinct brain regions (Betzel, 2022; Dhamala et al., 2021; Voss et al., 2013; Yarkoni and Westfall, 2017). As such, a network perspective capitalizing on the communication between different areas of the brain may aid in gaining a better understanding of age-related cognitive decline and the underlying sources of the high cognitive variance in healthy older adults, which will be more closely examined in the next section.

1.3 Functional network reorganization during the aging process

Functional network organization may be explored using RSFC, which may be computed between regions from resting-state functional MRI (rsfMRI) data (Sala-Llonch et al., 2015). In this context, RSFC refers to the time dependent coactivation of functionally related brain regions during rest, which is often represented by the Pearson's correlation coefficient between the spontaneous fluctuations of pairs of regions (Biswal et al., 1995; Sala-Llonch et al., 2015). To further quantify and specify functional network organization, graph-theoretical approaches may, for instance, be used, in which the brain is modelled as a graph composed of nodes and edges grouped into networks subserving specific functions (see

Figure 1) (Sporns et al., 2005; Stanley et al., 2013). These approaches may provide a mathematical description of networks and the connectivity between objects within a network

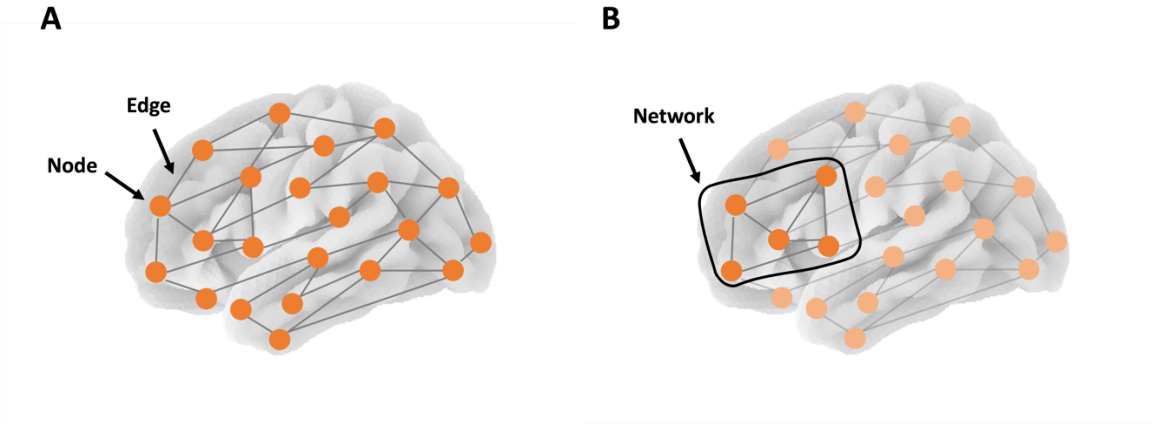

Figure 1. Overview network perspective on brain. [A] Illustration of brain graph with nodes and edges projected onto brain surface, [B] Illustration of brain graph with an exemplary network projected onto brain surface.

and allow the computation of specific measures dedicated to capture different network properties (Bullmore and Sporns, 2009; Bullmore and Bassett, 2011; Farahani et al., 2019; Rubinov and Sporns, 2010; Wig et al., 2011).

Generally, the brain appears to strive for a balance between integration and segregation, i.e. two basic principles underlying cognition and behaviour (Cabral et al., 2017; Perry et al., 2017). Segregation allows for specific information processing among a set of interrelated brain regions, while integration ensures the fast accommodation of discrete information from distinct brain networks (Rubinov and Sporns, 2010). During aging, the brain seems to experience a shift in the balance between integration and segregation, i.e. within- and inter-network RSFC, which has been related to cognitive performance differences in older age (Andrews-Hanna et al., 2007; Chan et al., 2014; Chong et al., 2019; Fjell et al., 2015; Grady et al., 2016; Nashiro et al., 2017; Onoda et al., 2012; Stumme et al., 2020). Particularly, a recurrent and stable finding across aging studies relates to decreases in within- and increases in inter-network RSFC hinting at networks becoming less segregated with age (Andrews-Hanna et al., 2007; Betzel et al., 2014; Chan et al., 2014; Ferreira et al., 2016; Geerligs et al., 2015; Grady et al., 2016). In turn, networks tend to communicate more strongly with each other and become more integrated with age (Andrews-Hanna et al., 2007; Betzel et al., 2014; Chan et al., 2014; Ferreira et al., 2016; Geerligs et al., 2015; Grady et al., 2016). Across studies, a reduced specialized information processing (segregation) and more communication across networks (integration) is linked

to lower cognitive performance in older ages (Andrews-Hanna et al., 2007; Bagarinao et al., 2019; Chan et al., 2014; Chong et al., 2019; Fjell et al., 2015; Grady et al., 2016; Ng et al., 2016; Onoda et al., 2012; Stumme et al., 2020). For instance, lower episodic memory has been related to a decreased specialization, i.e. lower segregation of associative networks, e.g. default mode (DMN), frontoparietal (FPN), dorsal attention (DAN) and ventral attention (VAN) network (Chan et al., 2014). In turn, better fluid cognitive performance and learning rates have been associated with higher segregation of the VAN (Hausman et al., 2020; Iordan et al., 2018). Furthermore, Stumme et al. (2020) have found a link between lower within- and inter-network RSFC in primary processing networks, i.e. visual (VN) and somatomotor (SMN) network, as well as higher inter-network RSFC between higher order networks, e.g. DAN and VAN, and lower cognitive performance in healthy older adults (Stumme et al., 2020). These findings support the dedifferentiation theory in aging, in which the functional system is less able to use specialized modes of processing and express less variation in their activity patterns at higher ages accompanied by reduced task performance (Chan et al., 2017, 2014; Ferreira et al., 2016; Goh, 2011; Nashiro et al., 2017; Park et al., 2004; Spreng et al., 2016; Spreng and Turner, 2019). Findings from longitudinal studies, further, support those from cross-sectional investigations. For example, it has been demonstrated that a decline in segregation of the FPN and an increased integration between the DMN and the FPN are related to declines in processing speed (Malagurski et al., 2020; Ng et al., 2016). Furthermore, a similar pattern of system segregation being beneficial for cognition, i.e. attenuated cognitive impairment, has also been encountered in individuals with neurodegenerative pathology (Ewers et al., 2021). Thus, previous research suggests a link between functional network architecture and cognitive performance in older age. Collectively, these findings hint at the potential use of functional brain network information, i.e. within- and inter-RSFC estimates, as imaging markers for individual cognitive functioning in healthy older adults, which has not been investigated so far.

Although functional brain network information may be a suitable candidate in the search for a biomarker for age-related cognitive decline, the underlying mechanisms and the origin of age-related functional network reorganizations accompanied by cognitive decline still remain unclear. In this context, the closer examination of brain structural information and with it of other brain modalities may provide further insight into potential root causes for these functional changes. In a similar vein, it has been suggested that functional brain data may not fully account for cognitive performance differences in older age (Alm et al., 2022; Damoiseaux, 2017; Fjell et al., 2016; Patel et al., 2022). Instead, it appears that brain structural information, e.g. SC and grey matter volume (GMV), may also explain their share

of variance in cognition in healthy older adults (Cox et al., 2019; Ritchie et al., 2015). As such, a multimodal perspective may allow for a more complete description of brain-behaviour relationships in older age. Thus, in the next section the focus will shift from a unimodal to a multimodal perspective on age-related cognitive decline in an attempt to explain the high inter-individual variability among older adults and its potential benefits in ML cognition prediction in healthy older adults.

1.4 A multimodal perspective on age-related cognitive decline

Aging has been found to affect all aspects of the system-level brain organization, i.e. brain structure, function and connectivity. Thus, focusing only on one modality will most likely not fully explain cognitive performance differences and with it the high inter-individual variability in normal aging. It may, in turn, neglect that the functional network organization does not exist in isolation, but possesses a structural backbone facilitating the communication between regions. For instance, the brains' grey matter (GM), composed of neuronal cell bodies forming the cerebral cortex, sustains the processing capacity of the brain (Colom et al., 2010). In turn, the brains' white matter (WM) allows for the effective transfer of information across the brain via major white matter pathways or tracts (Colom et al., 2010).

Focusing at first on gaining a greater understanding of the root causes for age-related shifts in functional network architecture and the associated cognitive performance declines, the closer investigation of the structural network organization may be of help. This is due to the fact that structural networks are thought to be closely coupled to functional networks and to provide a framework for functional network organization (Baum et al., 2020; Honey et al., 2009; O'Reilly et al., 2013; Suárez et al., 2020; Voineskos et al., 2012). Thereby, connectivity in a structural network may be characterized by diffusion-weighted MRI (dMRI), which is sensitive to the diffusion of water molecules in the brain and measures the diffusivity direction (Beaulieu, 2002; Damoiseaux and Greicius, 2009). This information can, then, be used to deduce the orientation of the brain's white matter tracts (Beaulieu, 2002; Damoiseaux and Greicius, 2009). Along the lines, SC represents the anatomical or physical links, i.e. white matter fibre tracts, between brain regions, which may be reconstructed using fibre tracking or tractography and may be captured by streamline counts between each pair of regions (Alfaro-Almagro et al., 2018; Behrens et al., 2007; Fornito et al., 2013; Jbabdi and Johansen-Berg, 2011; Sarwar et al., 2019; Sotiropoulos and Zalesky, 2019; Yeh et al., 2021).Turning back to the aging context, declines in SC and reductions in the efficiency of structural networks in the course of aging have been reported across studies (Bennett and Madden, 2014; Brickman et al., 2012; Li et al., 2020; Madden et al., 2012, 2009; Salami et

al., 2012; Wen et al., 2011). Particularly, disruptions of both the integration and segregation of structural brain networks may be encountered in aging, which have been linked to lower cognitive performance in older age (Li et al., 2020). These age-related structural network alterations, in turn, may be related to encountered shifts in functional network reorganization. Nevertheless, the exact relationship between RSFC and SC changes in aging and its connection to cognition is still highly debated.

In this context, prior studies have mostly separately addressed changes in brain function and structure in the aging process (Alm et al., 2022; Damoiseaux, 2017; Fjell et al., 2016; Jockwitz and Caspers, 2021). In turn, joint investigations of structure-function relationships in aging and their link to cognitive performance differences in older age remain relatively scarce. Prior joint research has suggested that the underlying SC may to a certain degree exert an influence on functional network organization (Betzel et al., 2014; Madden et al., 2020; Straathof et al., 2019; Zimmermann et al., 2016), although it should be mentioned that results appear to be mixed in this regard (Fjell et al., 2017; Hirsiger et al., 2016; Tsang et al., 2017). Thus, SC alterations in aging may potentially offer an explanation for age-related functional reorganization, i.e. shifts in the balance between integration and segregation, accompanied by cognitive decline (Betzel et al., 2014; Madden et al., 2020; Straathof et al., 2019; Zimmermann et al., 2016). Nevertheless, the interrelation between RSFC and SC changes during aging linked to cognition has not been comprehensively investigated so far in older age. Further research on this may, however, shed light on possible root causes for functional network shifts and allow for examining the sources for the high inter-individual variability in aging in more detail. As such, laying the foundation and providing further support for using multimodal data in a next step in a prediction setting.

Functional and structural network architecture may be further complemented by information from GM to explain cognitive performance differences in older age. The aging process has been associated with extensive structural decline, e.g. loss in GMV, measured by structural MRI (sMRI). In turn, greater regional atrophy has been related to lower performance in specific cognitive functions (Fjell and Walhovd, 2010; Jessen et al., 2006; Kennedy and Raz, 2009; Lemaitre et al., 2012; Persson et al., 2006; Raz et al., 2005; Raz and Rodrigue, 2006; Salat, 2004; Whalley et al., 2004). It has, for instance, been shown that declines in executive functions were related to greater atrophy in the prefrontal cortex (PFC), while reductions in volume of the medial temporal lobe (MTL) and hippocampus were associated with reduced episodic memory performance in older adults (Jessen et al., 2006; Persson et al., 2006; Raz and Rodrigue, 2006). Thus, not only functional and structural network architecture may explain unique variance in cognitive performance and

provide information relevant for prediction, but also brain structural data (Cox et al., 2019; Ritchie et al., 2015).

Ultimately, both brain structure and function support cognitive functioning. The different characteristics of brain organization uniquely contribute to our comprehension of the aging process and offer the possibility to examine distinct sources for the high inter-individual variability in cognition. Thus, they conjointly tend to describe age-related cognitive changes more comprehensively than on their own (McConathy and Sheline, 2015; Pacheco et al., 2015; Tomasi and Volkow, 2012; Vieira et al., 2022a). For example, it has been shown that both RSFC of the VAN and the WM microstructure, i.e. radial diffusivity, of particular MTL regions are separately related to memory performance in older adults (Alm et al., 2022). Findings from longitudinal settings further have revealed that each connectivity measure, i.e. RSFC and SC, may explain a substantial amount of unique variance in age-related cognitive decline and distinct cortical measures, i.e. GM and WM information, may differentially relate to specific patterns of individual longitudinal cognitive change (Fjell et al., 2016; Patel et al., 2022).

Complementing functional network information with those from brain structure, i.e. GMV, and structural network architecture, i.e. SC estimates, thus, may add unique and highly relevant information to the ML setting that might not be covered by brain functional data alone. ML models based on multimodal data may, hence, more completely capture the relation between brain and cognition in older age. As such, a multimodal approach may encourage the establishment of a more accurate and dependable marker for age-related cognitive decline, which has not yet been investigated comprehensively in normal older adults. In the next section, the current state of the field with regards to classification and prediction of cognitive functioning in healthy older adults from imaging data, i.e. unimodal and multimodal, will be outlined in more detail. Before turning to these results, a general introduction to ML will be provided to allow for the contextualization of subsequent ML findings.

1.5 Introduction to ML

The last decades have been marked by many technological advances. One of the major advances has been the shifting of attention to artificial intelligence and with it to machine learning (ML) methods. Use cases extend across different sectors from business applications to medical questions (Davenport and Ronanki, 2018). ML methods have also rapidly entered the neuroimaging field and have been increasingly adopted in a great variety of studies. ML methods as analytic tools develop techniques and algorithms to automatically find patterns or information in data (Hastie et al., 2009; Koutsouleris et al., 2016). In this

context, they may be an optimal choice in the study of biomarkers as they succeed at handling complex data, identifying associations, which may go undetected by univariate methods, and making assessments at the individual level (Dadi et al., 2019; Orrù et al., 2012; Woo et al., 2017; Zarogianni et al., 2013).

ML is commonly divided into two approaches, i.e. supervised and unsupervised learning. The focus in this dissertation will be with supervised ML, as we possess a labelled dataset consisting of input data and the respective correct outputs or target values for a ML model to train on. Supervised ML may be further divided into classification and regression (see Figure 2).

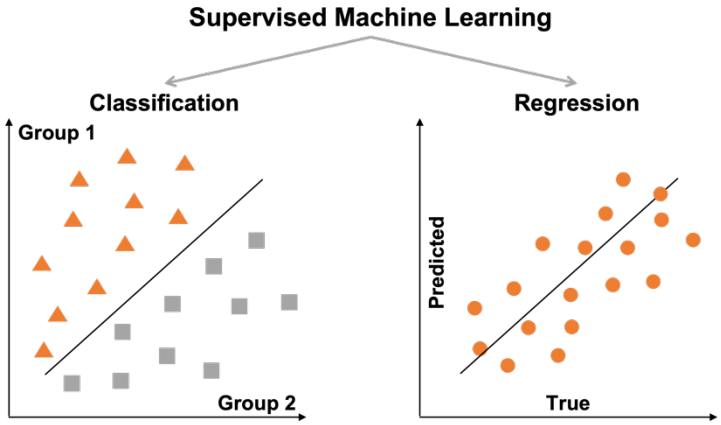

Figure 2. Overview Supervised ML.

Classification aims at predicting different group memberships from input data, e.g. patient group vs. healthy control group, while regression is aimed at predicting a continuous target from input data, e.g. age prediction (see Figure 2) (Orrù et al., 2012). Over the past decades, a variety of different classification and regression algorithms have been developed and introduced to the neuroimaging field (Cui and Gong, 2018; Mwangi et al., 2014). While the different ML algorithms have a similar goal, they use different approaches to provide a solution to a circumscribed problem (Cui and Gong, 2018; Mwangi et al., 2014). In this context, recent studies have compared prediction performances between different algorithms for different ML targets (Cui and Gong, 2018; Jollans et al., 2019). Results have suggested that despite performance differences between algorithms, deriving definite conclusions about the optimal algorithm is difficult and algorithm-related differences depend on the data set used for ML classification and prediction (Cui and Gong, 2018; Jollans et al., 2019). It, thus, appears advisable to examine ML performance across a range of different algorithms to ensure generalizability of results.

In general, the subsequent steps are followed to establish a ML model: (a) an ML algorithm is first trained on a training data set to establish a decision rule and (b) then applied to a new independent test data set to be evaluated. For performance estimation,

cross-validation (CV) is typically chosen as the most appropriate method for model evaluation (Varoquaux et al., 2017). It makes use of resampling to obtain training and test data. In k-fold CV, a particular form of CV, data is split into k folds. One fold is iteratively used as test data, while the remaining folds together form the training data. For example, in 5-fold CV, the data is split into five parts. In the first iteration, one fold is used as the test data, while the remaining four folds constitute the training data. This is repeated until each individual fold has served as test fold once. For each training/test set, a model is trained, evaluated on the test data and a prediction error is obtained (Gabrieli et al., 2015). To retrieve an estimate of generalization ability, prediction performance is, then, averaged across the number of splits. The current gold standard for performance estimation, if external validation is not feasible, is the use of a nested CV scheme. It allows tuning hyperparameters, i.e. parameters that allow configuring the ML algorithm to the data and with it regulate the learning process (Arbabshirani et al., 2017; Bergstra et al., 2013; Lemm et al., 2011; Sipper, 2022), in an inner CV loop and evaluating the generalization ability in an outer CV loop, while preventing data leakage (see Figure 3) (Filzmoser et al., 2009; Lemm et al., 2011).

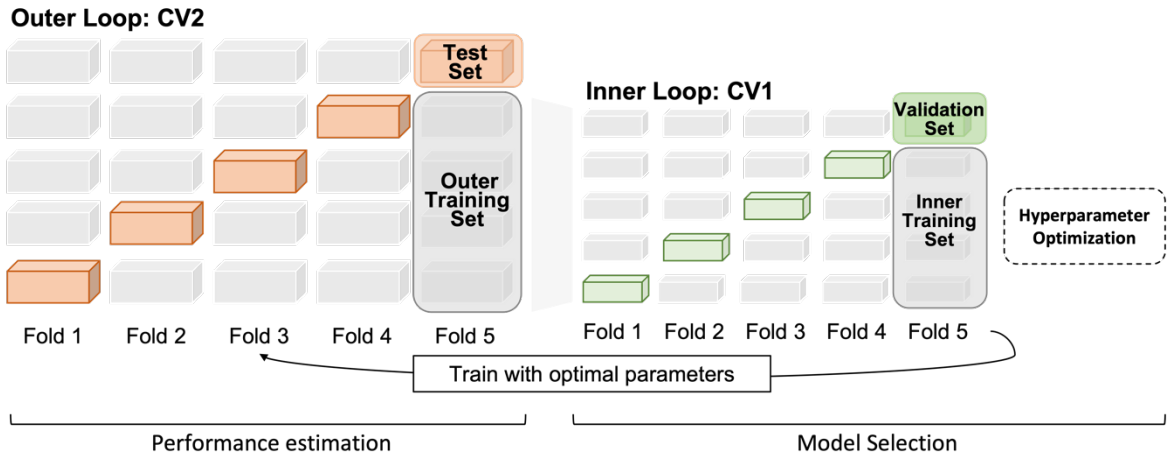

Figure 3. Illustration nested cross-validation (CV).

In nested CV, data is split into training and test sets on both an outer (CV2) and an inner (CV1) loop as it avoids biased estimations of performance (Lemm et al., 2011). Hyperparameters are tuned on the inner loop based on the inner CV performance, whereas in the outer loop established models are examined according to their generalization ability (see Figure 3) (Lemm et al., 2011). Due to its ability to tackle some of the biases and issues in performance evaluation, nested CV has become frequently implemented in neuroimaging ML studies and is considered essential, when one desires to tune hyperparameters (Varoquaux et al., 2017). Some studies have additionally opted to repeat the whole CV

cycle, e.g. using repeated nested CV, for a given number of times to address potential biases based on the initial splitting of the data and to obtain an even more generalizable estimate of performance (Franzmeier et al., 2020; Kong et al., 2019; Koutsouleris et al., 2014, 2012). All of the aforementioned measures are undertaken to reduce overoptimistic results and to better approximate the true performance of a ML model.

Importantly, ML performance has been found to be impacted by a variety of different factors. For instance, sample size and characteristics, feature selection steps, and the deconfounding strategy may all affect classification and prediction accuracies (Arbabshirani et al., 2017; Cui and Gong, 2018; Guyon and Elisseeff, 2003; Hua et al., 2009; Jollans et al., 2019; Mwangi et al., 2014). Up to date, the field of ML using neuroimaging data is lacking a standard ML pipeline, which might be due to the high variability in data sets (Paulus and Thompson, 2021). Thus, it appears warranted to systematically assess different analytical options, when addressing neuroimaging questions with a ML approach. After providing a general introduction to ML and its use in neuroimaging, the following two subsections will provide an overview of the current research state regarding classification and prediction of cognitive performance differences in older age based on functional brain network (i.e. unimodal) data (1.5.1) and multimodal brain data (1.5.2).

1.5.1 Unimodal prediction of cognitive abilities in normal aging

With the rise of large neuroimaging cohorts, we have entered a time with access to ample data that is required for training reliable and generalizable ML models, which tackle complex neuroscientific questions (Varoquaux et al., 2017). As such, research efforts have also turned to the investigation of brain-behaviour relationships and the prediction of cognitive abilities using ML approaches. Due to the well-established relation between behavioural constructs and functional networks, a multitude of studies have concentrated on the use of RSFC data in ML classification and prediction (Khosla et al., 2019). Most of the studies so far have concentrated on the prediction of cognitive ability in younger adults. For example, general intelligence could be successfully predicted from RSFC patterns in a large sample of younger adults from the Human Connectome Project (HCP) and a developmental cohort from the Adolescent Brain Cognitive Development (ABCD) consortium (Dubois et al., 2018; Sripada et al., 2020b). In healthy older adults, initial promising results have already been obtained in the prediction of specific cognitive functions using mainly RSFC matrices, either covering the whole brain or specific networks (Gao et al., 2020; He et al., 2020; Jiang et al., 2022; Kwak et al., 2021a; Pläschke et al., 2020; Wu et al., 2022). For instance, Pläschke et al. (2020) showed that working memory performance could be successfully predicted by specific RSFC patterns in meta-analytically defined brain

networks in an older age group using relevance vector regression (RVR). Furthermore, Gao et al. (2020) demonstrated that processing speed could be successfully predicted from RSFC data in older adults using a connectome-prediction model. Along the lines, RSFC effectively predicted neuropsychological test performances, e.g. amongst others Trail Making Test A and B, semantic fluency, digit span and Boston naming test, and fluid intelligence in three large samples across the lifespan and in older age using different ML approaches (He et al., 2020; Jiang et al., 2022; Kwak et al., 2021a). However, functional brain network data, i.e. within- and inter-network RSFC estimates, which capture more specifically information on network integration and segregation than RSFC matrices and have been shown to relate to cognitive performance differences in normal aging, has not been investigated yet as input features to ML (Stumme et al., 2020). In clinical settings, RSFC graph metrics targeting basic principles of network organization have already been successfully used as diagnostic marker to distinguish between healthy older adults and patients with neurodegenerative diseases, i.e. Alzheimer's disease (AD) and mild cognitive impairment (MCI) (Hojjati et al., 2017; Khazaee et al., 2016). Whether this also holds true for healthy older adults, remains to be examined.

1.5.2 Multimodal prediction of cognitive abilities in normal aging

While cognitive abilities may already be successfully predicted from one modality, a more complete picture may arise from a multimodal perspective. Given cognition may rely on different neurobiological substrates, i.e. brain structure, function and connectivity, a multimodal approach may, thus, characterize these brain-behaviour relationships more comprehensively and support the development of a more reliable, inclusive and potentially powerful marker for age-related cognitive decline (Dhamala et al., 2021). Research has lately started on this objective of integrating information across modalities in ML classification and prediction studies (Dhamala et al., 2021; Dyrba et al., 2015; Engemann et al., 2020; Hojjati et al., 2019, 2018; Liem et al., 2017; Rahim et al., 2016; Rasero et al., 2021; Tsapanou et al., 2020; Wee et al., 2012; Xifra-Porxas et al., 2021). Initial encouraging results emphasize that the use of multimodal data may be beneficial for ML performance. For example, Rasero et al. (2021) found improved prediction accuracies of different cognitive abilities, i.e. global and domain-specific cognition, from multimodal data, i.e. RSFC, GMV, cortical thickness, surface area and local connectome features, in a large sample of healthy young adults from the HCP. Across the life span, Tsapanou et al. (2020) have shown that more variance in fluid intelligence and vocabulary is explained by integrating information from white and grey matter than by single modalities. In healthy older adults, evidence on a multimodal benefit is limited. In this context, initial findings from the

UK Biobank suggest that fluid intelligence may be successfully predicted from multimodal brain imaging data, i.e. brain volumetric data, white matter information and RSFC (Dadi et al., 2021). Further support for a predictability benefit for multimodal data in older samples comes from investigations into neurodegenerative diseases (Dyrba et al., 2015; Hojjati et al., 2018, 2018; Wee et al., 2012). Better classifiability of patients with MCI and AD from healthy controls (HC) was reached for a combination of RSFC- and SC-derived graph metrics, which encompass information on network integration and segregation, compared to single modalities (Hojjati et al., 2019, 2018). As such, prior research suggests that using different combinations of multimodal data may be helpful in cognitive prediction settings in aging. It, however, remains to be investigated whether specifically integrating information from brain network architecture, i.e. RSFC and SC estimates, and brain morphology, i.e. region-wise GMV, may improve prediction performance of cognitive performance differences in healthy older individuals compared to single modalities. On the basis of findings suggesting that changes in all three modalities are linked to cognitive performances differences in older age, the combination of information is expected to explain more variance in cognition than each of them on their own (Dadi et al., 2021; Rasero et al., 2021; Vieira et al., 2022a).

1.6 Ethics approval

The 1000BRAINS study protocol was approved by the ethics committee of the University of Duisburg-Essen (reference number: 11-4678, 12-5199-BO). The study procedures comply with the Declaration of Helsinki and informed consent was obtained from all participants prior to participation in 1000BRAINS.

1.7 Aim of the studies

This dissertation is intended to advance the search for an imaging marker for age-related cognitive decline, provide new insights into the predictive power of imaging data for cognitive performance prediction in normal aging and a greater understanding of the structure-function relation in aging and its link to cognition. In detail, it is aimed at investigating (1) whether RSFC estimates of within- and inter-network connectivity may reliably classify and predict cognitive performance differences, (2) how RSFC and SC patterns as well as cognitive performance are interrelated in aging and (3) whether the combination of region-wise GMV, RSFC and SC estimates may lead to better prediction performance of different cognitive targets compared to single modalities using a systematic evaluation of different ML approaches in large samples of healthy older adults from the 1000BRAINS study. Thus, adding to laying a foundation for the development of a prospective marker for age-related cognitive decline.

2 Study 1

Classification and prediction of cognitive performance differences in older age based on brain network patterns using a machine learning approach

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RESEARCH

Classification and prediction of cognitive performance differences in older age based on brain network patterns using a machine learning approach

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Keywords: Cognition, Aging, Resting-state functional connectivity, Graph-theoretical analyses, Machine learning

ABSTRACT

Age-related cognitive decline varies greatly in healthy older adults, which may partly be explained by differences in the functional architecture of brain networks. Resting-state functional connectivity (RSFC) derived network parameters as widely used markers describing this architecture have even been successfully used to support diagnosis of neurodegenerative diseases. The current study aimed at examining whether these parameters may also be useful in classifying and predicting cognitive performance differences in the normally aging brain by using machine learning (ML). Classifiability and predictability of global and domain-specific cognitive performance differences from nodal and network-level RSFC strength measures were examined in healthy older adults from the 1000BRAINS study (age range: 55–85 years). ML performance was systematically evaluated across different analytic choices in a robust cross-validation scheme. Across these analyses, classification performance did not exceed 60% accuracy for global and domain-specific cognition. Prediction performance was equally low with high mean absolute errors (*MAE*s ≥ 0.75) and low to none explained variance ($R^2 \leq 0.07$) for different cognitive targets, feature sets, and pipeline configurations. Current results highlight limited potential of functional network parameters to serve as sole biomarker for cognitive aging and emphasize that predicting cognition from functional network patterns may be challenging.

AUTHOR SUMMARY

In recent years, new insights into brain network communication related to cognitive performance differences in older age have been gained. Simultaneously, an increasing number of studies has turned to machine learning (ML) approaches for the development of biomarkers in health and disease. Given the increasing aging population and the impact cognition has on the quality of life of older adults, automated markers for cognitive aging gain importance. This study addressed the classification and prediction power of resting-state functional connectivity (RSFC) strength measures for cognitive performance in healthy older adults using a battery of

standard ML approaches. Classifiability and predictability of cognitive abilities was found to be low across analytic choices. Results emphasize limited potential of these metrics as sole biomarker for cognitive aging.

INTRODUCTION

Healthy older adults vary greatly in the extent to which they experience age-related cognitive decline (Habib et al., 2007). While some older adults seem to maintain their cognitive abilities until old age, others show higher rates of cognitive decline during the aging process (Cabeza, 2001; Damoiseaux et al., 2008; Hedden & Gabrieli, 2004; Raz, 2000; Raz & Rodrigue, 2006). In light of the continuously growing aging population, the impact of cognitive decline on everyday functioning of older adults has gained momentum in research (Avery et al., 2020; Deary et al., 2009; Depp & Jeste, 2006; Fountain-Zaragoza et al., 2019; Luciano et al., 2009; Vieira et al., 2022).

In this context, differences in the functional architecture of brain networks have been identified as a potential source of variance explaining cognitive performance differences during aging (Chan et al., 2014; Stumme et al., 2020). Age-related differences have been linked to changes in resting-state functional connectivity (RSFC) of major resting-state networks, for example, the default mode network (DMN), the sensorimotor network (SMN), and the fronto-parietal and visual networks (Andrews-Hanna et al., 2007; Chong et al., 2019; Ng et al., 2016; Stumme et al., 2020). In detail, age-related cognitive decline is associated with both decreases in the functional specialization of brain networks (reduced network segregation) and increasingly shared coactivation patterns between functional brain networks (increased network integration) (Andrews-Hanna et al., 2007; Chan et al., 2014; Chong et al., 2019; Fjell et al., 2015; Grady et al., 2016; Ng et al., 2016; Onoda et al., 2012; Stumme et al., 2020). Furthermore, RSFC differences in older age may differentiate between healthy older adults and individuals suffering from mild cognitive impairment (MCI) or Alzheimer's disease (AD). For instance, both MCI and AD have been related to reduced RSFC within the DMN and SMN, the degeneration of specific brain hubs, and aberrant functional brain network organization (Dai et al., 2015; Farahani et al., 2019; Sanz-Arigita et al., 2010; Supekar et al., 2008; Wang et al., 2013).

Machine learning (ML):
Set of methods used to automatically find patterns in data that allow classification and prediction.

Given the role of RSFC network patterns in cognition in healthy and pathological aging, research on neurodegenerative diseases has started to embark on the development of diagnostic biomarker for automatic patient classification based on RSFC. For the development of diagnostic biomarkers, machine learning (ML) methods may be particularly suited. This is due to their ability to deal with high-dimensional data and to detect spatially distributed effects in the brain that might otherwise not be detected using univariate approaches (Dadi et al., 2019; Orrù et al., 2012; Woo et al., 2017; Zarogianni et al., 2013). In this context, RSFC-derived metrics capturing network integration and segregation have already been successfully used as diagnostic markers for MCI and AD, using ML approaches (Hojjati et al., 2017; Khazaee et al., 2016). In healthy older populations, functional network measures have also provided new insights into brain network communication related to cognitive performance differences (Chan et al., 2014; Chong et al., 2019; Stumme et al., 2020). Specifically, a previous study has demonstrated that shifts in within- and inter-network connectivity may be linked to differences in cognitive performance in older age (Stumme et al., 2020). Thus, RSFC network properties may also constitute potential meaningful candidates in search for a marker for nonpathological age-related cognitive decline (Chan et al., 2014; Stumme et al., 2020).

Previous studies have mainly used RSFC matrices, either containing information across the whole-brain or within specific networks, as input features to ML revealing initial promising results in the prediction of different cognitive facets in older adults (Avery et al., 2020; He

et al., 2020; Kwak et al., 2021; Pläschke et al., 2020). For instance, it has been shown that working memory performance could be predicted by specific RSFC patterns in meta-analytically defined brain networks in an older but not younger age group by using relevance vector regression (RVR) (Pläschke et al., 2020). Furthermore, a variety of neuropsychological test scores and fluid intelligence could be successfully predicted from RSFC in large older samples using ML (He et al., 2020; Kwak et al., 2021). Nevertheless, it remains unclear if RSFC strength measures targeting network integration and segregation may provide additional useful information in classifying and predicting global and domain-specific cognitive performance in older adults (Avery et al., 2020; Dubois et al., 2018; He et al., 2020; Kwak et al., 2021; Pläschke et al., 2020). Further knowledge in this context may be helpful on the road to building a reliable and accurate biomarker for cognitive performance in healthy older adults that could ultimately be used to predict prospective cognitive decline. The current investigation, therefore, aims to systematically examine whether RSFC strength parameters, capturing within- and inter-network connectivity, may reliably classify and predict cognitive performance differences in a large sample of older adults (age: 55–85) from the 1000BRAINS study by using a battery of standard ML approaches.

MATERIALS AND METHODS

Participants

Data for the current investigation stems from the 1000BRAINS project (Caspers et al., 2014), an epidemiologic population-based study examining variability of brain structure and function during aging in relation to behavioral, environmental, and genetic factors. The 1000BRAINS sample was drawn from the 10-year follow-up cohort of the Heinz Nixdorf Recall Study and the associated MultiGeneration study (Schmermund et al., 2002). As 1000BRAINS aims at the characterization of the aging process in the general population, no exclusion criteria other than eligibility for MR measurements (Caspers et al., 2014) were applied. In the current study, 966 participants were included within the age range 55 to 85 years. From this initial sample, 99 participants were excluded due to missing resting-state functional magnetic resonance imaging (fMRI) data or failed preprocessing. Furthermore, 25 participants were excluded due to insufficient quality of the preprocessed functional data described in further detail below (see Data Acquisition and Preprocessing section). Another 27 participants with missing scores on the DemTect, a dementia screening test, or those scoring smaller or equal to 8 were excluded due to the possibility of substantial cognitive impairment (Kalbe et al., 2004). Finally, two participants were excluded due to more than three missing values within the neuropsychological assessment (see Cognitive Performance section). This resulted in an initial (unmatched) sample of 813 participants (372 females, M_{age} = 66.99, SD_{age} = 6.70; see Table 1A and Figure 1: Sample). All subjects provided written consent prior to inclusion and the study protocol of 1000BRAINS was approved by the Ethics Committee of the University of Essen, Germany.

Table 1. Demographic information for unmatched and matched samples regarding age, educational level, and risk of dementia

	A. Unmatched sample				B. Matched sample			
	N	Age	Education	DemTect	*N*	Age	Education	DemTect
Female	372	66.38 (6.53)	5.93 (1.84)	15.42 (2.29)	232	65.33 (5.48)	5.88 (1.7)	15.43 (2.22)
Male	441	67.5 (6.8)	6.95 (1.91)	14.38 (2.33)	286	67.81 (6.44)	6.96 (1.87)	14.45 (2.25)
Total	813	66.99 (6.70)	6.48 (1.94)	14.86 (2.37)	518	66.7 (6.15)	6.48 (1.87)	14.89 (2.29)

Note. Mean displayed with standard deviation (*SD*) appearing in parentheses.

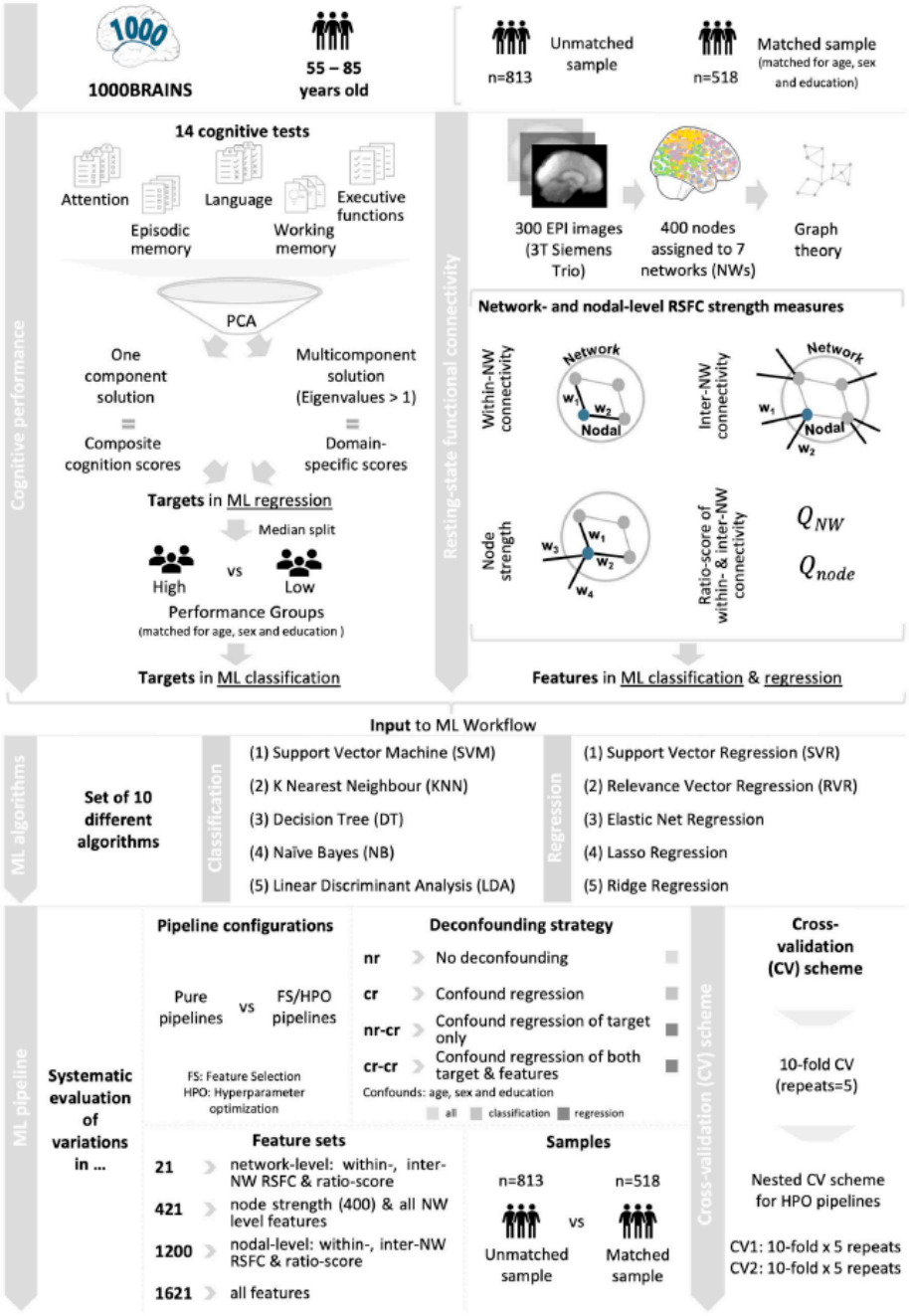

Figure 1. Schematic overview of workflow.

Cognitive Performance

All subjects underwent a large neuropsychological assessment testing the cognitive domains attention, executive functions, episodic memory, working memory (WM), and language (for further details, see Caspers et al., 2014). Fourteen cognitive variables targeting selective attention, processing speed, figural and verbal fluency, problem solving, vocabulary, WM, and episodic memory were selected for the purpose of the current study (see Figure 1: Cognitive performance). Further information on the tests and variables chosen in the current investigation are found in Supporting Information Table S1. In case of missing values (more than three missing values led to exclusion) in the neuropsychological assessment, missing values were replaced by the median for respective sex (males, females) and age groups (55–64 years, 65–74 years, 75–85 years). Imputation of missing values was performed to avoid further loss of information and power. In a next step, raw scores from all 14 neuropsychological tests used in the analysis were transformed into *z*-scores. For interpretability purposes, scores for neuropsychological tests with higher values meaning lower performance (i.e., time to complete the tasks or number of errors made) were inverted.

Global cognition:
General cognitive ability that encompasses cognitive functioning across different domains.

Neuropsychological test performance was reduced to cognitive composite scores using principal component analysis (PCA). To disentangle effects specific to certain cognitive facets, global and domain-specific cognitive performance were examined (Tucker-Drob, 2011). PCA was used to extract a one-component solution for global cognition and a multicomponent solution for cognitive subdomains based on eigenvalues >1. Lastly, varimax rotation was applied to enhance the interpretability of extracted components. Individual global and domain-specific component scores obtained from the PCA were used as targets in ML prediction of cognitive performance differences.

For classification of cognitive performance differences, the initial (unmatched) sample was separated into high- and low-performing groups. To do so, a median split was performed based on each of the three cognitive component scores (as extracted in the PCA). To remove the effect of potential confounders, the high- and low-performance groups derived from global cognition were additionally matched with respect to age, sex, and educational level by using propensity score matching, which constitutes a statistical approach to match participants based on their propensity scores (McDermott et al., 2016; Randolph et al., 2014; Stern et al., 1994; Vemuri et al., 2014). This led to a matched sample with $N = 518$ (232 females, $M_{age} = 66.7$, $SD_{age} = 6.15$; see Table 1B and Figure 1: Sample and Cognitive performance). Further demographic information regarding age, educational level, and sex distribution between high- and low-performance groups in the unmatched and matched sample can be found in Table 2. All cognitive analyses were performed using IBM SPSS Statistics 26 (https://www.ibm.com/de-de/analytics/spss-statistics-software) and customized Python (Version 3.7.6) and R scripts (Version 4.00).

Functional Imaging

Data acquisition and preprocessing. Imaging data was acquired using a 3T Siemens Tim-TRIO MR scanner with a 32-channel head coil. Out of the whole MR imaging protocol (for details, see Caspers et al. 2014), the current study used for surface reconstruction the 3D high-resolution T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) (176 slices, slice thickness = 1 mm, TR = 2,250 ms, TE = 3.03 ms, FoV = 256 × 256 mm^2, flip angle = 9°, voxel resolution = 1 × 1 × 1 mm^3); and for resting-state analyses, the 11:30 minutes resting-state fMRI with 300 EPI (gradient-echo planar imaging) volumes (slices 36, slice thickness = 3.1 mm, TR = 2,200 msec, TE = 30 msec, FoV = 200 × 200 mm^2, voxel resolution = 3.1 × 3.1 × 3.1 mm^3). During the resting-state scan, participants were instructed to keep their eyes closed, to relax and let their mind wander, but not to fall asleep. This was checked during a postscan debriefing.

Table 2. Differences in cognitive scores, age, educational level, and sex distribution between high- and low-performance groups in the unmatched and matched sample

		COGNITIVE COMPOSITE					NON-VERBAL MEMORY & EXECUTIVE					VERBAL MEMORY & LANGUAGE				
		Group					Group					Group				
		Low	High	t	p	df	Low	High	t	p	df	Low	High	t	p	df
Unmatched Sample	Cog. Score	−.79 (0.72)	.79 (0.47)	−37.17	<0.001	697.9	−.78 (0.68)	.78 (0.56)	−36.02	<0.001	784.8	−.81 (0.60)	.80 (0.59)	−36.67	<0.001	811
	Age	69.49 (6.43)	64.49 (5.99)	11.48	<0.001	811	69.24 (6.58)	64.72 (6.02)	10.28	<0.001	805.1	68.09 (6.72)	65.89 (6.5)	4.74	<0.001	811
	Education	5.84 (1.76)	7.13 (1.91)	−10.51	<0.001	805.0	6.03 (1.88)	6.94 (1.9)	−6.87	<0.001	810.8	5.97 (1.76)	7.00 (1.99)	−7.81	<0.001	800
	Males	206	235	–	–	–	187	254	–	–	–	245	196	–	–	–
	Females	200	172	–	–	–	220	152	–	–	–	161	211	–	–	–
Matched Sample	Cog. Score	−.66 (0.63)	.71 (0.44)	−28.67	<0.001	460.2	−.68 (0.61)	.75 (0.54)	−28.35	<0.001	516	−.74 (0.54)	.74 (0.53)	−31.24	<0.001	516
	Age	67.06 (6.1)	66.34 (6.2)	1.32	0.19	516	67.69 (6.20)	65.74 (5.95)	3.65	<0.001	516	66.63 (6.01)	66.77 (6.29)	−.25	.81	516
	Education	6.39 (1.82)	6.56 (1.92)	−.1.06	0.29	516	6.31 (1.85)	6.64 (1.88)	−2.01	<0.05	516	6.3 (1.77)	6.67 (1.96)	−2.25	<0.05	506.1
	Males	143	143	–	–	–	127	159	–	–	–	165	121	–	–	–
	Females	116	116	–	–	–	128	104	–	–	–	99	133	–	–	–

Note. Standard deviation (*SD*) appears in parentheses. Cog. Score = cognitive score. Unmatched sample: global: $X^2(1) = 4.01$, $p < .05$; memory and executive: $X^2(1) = 22.61$, $p < .001$; language: $X^2(1) = 12.16$, $p < .001$; Matched Sample: global: $X^2(1) = 0$, $p = 1$; memory and executive: $X^2(1) = 5.94$, $p < .05$; language: $X^2(1) = 11.56$, $p < .001$.

Preprocessing steps closely followed those from Stumme and colleagues (2020). During preprocessing, the first four volumes from the 300 EPI were removed for each participant. All functional images were corrected for head movement using a two-pass procedure. First, all volumes were aligned to the first image and then to the mean image using affine registration. Spatial normalization to the MNI152 template (2-mm-voxel size) of all functional images was achieved by using a "unified segmentation" approach as previous studies have shown increased registration accuracies compared to normalization based on T1-weighted images (Ashburner & Friston, 2005; Calhoun et al., 2017; Dohmatob et al., 2018). Furthermore, ICA-AROMA, that is, ICA-based automatic removal of motion artifacts (Pruim et al., 2015), which constitutes a data-driven method for the identification and removal of motion-related components from MRI data, was applied. Additionally, global signal regression (GSR) was performed in order to minimize the association between motion and RSFC (Burgess et al., 2016; Ciric et al., 2017; Parkes et al., 2018). Moreover, GSR has been found to improve behavioral prediction performance and to enhance the link between RSFC and behavior (Li et al., 2019). In a final step, a band-pass filter was applied (0.01–0.1 Hz). As a quality check for our preprocessing, further steps were implemented. Initially, we checked for potential misalignments in the mean functional AROMA data with the check sample homogeneity option in the Computational Anatomy Toolbox (CAT 12) (Gaser et al., 2022). Participants detected as outliers with >2 *SD* away from the mean were excluded. Additionally, we checked for volume-wise severe intensity dropouts (DVARS) in the preprocessed data by using an algorithm by Afyouni and Nichols (2018). For each participant, *p* values for spikes are generated, and participants with more than 10% of the 300 volumes detected as dropouts were excluded from further analyses. To check the quality control applied, we assessed the correlation between age and motion after the application of AROMA and the exclusion of deviating participants and found it to be nonsignificant (percentage (%) of corrupted volumes * age, $r = .03$, $p = .39$).

Functional connectivity analyses. For connectivity analyses, the 400-node cortical parcellation by Schaefer and colleagues (2018) was adopted. The 400 regions of interest from the parcellation scheme can be allocated to seven network parcels of known functional resting-state networks (Yeo et al., 2011). These include the visual, sensorimotor, limbic, fronto-parietal, default mode, dorsal, and ventral attention network.

A whole-brain graph was established from functional data (Rubinov & Sporns, 2010). This included, (i) a mean time series extraction for each node using fslmeants (Smith et al., 2004), (ii) individual edge definition as the Pearson's correlation of respective average time series of two nodes, (iii) a statistical significance test of each correlation coefficient using the Fourier transform and permutation testing (repeats = 1,000) with nonsignificant edges at $p \geq 0.05$ being set to zero (Stumme et al., 2020; Zalesky et al., 2012), and (iv) Fisher's *r*-to-*z*-transformation applied to the 400 × 400 adjacency matrix. Furthermore, since there is still debate about the true nature of anticorrelations in the brain, only positive correlations were considered in subsequent analyses (negative correlations were set to zero) (Murphy et al., 2009; Murphy & Fox, 2017; Saad et al., 2012). Finally, no further thresholding related to network density or network size was applied to the brain graph as it may, in addition to controlling the absolute number of edges, also increase the number of false positives and induce systematic differences in overall RSFC (Stumme et al., 2020; van den Heuvel et al., 2017; van Wijk et al., 2010). For the estimation of strength measures, the final network used, thus, may be described as a positively weighted network.

In a next step, connectivity estimates were calculated using the software bctpy with network parameters defined as in Rubinov and Sporns (2010) (https://pypi.org/project/bctpy/). All metrics estimated in the current investigation are based on the estimation of strength

Inter-network RSFC:
Connectivity strength estimate of one node (nodal) or all nodes (network) within a network to all nodes outside its network.

Ratio-score:
A metric capturing within-network RSFC of one node (nodal) or all nodes (network) within a network in relation to its inter-network RSFC.

Within-network RSFC:
Connectivity strength estimate of one node (nodal) or all nodes (network) within a network to all nodes within its network.

Feature set:
The specific combination of input features used in ML.

values, which do not appear to be distorted by varying amounts of edges and have been shown to reliably quantify networks (Finn et al., 2015). In total, seven parameters were computed for later use in ML. Within- and inter-network RSFC as well as a ratio-score indicating network segregation were obtained at both network and nodal level (see Figure 1: RSFC; for further details on network parameters, see Stumme et al., 2020). Within-network RSFC was defined as the sum of strength values from all nodes (network) or one node (nodal) within a network to all nodes within its related network divided by the number of existing edges in the network (network: 7 features; nodal: 400 features). Inter-network RSFC referred to the sum of strength values from all nodes (network) or one node (nodal) within a network to all nodes outside its network divided by the number of all edges in the network (network: 7 features; nodal: 400 features). The ratio-score captured within-network RSFC of all nodes (network) or one node (nodal) in relation to its inter-network RSFC (network: 7 features; nodal: 400 features). Additionally, the strength of each node was calculated as the sum of all connectivity weights attached to a node (i.e., 400 features). In total, the feature vector for each subject consisted of 1,621 features ($4 \times 400 = 1{,}600$ nodal features and $3 \times 7 = 21$ network-level features). From this, four different feature sets were derived and used in ML (21 features: all network-level features; 421 features: node strength and all network-level features; 1,200 features: nodal within- and inter-network and ratio of within/inter-network RSFC; 1,621 features: all features).

Systematic Application of a Battery of Standard Machine Learning Approaches

ML was used to assess whether RSFC strength measures can be used to distinguish (i.e., classification) and predict (i.e., regression) cognitive performance differences in older adults. As there is currently no agreement on a standard ML pipeline using neuroimaging data given the high variability in dataset properties, we systematically evaluated different analytical choices (see Figure 1: ML algorithms and pipeline). Performance of different ML algorithms, pipeline compositions, extents of deconfounding, and variations in feature set and sample sizes were assessed (Arbabshirani et al., 2017; Cui & Gong, 2018; Khazaee et al., 2016; Mwangi et al., 2014; Paulus & Thompson, 2021; Pervaiz et al., 2020). As such, we tested a total of 556 unique pipelines in the classification (406 pipelines) and regression (150 pipelines) setting. The scikit-learn library (version: 0.22.1) in Python (Version 3.7.6) (Pedregosa et al., 2011; https://scikit-learn.org/stable/index.html) was used for all ML analyses unless specified.

ML algorithms. For classification, Five different algorithms were examined: support vector machine (SVM), K-nearest while (KNN), decision tree (DT), naïve Bayes (NB) and linear discriminant analysis (LDA). Further information on the algorithms can be found in the Supporting Information Methods.

For regression, five different algorithms were assessed: support vector regression (SVR), RVR, Ridge regression (Ridge), least absolute shrinkage and selection operator regression (LASSO), and elastic net regression (Elastic Net) (Cui & Gong, 2018). The package scikit-rvm compatible with scikit-learn by James Ritchie (https://github.com/JamesRitchie/scikit-rvm) was used for RVR computation. Further information on the regression algorithms can be found in the Supporting Information Methods.

Basic ML pipeline. The basic ML pipeline was constructed as follows: the previously calculated connectivity estimates were used as input features for the ML workflow. Targets varied between classification (high vs. low cognitive performance group; matched sample) and regression (global and domain-specific cognitive scores; unmatched sample) (see Cognitive

Pipeline configuration:
A specific setup of an ML pipeline to be tested in the analysis.

Domain-specific cognition:
Cognitive processes that are linked and dedicated to specific mental abilities, e.g., executive and memory functions.

Performance section in Materials and Methods). Input features were scaled to unit variance in a first step in all pipeline configurations within the cross-validation setting. All models were evaluated using a repeated 10-fold cross-validation (CV) (five repeats). In case of an additional hyperparameter optimization (HPO) step, a repeated nested CV scheme was implemented for selecting optimal parameters (outer and inner loop: 10 folds × 5 repeats) (see Figure 1: CV scheme; Lemm et al., 2011). This was done to avoid data leakage and to obtain an unbiased estimate of the generalization performance of complete models (Lemm et al., 2011). Balanced accuracy (BAC) was used to assess classification performance. It was chosen to account for potential group size differences in domain-specific cognition. Sensitivity and specificity were also calculated to provide a more complete picture and can be found in the Supporting Information. Mean absolute error (*MAE*) and coefficient of determination (R^2) were computed in the prediction setting.

Systematic evaluation of ML pipeline options. Regarding pipeline configurations, different pipeline configurations were investigated. Performance of baseline models were compared to those from pipelines with feature selection (FS) and HPO as they have been found to greatly impact ML performance (Brown & Hamarneh, 2016; Guyon & Elisseeff, 2003; Hua et al., 2009; Mwangi et al., 2014). For baseline models, algorithms were run with default settings from scikit-learn without additional FS and HPO steps (pure pipeline). If FS was not performed in conjunction with HPO, default parameters were equally used. We investigated different FS methods in the present study (Mwangi et al., 2014).

For classification, two univariate filters, that is, ANOVA *F*-test and mutual information, were compared to L1-based (using a linear SVM) and hybrid FS. For the univariate filters, the top 10% of features were selected. Furthermore, L1-based (i.e., regularization) FS using a linear SVM to create sparse models in combination with the five classifiers was examined. Finally, a hybrid FS method, which combines both filter and wrapper methods, was considered (Kazeminejad & Sotero, 2019; Khazaee et al., 2016). Initially, a univariate filter (ANOVA *F*-test) was applied selecting 50% of the top performing features. On the remaining half of the features, a sequential forward floating selection wrapper was used to determine the top 10 features contributing to the classification using the mlxtend package for Python (Khazaee et al., 2016; Pudil et al., 1994; Raschka, 2018). FS was always performed on the training set.

Different FS methods were also examined in ML regression. A univariate correlation–based filter was applied in case of SVR, RVR, and Ridge regression (Finn et al., 2015; Guyon & Elisseeff, 2003). Again the top 10% of features were selected. In contrast, LASSO and Elastic Net regression are embedded FS algorithms. Due to their regularization penalty, only features with a high discriminatory power will have a nonzero weight and will contribute to the task at hand (Zou & Hastie, 2005). Thus, they enforce sparsity and with it integrate FS in their optimization problem (Mwangi et al., 2014).

In terms of HPO, three of the five classification algorithms had hyperparameters to be tuned, that is, SVM, KNN, and DT. HPO was carried out for (i) regularization parameter C for SVM (10^{-4} to 10^{1}, 10 steps, logarithmic scale) for linear, radial basis function (RBF) and polynomial (poly) kernel, (ii) maximum tree depth (4, 6, 8, 10, 20, 40, None) and optimum criterion (gini impurity vs entropy) for DT, and (iii) number of neighbors for KNN (1, 3, 5, 7, 9, 11,13, 15, 17, 19, 21, 23, 25). HPO was assessed with and without additional FS (ANOVA *F*-test) in classification. The following hyperparameters were tuned in ML prediction: (i) regularization parameter lambda λ for LASSO and Ridge regression (LASSO: 10^{-1} to 10^{2}, Ridge: 10^{-3} to 10^{5}, 10 steps, logarithmic scale); (ii) parameters lambda, λ, and alpha, α, for Elastic Net

(λ : 10^{-1} to 10^{2}, 10 steps, logarithmic scale; α: 0 to 1, 10 steps); and (iii) regularization parameter C for SVR (10^{-4} to 10^{1}, 10 steps, logarithmic scale) and kernel type (linear, RBF, and poly). HPO was assessed in conjunction with FS in prediction as some algorithms incorporated embedded feature selection. All HPO was performed on the inner loop using grid search assessing the performance of all parameter combinations and choosing the best one in terms of inner loop performance. All pipeline options were explored for feature sets without (nr condition) and with deconfounding (cr, nr-cr, cr-cr condition) applied.

Deconfounding strategy: The approach of how to control for the impact of potential confounders, e.g., age or sex.

For deconfounding strategy, if deconfounding was applied, the covariates age, sex and educational level were regressed from features/targets. To avoid data leakage, confound regression was always carried out within the ML pipeline. Following Rasero and colleagues (2021), confounders were regressed from targets/features by using a linear regression model, which was fit using only the training set and then applied to both training and test data to obtain residuals. Different extents of deconfounding (nr = no deconfounding; classification: cr = confounders regressed from features; regression: nr-cr = confounders regressed from targets, cr-cr = confounders regressed from both features and targets) were implemented to assess its impact on ML performance (Pervaiz et al., 2020).

For ML validation analyses, we performed several further analyses to validate our ML approach. First, we investigated the influence of a finer grained parcellation on ML performance (Dadi et al., 2019; Khazaee et al., 2016). Therefore, we compared ML performance results obtained from using a 400-node and 800-node parcellation (Schaefer et al., 2018). Additionally, ML performance was explored separately in males and females, given the well-established gender differences in RSFC and its potential impact on ML performance (Nostro et al., 2018; Stumme et al., 2020; Weis et al., 2019). Furthermore, we examined whether the inclusion of information from negative correlations in terms of functional connectivity may alter ML performance results. In this context, we calculated our strength measures based on (i) the absolute values from both positive and negative correlations and (ii) only on the absolute values from negative correlations and used these separately as features to ML. Additionally, we investigated how classification performance changes when only extreme groups, defined as the highest and lowest 25% of individuals scoring on the global cognition component, are included (Dadi et al., 2021; Vieira et al., 2022). Classification performance was examined in unmatched and matched (for age, sex, and education) samples (see Supporting Information Tables S2–S3). In terms of validating our pipeline, we tested our ML pipelines in the context of age, which has repeatedly been shown to be successfully predicted from RSFC patterns (Liem et al., 2017; Meier et al., 2012; Pläschke et al., 2017; Vergun et al., 2013). To adapt this to our classification setting, we examined the classification of extreme age groups (old vs. young; see Supporting Information Tables S4–S5) in feature set 421 (Vieira et al., 2022). In the prediction setting, age was predicted continuously. Prediction analyses were carried out for extreme groups, the unmatched sample and the whole age range of the 1000BRAINS cohort (18–85 age) (see Supporting Information Tables S4–S5).

Model Comparisons and Statistical Analyses

To assess the reliability and stability of the derived principal components (PCs), we performed two additional analyses. First, we checked for the robustness of the PCA against the imputation of missing values on different cognitive tests. Therefore, we obtained a validation sample, in which all participants with missing values in any of the cognitive tests were excluded from the unmatched sample (N = 749, 343 females, M_{age} = 66.86, SD_{age} = 6.62). Then, we compared component loadings from the original PCA results to the recalculated ones in the validation sample by calculating Pearson's correlations. Second, we turned to the stability of the PCs

across data splits to address the dependency between training and test sets introduced by performing PCA as a first step in the analysis outside of the ML framework. In case of stability of PCs, we may assume that this dependency will not affect our results. Therefore, we additionally divided the data into two subsamples (random split-half procedure was implemented; Sripada et al., 2020b; Thompson et al., 2019) and performed a PCA on each sample separately. Component loadings from the split halves were compared to the original loadings by computing Pearson's correlations (see Supporting Information Tables S9–S10).

To assess the relation between cognitive scores derived from PCA and potential confounding factors, we calculated partial correlations between all cognitive scores (global and domain specific) and age (corrected for education and sex) as well as education (corrected for age and sex) in the unmatched sample. Furthermore, to examine sex differences in cognitive scores, a multivariate analysis of covariance (MANCOVA) was computed with cognitive scores as dependent variables, sex as the independent variable, and the inclusion of age and education as covariates.

For checking the quality of the dichotomization into a high- and low-performance group, we performed independent samples *t*-tests to test for significant differences in cognitive performance (global and domain specific) between high- and low-performance groups in the unmatched and matched sample. Additionally, we assessed the relation between confounding factors and group membership. Thus, we performed independent samples *t*-test to examine group differences in terms of age and education and chi-square tests for independence to assess differences in the sex distribution across high- and low-performance groups in unmatched and matched samples.

To contextualize ML performance and obtain a chance-level prediction equivalent, we compared ML model estimations to those from a reference model, that is, dummy classifier and regressor, given the low computational costs of dummy estimates and their similarity in distribution to approaches based on permutation (Engemann et al., 2020; Vieira et al., 2022). In this case, the percentage of folds, for which the ML models were better than the reference model in terms of accuracy (classification) and R^2 (regression), was calculated with higher percentages (>80%) indicating robust outperformance of the reference model.

RESULTS

We performed twofold analyses to investigate whether cognitive performance differences could be distinguished and predicted based on RSFC strength measures. In a first step, a simple classification setting was chosen to examine if high- and low-performance groups can be accurately classified from RSFC strength parameters using different ML pipeline configurations, analytic choices, and feature sets. In a second step, we sought to address if the continuous prediction of cognitive scores leads to ML performance differences compared to the classification. Thus, we implemented a regression framework to analyze, whether cognitive performance differences could be predicted from RSFC strength measures.

Cognitive Performance Across Unmatched and Matched Samples

A one-component solution for global cognition and a multicomponent solution for cognitive subdomains based on the eigenvalue criterion (eigenvalue > 1) were extracted. Data suitability for PCA was tested with the Kaiser–Meyer–Olkin (KMO) index examining the extent of common variability. With a value of KMO = 0.91, data appeared suitable for PCA. Component scores from the one-component solution were stored as the COGNITIVE COMPOSITE (i.e., global cognition) score for each individual (see Figure 2 and Supporting Information Tables S6 and S7 and Figure S8). With regards to domain-specific cognitive scores, two components could

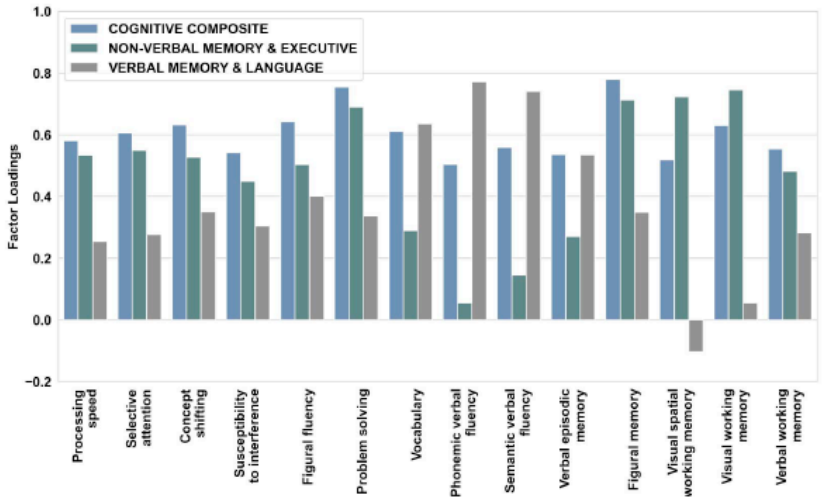

Figure 2. Factor loadings of each cognitive function on the one-component and multicomponent solution extracted from PCA analysis (after varimax rotation).

be discovered from the PCA (see Figure 2 and Supporting Information Tables S6 and S7). The first component mainly covered performance in visual spatial and spatial WM, figural memory, problem solving, selective attention, and processing speed (NON-VERBAL MEMORY & EXECUTIVE component; see Figure 2 and Supporting Information Table S7). The second component centrally reflected performance on semantic and phonemic verbal fluency, vocabulary, and verbal episodic memory (VERBAL MEMORY & LANGUAGE component; see Figure 2 and Supporting Information Table S7). In terms of robustness and stability of PCs, component loadings for all three extracted components were highly similar across the original sample, the random split half samples and the validation sample ($r > 0.86$, $p > 0.01$; Supporting Information Tables S9 and S10) indicating that PCs appear stable across subsets of data and robust against the imputation of missing values. Age was significantly negatively correlated with global and domain-specific cognitive performance scores (controlled for sex and educational level; COGNITIVE COMPOSITE: $r = -.48$, $p < .001$; NON-VERBAL MEMORY & EXECUTIVE: $r = -.43$, $p < .001$; VERBAL MEMORY & LANGUAGE: $r = -.19$, $p < .001$). Higher educational level was significantly associated with higher global and domain-specific cognitive performance (COGNITIVE COMPOSITE: $r = .40$, $p < .001$; NON-VERBAL MEMORY & EXECUTIVE: $r = .21$, $p < .001$; VERBAL MEMORY & LANGUAGE: $r = .35$, $p < .001$; controlled for age and sex). A multivariate analysis of covariance (MANCOVA) with age and education as covariates revealed males to perform significantly better than females on the NON-VERBAL MEMORY & EXECUTIVE component ($F(1, 809) = 30.22$, $p < .001$, $\eta_p^2 = 0.036$), while females outperformed males on the VERBAL MEMORY & LANGUAGE component ($F(1, 809) = 46.11$, $p < .001$, $\eta_p^2 = 0.056$). In turn, no sex differences were found for global cognition (COGNITIVE COMPOSITE: $F(1, 809) = 0.024$, $p = .877$, $\eta_p^2 = 0.0$). Component scores (global and domain-specific) obtained from PCA were used as targets in ML prediction.

For classification of cognitive performance differences, high- and low-performance groups were created by a median split after the extraction of participants' component scores (as extracted in the PCA). High- and low-performance groups in the initial (unmatched) sample

differed significantly in global and domain-specific cognitive performance, as well as in terms of age, educational level, and sex (see Table 2). The high-performing group was found to be significantly younger and better educated than the low-performing group (see Table 2). More males than females were represented in the high-performance group for the COGNITIVE COMPOSITE and the NON-VERBAL MEMORY & EXECUTIVE component (see Table 2). The reversed pattern was found for the VERBAL MEMORY & LANGUAGE component (see Table 2).

To control for the impact of confounding factors, high- and low-performance groups of the COGNITIVE COMPOSITE component were matched on age, educational level, and sex. This led to a matched subsample (N = 518; see Figure 1: Sample and Table 1B). High- and low-performance groups again differed significantly in their global and domain-specific cognitive performance (see Table 2). No significant group differences were encountered in terms of age, educational level and sex distribution for the COGNITIVE COMPOSITE component (see Table 2). Participants in the low-performance group on the NON-VERBAL MEMORY & EXECUTIVE and VERBAL MEMORY & LANGUAGE component were found to be significantly less educated than participants in the high-performance group. A similar significant pattern for differences in the sex distribution was encountered as in the unmatched sample (see Table 2). Group memberships (high vs. low) were used as targets in ML classification.

Classification Results

Classification performance across global cognition and cognitive domains. ML was used in a first step to assess the usefulness of RSFC strength measures to distinguish cognitive performance differences in older adults. All algorithms were first implemented in a feature set with 421 features to examine classification performance of global and domain-specific cognitive performance differences in the matched sample. Across all implemented ML pipelines with and without univariate feature selection (FS), performance did not exceed 60% accuracy (see Figure 3A and Supporting Information Table S11). Mean BACs ranged between 48.68% to 58.33% for global cognition and 50.21% to 58.44% for domain-specific cognition. These results were further supported by the comparison to the dummy classifier. The majority of models did not outperform the dummy classifier in more than 80% of folds. Higher accuracies compared to the dummy were achieved mainly in no more than 50% to 80% of folds, suggesting rather modest overall performance and limitations in reliability (see Supporting Information Table S12). Classification accuracies for the NON-VERBAL MEMORY & EXECUTIVE component were marginally higher than for the VERBAL MEMORY & LANGUAGE component, which was also supported by results from comparisons to the dummy estimate (see Figure 3A and Supporting Information Tables S11–S13). No systematic differences between models based on features with (cr) or without (nr) deconfounding, that is, controlling for the effects of age, sex, and education on features, could be observed (Figure 3A). Initial results suggested poor discriminatory power of RSFC strength measures for global and domain-specific cognitive performance differences in a large population-based older sample.

Classification performance across different pipeline configurations for global cognition. To examine the impact of different pipeline configurations, we investigated ML performance in a pure pipeline, that is, without FS, and in FS/hyperparameter optimization (HPO) pipelines, that is, additional step of feature selection (FS) and HPO, for global cognition. All algorithms were first implemented in a pure pipeline using 421 features. Baseline results revealed classification accuracies between 48.68% to 58.33% (see Figure 3B). Baseline results were then compared to those from different FS/HPO pipelines. Estimations from FS/HPO pipelines were found to be

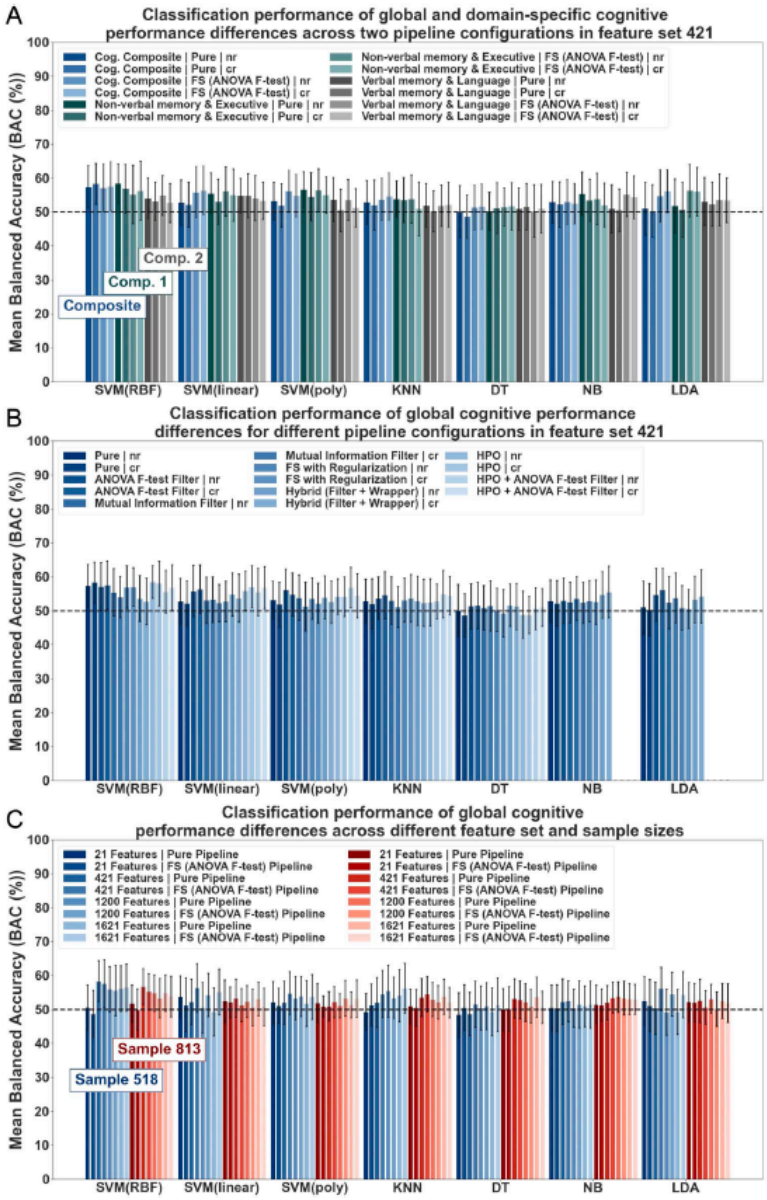

Figure 3. Classification performance results of cognitive performance differences (based on global and domain-specific scores) from RSFC strength measures. Classification results across algorithms: Support Vector Machine (SVM) with Radial Basis Function (RBF), linear and polynomial (poly) kernel, K-Nearest Neighbour (KNN), Decision Tree (DT), Naïve Bayes (NB), Linear Discriminant Analysis (LDA). Results shown for (A) different targets (cognitive composite and cognitive components), (B) pipeline configurations (pure (no FS/HPO) vs. FS/HPO pipelines), (C) samples (matched vs. unmatched sample) and feature set sizes (21, 421, 1,200, 1,621). Error bars correspond to standard deviation (*SD*); nr = no confound regression applied to features; cr = age, sex, and education regressed from features; unless otherwise specified, cr condition showed.

similar to baseline estimations (M_{BAC} range: 48.77–58.46%; in 42–96 % of folds BAC > dummy classifier; see Figure 3B and Supporting Information Tables S14–S16). Thus, additional pipeline steps, that is, FS and HPO, which are commonly found to enhance performance, did not substantially increase classification accuracies in the current study (Brown & Hamameh, 2016; Mwangi et al., 2014).

Classification performance across different feature sets and sample sizes for global cognition. Classification performance for global cognition was also examined for varying feature sets (i.e., 21, 421, 1,200, 1,621) and sample sizes (matched vs. unmatched). No performance improvements could be observed for greater feature set sizes (Feature sets 21 and 421: M_{BAC} range: 48.42–59.31%, in 34–98% of folds BAC > dummy classifier; feature sets 1,200 and 1,621: M_{BAC} range: 48.96–58.72%, in 38–94% of folds BAC > dummy classifier) in both samples across pipeline configurations and algorithms (see Figure 3C and Supporting Information Tables S17–S20). A small difference between samples emerged in the nr condition. Relatively higher accuracies across feature sets were found in the nr condition of the unmatched sample than in the matched sample (Unmatched sample: M_{BAC} range nr: 49.33–59.31%, in 44–98% of folds BAC > dummy classifier; Matched sample: M_{BAC} range nr: 48.96–57.41%, in 40–86% of folds BAC > dummy classifier; see Supporting Information Tables S17–S20). This effect was no longer found in the cr condition (Unmatched sample: M_{BAC} range cr: 50.00–56.81%, in 42–94% of folds BAC > dummy classifier; Matched sample: M_{BAC} range cr: 48.42–58.33%, in 34–94% of folds BAC > dummy classifier; see Figure 3C and Supporting Information Tables S17–S20). ML performance in this specific case (nr condition/unmatched sample), however, is most likely influenced by confounds. Overall, findings suggest that increasing feature set and sample size may not systematically aid classification performance in our study. It, however, further underlines the relatively low discriminatory power of the specific RSFC strength measures for the research question at stake.

Regression

Prediction performance of global cognition and cognitive domains across pipeline configurations. In a second step, ML was used to assess whether RSFC strength measures can be used to continuously predict cognitive performance in older adults. ML prediction performance of global and domain-specific cognition from RSFC strength measures was initially evaluated in feature set 421 in the unmatched sample. Across pipeline configurations and deconfounding strategies, MAEs obtained for global and domain-specific cognition were high, ranging between 0.76 and 1.14 (see Figure 4A). Simultaneously, the coefficient of determination (R^2) was found to be low (≤0.06) or even negative, indicating that predicting the mean of cognitive scores would have yielded better results than our model's predictions (see Figure 4B and Supporting Information Tables S21 and S22). The NON-VERBAL MEMORY & EXECUTIVE component revealed slightly lower MAE and higher R^2 than the VERBAL MEMORY & LANGUAGE component across conditions (see Figure 4A and B and Supporting Information Tables S21 and S22). Nevertheless, predictability compared to global cognition was similar in range. Furthermore, results were comparable for different algorithms except for Ridge regression in pure pipelines, which showed markedly elevated MAE, and reduced explained variance for all targets for default values of the hyperparameter lambda (see Supporting Information Table S21). Manual adjustment of the hyperparameter led to similar performance to other algorithms (see Figure 4A and B and Supporting Information Table S21). No systematic predictive performance differences were found for FS and HPO pipelines (see Figure 4A and B and Supporting Information Tables S21 and S22). In terms of different extents of deconfounding, the nr condition

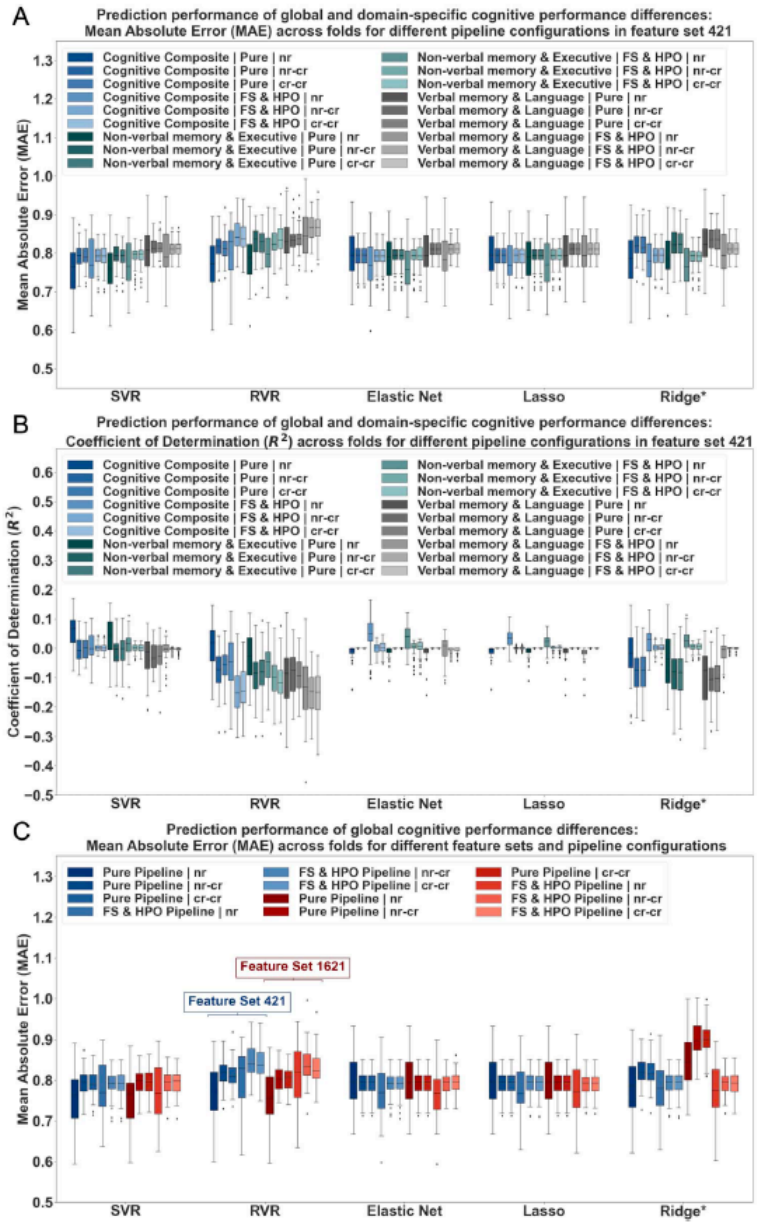

Figure 4. Regression performance results of cognitive performance differences (based on global and domain-specific cognitive scores) from RSFC strength measures. Regression performance across algorithms: Support Vector Regression (SVR), Relevance Vector Regression (RVR), Elastic Net, LASSO and Ridge Regression. Results shown for (A and B) cognitive composite and cognitive component scores, (A and C) different pipeline configurations (pure (no FS/HPO) vs. FS and HPO pipelines), and (C) feature set sizes (421, 1621) (C). Ridge*: default values in pure pipeline manually adjusted; nr = no confound regression; nr-cr = age, sex, and education regressed from target; cr-cr = age, sex, and education regressed from target and features.

resulted in slightly better prediction results compared to the other two conditions (nr: MAEs ≥ 0.76; $R^2 \leq 0.06$; nr-cr and cr-cr: MAEs ≥ 0.79; $R^2 \leq 0.00$; see Supporting Information Table S21). This was also reflected in an improved robustness against the dummy regressor (see Figure 4C and Supporting Information Table S22). Nevertheless, it should be kept in mind that still only a limited number of models were consistently outperforming the dummy estimates in more than 80% of folds. Jointly, these results suggest that RSFC strength measures may not contain sufficient information to reliably predict global and domain-specific cognitive performance in older adults from a population-based cohort.

Prediction performance across varying feature set sizes for global cognition. Feature set size did only have minimal impact in the classification setting. To verify the impact of varying feature combinations and number of features in ML prediction, feature set 421, which was used for comparability purposes throughout the analyses, and 1,621, which contains all possible features, were chosen for closer examination in the regression setting. Thus, ML performance estimations were examined in different pipeline configurations for global cognition. Across feature sets and deconfounding strategies, the *MAE* was again found to be high (≥0.75) and the coefficient of determination to be low (≤0.07) (see Supporting Information Tables S23 and S24). The impact of different algorithms, pipeline configurations, and extents of deconfounding on ML performance was again found to be minimal and to follow a similar pattern as before (see Figure 4C). No significant performance differences in terms of *MAE* and R^2 emerged for different feature set sizes (see Figure 4C and Supporting Information Tables S23 and S24). Thus, findings suggest in addition to minimal discriminatory power also low predictive potential of cognitive performance differences in healthy older adults across feature sets, deconfounding strategies, and pipeline configurations from RSFC strength measures.

Validation Analyses

Finally, we investigated the impact of a finer grained parcellation on ML performance. Results suggest that a higher granularity has only little impact on ML performance. Classification accuracies ranged between 47.79% and 56.53% across feature sets and pipeline configurations for the 800-node parcellation (see Supporting Information Tables S25 and S26 and Figure S28A), compared to the 48.42% to 58.33% range obtained for the 400-node parcellation. Prediction performance was found to be equally low as in the initial parcellation with high *MAE*s (≥0.75) and low to none explained variance ($R^2 \leq 0.07$) for different feature sets and pipeline configurations (see Supporting Information Table S27 and Figure S28B). Thus, no benefit of a higher granularity was observed. Furthermore, ML performance was examined in males and females separately. Classification performance in male and female samples equally did not exceed 60% accuracy for global cognition (M_{BAC}: 49.69–55.57%; see Supporting Information Tables S29 and S30 and Figure S32A). Prediction performance in male and female samples revealed comparable high *MAE*s (≥0.73) and low R^2 (≤0.04) (see Supporting Information Table S31 and Figure S32B). Findings, hence, further emphasize results found in the main analysis. Moreover, classification and prediction performance was assessed using connectivity estimates based on (i) positive and negative correlations and (ii) only negative correlations. For connectivity estimates based on positive and negative correlation values, classification performance varied between 47.91% to 56.25% BAC for global cognition across algorithms, feature sets and pipeline configurations (see Supporting Information Table S33 and Figure S35A). Prediction performance equally resembled results from the main analysis (*MAE*s ≥ 0.75; $R^2 \leq$ 0.08; see Supporting Information Table S34 and Figure S35B). A similar pattern of results emerged for strength measures derived from negative correlations. Classification performance varied between 48.42% to 54.73% BAC for global cognition across algorithms, feature sets,

and pipeline configurations (see Supporting Information Table S36). In turn, prediction performance was found to be equally low (*MAE*s ≥ 0.77; $R^2 \leq 0.05$; see Supporting Information Table S37). Adding further information from anticorrelations, thus, did not appear to improve ML performance. Furthermore, we investigated classification performance in extreme cognitive groups. Across samples, pipelines, feature sets, and algorithms, classification performance ranged between 49.70% to 62.50% BAC (see Supporting Information Tables S38 and S39). Although slightly better classification results were achieved for extreme cognitive groups, overall performance remained limited. This suggests that low classification results may not be primarily driven by difficulties in identifying participants close to the median and provides further sustenance to our findings from the main analyses. An age prediction and classification framework was chosen for validating our ML pipeline. In the classification of extreme age groups, highest classification performance was obtained for linear SVM in the pure and HPO pipeline with 85.13% and 83.13% accuracy, respectively (see Supporting Information Table S40). For the continuous prediction of age, RSFC strength measures were found to overall predict age reasonably well with R^2 in the best cases ranging between 0.3 and 0.4 (extreme and whole sample across age spectrum; see Supporting Information Table S41). In comparison to dummy estimates, these models also showed reliably higher performance (see Supporting Information Table S42). While the obtained *MAE*s across samples were not competitive with those reported in the literature, results from the validation analyses, nevertheless, generally support the view that the current pipeline may yield reasonable prediction and classification performances (Liem et al., 2017; Pläschke et al., 2017; Vergun et al., 2013; Vieira et al., 2022). Thus, the low ML performance estimates may be specific to the setting of classifying and predicting cognitive performance differences from RSFC strength measures in healthy older adults rather than a general finding pertained to the ML setup, parcellation granularity, sampling, or features.

DISCUSSION

The aim of the current investigation was to examine whether global and domain-specific cognitive performance differences may be successfully distinguished and predicted from RSFC strength measures in a large sample of older adults by using a systematic assessment of standard ML approaches. Results showed that classification and regression performance failed to reach adequate discriminatory and predictive power at the individual level. Importantly, these results persisted across different feature sets, algorithms, and pipeline configurations.

The present findings add to the notion that predicting cognition from the functional network architecture may yield heterogeneous findings (Dubois et al., 2018; Finn et al., 2015; Rasero et al., 2021; Vieira et al., 2022). For instance, RSFC patterns expressed in functional connectivity matrices have been shown to explain up to 20% of variance in a composite cognition score (NIH Cognitive Battery) and in a general intelligence factor (factor analysis) in two samples of the Human Connectome Project (HCP) S1200 young adult release (Dhamala et al., 2021; Dubois et al., 2018). In contrast, global cognition (NIH Cognitive Battery; cf. Dhamala et al., 2021) was predicted to a notably smaller degree from RSFC in young adults (median $R^2 = 0.016$) (Rasero et al., 2021). In older adults, Vieira et al., (2022) reported RSFC to not predict prospective global cognitive decline, that is, change in two clinical assessments (OASIS-3 project; median $R^2_{MMSE} = 0$; median $R^2_{CDR} = 0.01$). Our results further emphasize that across different analytic choices RSFC strength measures may not reliably capture cognitive performance variations in older aged adults. In light of our goal of robust and accurate classification and prediction at the individual level, the minimum acceptable prediction accuracy is achieved only if the model outperforms the dummy estimate in more than 80% of the

folds. This threshold is not met by the majority of our classification and prediction models, hinting at a limited potential as biomarker for age-related cognitive decline. Validation analyses further highlight the specificity of our results to cognitive abilities. RSFC strength measures could be used to successfully classify extreme age groups and moderately predict age (Meier et al., 2012; Pläschke et al., 2017; Vergun et al., 2013). RSFC patterns underlying cognition, however, may be more difficult to discern with current analytic tools, leading to mixed or null results. It should be stressed that null results may be highly informative as they provide important insights for future research, support a more realistic and unbiased view on brain-behavior relations, and allow for learning from experiences across the field (Janssen et al., 2018; Masouleh et al., 2019). Nevertheless, they tend to be underreported in the literature, leading to a potential publication bias (Janssen et al., 2018).

Successful prediction or classification of cognitive functioning from RSFC patterns has been reported previously (Dhamala et al., 2021; Dubois et al., 2018; Hojjati et al., 2017; Khazaee et al., 2016; Rosenberg et al., 2016; Yoo et al., 2018). One possible explanation for the fact that the results could not be replicated is related to the composition of the sample. Most previous studies reporting satisfactory ML performance focused on younger cohorts or patient populations (Dhamala et al., 2021; Dubois et al., 2018; Hojjati et al., 2017; Khazaee et al., 2016; Rosenberg et al., 2016; Yoo et al., 2018). In comparison to younger samples ($M_{age} < 30$), low discriminatory and predictive power in the current study may be attributable to a more complex link between RSFC and cognition evolving during the aging process (Dhamala et al., 2021; Dubois et al., 2018; Rosenberg et al., 2016; Yoo et al., 2018). Aging is not only associated with cognitive decline and functional network reorganization, but also with an increasing interindividual variability (Andrews-Hanna et al., 2007; Chan et al., 2014; Chong et al., 2019; Fjell et al., 2015; Grady et al., 2016; Habib et al., 2007; Hartshorne & Germine, 2015; Hedden & Gabrieli, 2004; Mowinckel et al., 2012; Ng et al., 2016; Onoda et al., 2012; Stumme et al., 2020). Consequently, the RSFC patterns that explain cognitive performance levels in older adults are more difficult to identify (Scarpazza et al., 2020).

When comparing promising patient classification results to the current results, effect sizes might be responsible for the unsatisfactory ML performance (Amaefule et al., 2021; Cui & Gong, 2018; Kwak et al., 2021). For example, patients with MCI and AD show markedly altered functional network organization compared to cognitively normal older adults (Badhwar et al., 2017; Brier et al., 2014; Buckner et al., 2009; Greicius et al., 2004; Sanz-Arigita et al., 2010; Wang et al., 2013). The sizable alterations related to pathological aging are reflected in encouraging results in patient classification (de Vos et al., 2018; Dyrba et al., 2015; Hojjati et al., 2017; Khazaee et al., 2016; Teipel et al., 2017). For instance, ML performance in patient classification (HC vs. MCI vs. AD) based on RSFC graph metrics reached above 88% accuracy (Hojjati et al., 2017; Khazaee et al., 2016). Nevertheless, these effect sizes may not be found for healthy older populations. For instance, cognition could be significantly predicted in samples of cognitive normal and clinically impaired older adults from whole-brain RSFC patterns (r = 0.08–0.44) (Kwak et al., 2021). However, prediction accuracy dropped substantially once models were trained only on clinically unimpaired older adults (r = −0.04–0.24) (Kwak et al., 2021). Accurate cognitive performance prediction from RSFC patterns in older aged adults without the inclusion of clinical populations may, hence, be impeded by small effect sizes.

Another aspect that needs to be addressed when discussing the low ML performance concerns the cognitive parameters used. Most studies including older cohorts have focused on specific cognitive abilities (Avery et al., 2020; Fountain-Zaragoza et al., 2019; Gao et al., 2020; Kwak et al., 2021; Pläschke et al., 2020). For instance, WM capacity could be successfully predicted from meta-analytically defined RSFC networks in older individuals (Pläschke

et al., 2020). This may be due to a more explicit mapping of RSFC patterns to specific cognitive abilities than for general or clustered cognitive abilities, which we were interested in (Avery et al., 2020; Gao et al., 2020; Kwak et al., 2021).

Furthermore, most prior studies have used pair-wise functional connectivity as input features (Avery et al., 2020; Dhamala et al., 2021; Dubois et al., 2018; Gao et al., 2020; He et al., 2020; Pläschke et al., 2020). We used functional connectivity estimates linked to cognitive performance differences in aging and with promising classification performance in neurodegenerative diseases (Chan et al., 2014; Hausman et al., 2020; Hojjati et al., 2017; Iordan et al., 2018; Khazaee et al., 2016; Malagurski et al., 2020; Ng et al., 2016; Stumme et al., 2020). Findings highlight that for reliably detecting cognitive performance differences in normally aging individuals, the additional dimensionality reduction inherent to the calculation of RSFC strength values may be too extensive, that is, relevant information for ML was lost during the computation (Cui & Gong, 2018; Lei et al., 2020). Also, redundancy of feature information, that is, within- and inter-network connectivity, may have resulted in poorer ML performance, especially in larger feature sets (Mwangi et al., 2014).

Methodological Considerations and Future Outlook

While the current investigation concentrated on RSFC strength measures, future studies might use other imaging features, that is, more complex graph metrics, such as betweenness centrality or modularity, multimodal or task-based fMRI data, to improve the prediction of cognitive performance in older age (Draganski et al., 2013; Gbadeyan et al., 2022; McConathy & Sheline, 2015; Pacheco et al., 2015; Sripada et al., 2020b; Vieira et al., 2022). For example, prior research has shown that global cognitive abilities could be better predicted from task-based than resting-state fMRI data in large samples of younger adults from the HCP dataset (Greene et al., 2018; Sripada et al., 2020a). Along these lines, it may be interesting to investigate whether task-based fMRI data in these circumstances also outperforms RSFC in older adults. Likewise, it is also warranted to keep a distinction between basic research and clinical applicability. Classification and prediction results might already be informative, if they are statistically significant in healthy subjects; however, they may not be practically relevant for the clinical context.

Furthermore, only cross-sectional data has been used in the current investigation. Although important insights can be gained cross-sectionally, the investigation of longitudinal data becomes indispensable in the biomarker development for prospective age-related cognitive decline (Davatzikos et al., 2009; Liem et al., 2021). Initial efforts to predict future cognitive decline from imaging and nonimaging data have revealed promising results (Vieira et al., 2022).

A further methodological consideration pertains to the choice of data preparation steps, for example, the parcellation scheme and choice of network assignment (Dubois et al., 2018). In the current investigation, a functional network parcellation derived from younger brains was used, which directly links brain networks to behavioral processing and is commonly used in lifespan studies (Schaefer et al., 2018; Yeo et al., 2011). Although ML performance in the current study was low regardless of data preparation, that is, parcellation granularity, and ML model choices, future studies are warranted to examine generalizability to other population-based cohorts of older aged adults and other functional network divisions.

Conclusions

The present study addressed the biomarker potential of RSFC strength measures for cognitive performance differences in normal aging in a systematic evaluation of standard ML approaches. Present results across different analytic choices emphasize that the potential of

RSFC strength measures as sole biomarker for age-related cognitive decline may be limited. Findings add to past research demonstrating that reliable cognitive performance prediction and distinction in healthy older adults based on RSFC strength measures may be challenging due to small effects, high heterogeneity, and the removal of relevant information during the computation of these parameters. Although current results are far from promising, they still may prove useful in providing guidance on future research targets. Specifically, multimodal and longitudinal approaches appear warranted in future studies developing a robust biomarker for cognitive performance in healthy aging.

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SUPPORTING INFORMATION

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AUTHOR CONTRIBUTIONS

Camilla Krämer: Conceptualization; Formal analysis; Methodology; Visualization; Writing – original draft; Writing – review & editing. Johanna Stumme: Formal analysis; Methodology; Writing – review & editing. Lucas da Costa Campos: Formal analysis; Methodology; Writing – review & editing. Christian Rubbert: Methodology; Writing – review & editing. Julian Caspers: Conceptualization; Methodology; Writing – review & editing. Svenja Caspers: Conceptualization; Funding acquisition; Resources; Supervision; Writing – review & editing. Christiane Jockwitz: Conceptualization; Methodology; Supervision; Writing – review & editing.

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REFERENCES

Afyouni, S., & Nichols, T. E. (2018). Insight and inference for DVARS. *NeuroImage*, *172*, 291–312. https://doi.org/10.1016/j.neuroimage.2017.12.098, PubMed: 29307608

Amaefule, C. O., Dyrba, M., Wolfsgruber, S., Polcher, A., Schneider, A., Fliessbach, K., Spottke, A., Meiberth, D., Preis, L., Peters, O., Incesoy, E. I., Spruth, E. J., Priller, J., Altenstein, S., Bartels, C., Wiltfang, J., Janowitz, D., Bürger, K., Laske, C., … Teipel, S. J. (2021). Association between composite scores of domain-specific cognitive functions and regional patterns of atrophy and functional connectivity in the Alzheimer's disease spectrum. *NeuroImage: Clinical*, *29*, 102533. https://doi.org/10.1016/j.nicl.2020.102533, PubMed: 33360018

Andrews-Hanna, J. R., Snyder, A. Z., Vincent, J. L., Lustig, C., Head, D., Raichle, M. E., & Buckner, R. L. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron*, *56*(5), 924–935. https://doi.org/10.1016/j.neuron.2007.10.038, PubMed: 18054866

Arbabshirani, M. R., Plis, S., Sui, J., & Calhoun, V. D. (2017). Single subject prediction of brain disorders in neuroimaging: Promises and pitfalls. *NeuroImage*, *145*, 137–165. https://doi.org/10.1016/j.neuroimage.2016.02.079, PubMed: 27012503

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *NeuroImage*, *26*(3), 839–851. https://doi.org/10.1016/j.neuroimage.2005.02.018, PubMed: 15955494

Avery, E. W., Yoo, K., Rosenberg, M. D., Greene, A. S., Gao, S., Na, D. L., Scheinost, D., Constable, T. R., & Chun, M. M. (2020). Distributed patterns of functional connectivity predict working memory performance in novel healthy and memory-impaired individuals. *Journal of Cognitive Neuroscience*, *32*(2), 241–255. https://doi.org/10.1162/jocn_a_01487, PubMed: 31659926

Badhwar, A., Tam, A., Dansereau, C., Orban, P., Hoffstaedter, F., & Bellec, P. (2017). Resting-state network dysfunction in Alzheimer's disease: A systematic review and meta-analysis. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *8*(1), 73–85. https://doi.org/10.1016/j.dadm.2017.03.007, PubMed: 28560308

Brier, M. R., Thomas, J. B., Fagan, A. M., Hassenstab, J., Holtzman, D. M., Benzinger, T. L., Morris, J. C., & Ances, B. M. (2014). Functional connectivity and graph theory in preclinical Alzheimer's disease. *Neurobiology of Aging*, *35*(4), 757–768. https://doi.org/10.1016/j.neurobiolaging.2013.10.081, PubMed: 24216223

Brown, C. J., & Hamarneh, G. (2016). Machine learning on human connectome data from MRI. *ArXiv:1611.08699*. https://doi.org/10.48550/arXiv.1611.08699

Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., Andrews-Hanna, J. R., Sperling, R. A., & Johnson, K. A. (2009). Cortical hubs revealed by intrinsic functional connectivity: Mapping, assessment of stability, and relation to Alzheimer's disease. *Journal of Neuroscience*, *29*(6), 1860–1873. https://doi.org/10.1523/JNEUROSCI.5062-08.2009, PubMed: 19211893

Burgess, G. C., Kandala, S., Nolan, D., Laumann, T. O., Power, J. D., Adeyemo, B., Harms, M. P., Petersen, S. E., & Barch, D. M. (2016). Evaluation of denoising strategies to address motion-correlated artifacts in resting-state functional magnetic resonance imaging data from the Human Connectome Project. *Brain Connectivity*, *6*(9), 669–680. https://doi.org/10.1089/brain.2016.0435, PubMed: 27571276

Cabeza, R. (2001). Cognitive neuroscience of aging: Contributions of functional neuroimaging. *Scandinavian Journal of Psychology*, *42*(3), 277–286. https://doi.org/10.1111/1467-9450.00237, PubMed: 11501741

Calhoun, V. D., Wager, T. D., Krishnan, A., Rosch, K. S., Seymour, K. E., Nebel, M. B., Mostofsky, S. H., Nyalakanai, P., & Kiehl, K. (2017). The impact of T1 versus EPI spatial normalization templates for fMRI data analyses. *Human Brain Mapping*, *38*(11), 5331–5342. https://doi.org/10.1002/hbm.23737, PubMed: 28745021

Caspers, S., Moebus, S., Lux, S., Pundt, N., Schütz, H., Mühleisen, T. W., Gras, V., Eickhoff, S. B., Romanzetti, S., Stöcker, T., Stirnberg, R., Kirlangic, M. E., Minnerop, M., Pieperhoff, P., Mödder, U., Das, S., Evans, A. C., Jöckel, K.-H., Erbel, R., … Amunts, K. (2014). Studying variability in human brain aging in a population-based German cohort-rationale and design of 1000BRAINS. *Frontiers in Aging Neuroscience*, *6*, 149. https://doi.org/10.3389/fnagi.2014.00149, PubMed: 25071558

Chan, M. Y., Park, D. C., Savalia, N. K., Petersen, S. E., & Wig, G. S. (2014). Decreased segregation of brain systems across the healthy adult lifespan. *Proceedings of the National Academy of Sciences*, *111*(46), E4997–E5006. https://doi.org/10.1073/pnas.1415122111, PubMed: 25368199

Chong, J. S. X., Ng, K. K., Tandi, J., Wang, C., Poh, J.-H., Lo, J. C., Chee, M. W. L., & Zhou, J. H. (2019). Longitudinal changes in the cerebral cortex functional organization of healthy elderly. *Journal of Neuroscience*, *39*(28), 5534–5550. https://doi.org/10.1523/JNEUROSCI.1451-18.2019, PubMed: 31109962

Ciric, R., Wolf, D. H., Power, J. D., Roalf, D. R., Baum, G. L., Ruparel, K., Shinohara, R. T., Elliott, M. A., Eickhoff, S. B., Davatzikos, C., Gur, R. C., Gur, R. E., Bassett, D. S., & Satterthwaite, T. D. (2017). Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity. *NeuroImage*, *154*, 174–187. https://doi.org/10.1016/j.neuroimage.2017.03.020, PubMed: 28302591

Cui, Z., & Gong, G. (2018). The effect of machine learning regression algorithms and sample size on individualized behavioral prediction with functional connectivity features. *NeuroImage*, *178*, 622–637. https://doi.org/10.1016/j.neuroimage.2018.06.001, PubMed: 29870817

Dadi, K., Rahim, M., Abraham, A., Chyzhyk, D., Milham, M., Thirion, B., & Varoquaux, G. (2019). Benchmarking functional connectome-based predictive models for resting-state fMRI. *NeuroImage*, *192*, 115–134. https://doi.org/10.1016/j.neuroimage.2019.02.062, PubMed: 30836146

Dadi, K., Varoquaux, G., Houenou, J., Bzdok, D., Thirion, B., & Engemann, D. (2021). Population modeling with machine learning can enhance measures of mental health. *GigaScience*, *10*(10), giab071. https://doi.org/10.1093/gigascience/giab071, PubMed: 34651172

Dai, Z., Yan, C., Li, K., Wang, Z., Wang, J., Cao, M., Lin, Q., Shu, N., Xia, M., Bi, Y., & He, Y. (2015). Identifying and mapping connectivity patterns of brain network hubs in Alzheimer's disease. *Cerebral Cortex*, *25*(10), 3723–3742. https://doi.org/10.1093/cercor/bhu246, PubMed: 25331602

Damoiseaux, J. S., Beckmann, C. F., Arigita, E. J. S, Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Rombouts, S. A. R. B. (2008). Reduced resting-state brain activity in the "default network" in normal aging. *Cerebral Cortex*, *18*(8), 1856–1864. https://doi.org/10.1093/cercor/bhm207, PubMed: 18063564

Davatzikos, C., Xu, F., An, Y., Fan, Y., & Resnick, S. M. (2009). Longitudinal progression of Alzheimer's-like patterns of atrophy in normal older adults: The SPARE-AD index. *Brain*, *132*(8), 2026–2035. https://doi.org/10.1093/brain/awp091, PubMed: 19416949

de Vos, F., Koini, M., Schouten, T. M., Seiler, S., van der Grond, J., Lechner, A., Schmidt, R., de Rooij, M., & Rombouts, S. A. R. B. (2018). A comprehensive analysis of resting state fMRI measures to classify individual patients with Alzheimer's disease. *NeuroImage*, *167*, 62–72. https://doi.org/10.1016/j.neuroimage.2017.11.025, PubMed: 29155080

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., Penke, L., Rafnsson, S. B., & Starr, J. M. (2009). Age-associated cognitive decline. *British Medical Bulletin*, *92*(1), 135–152. https://doi.org/10.1093/bmb/ldp033, PubMed: 19776035

Depp, C. A., & Jeste, D. V. (2006). Definitions and predictors of successful aging: A comprehensive review of larger quantitative studies. *The American Journal of Geriatric Psychiatry*, *14*(1), 6–20. https://doi.org/10.1097/01.JGP.0000192501.03069.bc, PubMed: 16407577

Dhamala, E., Jamison, K. W., Jaywant, A., Dennis, S., & Kuceyeski, A. (2021). Distinct functional and structural connections predict

crystallised and fluid cognition in healthy adults. *Human Brain Mapping*, *42*(10), 3102–3118. https://doi.org/10.1002/hbm.25420, PubMed: 33830577

Dohmatob, E., Varoquaux, G., & Thirion, B. (2018). Inter-subject registration of functional images: Do we need anatomical images? *Frontiers in Neuroscience*, *12*, 64. https://doi.org/10.3389/fnins.2018.00064, PubMed: 29497357

Draganski, B., Lutti, A., & Kherif, F. (2013). Impact of brain aging and neurodegeneration on cognition: Evidence from MRI. *Current Opinion in Neurology*, *26*(6), 640–645. https://doi.org/10.1097/WCO.0000000000000029, PubMed: 24184970

Dubois, J., Galdi, P., Paul, L. K., & Adolphs, R. (2018). A distributed brain network predicts general intelligence from resting-state human neuroimaging data. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *373*(1756), 20170284. https://doi.org/10.1098/rstb.2017.0284, PubMed: 30104429

Dyrba, M., Grothe, M., Kirste, T., & Teipel, S. J. (2015). Multimodal analysis of functional and structural disconnection in Alzheimer's disease using multiple kernel SVM: Functional and structural disconnection in AD. *Human Brain Mapping*, *36*(6), 2118–2131. https://doi.org/10.1002/hbm.22759, PubMed: 25664619

Engemann, D. A., Kozynets, O., Sabbagh, D., Lemaître, G., Varoquaux, G., Liem, F., & Gramfort, A. (2020). Combining magnetoencephalography with magnetic resonance imaging enhances learning of surrogate-biomarkers. *ELife*, *9*, e54055. https://doi.org/10.7554/eLife.54055, PubMed: 32423528

Farahani, F. V., Karwowski, W., & Lighthall, N. R. (2019). Application of graph theory for identifying connectivity patterns in human brain networks: A systematic review. *Frontiers in Neuroscience*, *13*, 585. https://doi.org/10.3389/fnins.2019.00585, PubMed: 31249501

Finn, E. S., Shen, X., Scheinost, D., Rosenberg, M. D., Huang, J., Chun, M. M., Papademetris, X., & Constable, R. T. (2015). Functional connectome fingerprinting: Identifying individuals using patterns of brain connectivity. *Nature Neuroscience*, *18*(11), 1664–1671. https://doi.org/10.1038/nn.4135, PubMed: 26457551

Fjell, A. M., Sneve, M. H., Grydeland, H., Storsve, A. B., de Lange, A.-M. G., Amlien, I. K., Røgeberg, O. J., & Walhovd, K. B. (2015). Functional connectivity change across multiple cortical networks relates to episodic memory changes in aging. *Neurobiology of Aging*, *36*(12), 3255–3268. https://doi.org/10.1016/j.neurobiolaging.2015.08.020, PubMed: 26363813

Fountain-Zaragoza, S., Samimy, S., Rosenberg, M. D., & Prakash, R. S. (2019). Connectome-based models predict attentional control in aging adults. *NeuroImage*, *186*, 1–13. https://doi.org/10.1016/j.neuroimage.2018.10.074, PubMed: 30394324

Gao, M., Wong, C. H. Y., Huang, H., Shao, R., Huang, R., Chan, C. C. H., & Lee, T. M. C. (2020). Connectome-based models can predict processing speed in older adults. *NeuroImage*, *223*, 117290. https://doi.org/10.1016/j.neuroimage.2020.117290, PubMed: 32871259

Gaser, C., Dahnke, R., Thompson, P. M., Kurth, F., Luders, E., & Alzheimer's Disease Neuroimaging Initiative. (2022). CAT—A computational anatomy toolbox for the analysis of structural MRI data. *bioRxiv*. https://doi.org/10.1101/2022.06.11.495736

Gbadeyan, O., Teng, J., & Prakash, R. S. (2022). Predicting response time variability from task and resting-state functional connectivity in the aging brain. *NeuroImage*, *250*, 118890. https://doi.org/10.1016/j.neuroimage.2022.118890, PubMed: 35007719

Grady, C., Sarraf, S., Saverino, C., & Campbell, K. (2016). Age differences in the functional interactions among the default, fronto-parietal control, and dorsal attention networks. *Neurobiology of Aging*, *41*, 159–172. https://doi.org/10.1016/j.neurobiolaging.2016.02.020, PubMed: 27103529

Greene, A. S., Gao, S., Scheinost, D., & Constable, R. T. (2018). Task-induced brain state manipulation improves prediction of individual traits. *Nature Communications*, *9*(1), 2807. https://doi.org/10.1038/s41467-018-04920-3, PubMed: 30022026

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. *Proceedings of the National Academy of Sciences*, *101*(13), 4637–4642. https://doi.org/10.1073/pnas.0308627101, PubMed: 15070770

Guyon, I., & Elisseeff, A. (2003). An introduction to variable and feature selection. *Journal of Machine Learning Research*, *3*, 1157–1182.

Habib, R., Nyberg, L., & Nilsson, L.-G. (2007). Cognitive and non-cognitive factors contributing to the longitudinal identification of successful older adults in the *Betula* study. *Aging, Neuropsychology, and Cognition*, *14*(3), 257–273. https://doi.org/10.1080/13825580600582412, PubMed: 17453560

Hartshorne, J. K., & Germine, L. T. (2015). When does cognitive functioning peak? The asynchronous rise and fall of different cognitive abilities across the life span. *Psychological Science*, *26*(4), 433–443. https://doi.org/10.1177/0956797614567339, PubMed: 25770099

Hausman, H. K., O'Shea, A., Kraft, J. N., Boutzoukas, E. M., Evangelista, N. D., Van Etten, E. J., Bharadwaj, P. K., Smith, S. G., Porges, E., Hishaw, G. A., Wu, S., DeKosky, S., Alexander, G. E., Marsiske, M., Cohen, R., & Woods, A. J. (2020). The role of resting-state network functional connectivity in cognitive aging. *Frontiers in Aging Neuroscience*, *12*, 177. https://doi.org/10.3389/fnagi.2020.00177, PubMed: 32595490

He, T., Kong, R., Holmes, A. J., Nguyen, M., Sabuncu, M. R., Eickhoff, S. B., Bzdok, D., Feng, J., & Yeo, B. T. T. (2020). Deep neural networks and kernel regression achieve comparable accuracies for functional connectivity prediction of behavior and demographics. *NeuroImage*, *206*, 116276. https://doi.org/10.1016/j.neuroimage.2019.116276, PubMed: 31610298

Hedden, T., & Gabrieli, J. D. E. (2004). Insights into the ageing mind: A view from cognitive neuroscience. *Nature Reviews Neuroscience*, *5*(2), 87–96. https://doi.org/10.1038/nrn1323, PubMed: 14735112

Hojjati, S. H., Ebrahimzadeh, A., Khazaee, A., & Babajani-Feremi, A. (2017). Predicting conversion from MCI to AD using resting-state fMRI, graph theoretical approach and SVM. *Journal of Neuroscience Methods*, *282*, 69–80. https://doi.org/10.1016/j.jneumeth.2017.03.006, PubMed: 28286064

Hua, J., Tembe, W. D., & Dougherty, E. R. (2009). Performance of feature-selection methods in the classification of high-dimension data. *Pattern Recognition*, *42*(3), 409–424. https://doi.org/10.1016/j.patcog.2008.08.001

Iordan, A. D., Cooke, K. A., Moored, K. D., Katz, B., Buschkuehl, M., Jaeggi, S. M., Jonides, J., Peltier, S. J., Polk, T. A., & Reuter-Lorenz, P. A. (2018). Aging and network properties: Stability over time and links with learning during working memory training. *Frontiers in Aging Neuroscience*, *9*, 419. https://doi.org/10.3389/fnagi.2017.00419, PubMed: 29354048

Janssen, R. J., Mourão-Miranda, J., & Schnack, H. G. (2018). Making individual prognoses in psychiatry using neuroimaging and machine learning. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3*(9), 798–808. https://doi.org/10.1016/j.bpsc.2018.04.004, PubMed: 29789268

Kalbe, E., Kessler, J., Calabrese, P., Smith, R., Passmore, A. P., Brand, M., & Bullock, R. (2004). DemTect: A new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. *International Journal of Geriatric Psychiatry*, *19*(2), 136–143. https://doi.org/10.1002/gps.1042, PubMed: 14758579

Kazeminejad, A., & Sotero, R. C. (2019). Topological properties of resting-state fMRI functional networks improve machine learning-based autism classification. *Frontiers in Neuroscience*, *12*, 1018. https://doi.org/10.3389/fnins.2018.01018, PubMed: 30686984

Khazaee, A., Ebrahimzadeh, A., & Babajani-Feremi, A. (2016). Application of advanced machine learning methods on resting-state fMRI network for identification of mild cognitive impairment and Alzheimer's disease. *Brain Imaging and Behavior*, *10*(3), 799–817. https://doi.org/10.1007/s11682-015-9448-7, PubMed: 26363784

Kwak, S., Kim, H., Kim, H., Youm, Y., & Chey, J. (2021). Distributed functional connectivity predicts neuropsychological test performance among older adults. *Human Brain Mapping*, *42*(10), 3305–3325. https://doi.org/10.1002/hbm.25436, PubMed: 33960591

Lei, D., Pinaya, W. H. L., van Amelsvoort, T., Marcelis, M., Donohoe, G., Mothersill, D. O., Corvin, A., Gill, M., Vieira, S., Huang, X., Lui, S., Scarpazza, C., Young, J., Arango, C., Bullmore, E., Qiyong, G., McGuire, P., & Mechelli, A. (2020). Detecting schizophrenia at the level of the individual: Relative diagnostic value of whole-brain images, connectome-wide functional connectivity and graph-based metrics. *Psychological Medicine*, *50*(11), 1852–1861. https://doi.org/10.1017/S0033291719001934, PubMed: 31391132

Lemm, S., Blankertz, B., Dickhaus, T., & Müller, K.-R. (2011). Introduction to machine learning for brain imaging. *NeuroImage*, *56*(2), 387–399. https://doi.org/10.1016/j.neuroimage.2010.11.004, PubMed: 21172442

Li, J., Kong, R., Liégeois, R., Orban, C., Tan, Y., Sun, N., Holmes, A. J., Sabuncu, M. R., Ge, T., & Yeo, B. T. T. (2019). Global signal regression strengthens association between resting-state functional connectivity and behavior. *NeuroImage*, *196*, 126–141. https://doi.org/10.1016/j.neuroimage.2019.04.016, PubMed: 30974241

Liem, F., Geerligs, L., Damoiseaux, J. S., & Margulies, D. S. (2021). Functional connectivity in aging. In *Handbook of the psychology of aging* (pp. 37–51). Elsevier. https://doi.org/10.1016/B978-0-12-816094-7.00010-6

Liem, F., Varoquaux, G., Kynast, J., Beyer, F., Kharabian Masouleh, S., Huntenburg, J. M., Lampe, L., Rahim, M., Abraham, A., Craddock, R. C., Riedel-Heller, S., Luck, T., Loeffler, M., Schroeter, M. L., Witte, A. V., Villringer, A., & Margulies, D. S. (2017). Predicting brain-age from multimodal imaging data captures cognitive impairment. *NeuroImage*, *148*, 179–188. https://doi.org/10.1016/j.neuroimage.2016.11.005, PubMed: 27890805

Luciano, M., Gow, A. J., Harris, S. E., Hayward, C., Allerhand, M., Starr, J. M., Visscher, P. M., & Deary, I. J. (2009). Cognitive ability at age 11 and 70 years, information processing speed, and APOE variation: The Lothian Birth Cohort 1936 study. *Psychology and Aging*, *24*(1), 129–138. https://doi.org/10.1037/a0014780, PubMed: 19290744

Malagurski, B., Liem, F., Oschwald, J., Mérillat, S., & Jäncke, L. (2020). Functional dedifferentiation of associative resting state networks in older adults—A longitudinal study. *NeuroImage*, *214*, 116680. https://doi.org/10.1016/j.neuroimage.2020.116680, PubMed: 32105885

Masouleh, S. K., Eickhoff, S. B., Hoffstaedter, F., Genon, S., & Alzheimer's Disease Neuroimaging Initiative. (2019). Empirical examination of the replicability of associations between brain structure and psychological variables. *ELife*, *8*, e43464. https://doi.org/10.7554/eLife.43464, PubMed: 30864950

McConathy, J., & Sheline, Y. I. (2015). Imaging biomarkers associated with cognitive decline: A review. *Biological Psychiatry*, *77*(8), 685–692. https://doi.org/10.1016/j.biopsych.2014.08.024, PubMed: 25442005

McDermott, K. L., McFall, G. P., Andrews, S. J., Anstey, K. J., & Dixon, R. A. (2016). Memory resilience to Alzheimer's genetic risk: Sex effects in predictor profiles. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *72*(6), 937–946. https://doi.org/10.1093/geronb/gbw161, PubMed: 28025282

Meier, T. B., Desphande, A. S., Vergun, S., Nair, V. A., Song, J., Biswal, B. B., Meyerand, M. E., Birn, R. M., & Prabhakaran, V. (2012). Support vector machine classification and characterization of age-related reorganization of functional brain networks. *NeuroImage*, *60*(1), 601–613. https://doi.org/10.1016/j.neuroimage.2011.12.052, PubMed: 22227886

Mowinckel, A. M., Espeseth, T., & Westlye, L. T. (2012). Network-specific effects of age and in-scanner subject motion: A resting-state fMRI study of 238 healthy adults. *NeuroImage*, *63*(3), 1364–1373. https://doi.org/10.1016/j.neuroimage.2012.08.004, PubMed: 22992492

Murphy, K., Birn, R. M., Handwerker, D. A., Jones, T. B., & Bandettini, P. A. (2009). The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced? *NeuroImage*, *44*(3), 893–905. https://doi.org/10.1016/j.neuroimage.2008.09.036, PubMed: 18976716

Murphy, K., & Fox, M. D. (2017). Towards a consensus regarding global signal regression for resting state functional connectivity MRI. *NeuroImage*, *154*, 169–173. https://doi.org/10.1016/j.neuroimage.2016.11.052, PubMed: 27888059

Mwangi, B., Tian, T. S., & Soares, J. C. (2014). A review of feature reduction techniques in neuroimaging. *Neuroinformatics*, *12*(2), 229–244. https://doi.org/10.1007/s12021-013-9204-3, PubMed: 24013948

Ng, K. K., Lo, J. C., Lim, J. K. W., Chee, M. W. L., & 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. https://doi.org/10.1016/j.neuroimage.2016.03.029, PubMed: 27001500

Nostro, A. D., Müller, V. I., Varikuti, D. P., Pläschke, R. N., Hoffstaedter, F., Langner, R., Patil, K. R., & Eickhoff, S. B. (2018). Predicting personality from network-based resting-state functional

connectivity. *Brain Structure and Function*, *223*(6), 2699–2719. https://doi.org/10.1007/s00429-018-1651-z, PubMed: 29572625

Onoda, K., Ishihara, M., & Yamaguchi, S. (2012). Decreased functional connectivity by aging is associated with cognitive decline. *Journal of Cognitive Neuroscience*, *24*(11), 2186–2198. https://doi.org/10.1162/jocn_a_00269, PubMed: 22784277

Orrù, G., Pettersson-Yeo, W., Marquand, A. F., Sartori, G., & Mechelli, A. (2012). Using support vector machine to identify imaging biomarkers of neurological and psychiatric disease: A critical review. *Neuroscience & Biobehavioral Reviews*, *36*(4), 1140–1152. https://doi.org/10.1016/j.neubiorev.2012.01.004, PubMed: 22305994

Pacheco, J., Goh, J. O., Kraut, M. A., Ferrucci, L., & Resnick, S. M. (2015). Greater cortical thinning in normal older adults predicts later cognitive impairment. *Neurobiology of Aging*, *36*(2), 903–908. https://doi.org/10.1016/j.neurobiolaging.2014.08.031, PubMed: 25311277

Parkes, L., Fulcher, B., Yücel, M., & Fornito, A. (2018). An evaluation of the efficacy, reliability, and sensitivity of motion correction strategies for resting-state functional MRI. *NeuroImage*, *171*, 415–436. https://doi.org/10.1016/j.neuroimage.2017.12.073, PubMed: 29278773

Paulus, M. P., & Thompson, W. K. (2021). Computational approaches and machine learning for individual-level treatment predictions. *Psychopharmacology*, *238*, 1231–1239. https://doi.org/10.1007/s00213-019-05282-4, PubMed: 31134293

Pedregosa, F., Varoquaux, G., Gramfort, A., Michel, V., Thirion, B., Grisel, O., Blondel, M., Prettenhofer, P., Weiss, R., Dubourg, V., Vanderplas, J., Passos, A., Cournapeau, D., Brucher, M., Perrot, M., & Duchesnay, E. (2011). Scikit-learn: Machine learning in Python. *Journal of Machine Learning Research*, *12*, 2825–2830.

Pervaiz, U., Vidaurre, D., Woolrich, M. W., & Smith, S. M. (2020). Optimising network modelling methods for fMRI. *NeuroImage*, *211*, 116604. https://doi.org/10.1016/j.neuroimage.2020.116604, PubMed: 32062083

Pläschke, R. N., Cieslik, E. C., Müller, V. I., Hoffstaedter, F., Plachti, A., Varikuti, D. P., Goosses, M., Latz, A., Caspers, S., Jockwitz, C., Moebus, S., Gruber, O., Eickhoff, C. R., Reetz, K., Heller, J., Südmeyer, M., Mathys, C., Caspers, J., Grefkes, C., … Eickhoff, S. B. (2017). On the integrity of functional brain networks in schizophrenia, Parkinson's disease, and advanced age: Evidence from connectivity-based single-subject classification: Schizophrenia, Parkinson's disease and aging classification. *Human Brain Mapping*, *38*(12), 5845–5858. https://doi.org/10.1002/hbm.23763, PubMed: 28876500

Pläschke, R. N., Patil, K. R., Cieslik, E. C., Nostro, A. D., Varikuti, D. P., Plachti, A., Lösche, P., Hoffstaedter, F., Kalenscher, T., Langner, R., & Eickhoff, S. B. (2020). Age differences in predicting working memory performance from network-based functional connectivity. *Cortex*, *132*, 441–459. https://doi.org/10.1016/j.cortex.2020.08.012, PubMed: 33065515

Pruim, R. H. R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J. K., & Beckmann, C. F. (2015). ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. *NeuroImage*, *112*, 267–277. https://doi.org/10.1016/j.neuroimage.2015.02.064, PubMed: 25770991

Pudil, P., Novovičová, J., & Kittler, J. (1994). Floating search methods in feature selection. *Pattern Recognition Letters*, *15*(11), 1119–1125. https://doi.org/10.1016/0167-8655(94)90127-9

Randolph, J. J., Falbe, K., Manuel, A. K., & Balloun, J. L. (2014). A step-by-step guide to propensity score matching in R. *Practical Assessment, Research & Evaluation*, *19*(18), 1–6.

Raschka, S. (2018). MLxtend: Providing machine learning and data science utilities and extensions to Python's scientific computing stack. *Journal of Open Source Software*, *3*(24), 638. https://doi.org/10.21105/joss.00638

Rasero, J., Sentis, A. I., Yeh, F.-C., & Verstynen, T. (2021). Integrating across neuroimaging modalities boosts prediction accuracy of cognitive ability. *PLOS Computational Biology*, *17*(3), e1008347. https://doi.org/10.1371/journal.pcbi.1008347, PubMed: 33667224

Raz, N. (2000). Aging of the brain and its impact on cognitive performance: Integration of structural and functional findings. In *The handbook of aging and cognition* (2nd ed., pp. 1–90). Mahwah, NJ: Lawrence Erlbaum Associates Publishers.

Raz, N., & Rodrigue, K. M. (2006). Differential aging of the brain: Patterns, cognitive correlates and modifiers. *Neuroscience & Biobehavioral Reviews*, *30*(6), 730–748. https://doi.org/10.1016/j.neubiorev.2006.07.001, PubMed: 16919333

Rosenberg, M. D., Finn, E. S., Scheinost, D., Papademetris, X., Shen, X., Constable, R. T., & Chun, M. M. (2016). A neuromarker of sustained attention from whole-brain functional connectivity. *Nature Neuroscience*, *19*(1), 165–171. https://doi.org/10.1038/nn.4179, PubMed: 26595653

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, *52*(3), 1059–1069. https://doi.org/10.1016/j.neuroimage.2009.10.003, PubMed: 19819337

Saad, Z. S., Gotts, S. J., Murphy, K., Chen, G., Jo, H. J., Martin, A., & Cox, R. W. (2012). Trouble at rest: How correlation patterns and group differences become distorted after global signal regression. *Brain Connectivity*, *2*(1), 25–32. https://doi.org/10.1089/brain.2012.0080, PubMed: 22432927

Sanz-Arigita, E. J., Schoonheim, M. M., Damoiseaux, J. S., Rombouts, S. A. R. B., Maris, E., Barkhof, F., Scheltens, P., & Stam, C. J. (2010). Loss of 'small-world' networks in Alzheimer's disease: Graph analysis of fMRI resting-state functional connectivity. *PLoS One*, *5*(11), e13788. https://doi.org/10.1371/journal.pone.0013788, PubMed: 21072180

Scarpazza, C., Ha, M., Baecker, L., Garcia-Dias, R., Pinaya, W. H. L., Vieira, S., & Mechelli, A. (2020). Translating research findings into clinical practice: A systematic and critical review of neuroimaging-based clinical tools for brain disorders. *Translational Psychiatry*, *10*(1), 107. https://doi.org/10.1038/s41398-020-0798-6, PubMed: 32313006

Schaefer, A., Kong, R., Gordon, E. M., Laumann, T. O., Zuo, X.-N., Holmes, A. J., Eickhoff, S. B., & Yeo, B. T. T. (2018). Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. *Cerebral Cortex*, *28*(9), 3095–3114. https://doi.org/10.1093/cercor/bhx179, PubMed: 28981612

Schmermund, A., Möhlenkamp, S., Stang, A., Grönemeyer, D., Seibel, R., Hirche, H., Mann, K., Siffert, W., Lauterbach, K., Siegrist, J., Jöckel, K.-H., & Erbel, R. (2002). Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: Rationale and design of the Heinz Nixdorf RECALL Study. *American Heart Journal*, *144*(2), 212–218. https://doi.org/10.1067/mhj.2002.123579, PubMed: 12177636

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*, S208–S219. https://doi.org/10.1016/j.neuroimage.2004.07.051, PubMed: 15501092

Sripada, C., Angstadt, M., Rutherford, S., Taxali, A., & Shedden, K. (2020a). Toward a "treadmill test" for cognition: Improved prediction of general cognitive ability from the task activated brain. *Human Brain Mapping*, *41*(12), 3186–3197. https://doi.org/10.1002/hbm.25007, PubMed: 32364670

Sripada, C., Rutherford, S., Angstadt, M., Thompson, W. K., Luciana, M., Weigard, A., Hyde, L. H., & Heitzeg, M. (2020b). Prediction of neurocognition in youth from resting state fMRI. *Molecular Psychiatry*, *25*(12), 3413–3421. https://doi.org/10.1038/s41380-019-0481-6, PubMed: 31427753

Stern, Y., Gurland, B., Tatemichi, T. K., Tang, M. X., Wilder, D., & Mayeux, R. (1994). Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA: The Journal of the American Medical Association*, *271*(13), 1004–1010. https://doi.org/10.1001/jama.1994.03510370056032, PubMed: 8139057

Stumme, J., Jockwitz, C., Hoffstaedter, F., Amunts, K., & Caspers, S. (2020). Functional network reorganization in older adults: Graph-theoretical analyses of age, cognition and sex. *NeuroImage*, *214*, 116756. https://doi.org/10.1016/j.neuroimage.2020.116756, PubMed: 32201326

Supekar, K., Menon, V., Rubin, D., Musen, M., & Greicius, M. D. (2008). Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Computational Biology*, *4*(6), e1000100. https://doi.org/10.1371/journal.pcbi.1000100, PubMed: 18584043

Teipel, S. J., Grothe, M. J., Metzger, C. D., Grimmer, T., Sorg, C., Ewers, M., Franzmeier, N., Meisenzahl, E., Klöppel, S., Borchardt, V., Walter, M., & Dyrba, M. (2017). Robust detection of impaired resting state functional connectivity networks in Alzheimer's disease using elastic net regularized regression. *Frontiers in Aging Neuroscience*, *8*, 318. https://doi.org/10.3389/fnagi.2016.00318, PubMed: 28101051

Thompson, W. K., Barch, D. M., Bjork, J. M., Gonzalez, R., Nagel, B. J., Nixon, S. J., & Luciana, M. (2019). The structure of cognition in 9 and 10 year-old children and associations with problem behaviors: Findings from the ABCD study's baseline neurocognitive battery. *Developmental Cognitive Neuroscience*, *36*, 100606. https://doi.org/10.1016/j.dcn.2018.12.004, PubMed: 30595399

Tucker-Drob, E. M. (2011). Global and domain-specific changes in cognition throughout adulthood. *Developmental Psychology*, *47*(2), 331–343. https://doi.org/10.1037/a0021361, PubMed: 21244145

van den Heuvel, M. P., de Lange, S. C., Zalesky, A., Seguin, C., Yeo, B. T. T., & Schmidt, R. (2017). Proportional thresholding in resting-state fMRI functional connectivity networks and consequences for patient-control connectome studies: Issues and recommendations. *NeuroImage*, *152*, 437–449. https://doi.org/10.1016/j.neuroimage.2017.02.005, PubMed: 28167349

van Wijk, B. C. M., Stam, C. J., & Daffertshofer, A. (2010). Comparing brain networks of different size and connectivity density using graph theory. *PLoS One*, *5*(10), e13701. https://doi.org/10.1371/journal.pone.0013701, PubMed: 21060892

Vemuri, P., Lesnick, T. G., Przybelski, S. A., Machulda, M., Knopman, D. S., Mielke, M. M., Roberts, R. O., Geda, Y. E., Rocca, W. A., Petersen, R. C., & Jack, C. R. (2014). Association of lifetime intellectual enrichment with cognitive decline in the older population. *JAMA Neurology*, *71*(8), 1017–1024. https://doi.org/10.1001/jamaneurol.2014.963, PubMed: 25054282

Vergun, S., Deshpande, A. S., Meier, T. B., Song, J., Tudorascu, D. L., Nair, V. A., Singh, V., Biswal, B. B., Meyerand, M. E., Birn, R. M., & Prabhakaran, V. (2013). Characterizing functional connectivity differences in aging adults using machine learning on resting state fMRI data. *Frontiers in Computational Neuroscience*, *7*, 38. https://doi.org/10.3389/fncom.2013.00038, PubMed: 23630491

Vieira, B. H., Liem, F., Dadi, K., Engemann, D. A., Gramfort, A., Bellec, P., Craddock, R. C., Damoiseaux, J. S., Steele, C. J., Yarkoni, T., Langer, N., Margulies, D. S., & Varoquaux, G. (2022). Predicting future cognitive decline from non-brain and multimodal brain imaging data in healthy and pathological aging. *Neurobiology of Aging*, *118*, 55–65. https://doi.org/10.1016/j.neurobiolaging.2022.06.008, PubMed: 35878565

Wang, J., Zuo, X., Dai, Z., Xia, M., Zhao, Z., Zhao, X., Jia, J., Han, Y., & He, Y. (2013). Disrupted functional brain connectome in individuals at risk for Alzheimer's disease. *Biological Psychiatry*, *73*(5), 472–481. https://doi.org/10.1016/j.biopsych.2012.03.026, PubMed: 22537793

Weis, S., Hodgetts, S., & Hausmann, M. (2019). Sex differences and menstrual cycle effects in cognitive and sensory resting state networks. *Brain and Cognition*, *131*, 66–73. https://doi.org/10.1016/j.bandc.2017.09.003, PubMed: 29030069

Woo, C.-W., Chang, L. J., Lindquist, M. A., & Wager, T. D. (2017). Building better biomarkers: Brain models in translational neuroimaging. *Nature Neuroscience*, *20*(3), 365–377. https://doi.org/10.1038/nn.4478, PubMed: 28230847

Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., Polimeni, J. R., Fischl, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125–1165. https://doi.org/10.1152/jn.00338.2011, PubMed: 21653723

Yoo, K., Rosenberg, M. D., Hsu, W.-T., Zhang, S., Li, C.-S. R., Scheinost, D., Constable, R. T., & Chun, M. M. (2018). Connectome-based predictive modeling of attention: Comparing different functional connectivity features and prediction methods across datasets. *NeuroImage*, *167*, 11–22. https://doi.org/10.1016/j.neuroimage.2017.11.010, PubMed: 29122720

Zalesky, A., Fornito, A., & Bullmore, E. (2012). On the use of correlation as a measure of network connectivity. *NeuroImage*, *60*(4), 2096–2106. https://doi.org/10.1016/j.neuroimage.2012.02.001, PubMed: 22343126

Zarogianni, E., Moorhead, T. W. J., & Lawrie, S. M. (2013). Towards the identification of imaging biomarkers in schizophrenia, using multivariate pattern classification at a single-subject level. *NeuroImage: Clinical*, *3*, 279–289. https://doi.org/10.1016/j.nicl.2013.09.003, PubMed: 24273713

Zou, H., & Hastie, T. (2005). Regularization and variable selection via the elastic net. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, *67*(2), 301–320. https://doi.org/10.1111/j.1467-9868.2005.00503.x

3 Study 2

Interrelating differences in structural and functional connectivity in the older adult's brain

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RESEARCH ARTICLE

WILEY

Interrelating differences in structural and functional connectivity in the older adult's brain

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Abstract

In the normal aging process, the functional connectome restructures and shows a shift from more segregated to more integrated brain networks, which manifests itself in highly different cognitive performances in older adults. Underpinnings of this reorganization are not fully understood, but may be related to age-related differences in structural connectivity, the underlying scaffold for information exchange between regions. The structure–function relationship might be a promising factor to understand the neurobiological sources of interindividual cognitive variability, but remain unclear in older adults. Here, we used diffusion weighted and resting-state functional magnetic resonance imaging as well as cognitive performance data of 573 older subjects from the 1000BRAINS cohort (55–85 years, 287 males) and performed a partial least square regression on 400 regional functional and structural connectivity (FC and SC, respectively) estimates comprising seven resting-state networks. Our aim was to identify FC and SC patterns that are, together with cognitive performance, characteristic of the older adults aging process. Results revealed three different aging profiles prevalent in older adults. FC was found to behave differently depending on the severity of age-related SC deteriorations. A functionally highly interconnected system is associated with a structural connectome that shows only minor age-related decreases. Because this connectivity profile was associated with the most severe age-related cognitive decline, a more interconnected FC system in older adults points to a process of dedifferentiation. Thus, functional network integration appears to increase primarily when SC begins to decline, but this does not appear to mitigate the decline in cognitive performance.

KEYWORDS
aging, cognitive performance, functional connectivity, multivariate analyses, structural connectivity

1 | INTRODUCTION

Age-related decreases in cognitive performance have been associated with numerous neural substrates (Hedden et al., 2016; MacDonald & Pike, 2021; Whalley et al., 2004) including age-related differences in the brain network configuration (for reviews, see, Damoiseaux, 2017; Salat, 2011; Sporns, 2013; Wig, 2017; Zuo et al., 2017). Brain networks comprise sets of brain regions (nodes) and their connections (edges) which together are associated with solving specific behavioral tasks (Schaefer et al., 2018; Smith et al., 2009; Yeo et al., 2011). Thereby, brain regions belonging to the same network are more highly connected (intra-network) as compared to regions outside its related network (inter-network). The entirety of all connected regions within and across networks forms the whole-brain connectome (Bullmore & Sporns, 2009, 2012; Fornito, 2016; Fornito et al., 2013) that seems to be subject to age-related reorganization in terms of both, functional as well as structural connectivity (FC and SC).

In young adults, an efficient functional network configuration, which is associated with high cognitive performance, is characterized by a balance between connections of regions belonging to the same and other networks (Bullmore & Sporns, 2012; Sadaghiani et al., 2015; Sporns, 2013; Wig, 2017). With increasing age, however, this segregated and specialized network configuration decomposes, showing a shift towards a higher network integration, that is, decreasing intra-network FC and increasing inter-network FC (Betzel et al., 2014; Cao et al., 2014; Chan et al., 2014; Ferreira et al., 2016; He et al., 2020; Mowinckel et al., 2012; Tsvetanov et al., 2016; Varangis et al., 2019). Across the adult lifespan, intra-network FC decreases predominantly pertain to higher-order networks, for example, the default mode network (DMN) and frontoparietal network. In contrast, primary processing networks, for example, the sensorimotor (SMN) and visual network (VN) remain rather stable (Betzel et al., 2014; Chan et al., 2014; Ferreira et al., 2016; Geerligs et al., 2015; Grady et al., 2016; Jockwitz & Caspers, 2021; Mowinckel et al., 2012; Siman-Tov et al., 2016; Spreng et al., 2016; Varangis et al., 2019). In older adults, though, differences in primary processing networks become highly apparent with age-related intra-network FC decreases together with FC increases with higher order networks (Edde et al., 2021; Perry et al., 2017; Stumme et al., 2020; Zonneveld et al., 2019).

The origins of these age-related FC changes, from segregated toward integrated networks, are not fully understood and their effect is ambiguously interpreted. On one hand, the functional recruitment of additional brain networks is understood as a compensation strategy in older adults, in which age-related decreases in intra-network FC may be compensated by functional adaptations (Cabeza et al., 2002; Marstaller et al., 2015; Pistono et al., 2021; Reuter-Lorenz & Cappell, 2008) to countervail cognitive performance decline (Bartres-Faz & Arenaza-Urquijo, 2011; Spreng & Turner, 2019; Stern, 2002, 2009). On the other hand, age-related shifts toward increasing inter-network connectivity are thought to result from longer latencies in dynamic functional states, that is, a decreased variance in functional dynamics across time (Battaglia et al., 2020; Naik et al., 2017). A functional system with less variance in functional dynamics is understood as a dedifferentiated system in which the ability to recruit specialized neural mechanisms and to switch between brain states is reduced, followed by a cognitive decline (Chan et al., 2014, 2017; Colcombe et al., 2005; Goh, 2011; Nashiro et al., 2017; Park et al., 2004). In fact, the origin of these age-related functional reorganizations and the underlying mechanism, being it compensation or dedifferentiation, still remains unclear. To further elucidate this, the additional analysis of SC could be helpful as it provides the structural framework for FC.

SC was found to decrease across aging, spanning the whole brain but with a particular vulnerability of the frontal lobe (Antonenko & Floel, 2014; Betzel et al., 2014; Gunning-Dixon et al., 2009; Puxeddu et al., 2020; Westlye et al., 2010; Zhao et al., 2015; Zuo et al., 2017). In a recent study of older adults, age-related disruption of the structural connectome was found to impair both network segregation and network integration (Li et al., 2020). As such, age-related alterations in SC may relate to the disrupted balance between network integration and segregation in FC. So far, the interrelation between SC and FC and their differences across aging are still a matter of debate. While there exist many studies characterizing age-related differences in terms of functional and structural networks in isolation (for reviews, see, Damoiseaux, 2017; Jockwitz & Caspers, 2021; Wig, 2017; Zuo et al., 2017), there are fewer studies that have jointly examined FC and SC in the aging process (for review, see, Lynn & Bassett, 2019; Straathof et al., 2019). Results on the direct relation between FC and SC in terms of age-related differences appear mixed. On the one hand, FC and SC were found to change mostly independently across the lifespan (Fjell et al., 2017; Hirsiger et al., 2016; Tsang et al., 2017) as well as in older adults (Hirsiger et al., 2016) indicating that SC only weakly influences or constricts age-related differences in FC. On the other hand, studies suggest that SC and FC are interrelated, and that during adolescence changes in the structural connectome are associated with the development and specialization of functional systems (Baum et al., 2020). Across the lifespan, Zimmermann et al. (2016) found increasing age to be accompanied by a greater coupling between SC and FC, which may be explained by the fact that more strongly integrated functional systems (as present in older adults) were found to be more strongly rely on existing structural pathways (Fukushima et al., 2018). With regards to cognitive performance, Davis et al. (2012) found that functional overactivation in older adults during task execution, for example, in contralateral regions, depends on the integrity of the interhemispheric SC. This suggests that functional restructuring in older adults is related to SC in the sense that the ability to recruit additional brain areas, that is, to meet increasing task demands, is mediated by the underlying SC. To date, however, no study has looked at the relationship between whole-brain structural, functional connectivity, and cognition in older adults. By analyzing this triad, we aim to shed light on the possible causes of the functional shift in older adults.

Specifically, we took advantage of a large sample of older adults from the 1000BRAINS study to investigate SC and FC differences that are jointly age-characteristic and related to cognition. To

TABLE 1 Descriptives of the study sample

		Age in years			Education		
	n, proportion in %	Mean (SD)	Min	Max	Mean (SD)	Min	Max
All	573, 100%	66.9 (6.7)	55.1	85.4	6.5 (1.9)	3	10
Male	287, 50.1%	67.6 (7.0)	55.1	85.4	7.1 (1.9)	3	10
Female	286, 49.9%	66.2 (6.4)	55.2	85.4	6.0 (1.9)	3	10

investigate this, we used partial least squares regression (PLSR) (Mevik et al., 2018), which, in contrast to univariate approaches, has the great potential to effectively deal with high dimensional data. PLSR capitalizes on the potential to detect interrelations between various predictor variables such as region-wise connectivity estimates (comprising all networks) and cognition (Chen et al., 2019; Krishnan et al., 2011; McIntosh & Lobaugh, 2004; Yoo et al., 2018). PLSR decomposes predictor variables (cognition, SC, and FC estimates) into smaller sets of independent components, that is, aging profiles, that are maximally correlated with age. These aging profiles unveil region-wise estimates of SC and FC that are together related to cognition and particularly age-characteristic. As we investigate an older adult sample (55–85 years), we assume low FC of primary processing networks together with high FC between higher-order networks to be age-characteristic. With respect to SC, we hypothesize that older adults have lower connectivity overall, particularly in regions of the frontal lobe. How region-wise age-related SC and FC differences are interrelated, tough, is uncertain and analyzed from an explanatory, holistic perspective.

2 | METHODS

2.1 | Subjects

The subjects of the current study are drawn from 1000BRAINS (Caspers et al., 2014), a large longitudinal population-based cohort study investigating the interindividual variability in brain structure, function, and connectivity and its relations to behavioral, environmental, and genetic factors. Subjects included in 1000BRAINS were recruited from the 10-year follow-up of the epidemiological population-based Heinz Nixdorf Recall Study, a study investigating risk factors for atherosclerosis, cardiovascular disease, cardiac infarction, and cardiac death (Schmermund et al., 2002). 1000BRAINS aims at characterizing the aging process at the level of the general population, therefore no exclusion criteria other than eligibility for MR measurements (Caspers et al., 2014) were applied. 1000BRAINS comprises 969 older adults aged between 55 and 88 years of one measurement time point, as relevant for the current cross-sectional study design. From the initial sample, 114 participants had to be excluded due to preprocessing failure caused by artifacts in structural T1 scans, problems during normalization procedure, or insufficient AROMA-denoising ($n = 98$). Subsequently, functional data were quality checked and excluded in cases of insufficient quality ($n = 16$, see Section 2.2.2 for description of quality control). Of these 855 participants, 720 subjects also had diffusion-weighted images available, from which another 69 were excluded after quality control of the diffusion-weighted images (see Section 2.2.1 for the description of quality control). Finally, participants with missing information on education ($n = 1$), the dementia screening test ($n = 13$, DemTect; Kalbe et al., 2004), or those with indication for potential cognitive impairment (score of eight or lower, $n = 1$) according to the dementia screening test were excluded. After the exclusion of participants with more than three missing values in the cognitive performance tests as well as outliers (mean ± 3 * standard deviation[SD]), the final study sample comprises $n = 573$ subjects (Table 1). All subjects gave written informed consent prior to inclusion in 1000BRAINS. The study protocol of 1000BRAINS was approved by the Ethics Committee of the University of Essen, Germany. Due to local regulations of data acquisition and usage, data of 1000BRAINS are available upon request from the responsible principal investigator.

2.2 | Imaging

Magnetic resonance imaging was performed using a 3T Siemens TimTRIO MR scanner with a 32-channel head coil (Erlangen, Germany). For the investigation of SC and FC, different sequence images were included in the current study (see Caspers et al. (2014) for a detailed description of the 1000BRAINS study protocol): For surface reconstruction, a three-dimensional high-resolution T1 weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) anatomical scan was acquired [176 slices, slice thickness 1 mm, repetition time (TR) = 2250 ms, echo time (TE) = 3.03 ms, field of view (FoV) = $256 \times 256\ mm^2$, flip angle = 9°, voxel resolution $1 \times 1 \times 1\ mm^3$]. For structural connectivity analyses, high-angular resolution diffusion imaging (HARDI) data with the following parameters were used: (1) 120 directions dataset; EPI, TR = 8 s, TE = 112 ms, 13 b0-images (interleaved), 120 images with $b = 2700\ s/mm^2$, voxel resolution = $2.4 \times 2.4 \times 2.4\ mm^3$; (2) 60 direction subset (out of 120 direction dataset); EPI, TR = 6.3 s, TE = 81 ms, 7 b0-images (interleaved), 60 images with $b = 1000\ s/mm^2$, voxel resolution = $2.4 \times 2.4 \times 2.4\ mm^3$. For functional connectivity analysis, resting-state functional MRI data were acquired as a blood-oxygen level-dependent (BOLD) gradient-echo planar imaging (EPI) sequence with 36 transversally oriented slices (slice thickness 3.1 mm, TR = 2200 ms, TE = 30 ms, FoV = $200 \times 200\ mm^2$, voxel resolution $3.1 \times 3.1 \times 3.1\ mm^3$) was used, lasting for ~11 min and producing 300 volumes. During RS image acquisition, participants were instructed to keep their eyes closed, be relaxed, let their mind

wander, and to not fall asleep. The latter was assured by postscan debriefing.

2.2.1 | Structural image processing

For each participant, tissue probability maps (TPM) for grey matter (GM), white matter (WM) as well as corticospinal fluid (CSF) were computed from T1 data using the Computational Anatomy Toolbox (CAT12; Gaser & Dahnke, 2016) implemented in SPM12 (Ashburner, 2009; for a listing of software used see Table S1). To optimally extract the brain from the T1 data, brain masks were used created by superimposing the three probability maps and thresholding them at 0.5 (small enclosed holes were filled). Using the FSL toolbox (FMRIB Software Library: http://www.fmrib.ox.ac.uk/fsl; Jenkinson et al., 2012), the T1 brain image was bias field corrected, rigidly aligned to MNI152 template space, and resampled to 1.25 mm isotropic voxel size. These scans were then used as coregistration image for the subsequent alignment of the similarly resampled diffusion data (see below) to the MNI152 template [in accordance with standard pipelines as used in, e.g., the human connectome project (www.humanconnectomeproject.org) or the UK Biobank (www.ukbiobank.ac.uk)]. Diffusion MRI data (dMRI) were corrected for eddy current and motion artifacts including interpolation of slices with signal dropouts (Andersson et al., 2016; Andersson & Sotiropoulos, 2016). Visual quality control was performed to check for ghosting, remaining signal dropouts, or very noisy data. Suboptimal volumes or datasets were removed from further analyses ($n = 69$). For dMRI-T1 alignment, the first b0 images from each dMRI data with b1000 and b2700 were extracted and rigidly aligned to T1 dataset using mutual information as a cost function (Wells et al., 1996). Based on the corresponding transforms, all dMRI data were registered to the individual T1 space, separately for the two b-values. The realignment implicitly resampled the data to 1.25 mm and b-vectors were rotated according to the transformations. To account for susceptibility artifacts and optimize image registration, we computed Anisotropic Power Maps (APM; Dell'Acqua et al., 2014) from the b2700 dMRI data. Since the APM contrast is very similar to the T1 image, they provide an optimal basis for image registration. Accordingly, APMs were used to compute the nonlinear transformation from diffusion to anatomical space additionally taking EPI-induced distortions into account using ANTs (https://stnava.github.io/ANTs/). The derived nonlinear transformations were then used to transform the TPMs to diffusion space. Finally, the two datasets with b1000 and b2700 were merged into one single file and corrected for different echo times. This correction was computed by a voxel-wise multiplication of the b2700 data with the ratio of the nondiffusion-weighted data, respectively, for the two datasets. Subsequently, local modeling and probabilistic streamline tractography were performed using the MRtrix software package (Tournier et al., 2012) version 0.3.15. The constrained spherical deconvolution (CSD) local model was computed using multi-tissue CSD of multi-shell data (Jeurissen et al., 2014) using all shells and a maximal spherical harmonic order of 8. Ten million streamlines were computed with dynamic seeding in the grey-white matter interface for every subject using the probabilistic iFOD2 algorithm with a maximal length of 250 mm and a cut-off value of 0.06.

2.2.2 | Functional image processing

Functional image preprocessing was performed using the FSL toolbox (FMRIB Software Library: http://www.fmrib.ox.ac.uk/fsl; Jenkinson et al., 2012). For each participant, the first four echo-planar imaging (EPI) volumes were discarded. Using a two-pass procedure, all functional images were corrected for head movement using rigid-body registration. First, all volumes were aligned to the first image on which a mean image was created serving as the basis to which secondly, all volumes were aligned. To identify and remove motion-related independent components from functional MRI data, ICA-based Automatic Removal Of Motion Artifacts (ICA-AROMA; Pruim et al., 2015) was applied. According to current suggestions for minimizing the relationship between motion and resting-state FC (Burgess et al., 2016; Ciric et al., 2017; Parkes et al., 2018), AROMA was combined with global signal regression in the current study. Finally, all resting-state fMRI images were bandpass filtered (0.01–0.1 Hz) and registered to the standard space template (MNI152) using the unified segmentation approach (Ashburner & Friston, 2005). This was preferred to normalization based on T1 weighted images as previous studies indicated increased registration accuracies (Calhoun et al., 2017; Dohmatob et al., 2018). With AROMA particularly focusing on the correction of intensity artifacts induced by head motion, we further on took advantage of an established algorithm by Afyouni and Nichols (2018) to check for each participant's volume-wise severe intensity dropouts by generating p values for spikes (DVARS) on the already preprocessed functional data. In the current study, volumes with corrupted spikes are indicated and participants for which more than 10% of the 300 volumes (Stumme et al., 2020) were detected as dropouts were excluded from further analyses ($n = 8$). Further, based on the preprocessed mean AROMA functional data, we checked for potential misalignments by performing the "check sample homogeneity using standard deviation across sample" function provided by the CAT12 toolbox (Gaser & Dahnke, 2016) and excluded participants for which the individual image did not align to the MNI152 template (>2 SD, $n = 8$).

2.3 | Connectivity analyses

To analyze FC and SC data, we parcellated the whole brain into 400 different regions comprising seven networks [visual (VN), sensorimotor (SMN), limbic (LN), frontoparietal (FPN), default mode (DMN), dorsal (DAN), and ventral attention network (VAN)], as defined in Yeo et al. (2011) using the predefined cortical parcellation of Schaefer et al. (2018). This was done according to recent studies, which found a resolution of 300–600 nodes to be optimal for functional (Schaefer et al., 2018) and structural analyses (Varikuti et al., 2018).

In terms of FC, mean time-series spanning 296 time points (first four of in total 300 volumes were discarded) were extracted node-wise from the preprocessed resting-state fMRI data [fslmeants (Smith et al., 2004)] averaging the timeseries of all voxels corresponding to that node. FC between nodes was estimated using Pearson's product–moment correlation of the respective average BOLD time series resulting in a symmetric 400 × 400 matrix, with each entry (i.e., edge) representing a Pearson's correlation coefficient between the respective nodes. To minimize the number of edges caused by noise, we included the statistical significance of each correlation coefficient as an additional preprocessing step. Therefore, the observed time-series were randomized by taking its Fourier transform, scrambling its phase, and then inverting the transform (Stumme et al., 2020; Zalesky et al., 2012). This procedure was repeated 1000 times and followed by a permutation test (nonsignificant edges at $p \geq .05$ were set to zero). The adjacency matrix was then transformed into *z*-scores by applying a Fishers *r*-to-*z* transformation. Integrating both, positive as well as negative weights into the estimation of strength values leads to a mutual suppression by canceling each other out. Therefore, we separated the FC matrices, with one containing only positive correlations (FC_{pos}) and the second containing only the absolute values of negative correlations (FC_{neg}), with the other values set to zero in each case.

Regarding SC, the parcellation template was first warped to individual diffusion space by combining the nonlinear warps of the spatial T1 registration to MNI152 template and the distortion correction with the APMs. Since streamlines are generated seeding from the grey-white matter interface and the predefined parcellation scheme only covers cortical grey matter, we expanded the template adding voxels towards the grey-white matter boundary so that all regions also include the seeding points. To increase the biological accuracy of SC, we converted streamline counts between each pair of nodes into weighting factors using a cross-sectional area multiplier (SIFT-2; Smith et al., 2015). Finally, the derived 400 × 400 matrix was log10 transformed.

Each of the SC, FC_{pos} as well as FC_{neg} whole brain connectomes (i.e., 400 × 400 connectivity matrices) were then transformed into a triangular matrix (diagonal set to NaN) as only unidirectional information of edges was used. Based on the three different matrices, we calculated two different parameters for each node:

i. Intra-network connectivity estimate comprising the sum of weights (i.e., connectivity values) of edges from one node to all nodes within its corresponding network divided by the number of all edges in the network (for n nodes, there are $n^*[n-1]/2$ possible edges in a fully connected network)
ii. Inter-network connectivity estimate comprising the sum of edge weights from one node to all nodes outside its corresponding network divided by the number of the respective edges.

Thus, for each node, six different strength values were calculated, three intra-network (SC, FC_{pos}, and FC_{neg}) and three inter-network estimates (SC, FC_{pos}, and FC_{neg}), in total comprising 2400 connectivity values (400 nodes × 6 strength values) for each subject. Of note, density values for functional inter- and intra-network parameters can be found in Table S2.

2.4 | Cognitive performance

All subjects underwent comprehensive neuropsychological assessment addressing a wide range of cognitive functions including the domains of attention, episodic and working memory, executive as well as language functions (for a detailed description of neuropsychological tests, see, Caspers et al., 2014; Jockwitz et al., 2017; Stumme et al., 2020). In cases of one ($n = 31$) or two ($n = 6$) missing values in the neuropsychological assessment (≥3 missing values led to exclusion, see above), they were replaced by the appropriate median (calculated separately for sex and age decades: 55–64 years, 65–74 years, 75–80, and >85 years). Principal component analysis (PCA) was applied to reduce the neuropsychological data to one cognitive performance component (COG). Previously, data was tested on suitability for PCA, using the Kaiser–Meyer–Olkin (KMO) index indicating suitability of data for PCA (KMO = 0.89; Tabachnick et al., 2007).

2.5 | Statistics

To unveil FC and SC patterns that are, together with cognitive performance, characteristic for the older adults' aging process, we performed a partial least square regression (PLSR; Mevik et al., 2018) with COG, whole-brain region-wise SC, FC_{pos}, and FC_{neg} values as predictor variables (corrected for sex and education) and chronological age as the response variable. PLSR is a multivariate statistical approach that has the advantage of effectively dealing with multiple predictor variables that may even extend the number of observations and depict high collinearity (Haenlein & Kaplan, 2004; Krishnan et al., 2011; McIntosh & Lobaugh, 2004). In PLSR, predictor variables are decomposed into a smaller set of independent components (using a nonlinear iterative partial least squares algorithm, NIPALS) on which a least square regression is performed to define components that are maximally correlated with the response variable. Hence, within one component predictor variables (COG, SC, FC_{pos}, and FC_{neg}) are clustered in a unique combination, such that a unique amount of variance is used to explain the highest possible amount of variance in age. In the following, the components are called "aging profiles," that is, comprising both the connectivity predictors (connectivity profile) and the cognitive performance predictor.

To extract the number of components that explain a significant proportion of variance in age without overfitting the model, a permutation approach with cross-validation is included in PLSR (Mevik et al., 2018; Mevik & Wehrens, 2015). Thereby, PLSR is repeatedly calculated with the inclusion of different numbers of components, each run omitting one individual and determining cross-validated residual values (leave one out cross-validation to depict the difference between the actual response and predicted response value). For each

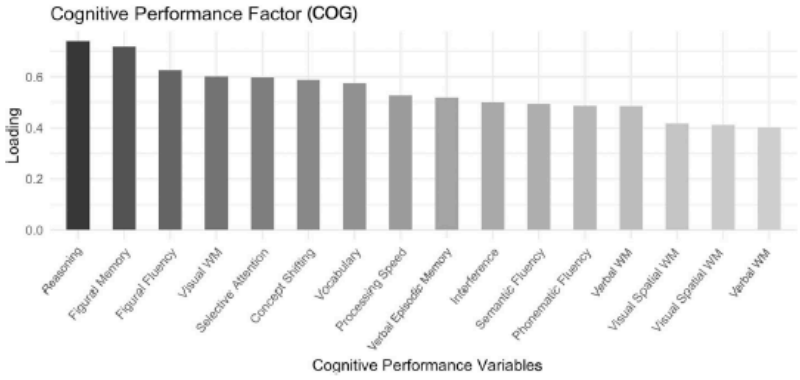


FIGURE 1 PCA derived factor loadings for the cognitive performance, ordered descendent according to the strength of loading. STM, short-term memory; WM, working memory

model (different number of components included), the root mean squared error of prediction (RMSEP) is calculated by summing all squared prediction errors. Based on the derived RMSEP for each component, a permutation test is used to determine the number of components to be included until there is no further significant improvement in predictive performance [$\alpha = .01$; for a detailed description of PLSR, also see, Mevik and Wehrens (2015) and Mevik et al. (2018)].

For each component, PLSR provides loading values for each predictor variable indicating the association between predictor and age (whether the predictor shows age-related connectivity increases or decreases). Components-derived loading values then reveal how region-wise connectivity estimates are combined, that is, how they are together age-characteristic. Furthermore, with COG being included as a predictor variable, components-derived connectivity profiles can additionally be related to cognitive performance.

To assure that results of the PLSR are applicable and robust across multiple datasets, we split the whole sample into 1000 different training (80%, $n = 458$) and test datasets (20%, $n = 115$), performed PLSR on the training datasets and applied the derived model to the remaining test datasets to predict age (based on their predictor variables). Further, to validate that PLSR on real data performs significantly better as compared to random data, we reran all analyses with 1000 null models (created by randomly scrambling age and connectivity estimates) and compared model performances. All PLSRs were additionally performed with only the inclusion of cognition and FC or cognition and SC. To ensure that the results are not dependent on the specific sample split that was used, we also performed the same analyses by using three other sample divisions (90/10%, 70/30%, and 60/40%). Finally, to ensure that results were robust to participant's health status, we reran PLSR with the additional inclusion of available covariates indicative of our participants' state of health [total grey matter volume (ml), white matter lesions (mm^3), blood pressure (mmHg), blood glucose concentration (%), and BMI (body mass index)]. For details, see Figure S1 and Table S3.

After model validation, the different PLSR-derived components, that is, aging profiles, were inspected. As stated above, for each of the 1000 permutations, PLSR provides loading values for each predictor variable in each component. To make the strength of loadings more easily interpretable across networks, we calculated network-wise average mean loading values (the average across all mean loading values within one network). With regards to previous literature indicating that the frontal lobe is structurally more sensitive to age-related decreases as compared to the rest of the brain, we statistically tested this by calculating the average mean loading values of regions located within the frontal lobe and compared these to the average mean loading values located in the rest of the brain using an undirected two-sample *t*-test (Figure S6).

3 | RESULTS

3.1 | Cognitive performance

Using PCA, we reduced the cognitive performances across 16 different cognitive test scores into one comprehensive cognitive performance component (Figure 1). Relating the cognitive factor to age, sex, and education revealed a significant negative correlation with age ($r = -.44$, $p < .001$, corrected for sex and education), a significant positive relation to education ($r = .40$, $p < .001$, corrected for age and sex), and no sex-related performance differences ($F = 2.31$, $p = .129$, corrected for age and education).

3.2 | PLSR—Model validation

Results from the PLSR model validation revealed that the inclusion of three components appears optimal in the current context, that is, the model explains sufficient variance, while preventing an overfitting of the model. Importantly, PLSR on real models performed significantly better as compared to null models [$RMSEP_{real(SD)} = 5.45$ (.07); $RMSEP_{null(SD)} = 7.68$ (.23); Figure 2a, Table 2]. Additively including information of the first, second, and third components revealed a successive increase of explained variance in age (first: $R^2 = 22.7\%$; second: $R^2 = 44.9\%$; third: $R^2 = 56.2\%$) and an increasing correlation

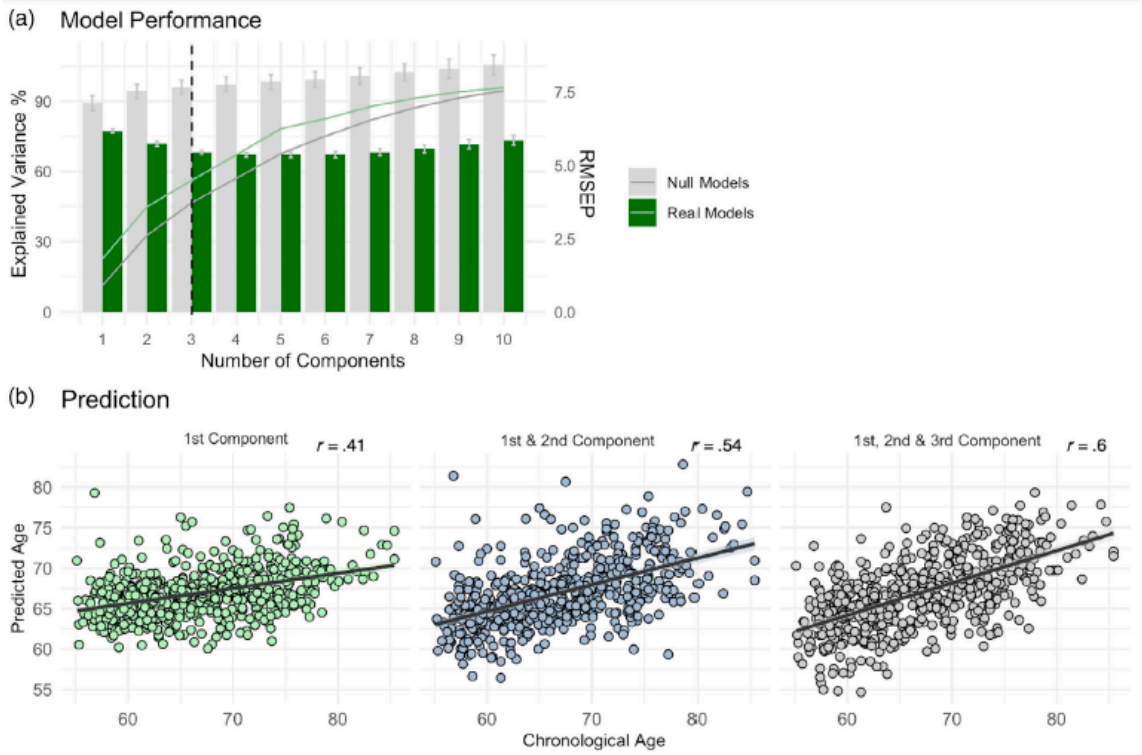


FIGURE 2 PLSR model description. (a) Model performance across 1000 real models (green) or null models (grey): RMSEP (SD) as bars and explained variance in age (%, R^2) as lines including up to 10 components. Dashed line indicating the utilized model in the current study. (b) Prediction accuracies derived from applying the PLSR model on 80% of the sample to unseen test datasets (20% of the sample): Correlation between predicted and chronological age including the information of only the first component, the first and second component, or all three components. Individual score values depict the mean scores across 1000 permutations

between predicted and chronological age (first: $r = .41$, $p < .001$; second: $r = .54$, $p < .001$, third: $r = .6$, $p < .001$; Figure 2b).

Of note, the inclusion of various covariates addressing the participants' health status did not result in any significant alterations of the presented effects (Figure S1, Table S3). Further, performing PLSR on different training and test sample sizes (60%/40%, 70%/30%, 80%/20%, 90%/10%) revealed highly comparable results across all sample splits (Figure S2, Tables S4–S6). Finally, PLSR based on either cognition with SC or cognition with FC revealed both models to significantly outperform null models, though with better model performances based on SC as compared to FC (Figure S2, Tables S5 and S6).

3.3 | PLSR: Aging profiles

The PLSR model validation revealed the variance in age to be described by three different components, that is, aging profiles. Within each component, predictor variables (COG and connectivity estimates) were combined in a unique way such that they show the highest possible correlation with age. All components show a negative correlation with age (first component: $r = .46$, $p < .001$, second component: $r = .5$, $p < .001$, third component: $r = .35$, $p < .001$; Figure 3a). Within each component, this age-related shift can comprise age-related increases or decreases of predictors, determined for each predictor variable separately and indicated by the respective loading value.

We found cognitive performance to be depicted by positive loading values in all components with an emphasis on the second component (first component: $COG_{mean(SD)} = .022$ (.002), second component: $COG_{mean(SD)} = .030$ (.005), third component: $COG_{mean(SD)} = .021$ (.002); Figure 3b) indicating that higher ages are related to lower global cognitive performance, especially in the second component.

Regarding the connectivity profiles, that is, how region-wise connectivity predictors are combined in each aging profile, we plotted region-wise mean loading values (the mean of a predictor's loading values derived from 1000 permutations) for intra- and inter-network SC, FC_{pos}, and FC_{neg} onto the brain surface (Figure 3c). While positive loading values indicate age-related connectivity decreases (blue color), negative loading values show the opposite association, that is, age-related connectivity increases (red color). Overall higher loading values

TABLE 2 Results of PLSR based on real or null models: RMSEP, % variance used of the predictor variables (SD), the % explained variance in age (SD) by the inclusion of up to 10 components

Component	1	2	3	4	5	6	7	8	9	10
Real models										
RMSEP	6.18 (0.07)	5.74 (0.09)	**5.45 (0.07)**	5.37 (0.08)	5.38 (0.09)	5.38 (0.1)	5.45 (0.12)	5.57 (0.13)	5.73 (0.16)	5.86 (0.17)
% used variance COG/connectivity (SD)	8.26 (0.3)	12.9 (0.8)	**19.51 (0.92)**	22.11 (0.36)	24.04 (0.36)	27.04 (0.7)	28.73 (0.76)	29.94 (0.45)	31.07 (0.27)	31.98 (0.23)
% explained variance age (SD)	22.71 (1.18)	44.93 (2.47)	56.18 (1.09)	67.05 (1.6)	78.24 (0.96)	82.46 (1.52)	87.68 (0.65)	91.24 (0.9)	93.96 (0.52)	95.78 (0.35)
Null models										
RMSEP	7.14 (0.25)	7.54 (0.24)	7.68 (0.23)	7.77 (0.25)	7.85 (0.24)	7.94 (0.27)	8.06 (0.28)	8.19 (0.3)	8.31 (0.32)	8.44 (0.34)
% used variance COG/connectivity (SD)	6.67 (1.87)	21.16 (1.36)	32.41 (1.5)	41.62 (1.54)	46.15 (1.3)	51.09 (0.87)	55.77 (0.7)	58.67 (0.5)	61.01 (0.35)	63.05 (0.19)
% explained variance age (SD)	11.34 (5.09)	32.74 (5.38)	46.63 (3.87)	57.03 (3.86)	67.62 (2.63)	75.06 (2.26)	81.8 (1.91)	87.18 (1.32)	91.38 (0.79)	94.47 (0.55)

Note: The cross-validated permutation approach of PLSR (Section 2) revealed three components to explain enough variance in an age without overfitting the model.

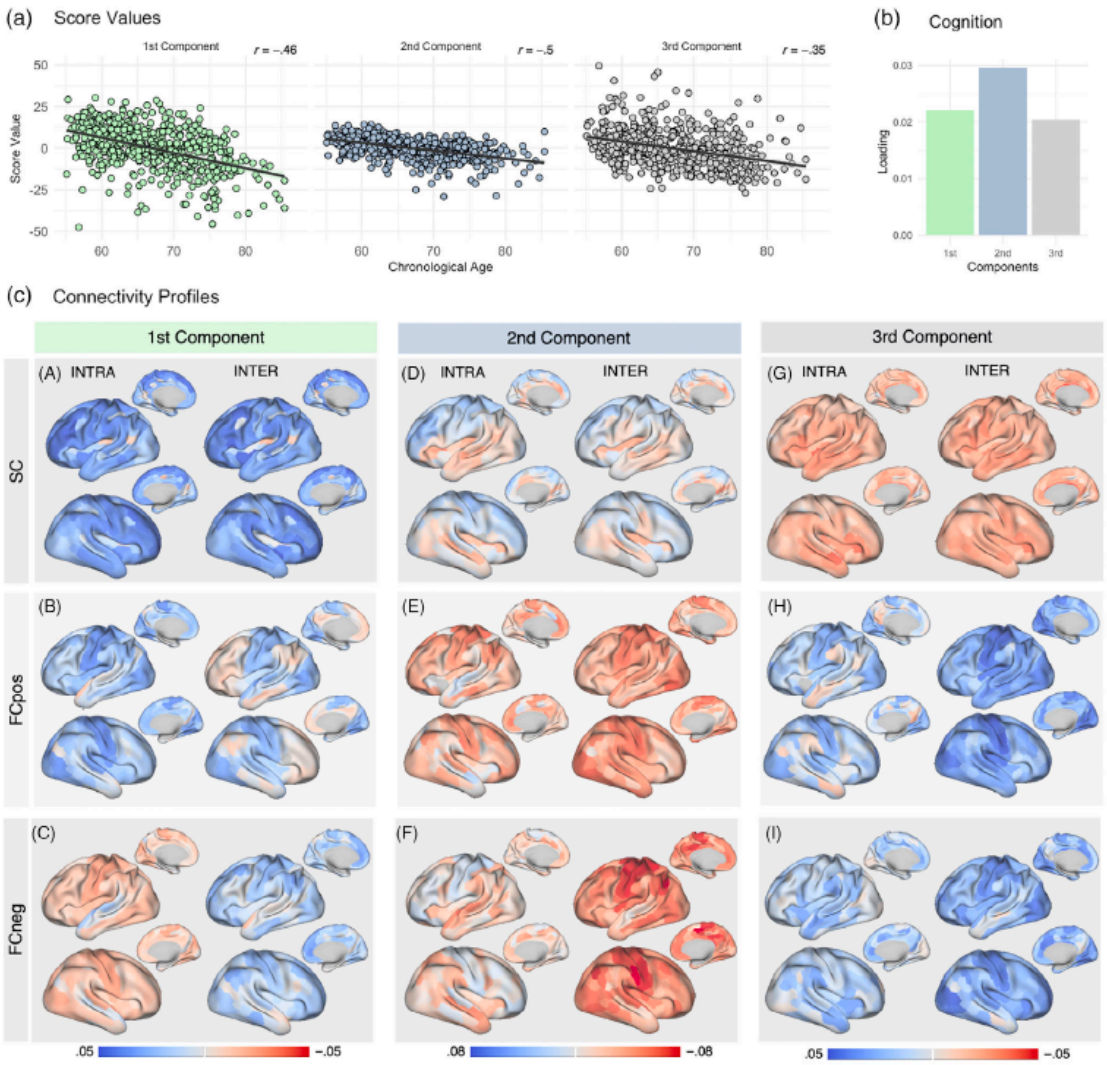
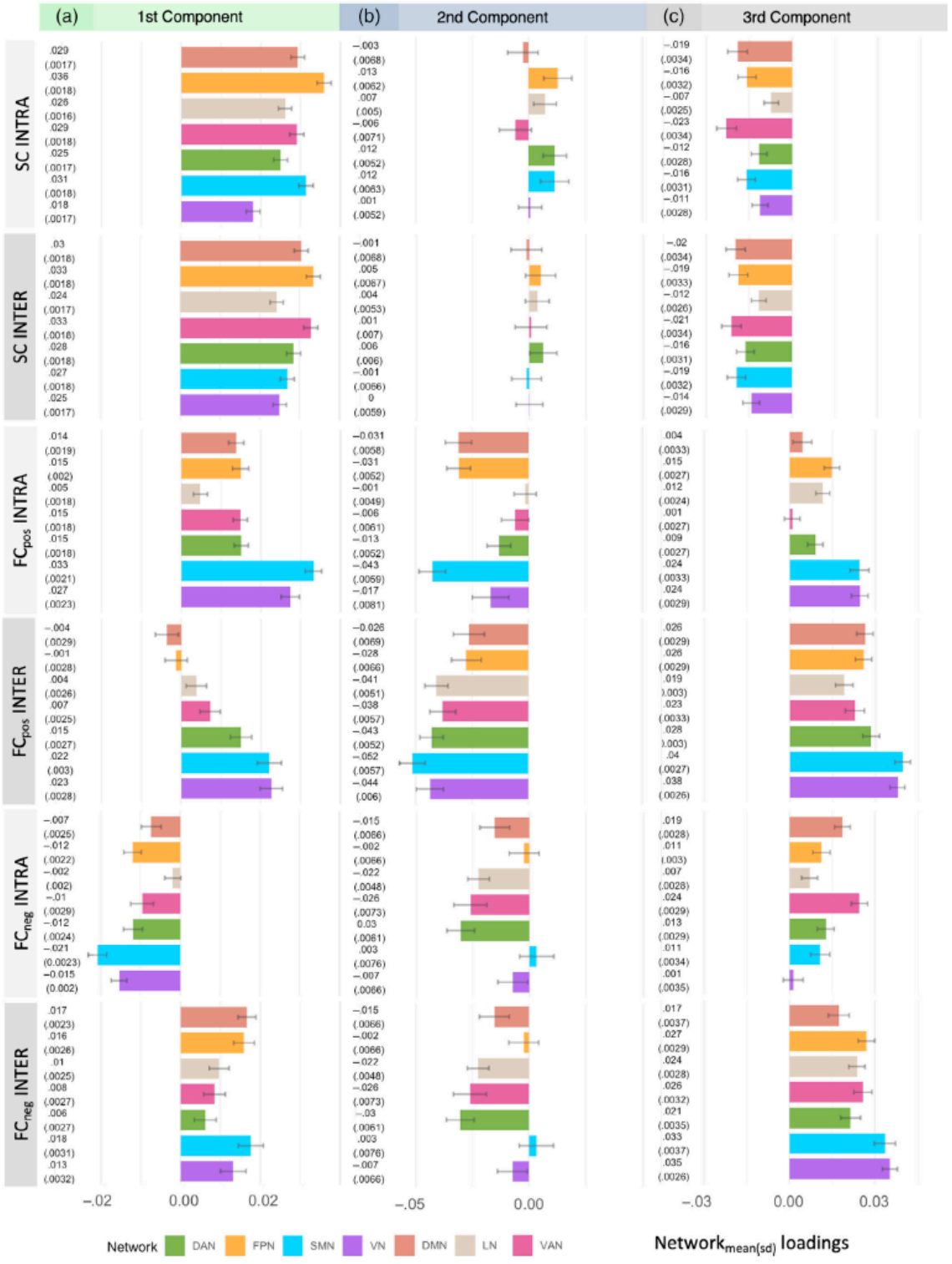


FIGURE 3 (a) Model derived individual score values for the first, second, and third components in relation to the participant's chronological age. (b) Loading values for cognitive performance in the first, second, and third components: Higher loadings indicate lower cognitive performance at higher ages. (c) Region-specific loading values for the first (A, B, C), second (D, E, F), and third component (G, H, I): Intra- and inter-network SC (A, D, G), FC_{pos} (B, E, H), and FC_{neg} (C, F, I) plotted onto the brain surface. Blue colors indicate lower and red colors higher connectivity values being characteristic for higher ages

indicate a stronger association with age underpinning these connectivity estimates to be highly age-characteristic. In the following sections, the three derived age-related connectivity profiles will be successively described by referring to the concurrent effects of SC, FC_{pos}, and FC_{neg}. As outlined in Section 2, network-wise mean loading values were calculated to make the strength of loadings more easily interpretable across networks (Figure 4). For results on region-wise loading, which are informative about the distribution of loadings within networks, refer to Figures S3–S5.

3.4 | First component

In the first component, 8% of the variance in the predictor variables is used to explain the highest variance in age (23%) indicating that this connectivity profile is most applicable to older adults. Within this component, older age is characterized by overall low SC. Looking at the region-wise loading values for SC (Figure 3c-A), age-related decreases seem to particularly affect the frontal lobe. Statistically comparing loading values in frontal brain areas to the rest of the brain


(a) 1st Component
(b) 2nd Component
(c) 3rd Component
SC INTRA
SC INTER
FCpos INTRA
FCpos INTER
FCneg INTRA
FCneg INTER
−.02 0.00 0.02
−.05 0.00
−.03 0.00 0.03
Network DAN FPN SMN VN DMN LN VAN
Networkmean(sd) loadings

indeed revealed intra-network SC ($t = 4.7$, $p < .001$) as well as inter-network SC ($t = 5.3$, $p < .001$) to be significantly higher in frontal brain parts (Figure S6). Network-wise, the FPN, DMN, and SMN are depicted by the strongest age-related decreases, while the FPN, DMN, and VAN are most sensitive in terms of age-related inter-network SC decreases. Because the FPN, SMN, DMN, and VAN have regions located in both frontal as well as more posterior brain parts, SC decreases seem to affect regions in the frontal lobe independent of their network affiliation.

This age-related decrease in SC is accompanied by overall age-related decreases of the intra-network FC_{pos} (Figure 3c-B) and increases of intra-network FC_{neg} (Figure 3c-C) pertaining to all networks distributed across the whole brain. Hence, while coactivations of regions within networks decrease with higher age, their anticorrelations show an opposite trajectory. Thereby, loading values of primary processing networks are notably high [FC_{pos}: $VN_{mean(SD)} = .027$ (.002), $SMN_{mean(SD)} = .033$ (.002); FC_{neg}: $VN_{mean(SD)} = .021$ (.002), $SMN_{mean(SD)} = .015$ (.002), Figure 4a] indicating the strongest age-related differences in both positive connections and anticorrelations. Concurrently, the inter-network FC_{pos} shows age-related decreases (Figure 3c-B). This, however, is not applicable to higher order networks: regions inside the VAN, LN, FPN, and DMN show age-related increases, mainly pertaining to the FPN and DMN [$FPN_{mean(SD)} = -.001$ (.003), $DMN_{mean(SD)} = -.004$ (.003); Figures 3c-B and 4a]. Anticorrelations show decreases across all networks indicating less network-specific coactivations, but more simultaneous activations of regions from different networks.

Cohesively, the first connectivity profile implies age-related decreases in SC and FC_{pos} accompanied by increasing anticorrelations within all networks and across the whole brain. Specifically, as the age-related decline of SC affects the whole brain, we see age-related decreases of the intra-network FC_{pos} in particularly primary processing networks together with age-related increases of inter-network FC_{pos} of higher-order networks. Regarding cognition, increasing age is associated with decreasing performance that is comparable to the third component and slightly less advanced compared to the second component [first component: $COG_{mean(SD)} = .022$ (.002), second component: $COG_{mean(SD)} = .030$ (.005), third component: $COG_{mean(SD)} = .021$ (.002); Figure 3b].

3.5 | Second component

In the second component, another 4% of the variance in the predictor variables is clustered such that it explains another 22% of the variance in age. In contrast to the first component, the second component comprises a connectivity profile in which age-related SC decreases only affect the frontal lobe and parts of the parietal lobe, while regions within the temporal, and occipital lobe and the insula remain rather stable (Figure 3c-D). This is applicable to both, intra- and inter-network SC. Accordingly, SC decreases in frontal brain areas are again significantly stronger as compared to the rest of the brain (intra-network SC: $t = 2.5$, $p = .015$; inter-network SC: $t = 2.7$, $p = .008$, Figure S6). Inspecting the loading values across networks (Figure 4b, Figure S4), each network comprises regions with positive as well as negative loading values indicating age-related differences of regions to be rather independent of their network affiliation.

In terms of FC, the second component FC_{pos} is (in contrast to the first component) overall high in older adults (Figure 3c-E). This is applicable to the FC_{pos} within- as well as between-networks, with an emphasis on the SMN (intra-network: $SMN_{mean(SD)} = .043$ (.006); inter-network: $SMN_{mean(SD)} = .052$ (.006); Figure 4b). Furthermore, especially between networks, anticorrelations show age-related increases, indicating that networks do not only show more coactivations, but also higher anticorrelations in higher ages (Figure 3c-F). Of note, comparing the intra-network SC and FC (left column in Figure 3c-D, E, F) one can see that regions which remain rather stable in SC across age (superior temporal lobe and insular) seem to show comparably low increases in FC_{pos} and FC_{neg}. In contrast, regions with stronger age-related decreases in SC show stronger increases in both, FC_{pos} as well as FC_{neg}. Remarkably, the second component is associated with the strongest age-related differences in cognitive performance as indicated by the highest COG loading value (Figure 3b).

3.6 | Third component

As compared to the first and second components, the third component explains less variance in age (11%) by using 7% of the variance of the predictors. Therefore, this connectivity profile is comparably less representative for older adults. Here, the SC show overall negative loading values indicating a stable SC system across age (Figure 3c-G) with no age-related SC decreases affecting either the intra- or inter-network SC of any networks (Figure 4c). Remarkably, this overall stable SC profile is clustered together with overall low FC_{pos} (Figure 3c-H) as well as low FC_{neg} (Figure 3c-I). Thereby, the intra- and inter-network FC_{pos}, as well as inter-network FC_{neg} of primary processing networks, show the strongest relations to age, indicating that these networks are most age-characteristic and showing the strongest age-related decreases [intra-network FC_{pos}: $VN_{mean(SD)} = .024$ (.003), $SMN_{mean(SD)} = .024$ (.003); inter-network FC_{pos}: $VN_{mean(SD)} = .038$ (.003), $SMN_{mean(SD)} = .040$ (.003); inter-network FC_{neg}: $VN_{mean(SD)} = .035$ (.003), $SMN_{mean(SD)} = .033$ (.004); Figure 4c]. In terms of cognitive performance, this connectivity profile is similar to the first component accompanied by cognitive performance decreases (Figure 3b).

FIGURE 4 Network-wise mean loading values (SD) for the first, second, and third components visualized as bar plots: Inter- and inter-network SC, FC_{pos}, and FC_{neg} (colored according to their respective network, from top to bottom: Brown = DMN, orange = FPN, grey = LN, pink = VAN, green = DAN, blue = SMN, violet = VN)

4 | DISCUSSION

As we age, the functional connectome undergoes a process of reorganization that manifests itself in a shift from segregated to more integrated brain networks and which was found to be relevant in terms of cognitive performance. The causes of this functional restructuring are not yet fully understood, but are related to differences in SC. Since SC is the underlying scaffold for information exchange between regions, age-related SC differences may explain age-related FC reorganizations. Here, we took advantage of a large cohort of older adults and performed a multivariate statistical approach (PLSR) on the participant's regions-wise FC, SC and global cognitive performance. Specifically, we examined how region-wise FC and SC are together age-characteristic and related to cognitive performance. In doing so, we aim to contribute to the understanding of age-related functional restructuring by considering SC differences that are associated with it.

Results of PLSR indicate that the variance in age is explained by three different aging profiles. Of note, sensitivity analyses indicate these aging profiles to be robust across multiple sample splits and independent of the overall health status of participants. In line with previous research PLSR with only cognition and SC explained more variance in age as compared to cognition and FC (Cole, 2020). Inspecting the aging profiles in detail revealed interesting interrelations of region-wise FC and SC estimates, which will be discussed as follows.

With regards to previous research, we assumed age-related decreases in SC across the whole brain with a particular focus on the frontal lobe. This is exactly what is captured by the first aging profile (first component). Here, SC across the whole brain was characteristic for higher ages and the strongest age-related decreases in SC pertain to the frontal lobe. These effects were very similar not only for the two hemispheres, but also for SC within and between networks. Hence, decreases affect the SC between any regions (in all networks), but especially those located in the frontal lobe. Previous results on lifespan changes indicate that white matter of the frontal lobe is particularly vulnerable to the aging process showing the greatest deteriorations across ages while white matter of temporal and occipital regions seem to be relatively preserved (Antonenko & Floel, 2014; Gunning-Dixon et al., 2009; Rojkova et al., 2016; Salat, 2011; Salat et al., 2005; Zhao et al., 2015). In the current sample of older adults, we found the first component to capture SC decreases that affect the whole brain. Thereby, decreases in frontal brain areas are indeed most age-specific, but the rest of the brain is additionally affected, though to a somewhat lesser extent. These effects may represent a more advanced picture of aging (in older adults as compared to lifespan samples) that has additionally affected SC in parietal and temporal regions.

This SC profile is clustered together with a FC profile that very much matches the typical FC aging pattern described in previous research on older adults (Edde et al., 2021; Perry et al., 2017; Stumme et al., 2020; Zonneveld et al., 2019). The functional profile of the first component is in line with our hypothesis that higher age is characterized by lower intra-network FC of particularly primary processing networks together with a higher integration between higher-order networks. The strongest age-related decreases of intra- and inter-network FC pertain to the VN and SMN indicating that in older adults a reduced FC_{pos} of particularly primary processing networks is characteristic for higher ages. Concurrently, higher order networks (especially the DMN and FPN) show higher positive inter-network FC at higher ages, perfectly reflecting the assumed age-related shift towards a stronger network integration of higher order networks (Betzel et al., 2014; Edde et al., 2021; Ferreira et al., 2016; He et al., 2020; Stumme et al., 2020; Tsvetanov et al., 2016; Varangis et al., 2019). Complementary to positive FC, FC anticorrelations within networks show overall age-related increases in FC which could indicate that regions within a network work less coherently at higher ages. However, these results must be viewed with caution, as anticorrelation within networks are rather unlikely and may be caused by a topographical deviation of older adults to the younger adults parcellation used in the current study (further discussed in the methodological considerations). In turn, anticorrelations between networks decrease, indicating a reduced ability to deactivate brain networks while activating another, and thus leading to a shift towards greater inter-network integration (Edde et al., 2021; Ferreira et al., 2016; Keller et al., 2015; Spreng et al., 2016). Current research agrees that lower intra-network FC is associated with lower performances, meaning that less coherent networks result in poorer cognitive functioning (Ewers et al., 2021; Fjell et al., 2015; Marques et al., 2016; Stumme et al., 2020).

In turn, inter-network FC increases can be interpreted in two ways: as a compensatory attempt or a dedifferentiation process. In terms of compensation, the additional functional recruitment of higher order networks may be understood as the attempt to more intensively involve additional control processes (e.g., monitoring, introspection, and attention processes) to maintain cognitive performances despite a decay of network coherence. A higher recruitment of brain regions may be accompanied by increasing wiring costs, but may also be accompanied by a higher cognitive reserve, that is, performance maintenance (Festini et al., 2018; Franzmeier et al., 2018). As discussed in Stumme et al. (2020), specific coactivations may indeed be beneficial for cognitive maintenance. However, with an increasing number of coactivations, specific access to the auxiliary functions and thus the compensatory purpose of the system may be lost and replaced by a rather dedifferentiated system. A functionally dedifferentiated system is characterized by a reduced distinctiveness of activity patterns throughout the brain (Edde et al., 2021; Ferreira et al., 2016; Keller et al., 2015; Spreng et al., 2016) limiting the access to specific cognitive processing, which is associated with impaired performances (Monteiro et al., 2019; Spreng & Turner, 2019). The first component is accompanied by age-related decreases in cognitive performance indicating that the additional recruitment of higher order networks during rest cannot hinder a cognitive decline. In view of the large age range (55–85 years), the strong cognitive changes in older subjects (Hedden & Gabrieli, 2004; Salthouse, 2019) and the widely affected SC decreases, a halt of cognitive loss is not to be expected. Collectively, the first component captures a connectivity profile in which both, FC and SC show their previously described typical age-related

differences in parallel. Accordingly, this aging profile explains the most variance in age.

The second component explains only slightly less variance in age as compared to the first component, indicating that there exists another aging profile that is particularly age-characteristic in older adults. Here, the overall SC is less affected by age with only the frontal lobe showing age-related decreases, while the parietal and occipital lobes remain stable. As discussed above, this may comprise a less advanced aging process (Antonenko & Floel, 2014; Gunning-Dixon et al., 2009; Rojkova et al., 2016; Salat, 2011; Salat et al., 2005; Zhao et al., 2015), in which SC decreases have not yet affected the whole brain. In the case of initially decreasing SC in the frontal lobe while simultaneously large parts of the brain remain structurally intact, the brain exhibits a functionally maximally interconnected system. In fact, previous work suggests a functional over-recruitment of brain areas to be a response to age-related structural changes that itself would cause a poor processing of cognitive functions (Marstaller et al., 2015; Park & Reuter-Lorenz, 2009; Pistono et al., 2021; Reuter-Lorenz & Park, 2014). In response to decreasing white matter pathways, the aging brain must seek alternative functional routes to maintain communication between regions (Naik et al., 2017). In this regard, overall high functional interactions could be an adaptive recalibration process resulting from the initial decline of the frontal lobe to maintain cognitive performance. Unlike the first component, the second component still has a large portion of SC paths that can be used to select alternate routes so that an exchange of information is maintained. However, because the second component is associated with the strongest age-related cognitive decline, this supports the dedifferentiation theory, in which specific access to desired functions is reduced (Edde et al., 2021; Ferreira et al., 2016; Keller et al., 2015; Spreng et al., 2016). As discussed above, in a compensation process we might expect more specific coactivations that recruit specific functions to maintain cognitive performance. As the recruitment of additional brain regions increases (either on purpose or due to necessary detours), increasing inter-network FC may no longer be supported, but rather result in a decreased functional diversity of brain networks. Hence, although a compensation process may have aspired, a supportive character of increasing coactivations may at some point be replaced by a decreased functional diversity of brain networks. In this context, it is highly interesting that more and more research additionally includes time into the analyses of brain function looking at functional connectivity dynamics (FCD), that is, how the FC varies across time. It has been found that with increasing age the time-dependent variance of functional states, called metastability, declines (Battaglia et al., 2020; Lou et al., 2019; Naik et al., 2017; Xia et al., 2019). Here, the functional activity is characterized by reduced differentiated activity states, meaning that a high proportion of functional systems are activated in parallel. A lower metastability is, thereby, characterized by a lower ability of the functional system to transition between different cognitive states, that is, if the whole system is similarly activated, the potential to switch between states diminishes. This is thought to reduce the capacity to also behaviorally switch between concepts and to slow the rate of functional adaptations to external influences (Escrichs et al., 2021; Lee et al., 2019; Xia et al., 2019). Computational models showed that reduced metastability is a response to SC decline (Deco & Kringelbach, 2016; Lavanga et al., 2022; Naik et al., 2017). Hence, the functionally highly interconnected system found in the second component could point towards a low capacity to switch between functional states potentially resulting from the incipient SC decline and would explain the strongest association with cognitive performance decline. Including FCD estimates in this context, thus, would be highly promising for future research.

It remains open why the brain associated with the most severe SC decline (as in the first component) does not show a highly interconnected functional system. Participants with minor SC deterioration may experience an onset of cognitive decline, that is find the everyday tasks more difficult, but still strive to maintain cognitive performance, which may then be addressed by an increase in functional interconnectivity (Gaviria et al., 2021). However, with regards to the "Compensation-related utilization of neural circuits hypothesis" (Reuter-Lorenz & Cappell, 2008), the functional capacity to respond to increasing task difficulty is exhausted at some point and the attempt to compensate for increasing task complexity by functional overactivation is no longer even considered. Further, an overall reduced SC in the first component limits the possibility of alternative routes and may logistically not allow information to be relayed via many different regions.

Following the course of descending severity of SC decline from the first over the second to the third component, the third component reflects a connectivity profile which we may consider as well preserved. In this case, higher age is depicted by comparably high SC, while the overall FC is low. Overall high SC points to a well-preserved underlying architecture that enables an efficient exchange of information between regions while consuming as little energy as possible (Lynn & Bassett, 2019). The associated resting brain exhibits rather weak FC both within and between all networks. Higher overall communication in the brain, that is, connectivity, requires higher energy consumption (Tomasi et al., 2013). At the same time, a highly interconnected functional system reduces the ability to efficiently switch between brain states (Chan et al., 2014, 2017; Colcombe et al., 2005; Goh, 2011; Nashiro et al., 2017; Park et al., 2004), which is associated with lower cognitive performance (Lavanga et al., 2022). Accordingly, the functional connectivity system of this third component could reflect a rather low-energy state of the resting brain, which at the same time may involve a high ability to efficiently adapt to external stimuli. However, this connectivity profile is comparatively less representative in older adults, which is plausible in light of previous results showing a continuous SC decline into old age (Cox et al., 2016; Gunning-Dixon et al., 2009; Li et al., 2020).

Collectively, we found three different connectivity profiles to be related to age in older adults. Each connectivity profile is depicted by different severity of SC decline. While a well-preserved SC system is accompanied by a comparably low interconnected functional system, a decline in SC seems to go along with an increase in the brain FC. The functionally highest interconnected system is present when the underlying white matter pathways are only slightly damaged. This

could indicate that an increasing FC is the reaction to an incipient decline of the underlying SC construct, which logistically allows the transmission of information in various detours. However, we found that the highest interconnected functional system was associated with the greatest decline in cognitive performance, indicating a shift towards higher network integration to represent a dedifferentiation process. In fact, the compensation and dedifferentiation theories do not cancel each other out. Instead, an interlocking process in which a beneficial compensation process is replaced by a steadily decreasing diversity of functional systems may be conceivable.

4.1 | Methodological considerations

The results of the present study are based on a cross-sectional design. The current cross-sectional design has the advantage of a large sample size representative of and thus, largely generalizable for, the general older population in West Germany. For capturing the intraindividual age-related changes in the relationship between SC and FC, however, longitudinal studies are warranted.

A potential limitation of the current study pertains to the specific functional network parcellation used, which is based on resting-state data from younger adults. Methods for such imaging-based brain parcellations improved considerably over the recent decade (Eickhoff et al., 2018). Nevertheless, so far, no whole brain network parcellation based on older adults exists integrating both, structural and functional information. Within the current study, we chose the current parcellation based on previous work on functional (Schaefer et al., 2018) and anatomical data (Varikuti et al., 2018) indicating fine-grained parcellations of 300–600 nodes to be optimal. Especially using fine-grained parcellations, however, transformation procedures between image modalities could influence inter-subjects' variance. Hence, changes in the parcellation granularity and further, the inclusion of subcortical structures would be interesting for future studies focusing on SC–FC relations during aging and their link to cognitive performance.

SC evolves, rearranges, and strengthens in developmental stages, after brain injuries as well as across the lifespan as a result of, for example, learning processes (Fields, 2005; Salat, 2011; Yeatman et al., 2014). However, in older ages, increases in SC are rather unlikely and may point to yet unresolved methodological constraints. In addition, tractography on diffusion imaging data is not a direct measurement, but only an estimation of anatomical connectivity (Sotiropoulos & Zalesky, 2019) known to under-represent long-distance white matter connections (de Reus & van den Heuvel, 2013). Across the aging process the paucity of long-distance connections even increases, which may foster increasing short-range connections (Puxeddu et al., 2020; Zhao et al., 2015). So far, a ground truth for structural connectomes has not yet been developed. To optimally picture the biological SC, we conducted streamlined filtering as an additional step in diffusion MRI denoising (Smith et al., 2015). Furthermore, particularly for SC, network properties are known to depend on the methodology applied, which potentially makes specific network results less generalizable (Qi et al., 2015).

As compared to previous studies on age prediction our model explains less variance in age. Although the validation process revealed our PLSR model to perform significantly better as compared to random data underpinning the model's prediction ability. So far, the optimal method for age prediction is still under debate (Smith et al., 2019). Predictions were found to perform best using structural brain volume data (Cole et al., 2017; Cole & Franke, 2017; Franke et al., 2010; Liem et al., 2017), while age prediction on connectivity data was found to perform significantly lower explaining about 40%–60% of the variance in age (Dosenbach et al., 2010; Han et al., 2014; Li et al., 2018; Vergun et al., 2013). With respect to the current study, the intended restriction to region-wise connectivity estimates limits the informative value for age prediction to only particular connectivity values. The inclusion of more specific connectivity measures, for example, individual edge weights, may potentially increase prediction accuracy.

Finally, it should be noted that FC anticorrelations imply a qualitatively distinct type of interaction between brain regions, which is not yet clearly interpretable (Chai et al., 2012; Fornito et al., 2013; Murphy & Fox, 2017). Negative correlations may be artificially induced, when using global signal regression in functional imaging preprocessing (Fox et al., 2009; Murphy et al., 2009; Murphy & Fox, 2017). Therefore, results on negative correlations have been included in this study as additional complementary evidence for the general relation between FC and SC, without demanding clear interpretability on its own.

5 | CONCLUSION

The normal aging process is accompanied by a restructuring of the functional connectome, characterized by a shift from more segregated to more integrated brain networks which was found to be important for changes in our cognitive performance. Causes of the functional restructuring remain unclear, but may be associated with age-related SC differences, depicting the underlying scaffold for information exchange between regions. By performing PLSR with FC and SC estimates as well as cognitive performance data from a large cohort of older adults, we investigated the interdependency of region-wise SC and FC differences and how these are, together with cognitive performance, characteristic of older adults' age. Our results revealed three different aging profiles to be prevalent in older adults. Overall, it appears that the frontal lobe of older adults is particularly affected by aging with respect to SC showing the greatest age-related decline. In terms of brain function, primary processing networks are most indicative of the older adult's age. In this context, the functional activity pattern seems to behave differently depending on the severity of SC deterioration. In a well-preserved structural connectome, the brain exhibits a less interconnected system at rest, characterized by particularly low connections between networks. In turn, when SC shows

minor age-related deteriorations affecting the frontal lobe, the brain exhibits a functionally maximally connected system. Because this connectivity pattern was associated with the most severe age-related cognitive decline, a more interconnected functional connectivity system in older adults points to a process of dedifferentiation.

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CONFLICT OF INTEREST

No competing interests were declared.

DATA AVAILABILITY STATEMENT

Due to local regulations of data acquisition and usage, data of 1000BRAINS are available upon request from the responsible PI.

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REFERENCES

Afyouni, S., & Nichols, T. E. (2018). Insight and inference for DVARS. *NeuroImage*, *172*, 291–312. https://doi.org/10.1016/j.neuroimage.2017.12.098

Andersson, J. L. R., Graham, M. S., Zsoldos, E., & Sotiropoulos, S. N. (2016). Incorporating outlier detection and replacement into a non-parametric framework for movement and distortion correction of diffusion MR images. *NeuroImage*, *141*, 556–572. https://doi.org/10.1016/j.neuroimage.2016.06.058

Andersson, J. L. R., & Sotiropoulos, S. N. (2016). An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *NeuroImage*, *125*, 1063–1078. https://doi.org/10.1016/j.neuroimage.2015.10.019

Antonenko, D., & Floel, A. (2014). Healthy aging by staying selectively connected: A mini-review. *Gerontology*, *60*(1), 3–9. https://doi.org/10.1159/000354376

Ashburner, J. (2009). Computational anatomy with the SPM software. *Magnetic Resonance Imaging*, *27*(8), 1163–1174. https://doi.org/10.1016/j.mri.2009.01.006

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *NeuroImage*, *26*(3), 839–851. https://doi.org/10.1016/j.neuroimage.2005.02.018

Bartres-Faz, D., & Arenaza-Urquijo, E. M. (2011). Structural and functional imaging correlates of cognitive and brain reserve hypotheses in healthy and pathological aging. *Brain Topography*, *24*(3–4), 340–357. https://doi.org/10.1007/s10548-011-0195-9

Battaglia, D., Boudou, T., Hansen, E. C. A., Lombardo, D., Chettouf, S., Daffertshofer, A., McIntosh, A. R., Zimmermann, J., Ritter, P., & Jirsa, V. (2020). Dynamic functional connectivity between order and randomness and its evolution across the human adult lifespan. *NeuroImage*, *222*, 117156. https://doi.org/10.1016/j.neuroimage.2020.117156

Baum, G. L., Cui, Z., Roalf, D. R., Ciric, R., Betzel, R. F., Larsen, B., Cieslak, M., Cook, P. A., Xia, C. H., Moore, T. M., Ruparel, K., Oathes, D. J., Alexander-Bloch, A. F., Shinohara, R. T., Raznahan, A., Gur, R. E., Gur, R. C., Bassett, D. S., & Satterthwaite, T. D. (2020). Development of structure-function coupling in human brain networks during youth. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(1), 771–778. https://doi.org/10.1073/pnas.1912034117

Betzel, R. F., Byrge, L., He, Y., Goni, J., Zuo, X. N., & Sporns, O. (2014). Changes in structural and functional connectivity among resting-state networks across the human lifespan. *NeuroImage*, *102*(Pt 2), 345–357. https://doi.org/10.1016/j.neuroimage.2014.07.067

Bullmore, E., & Sporns, O. (2009). Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nature Reviews. Neuroscience*, *10*(3), 186–198. https://doi.org/10.1038/nrn2575

Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. *Nature Reviews. Neuroscience*, *13*(5), 336–349. https://doi.org/10.1038/nrn3214

Burgess, G. C., Kandala, S., Nolan, D., Laumann, T. O., Power, J. D., Adeyemo, B., Harms, M. P., Petersen, S. E., & Barch, D. M. (2016). Evaluation of Denoising strategies to address motion-correlated artifacts in resting-state functional magnetic resonance imaging data from the human connectome project. *Brain Connectivity*, *6*(9), 669–680. https://doi.org/10.1089/brain.2016.0435

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: Compensatory brain activity in high-performing older adults. *NeuroImage*, *17*(3), 1394–1402. https://doi.org/10.1006/nimg.2002.1280

Calhoun, V. D., Wager, T. D., Krishnan, A., Rosch, K. S., Seymour, K. E., Nebel, M. B., Mostofsky, S. H., Nyalakanai, P., & Kiehl, K. (2017). The impact of T1 versus EPI spatial normalization templates for fMRI data analyses. *Human Brain Mapping*, *38*(11), 5331–5342. https://doi.org/10.1002/hbm.23737

Cao, M., Wang, J. H., Dai, Z. J., Cao, X. Y., Jiang, L. L., Fan, F. M., Song, X. W., Xia, M. R., Shu, N., Dong, Q., Milham, M. P., Castellanos, F. X., Zuo, X. N., & He, Y. (2014). Topological organization of the human brain functional connectome across the lifespan. *Developmental Cognitive Neuroscience*, *7*, 76–93. https://doi.org/10.1016/j.dcn.2013.11.004

Caspers, S., Moebus, S., Lux, S., Pundt, N., Schutz, H., Muhleisen, T. W., Gras, V., Eickhoff, S. B., Romanzetti, S., Stocker, T., Stirnberg, R., Kirlangic, M. E., Minnerop, M., Pieperhoff, P., Modder, U., Das, S., Evans, A. C., Jockel, K. H., Erbel, R., … Amunts, K. (2014). Studying variability in human brain aging in a population-based German cohort-rationale and design of 1000BRAINS. *Frontiers in Aging Neuroscience*, *6*, 149. https://doi.org/10.3389/fnagi.2014.00149

Chai, X. J., Castanon, A. N., Ongur, D., & Whitfield-Gabrieli, S. (2012). Anticorrelations in resting state networks without global signal regression. *NeuroImage*, *59*(2), 1420–1428. https://doi.org/10.1016/j.neuroimage.2011.08.048

Chan, M. Y., Alhazmi, F. H., Park, D. C., Savalia, N. K., & Wig, G. S. (2017). Resting-state network topology differentiates task signals across the adult life span. *The Journal of Neuroscience*, *37*(10), 2734–2745. https://doi.org/10.1523/JNEUROSCI.2406-16.2017

Chan, M. Y., Park, D. C., Savalia, N. K., Petersen, S. E., & Wig, G. S. (2014). Decreased segregation of brain systems across the healthy adult lifespan. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(46), E4997–E5006. https://doi.org/10.1073/pnas.1415122111

Chen, C., Cao, X., & Tian, L. (2019). Partial least squares regression performs well in MRI-based individualized estimations. *Frontiers in Neuroscience*, *13*, 1282. https://doi.org/10.3389/fnins.2019.01282

Ciric, R., Wolf, D. H., Power, J. D., Roalf, D. R., Baum, G. L., Ruparel, K., Shinohara, R. T., Elliott, M. A., Eickhoff, S. B., Davatzikos, C., Gur, R. C., Gur, R. E., Bassett, D. S., & Satterthwaite, T. D. (2017). Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity. *NeuroImage*, *154*, 174–187. https://doi.org/10.1016/j.neuroimage.2017.03.020

Colcombe, S. J., Kramer, A. F., Erickson, K. I., & Scalf, P. (2005). The implications of cortical recruitment and brain morphology for individual differences in inhibitory function in aging humans. *Psychology and Aging*, *20*(3), 363–375. https://doi.org/10.1037/0882-7974.20.3.363

Cole, J. H. (2020). Multimodality neuroimaging brain-age in UKbiobank: Relationship to biomedical, lifestyle, and cognitive factors. *Neurobiology of Aging*, *92*, 34–42.

Cole, J. H., & Franke, K. (2017). Predicting age using Neuroimaging: Innovative brain ageing biomarkers. *Trends in Neurosciences*, *40*(12), 681–690. https://doi.org/10.1016/j.tins.2017.10.001

Cole, J. H., Poudel, R. P. K., Tsagkrasoulis, D., Caan, M. W. A., Steves, C., Spector, T. D., & Montana, G. (2017). Predicting brain age with deep learning from raw imaging data results in a reliable and heritable biomarker. *NeuroImage*, *163*, 115–124. https://doi.org/10.1016/j.neuroimage.2017.07.059

Cox, S. R., Ritchie, S. J., Tucker-Drob, E. M., Liewald, D. C., Hagenaars, S. P., Davies, G., Wardlaw, J. M., Gale, C. R., Bastin, M. E., & Deary, I. J. (2016). Ageing and brain white matter structure in 3,513 UKbiobank participants. *Nature Communications*, *7*, 13629. https://doi.org/10.1038/ncomms13629

Damoiseaux, J. S. (2017). Effects of aging on functional and structural brain connectivity. *NeuroImage*, *160*, 32–40. https://doi.org/10.1016/j.neuroimage.2017.01.077

Davis, S. W., Kragel, J. E., Madden, D. J., & Cabeza, R. (2012). The architecture of cross-hemispheric communication in the aging brain: Linking behavior to functional and structural connectivity. *Cerebral Cortex*, *22*(1), 232–242. https://doi.org/10.1093/cercor/bhr123

de Reus, M. A., & van den Heuvel, M. P. (2013). The parcellation-based connectome: Limitations and extensions. *NeuroImage*, *80*, 397–404. https://doi.org/10.1016/j.neuroimage.2013.03.053

Deco, G., & Kringelbach, M. L. (2016). Metastability and coherence: Extending the communication through coherence hypothesis using a whole-brain computational perspective. *Trends in Neurosciences*, *39*(3), 125–135. https://doi.org/10.1016/j.tins.2016.01.001

Dell'Acqua, F., Lacerda, L., Catani, M., & Simmons, A. (2014). Anisotropic power maps: A diffusion contrast to reveal low anisotropy tissues from HARDI data. *Proceedings of the International Society for Magnetic Resonance in Medicine*, *22*, 29960–29967.

Dohmatob, E., Varoquaux, G., & Thirion, B. (2018). Inter-subject registration of functional images: Do we need anatomical images? *Frontiers in Neuroscience*, *12*, 64.

Dosenbach, N. U., Nardos, B., Cohen, A. L., Fair, D. A., Power, J. D., Church, J. A., Nelson, S. M., Wig, G. S., Vogel, A. C., & Lessov-Schlaggar, C. N. (2010). Prediction of individual brain maturity using fMRI. *Science*, *329*(5997), 1358–1361.

Edde, M., Leroux, G., Altena, E., & Chanraud, S. (2021). Functional brain connectivity changes across the human life span: From fetal development to old age. *Journal of Neuroscience Research*, *99*(1), 236–262. https://doi.org/10.1002/jnr.24669

Eickhoff, S. B., Yeo, B. T. T., & Genon, S. (2018). Imaging-based parcellations of the human brain. *Nature Reviews. Neuroscience*, *19*(11), 672–686. https://doi.org/10.1038/s41583-018-0071-7

Escrichs, A., Biarnes, C., Garre-Olmo, J., Fernandez-Real, J. M., Ramos, R., Pamplona, R., Brugada, R., Serena, J., Ramio-Torrenta, L., Coll-De-Tuero, G., Gallart, L., Barretina, J., Vilanova, J. C., Mayneris-Perxachs, J., Essig, M., Figley, C. R., Pedraza, S., Puig, J., & Deco, G. (2021). Whole-brain dynamics in aging: Disruptions in functional connectivity and the role of the Rich Club. *Cerebral Cortex*, *31*(5), 2466–2481. https://doi.org/10.1093/cercor/bhaa367

Ewers, M., Luan, Y., Frontzkowski, L., Neitzel, J., Rubinski, A., Dichgans, M., Hassenstab, J., Gordon, B. A., Chhatwal, J. P., Levin, J., Schofield, P., Benzinger, T. L. S., Morris, J. C., Goate, A., Karch, C. M., Fagan, A. M., McDade, E., Allegri, R., Berman, S., … the Dominantly Inherited Alzheimer Network. (2021). Segregation of functional networks is associated with cognitive resilience in Alzheimer's disease. *Brain*, *144*(7), 2176–2185. https://doi.org/10.1093/brain/awab112

Ferreira, L. K., Regina, A. C., Kovacevic, N., Martin Mda, G., Santos, P. P., Carneiro Cde, G., Kerr, D. S., Amaro, E., Jr., McIntosh, A. R., & Busatto, G. F. (2016). Aging effects on whole-brain functional connectivity in adults free of cognitive and psychiatric disorders. *Cerebral Cortex*, *26*(9), 3851–3865. https://doi.org/10.1093/cercor/bhv190

Festini, S. B., Zahodne, L., & Reuter-Lorenz, P. A. (2018). Theoretical perspectives on age differences in brain activation: HAROLD, PASA, CRUNCH—How do they STAC up? In *Oxford Research Encyclopedia of Psychology*. Oxford. https://doi.org/10.1093/acrefore/9780190236557.013.400

Fields, R. D. (2005). Myelination: An overlooked mechanism of synaptic plasticity? *The Neuroscientist*, *11*(6), 528–531.

Fjell, A. M., Sneve, M. H., Grydeland, H., Storsve, A. B., Amlien, I. K., Yendiki, A., & Walhovd, K. B. (2017). Relationship between structural and functional connectivity change across the adult lifespan: A longitudinal investigation. *Human Brain Mapping*, *38*(1), 561–573. https://doi.org/10.1002/hbm.23403

Fjell, A. M., Sneve, M. H., Grydeland, H., Storsve, A. B., de Lange, A. G., Amlien, I. K., Rogeberg, O. J., & Walhovd, K. B. (2015). Functional connectivity change across multiple cortical networks relates to episodic memory changes in aging. *Neurobiology of Aging*, *36*(12), 3255–3268. https://doi.org/10.1016/j.neurobiolaging.2015.08.020

Fornito, A. (2016). Graph theoretic analysis of human brain networks. In M. Filippi (Ed.), *fMRI techniques and protocols* (pp. 283–314). Springer. https://doi.org/10.1007/978-1-4939-5611-1_10

Fornito, A., Zalesky, A., & Breakspear, M. (2013). Graph analysis of the human connectome: Promise, progress, and pitfalls. *NeuroImage*, *80*, 426–444. https://doi.org/10.1016/j.neuroimage.2013.04.087

Fox, M. D., Zhang, D., Snyder, A. Z., & Raichle, M. E. (2009). The global signal and observed anticorrelated resting state brain networks. *Journal of Neurophysiology*, *101*(6), 3270–3283. https://doi.org/10.1152/jn.90777.2008

Franke, K., Ziegler, G., Kloppel, S., Gaser, C., & Alzheimer's Disease Neuroimaging Initiative. (2010). Estimating the age of healthy subjects from T1-weighted MRI scans using kernel methods: Exploring the influence of various parameters. *NeuroImage*, *50*(3), 883–892. https://doi.org/10.1016/j.neuroimage.2010.01.005

Franzmeier, N., Hartmann, J., Taylor, A. N. W., Araque-Caballero, M. A., Simon-Vermot, L., Kambeitz-Ilankovic, L., Burger, K., Catak, C., Janowitz, D., Muller, C., Ertl-Wagner, B., Stahl, R., Dichgans, M., Duering, M., & Ewers, M. (2018). The left frontal cortex supports reserve in aging by enhancing functional network efficiency.

Alzheimer's Research & Therapy, *10*(1), 28. https://doi.org/10.1186/s13195-018-0358-y

Fukushima, M., Betzel, R. F., He, Y., van den Heuvel, M. P., Zuo, X. N., & Sporns, O. (2018). Structure-function relationships during segregated and integrated network states of human brain functional connectivity. *Brain Structure & Function*, *223*(3), 1091–1106. https://doi.org/10.1007/s00429-017-1539-3

Gaser, C., & Dahnke, R. (2016). CAT—A computational anatomy toolbox for the analysis of structural MRI data. *Human Brain Mapping*, *2016*, 336–348.

Gaviria, J., Rey, G., Bolton, T., Delgado, J., Van De Ville, D., & Vuilleumier, P. (2021). Brain functional connectivity dynamics at rest in the aftermath of affective and cognitive challenges. *Human Brain Mapping*, *42*(4), 1054–1069. https://doi.org/10.1002/hbm.25277

Geerligs, L., Renken, R. J., Saliasi, E., Maurits, N. M., & Lorist, M. M. (2015). A brain-wide study of age-related changes in functional connectivity. *Cerebral Cortex*, *25*(7), 1987–1999. https://doi.org/10.1093/cercor/bhu012

Goh, J. O. (2011). Functional dedifferentiation and altered connectivity in older adults: Neural accounts of cognitive aging. *Aging and Disease*, *2*(1), 30.

Grady, C., Sarraf, S., Saverino, C., & Campbell, K. (2016). Age differences in the functional interactions among the default, frontoparietal control, and dorsal attention networks. *Neurobiology of Aging*, *41*, 159–172. https://doi.org/10.1016/j.neurobiolaging.2016.02.020

Gunning-Dixon, F. M., Brickman, A. M., Cheng, J. C., & Alexopoulos, G. S. (2009). Aging of cerebral white matter: A review of MRI findings. *International Journal of Geriatric Psychiatry*, *24*(2), 109–117. https://doi.org/10.1002/gps.2087

Haenlein, M., & Kaplan, A. M. (2004). A beginner's guide to partial least squares analysis. *Understanding Statistics*, *3*(4), 283–297.

Han, C. E., Peraza, L. R., Taylor, J.-P., & Kaiser, M. (2014). Predicting age across human lifespan based on structural connectivity from diffusion tensor imaging. In *Proceedings of the 2014 IEEE Biomedical Circuits and Systems Conference (BioCAS)*.

He, L., Wang, X., Zhuang, K., & Qiu, J. (2020). Decreased dynamic segregation but increased dynamic integration of the resting-state functional networks during Normal aging. *Neuroscience*, *437*, 54–63. https://doi.org/10.1016/j.neuroscience.2020.04.030

Hedden, T., & Gabrieli, J. D. (2004). Insights into the ageing mind: A view from cognitive neuroscience. *Nature Reviews. Neuroscience*, *5*(2), 87–96. https://doi.org/10.1038/nrn1323

Hedden, T., Schultz, A. P., Rieckmann, A., Mormino, E. C., Johnson, K. A., Sperling, R. A., & Buckner, R. L. (2016). Multiple brain markers are linked to age-related variation in cognition. *Cerebral Cortex*, *26*(4), 1388–1400. https://doi.org/10.1093/cercor/bhu238

Hirsiger, S., Koppelmans, V., Merillat, S., Liem, F., Erdeniz, B., Seidler, R. D., & Jancke, L. (2016). Structural and functional connectivity in healthy aging: Associations for cognition and motor behavior. *Human Brain Mapping*, *37*(3), 855–867. https://doi.org/10.1002/hbm.23067

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). Fsl. *NeuroImage*, *62*(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Jeurissen, B., Tournier, J. D., Dhollander, T., Connelly, A., & Sijbers, J. (2014). Multi-tissue constrained spherical deconvolution for improved analysis of multi-shell diffusion MRI data. *NeuroImage*, *103*, 411–426. https://doi.org/10.1016/j.neuroimage.2014.07.061

Jockwitz, C., & Caspers, S. (2021). Resting-state networks in the course of aging-differential insights from studies across the lifespan vs. amongst the old. *Pflügers Archiv*, *473*, 793–803. https://doi.org/10.1007/s00424-021-02520-7

Jockwitz, C., Caspers, S., Lux, S., Eickhoff, S. B., Jutten, K., Lenzen, S., Moebus, S., Pundt, N., Reid, A., Hoffstaedter, F., Jockel, K. H., Erbel, R., Cichon, S., Nothen, M. M., Shah, N. J., Zilles, K., & Amunts, K. (2017). Influence of age and cognitive performance on resting-state brain networks of older adults in a population-based cohort. *Cortex*, *89*, 28–44. https://doi.org/10.1016/j.cortex.2017.01.008

Kalbe, E., Kessler, J., Calabrese, P., Smith, R., Passmore, A. P., Brand, M., & Bullock, R. (2004). DemTect: A new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. *International Journal of Geriatric Psychiatry*, *19*(2), 136–143. https://doi.org/10.1002/gps.1042

Keller, J. B., Hedden, T., Thompson, T. W., Anteraper, S. A., Gabrieli, J. D., & Whitfield-Gabrieli, S. (2015). Resting-state anticorrelations between medial and lateral prefrontal cortex: Association with working memory, aging, and individual differences. *Cortex*, *64*, 271–280. https://doi.org/10.1016/j.cortex.2014.12.001

Krishnan, A., Williams, L. J., McIntosh, A. R., & Abdi, H. (2011). Partial least squares (PLS) methods for neuroimaging: A tutorial and review. *NeuroImage*, *56*(2), 455–475. https://doi.org/10.1016/j.neuroimage.2010.07.034

Lavanga, M., Stumme, J., Yalcinkaya, B. H., Fousek, J., Jockwitz, C., Sheheitli, H., Bittner, N., Hashemi, M., Petkoski, S., Caspers, S., & Jirsa, V. (2022). The virtual aging brain: A model-driven explanation for cognitive decline in older subjects. *bioRxiv (preprint)*. https://doi.org/10.1101/2022.02.17.480902

Lee, H., Golkowski, D., Jordan, D., Berger, S., Ilg, R., Lee, J., Mashour, G. A., Lee, U., & Re, C. S. G. (2019). Relationship of critical dynamics, functional connectivity, and states of consciousness in large-scale human brain networks. *NeuroImage*, *188*, 228–238. https://doi.org/10.1016/j.neuroimage.2018.12.011

Li, H., Satterthwaite, T. D., & Fan, Y. (2018). Brain age prediction based on resting-state functional connectivity patterns using convolutional neural networks. In *Proceedings of the 2018 IEEE 15th International Symposium on Biomedical Imaging (ISBI 2018)*.

Li, X., Wang, Y., Wang, W., Huang, W., Chen, K., Xu, K., Zhang, J., Chen, Y., Li, H., Wei, D., Shu, N., & Zhang, Z. (2020). Age-related decline in the topological efficiency of the brain structural connectome and cognitive aging. *Cerebral Cortex*, *30*(8), 4651–4661. https://doi.org/10.1093/cercor/bhaa066

Liem, F., Varoquaux, G., Kynast, J., Beyer, F., Kharabian Masouleh, S., Huntenburg, J. M., Lampe, L., Rahim, M., Abraham, A., Craddock, R. C., Riedel-Heller, S., Luck, T., Loeffler, M., Schroeter, M. L., Witte, A. V., Villringer, A., & Margulies, D. S. (2017). Predicting brain-age from multimodal imaging data captures cognitive impairment. *NeuroImage*, *148*, 179–188. https://doi.org/10.1016/j.neuroimage.2016.11.005

Lou, W., Wang, D., Wong, A., Chu, W. C. W., Mok, V. C. T., & Shi, L. (2019). Frequency-specific age-related decreased brain network diversity in cognitively healthy elderly: A whole-brain data-driven analysis. *Human Brain Mapping*, *40*(1), 340–351. https://doi.org/10.1002/hbm.24376

Lynn, C. W., & Bassett, D. S. (2019). The physics of brain network structure, function and control. *Nature Reviews Physics*, *1*(5), 318–332. https://doi.org/10.1038/s42254-019-0040-8

MacDonald, M. E., & Pike, G. B. (2021). MRI of healthy brain aging: A review. *NMR in Biomedicine*, *34*(9), e4564. https://doi.org/10.1002/nbm.4564

Marques, P., Moreira, P., Magalhaes, R., Costa, P., Santos, N., Zihl, J., Soares, J., & Sousa, N. (2016). The functional connectome of cognitive reserve. *Human Brain Mapping*, *37*(9), 3310–3322. https://doi.org/10.1002/hbm.23242

Marstaller, L., Williams, M., Rich, A., Savage, G., & Burianova, H. (2015). Aging and large-scale functional networks: White matter integrity, gray matter volume, and functional connectivity in the resting state. *Neuroscience*, *290*, 369–378. https://doi.org/10.1016/j.neuroscience.2015.01.049

McIntosh, A. R., & Lobaugh, N. J. (2004). Partial least squares analysis of neuroimaging data: Applications and advances. *NeuroImage*, *23*(Suppl 1), S250–S263. https://doi.org/10.1016/j.neuroimage.2004.07.020

Mevik, B.-H., & Wehrens, R. (2015). *Introduction to the pls package. Help section of the "Pls" package of R studio software* (pp. 1–23). R Foundation for Statistical Computing.

Mevik, B.-H., Wehrens, R., Liland, K. H., & Hiemstra, P. (2018). Package 'pls'. In (Version 2.7-0) [Computer Software]. Retrieved from https://github.com/bhmevik/pls.

Monteiro, T. S., King, B. R., Zivari Adab, H., Mantini, D., & Swinnen, S. P. (2019). Age-related differences in network flexibility and segregation at rest and during motor performance. *NeuroImage*, *194*, 93–104. https://doi.org/10.1016/j.neuroimage.2019.03.015

Mowinckel, A. M., Espeseth, T., & Westlye, L. T. (2012). Network-specific effects of age and in-scanner subject motion: A resting-state fMRI study of 238 healthy adults. *NeuroImage*, *63*(3), 1364–1373. https://doi.org/10.1016/j.neuroimage.2012.08.004

Murphy, K., Birn, R. M., Handwerker, D. A., Jones, T. B., & Bandettini, P. A. (2009). The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced? *NeuroImage*, *44*(3), 893–905. https://doi.org/10.1016/j.neuroimage.2008.09.036

Murphy, K., & Fox, M. D. (2017). Towards a consensus regarding global signal regression for resting state functional connectivity MRI. *NeuroImage*, *154*, 169–173. https://doi.org/10.1016/j.neuroimage.2016.11.052

Naik, S., Banerjee, A., Bapi, R. S., Deco, G., & Roy, D. (2017). Metastability in senescence. *Trends in Cognitive Sciences*, *21*(7), 509–521.

Nashiro, K., Sakaki, M., Braskie, M. N., & Mather, M. (2017). Resting-state networks associated with cognitive processing show more age-related decline than those associated with emotional processing. *Neurobiology of Aging*, *54*, 152–162. https://doi.org/10.1016/j.neurobiolaging.2017.03.003

Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., & Smith, M. R. (2004). Aging reduces neural specialization in ventral visual cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(35), 13091–13095. https://doi.org/10.1073/pnas.0405148101

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: Aging and neurocognitive scaffolding. *Annual Review of Psychology*, *60*, 173–196. https://doi.org/10.1146/annurev.psych.59.103006.093656

Parkes, L., Fulcher, B., Yucel, M., & Fornito, A. (2018). An evaluation of the efficacy, reliability, and sensitivity of motion correction strategies for resting-state functional MRI. *NeuroImage*, *171*, 415–436. https://doi.org/10.1016/j.neuroimage.2017.12.073

Perry, A., Wen, W., Kochan, N. A., Thalamuthu, A., Sachdev, P. S., & Breakspear, M. (2017). The independent influences of age and education on functional brain networks and cognition in healthy older adults. *Human Brain Mapping*, *38*(10), 5094–5114. https://doi.org/10.1002/hbm.23717

Pistono, A., Guerrier, L., Péran, P., Rafiq, M., Giméno, M., Bézy, C., Pariente, J., & Jucla, M. (2021). Increased functional connectivity supports language performance in healthy aging despite gray matter loss. *Neurobiology of Aging*, *98*, 52–62.

Pruim, R. H. R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J. K., & Beckmann, C. F. (2015). ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. *NeuroImage*, *112*, 267–277. https://doi.org/10.1016/j.neuroimage.2015.02.064

Puxeddu, M. G., Faskowitz, J., Betzel, R. F., Petti, M., Astolfi, L., & Sporns, O. (2020). The modular organization of brain cortical connectivity across the human lifespan. *NeuroImage*, *218*, 116974. https://doi.org/10.1016/j.neuroimage.2020.116974

Qi, S., Meesters, S., Nicolay, K., ter Haar Romeny, B. M., & Ossenblok, P. (2015). The influence of construction methodology on structural brain network measures: A review. *Journal of Neuroscience Methods*, *253*, 170–182.

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Current Directions in Psychological Science*, *17*(3), 177–182.

Reuter-Lorenz, P. A., & Park, D. C. (2014). How does it STAC up? Revisiting the scaffolding theory of aging and cognition. *Neuropsychology Review*, *24*(3), 355–370. https://doi.org/10.1007/s11065-014-9270-9

Rojkova, K., Volle, E., Urbanski, M., Humbert, F., Dell'Acqua, F., & Thiebaut de Schotten, M. (2016). Atlasing the frontal lobe connections and their variability due to age and education: A spherical deconvolution tractography study. *Brain Structure & Function*, *221*(3), 1751–1766. https://doi.org/10.1007/s00429-015-1001-3

Sadaghiani, S., Poline, J. B., Kleinschmidt, A., & D'Esposito, M. (2015). Ongoing dynamics in large-scale functional connectivity predict perception. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(27), 8463–8468. https://doi.org/10.1073/pnas.1420687112

Salat, D. H. (2011). The declining infrastructure of the aging brain. *Brain Connectivity*, *1*(4), 279–293. https://doi.org/10.1089/brain.2011.0056

Salat, D. H., Tuch, D. S., Greve, D. N., van der Kouwe, A. J., Hevelone, N. D., Zaleta, A. K., Rosen, B. R., Fischl, B., Corkin, S., Rosas, H. D., & Dale, A. M. (2005). Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiology of Aging*, *26*(8), 1215–1227. https://doi.org/10.1016/j.neurobiolaging.2004.09.017

Salthouse, T. A. (2019). Trajectories of normal cognitive aging. *Psychology and Aging*, *34*(1), 17–24. https://doi.org/10.1037/pag0000288

Schaefer, A., Kong, R., Gordon, E. M., Laumann, T. O., Zuo, X. N., Holmes, A. J., Eickhoff, S. B., & Yeo, B. T. T. (2018). Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. *Cerebral Cortex*, *28*(9), 3095–3114. https://doi.org/10.1093/cercor/bhx179

Schmermund, A., Mohlenkamp, S., Stang, A., Gronemeyer, D., Seibel, R., Hirche, H., Mann, K., Siffert, W., Lauterbach, K., Siegrist, J., Jockel, K. H., & Erbel, R. (2002). Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: Rationale and design of the Heinz Nixdorf RECALL study. Risk factors, evaluation of coronary calcium and lifestyle. *American Heart Journal*, *144*(2), 212–218. https://doi.org/10.1067/mhj.2002.123579

Siman-Tov, T., Bosak, N., Sprecher, E., Paz, R., Eran, A., Aharon-Peretz, J., & Kahn, I. (2016). Early age-related functional connectivity decline in high-order cognitive networks. *Frontiers in Aging Neuroscience*, *8*, 330. https://doi.org/10.3389/fnagi.2016.00330

Smith, R. E., Tournier, J. D., Calamante, F., & Connelly, A. (2015). SIFT2: Enabling dense quantitative assessment of brain white matter connectivity using streamlines tractography. *NeuroImage*, *119*, 338–351. https://doi.org/10.1016/j.neuroimage.2015.06.092

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., Filippini, N., Watkins, K. E., Toro, R., Laird, A. R., & Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(31), 13040–13045. https://doi.org/10.1073/pnas.0905267106

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*(Suppl 1), S208–S219. https://doi.org/10.1016/j.neuroimage.2004.07.051

Smith, S. M., Vidaurre, D., Alfaro-Almagro, F., Nichols, T. E., & Miller, K. L. (2019). Estimation of brain age delta from brain imaging. *NeuroImage*, *200*, 528–539. https://doi.org/10.1016/j.neuroimage.2019.06.017

Sotiropoulos, S. N., & Zalesky, A. (2019). Building connectomes using diffusion MRI: Why, how and but. *NMR in Biomedicine*, *32*(4), e3752. https://doi.org/10.1002/nbm.3752

Sporns, O. (2013). Network attributes for segregation and integration in the human brain. *Current Opinion in Neurobiology*, *23*(2), 162–171. https://doi.org/10.1016/j.conb.2012.11.015

Spreng, R. N., Stevens, W. D., Viviano, J. D., & Schacter, D. L. (2016). Attenuated anticorrelation between the default and dorsal attention networks with aging: Evidence from task and rest. *Neurobiology of Aging*, *45*, 149–160. https://doi.org/10.1016/j.neurobiolaging.2016.05.020

Spreng, R. N., & Turner, G. R. (2019). The shifting architecture of cognition and brain function in older adulthood. *Perspectives on Psychological Science*, *14*(4), 523–542.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, *8*(3), 448–460.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*(10), 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004

Straathof, M., Sinke, M. R., Dijkhuizen, R. M., & Otte, W. M. (2019). A systematic review on the quantitative relationship between structural and functional network connectivity strength in mammalian brains. *Journal of Cerebral Blood Flow and Metabolism*, *39*(2), 189–209. https://doi.org/10.1177/0271678X18809547

Stumme, J., Jockwitz, C., Hoffstaedter, F., Amunts, K., & Caspers, S. (2020). Functional network reorganization in older adults: Graph-theoretical analyses of age, cognition and sex. *NeuroImage*, *214*, 116756. https://doi.org/10.1016/j.neuroimage.2020.116756

Tabachnick, B. G., Fidell, L. S., & Ullman, J. B. (2007). *Using multivariate statistics* (Vol. 5). Pearson.

Tomasi, D., Wang, G. J., & Volkow, N. D. (2013). Energetic cost of brain functional connectivity. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(33), 13642–13647. https://doi.org/10.1073/pnas.1303346110

Tournier, J. D., Calamante, F., & Connelly, A. (2012). MRtrix: Diffusion tractography in crossing fiber regions. *International Journal of Imaging Systems and Technology*, *22*(1), 53–66. https://doi.org/10.1002/ima.22005

Tsang, A., Lebel, C. A., Bray, S. L., Goodyear, B. G., Hafeez, M., Sotero, R. C., McCreary, C. R., & Frayne, R. (2017). White matter structural connectivity is not correlated to cortical resting-state functional connectivity over the healthy adult lifespan. *Frontiers in Aging Neuroscience*, *9*, 144. https://doi.org/10.3389/fnagi.2017.00144

Tsvetanov, K. A., Henson, R. N., Tyler, L. K., Razi, A., Geerligs, L., Ham, T. E., Rowe, J. B., & Cambridge Centre for Ageing and Neuroscience. (2016). Extrinsic and intrinsic brain network connectivity maintains cognition across the lifespan despite accelerated decay of regional brain activation. *The Journal of Neuroscience*, *36*(11), 3115–3126. https://doi.org/10.1523/JNEUROSCI.2733-15.2016

Varangis, E., Habeck, C. G., Razlighi, Q. R., & Stern, Y. (2019). The effect of aging on resting state connectivity of predefined networks in the brain. *Frontiers in Aging Neuroscience*, *11*, 234. https://doi.org/10.3389/fnagi.2019.00234

Varikuti, D. P., Genon, S., Sotiras, A., Schwender, H., Hoffstaedter, F., Patil, K. R., Jockwitz, C., Caspers, S., Moebus, S., Amunts, K., Davatzikos, C., & Eickhoff, S. B. (2018). Evaluation of non-negative matrix factorization of grey matter in age prediction. *NeuroImage*, *173*, 394–410. https://doi.org/10.1016/j.neuroimage.2018.03.007

Vergun, S., Deshpande, A. S., Meier, T. B., Song, J., Tudorascu, D. L., Nair, V. A., Singh, V., Biswal, B. B., Meyerand, M. E., Birn, R. M., & Prabhakaran, V. (2013). Characterizing functional connectivity differences in aging adults using machine learning on resting state fMRI data. *Frontiers in Computational Neuroscience*, *7*, 38. https://doi.org/10.3389/fncom.2013.00038

Wells, W. M., Viola, P., Atsumi, H., Nakajima, S., & Kikinis, R. (1996). Multi-modal volume registration by maximization of mutual information. *Medical Image Analysis*, *1*(1), 35–51. https://doi.org/10.1016/s1361-8415(01)80004-9

Westlye, L. T., Walhovd, K. B., Dale, A. M., Bjornerud, A., Due-Tonnessen, P., Engvig, A., Grydeland, H., Tamnes, C. K., Ostby, Y., & Fjell, A. M. (2010). Life-span changes of the human brain white matter: Diffusion tensor imaging (DTI) and volumetry. *Cerebral Cortex*, *20*(9), 2055–2068. https://doi.org/10.1093/cercor/bhp280

Whalley, L. J., Deary, I. J., Appleton, C. L., & Starr, J. M. (2004). Cognitive reserve and the neurobiology of cognitive aging. *Ageing Research Reviews*, *3*(4), 369–382. https://doi.org/10.1016/j.arr.2004.05.001

Wig, G. S. (2017). Segregated Systems of Human Brain Networks. *Trends in Cognitive Sciences*, *21*(12), 981–996. https://doi.org/10.1016/j.tics.2017.09.006

Xia, Y., Chen, Q., Shi, L., Li, M., Gong, W., Chen, H., & Qiu, J. (2019). Tracking the dynamic functional connectivity structure of the human brain across the adult lifespan. *Human Brain Mapping*, *40*(3), 717–728. https://doi.org/10.1002/hbm.24385

Yeatman, J. D., Wandell, B. A., & Mezer, A. A. (2014). Lifespan maturation and degeneration of human brain white matter. *Nature Communications*, *5*, 4932. https://doi.org/10.1038/ncomms5932

Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zollei, L., Polimeni, J. R., Fischl, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125–1165. https://doi.org/10.1152/jn.00338.2011

Yoo, K., Rosenberg, M. D., Hsu, W. T., Zhang, S., Li, C. R., Scheinost, D., Constable, R. T., & Chun, M. M. (2018). Connectome-based predictive modeling of attention: Comparing different functional connectivity features and prediction methods across datasets. *NeuroImage*, *167*, 11–22. https://doi.org/10.1016/j.neuroimage.2017.11.010

Zalesky, A., Fornito, A., & Bullmore, E. (2012). On the use of correlation as a measure of network connectivity. *NeuroImage*, *60*(4), 2096–2106. https://doi.org/10.1016/j.neuroimage.2012.02.001

Zhao, T., Cao, M., Niu, H., Zuo, X. N., Evans, A., He, Y., Dong, Q., & Shu, N. (2015). Age-related changes in the topological organization of the white matter structural connectome across the human lifespan. *Human Brain Mapping*, *36*(10), 3777–3792. https://doi.org/10.1002/hbm.22877

Zimmermann, J., Ritter, P., Shen, K., Rothmeier, S., Schirner, M., & McIntosh, A. R. (2016). Structural architecture supports functional organization in the human aging brain at a regionwise and network level. *Human Brain Mapping*, *37*(7), 2645–2661. https://doi.org/10.1002/hbm.23200

Zonneveld, H. I., Pruim, R. H., Bos, D., Vrooman, H. A., Muetzel, R. L., Hofman, A., Rombouts, S. A., van der Lugt, A., Niessen, W. J., Ikram, M. A., & Vernooij, M. W. (2019). Patterns of functional connectivity in an aging population: The Rotterdam study. *NeuroImage*, *189*, 432–444. https://doi.org/10.1016/j.neuroimage.2019.01.041

Zuo, X. N., He, Y., Betzel, R. F., Colcombe, S., Sporns, O., & Milham, M. P. (2017). Human Connectomics across the life span. *Trends in Cognitive Sciences*, *21*(1), 32–45. https://doi.org/10.1016/j.tics.2016.10.005

SUPPORTING INFORMATION

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4 Study 3

Prediction of cognitive performance differences in older age from multimodal neuroimaging data

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ORIGINAL ARTICLE

Prediction of cognitive performance differences in older age from multimodal neuroimaging data

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Abstract Differences in brain structure and functional and structural network architecture have been found to partly explain cognitive performance differences in older ages. Thus, they may serve as potential markers for these differences. Initial unimodal studies, however, have reported mixed prediction results of selective cognitive variables based on these brain features using machine learning (ML). Thus, the aim of the current study was to investigate the general validity of cognitive performance prediction from imaging data in healthy older adults. In particular, the focus was with examining whether (1) multimodal information, i.e., region-wise grey matter volume (GMV), resting-state functional connectivity (RSFC), and structural connectivity (SC) estimates, may improve predictability of cognitive targets, (2) predictability differences arise for global cognition and distinct cognitive profiles, and (3) results generalize across different ML approaches in 594 healthy older adults (age range: 55–85 years) from the 1000BRAINS study. Prediction potential was examined for each modality and all multimodal combinations, with and without confound (i.e., age, education, and sex) regression across different analytic options,

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i.e., variations in algorithms, feature sets, and multimodal approaches (i.e., concatenation vs. stacking). Results showed that prediction performance differed considerably between deconfounding strategies. In the absence of demographic confounder control, successful prediction of cognitive performance could be observed across analytic choices. Combination of different modalities tended to marginally improve predictability of cognitive performance compared to single modalities. Importantly, all previously described effects vanished in the strict confounder control condition. Despite a small trend for a multimodal benefit, developing a biomarker for cognitive aging remains challenging.

Keywords Cognition · Aging · Machine learning · Multimodal analyses · Graph theoretical approaches

Introduction

The aging population experiences declines in many cognitive functions, e.g., memory and executive functions [1, 2]. In groups of healthy older adults, age-related cognitive decline has been partly explained by alterations in network architecture, structural (SC) and resting-state functional connectivity (RSFC) of major resting-state networks (RSNs), and grey matter (GM) atrophy [1, 3–13]. However, despite robust findings at the group level, cognitive performance has been found to vary greatly at the individual level [1, 14], particularly in the older ages. In light of the increasing aging population and high relevance of cognitive health for the quality of life of healthy older adults, research has turned to searching for a neuroimaging marker for individual cognitive ability in aging [11, 15–20].

Machine learning (ML) approaches may be particularly appropriate to search for an imaging marker for age-related cognitive decline. This is due to the fact that they may provide information at the individual level and may find patterns in high-dimensional data that might be difficult to capture with univariate methods [21]. Initial ML approaches investigating either resting-state functional connectivity (RSFC), structural connectivity, or grey matter volume (GMV), revealed mixed prediction performance of cognitive measures [15, 18, 19, 22–27]. For instance, by investigating SC, i.e., nodal global and local efficiency, Li et al. could successfully predict attention and executive function in a large sample of healthy older adults ($N = 633$, age range: 45–86 years) [25]. In turn, regional GMV was found to predict fluid reasoning abilities across the adult population ($N = 335$, age range: 20–80 years) in a study by Tsapanou et al. [26], while Hilger et al. revealed decidedly error-prone prediction of intelligence in a large sample of healthy adults ($N = 308$, age range: 18–60 years) [27]. Moreover, recent results from our group emphasize low classifiability and predictability of RSFC strength measures for both, global and domain-specific cognitive abilities, in a large sample of older adults (age range: 55–85 years) [24]. Thus, these partially promising results seem to be rather circumscribed to specific settings, as previous studies all differ in, e.g., their study characteristics, input modalities, and cognitive target variables. To make more general predictions of cognition based on imaging data, however, it may become necessary to directly compare prediction performance across different cognitive variables and input modalities within one sample and the same ML framework.

Furthermore, most previous studies have focused on a single modality in the prediction of cognitive ability in healthy older adults neglecting that brain-behavior relationships arise through the complex interplay between different organizational levels of the brain and its network architecture. Research on neurodegenerative diseases has recently started to integrate information across different modalities in diagnostic classification studies revealing a benefit for multimodal approaches in terms of ML performance [28–30]. For instance, a combination of functionally and structurally derived graph metrics, which may allow to specifically characterize the network architecture of the brain, led to better classification performance in distinguishing patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) from healthy controls (HC) [29, 30]. Results from combining multimodal data in healthy older adults and across the lifespan in the prediction of cognitive targets also appear promising [31–33]. For example, Xiao et al. have shown that multimodal imaging models, i.e., amplitude of low-frequency fluctuations (ALFF), fractional anisotropy (FA), and GMV, performed mostly better than unimodal ones in the prediction of visual working memory in a large sample across the lifespan (age range: 18–88 years) [33].

Furthermore, Dadi et al. have demonstrated that fluid intelligence could be predicted from brain volumetric measures, RSFC, and diffusion-derived parameters in a large sample of older adults from the UK Biobank (age range: 40–70 years) [31]. Nevertheless, it remains elusive, if combining information from a functional and structural network perspective, which has already been successfully employed in patient samples, combined with morphologic brain data, i.e., region-wise GMV, may lead to equally promising prediction results especially in higher older ages.

Finally, switching to a methodological perspective, prior studies have shown that prediction accuracies may be affected by the use of different algorithms, feature set sizes, feature selection steps, and deconfounding strategies [34–38]. There is currently no agreement on a standard ML pipeline using neuroimaging data [39] and given the high variability in ML approaches used throughout the field, it may become difficult to compare and discern informational value of each modality for prediction. It, thus, appears warranted to systematically evaluate different analytical choices and their impact on prediction performance.

The current study, hence, aimed at examining the general validity of the prediction of cognitive performance from imaging data in healthy older adults. Particularly, it was directed at investigating whether (1) combining information from a network perspective, i.e., RSFC and SC estimates, with morphological brain data, i.e., region-wise GMV, may lead to better predictability of different cognitive targets than unimodal models, (2) differences emerge in the prediction of global cognition and distinct cognitive profiles, and (3) results generalize across different ML pipeline configurations and approaches, i.e., different modality combinations, algorithms, feature sets, deconfounding analyses, and multimodal approaches, in a large sample of healthy older adults from the 1000BRAINS study.

Methods

Participants

Data for the current analyses was derived from the 1000BRAINS study [40], which aims at investigating age-related variability in brain structure and function in light of environmental, behavioural and genetic factors in an epidemiologic population-based design. The 10-year follow-up cohort of the Heinz Nixdorf Recall Study and the MultiGeneration Study was used to define the 1000BRAINS sample [41]. A total of 966 participants of the whole sample met the age criteria of the current study (age range: 55–85 years). Missing resting-state functional magnetic resonance imaging (fMRI), structural magnetic resonance imaging (sMRI), or diffusion-weighted imaging (DWI) data or failed preprocessing of functional and structural imaging data led to the exclusion of 248 participants from the initial sample. In a next step, 95 participants were excluded as preprocessed data did not meet quality standards described in more detail below. Further, 27 participants with missing values on the dementia screening test DemTect or scoring ≤ 8 were excluded in light of potential cognitive impairment [42]. More than three missing values in the neuropsychological assessment led to the exclusion of additional 2 participants. A final sample of 594 participants (296 females, $M_{age} = 66.88$ years, $SD_{age} = 6.67$, see Table 1) was used for further analyses. The study protocol of 1000BRAINS was approved by the Ethics Committee of the University of Essen, Germany, and all subjects provided written consent prior to inclusion.

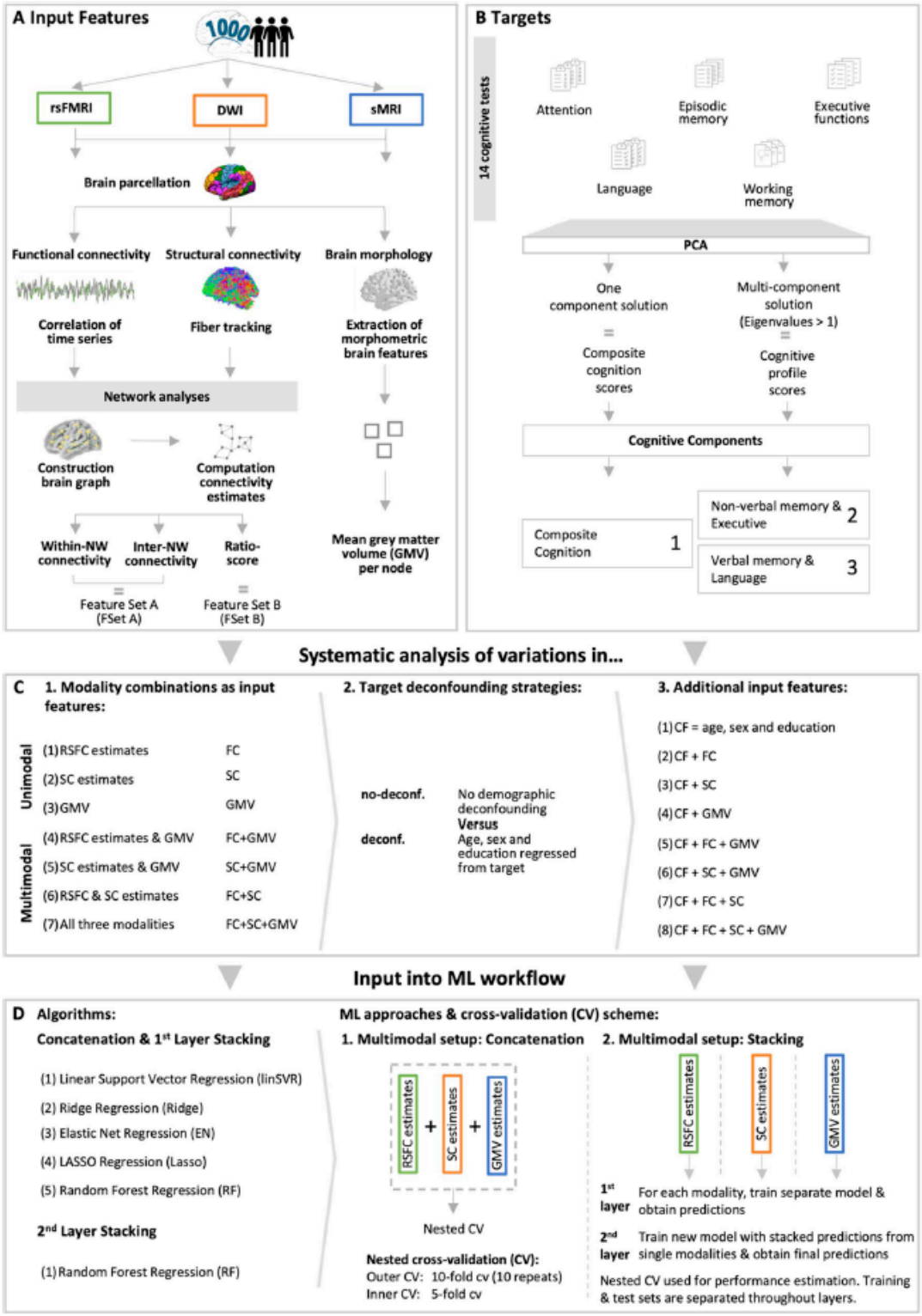
Functional and structural brain data

Functional and structural imaging data was acquired on a 3T Siemens Tim-TRIO MR scanner with a 32-channel head coil. A 3D high-resolution T1-weighted magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence was obtained for subsequent surface reconstruction and brain structural analyses (176 slices, slice thickness = 1 mm, TR = 2250 ms, TE = 3.03 ms, FoV = 256 × 256 mm^2,

Table 1 Demographic information of sample regarding age, educational level and risk of dementia

	N	Age (in years)	Education (measured by ISCED)	DemTect score
Female	296	66.26 (6.44)	5.99 (1.83)	15.55 (2.25)
Male	298	67.50 (6.84)	7.03 (1.91)	14.41 (2.34)
Total	594	66.88 (6.67)	6.51 (1.94)	14.98 (2.36)

Mean displayed with standard deviation (SD) appearing in parentheses


A Input Features
1000
rsFMRI
DWI
sMRI
Brain parcellation
Functional connectivity
Structural connectivity
Brain morphology
Correlation of time series
Fiber tracking
Extraction of morphometric brain features
Network analyses
Construction brain graph
Computation connectivity estimates
Within-NW connectivity
Inter-NW connectivity
Ratio-score
Mean grey matter volume (GMV) per node
Feature Set A (FSet A)
Feature Set B (FSet B)
B Targets
14 cognitive tests
Attention
Episodic memory
Executive functions
Language
Working memory
PCA
One component solution
Multi-component solution (Eigenvalues > 1)
Composite cognition scores
Cognitive profile scores
Cognitive Components
Composite Cognition 1
Non-verbal memory & Executive 2
Verbal memory & Language 3
Systematic analysis of variations in...
C
1. Modality combinations as input features:
Unimodal
(1) RSFC estimates FC
(2) SC estimates SC
(3) GMV GMV
Multimodal
(4) RSFC estimates & GMV FC+GMV
(5) SC estimates & GMV SC+GMV
(6) RSFC & SC estimates FC+SC
(7) All three modalities FC+SC+GMV
2. Target deconfounding strategies:
no-deconf. No demographic deconfounding
Versus
deconf. Age, sex and education regressed from target
3. Additional input features:
(1) CF = age, sex and education
(2) CF + FC
(3) CF + SC
(4) CF + GMV
(5) CF + FC + GMV
(6) CF + SC + GMV
(7) CF + FC + SC
(8) CF + FC + SC + GMV
Input into ML workflow
D Algorithms:
Concatenation & 1st Layer Stacking
(1) Linear Support Vector Regression (linSVR)
(2) Ridge Regression (Ridge)
(3) Elastic Net Regression (EN)
(4) LASSO Regression (Lasso)
(5) Random Forest Regression (RF)
2nd Layer Stacking
(1) Random Forest Regression (RF)
ML approaches & cross-validation (CV) scheme:
1. Multimodal setup: Concatenation
RSFC estimates + SC estimates + GMV estimates
Nested CV
Nested cross-validation (CV):
Outer CV: 10-fold cv (10 repeats)
Inner CV: 5-fold cv
2. Multimodal setup: Stacking
RSFC estimates
SC estimates
GMV estimates
1st layer For each modality, train separate model & obtain predictions
2nd layer Train new model with stacked predictions from single modalities & obtain final predictions
Nested CV used for performance estimation. Training & test sets are separated throughout layers.

◂**Fig. 1** Schematic overview of workflow

flip angle = 9°, voxel resolution = 1 × 1 × 1 mm^3). Resting-state fMRI was acquired for about 11 min resulting in 300 EPI (gradient-echo planar imaging) volumes (slices = 36, slice thickness = 3.1 mm, TR = 2200 ms, TE = 30 ms, FoV = 200 × 200 mm^2, voxel resolution = 3.1 × 3.1 × 3.1 mm^3). During the resting-state scan, participants were asked to keep their eyes closed, to relax and let their mind wander, but not to fall asleep. A post-scan debriefing was used as a check. Additionally, high-angular resolution diffusion imaging (HARDI) data was obtained using the following parameters: (i) 60 direction subset; EPI, TR = 6300 ms, TE = 81 ms, 7 b0-images (interleaved), 60 images with b = 1000 s/mm^2, voxel resolution = 2.4 × 2.4 × 2.4 mm^3; (ii) 120 direction subset; EPI, TR = 8000 ms, TE = 112 ms, 13 b0-images (interleaved), 120 images with b = 2700 s/mm^2, voxel resolution = 2.4 × 2.4 × 2.4mm^3.

Image preprocessing

The T1-weighted 3D anatomical images were preprocessed using the "recon-all" automated cortical reconstruction pipeline of the FreeSurfer 7.1.0 Software package [43] as described under http://surfer.nmr.mgh.harvard.edu. The original pipeline includes a range of brain parcellations derived from cortical surface models constructed from manually or automated labelled training sets. We adapted the original pipeline to also include the 400-node Schaefer parcellation, which is based on cortical surface models calculated from rsfMRI measurements of 1489 participants using a gradient weighted Markov random field approach [44]. First, the parcellation was transformed to individual subject space using FreeSurfer's mris_ca_label tool. Then, morphology values were gathered for every transformed node using FreeSurfer's mris_anatomical_stats tool. Afterwards measures, such as surface area, grey matter volume (GMV), and cortical thickness of every node for the left and right brain hemisphere, were summarized in separate tables using FreeSurfer's aparcstats2table utility. The GMV values for each node (= 400) were used as features in the ML pipeline (see Fig. 1: Features). To ensure data quality, mean GMV values were calculated and participants with values greater than 1.5 times the inter-quartile range were excluded from further analyses.

Functional and diffusion tensor images were preprocessed according to an established pipeline by [12]. For all functional images, this included (1) deletion of the first four EPI volumes, (2) head movement correction using a two-pass procedure, (2) application of ICA-based Automatic Removal of Motion Artifacts (ICA-AROMA) [45] combined with global signal regression, (3) application of a band-pass filter (0.01–0.1 Hz), and (4) registration to MNI152 template using a unified segmentation approach [46]. An additional quality check for the preprocessing of functional images was carried out according to [12], which included (1) checking for potential misalignments in the mean functional AROMA data with the check sample homogeneity option in the Computational Anatomy Toolbox (CAT12) [47] (participants identified as outliers with > 2 SD away from the mean excluded) and (2) checking for volume-wise severe intensity dropouts (DVARS) in the preprocessed data using an algorithm by [48] (participants with more than 10% of the 300 volumes detected as dropouts excluded).

Diffusion image processing involved (1) calculation of tissue probability maps (TPM) for grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) from T1 data using CAT12 toolbox [47], (2) extraction of brain from T1 data by using brain masks created by superimposing the three probability maps, (3) bias field correction of T1 data, rigid alignment to the MNI152 template and resampling to 1.25 mm isotropic voxel size, (4) correction of dMRI data for eddy currents and motion artefacts, (5) visual quality control to remove remaining noisy data, (6) alignment of dMRI data to individual T1 space, (7) computation of anisotropic power maps (APMs) from b2700 dMRI data for image registration, (8) transformation of TPMs to diffusion space via APMs, (9) merging of the two dMRI datasets (b1000 & b2700) into one, (10) computation of the constrained spherical deconvolution (CSD) model using multi-tissue CSD with multi-shell data [49], and (11) application of probabilistic streamline tractography and computation of 10 million streamlines with dynamic seeding at the grey-white matter interface using the iFOD2 algorithm (max. length = 250 mm; cut-off value = 0.06).

Functional and structural connectivity analyses

For connectivity analyses, the same protocol as in [12] was followed. The brain was parcellated into 400 cortical parcels according to [44], which were assigned to seven known resting-state networks (visual, sensorimotor, limbic, frontoparietal, default mode, dorsal, and ventral attention network) [50]. Each parcel served as nodes in the subsequent graph-theoretical analysis.

For both functional and structural connectivity, a 400 × 400 adjacency matrix for each participant was obtained. For functional data, each matrix entry reflected the Pearson's correlation of the average time series of two nodes. As an additional step, a statistical significant test of each correlation coefficient was performed making use of the Fourier transform and permutation testing (1000 repeats) to reduce the amount of spurious correlations [11, 12, 51]. Non-significant edges at $p \geq 0.05$ were set to zero. Afterwards, a Fisher's r-to-z-transformation was used to transform the 400 × 400 adjacency matrix. In subsequent analyses only positive correlations were considered and no further thresholding in terms of network size and network density was applied to the brain graph. Thus, a positively weighted network was used for the computation of connectivity estimates. For diffusion data, each matrix entry constituted a weighting factor derived from streamline counts between each pair of nodes using a cross-sectional area multiplier (SIFT-2) [52]. Before obtaining each matrix entry, the following steps were performed: (1) warping of the parcellation template to individual diffusion space using the combination of nonlinear warps of spatial T1 registration to MNI152 template and distortion correction with APMs, (2) expansion of template by adding voxels towards the grey-white matter boundary for seeding points to be included in regions. Ultimately, the diffusion matrix was log10 transformed.

In a final step, connectivity estimates were calculated from both functional and structural connectome data using the software *bctpy* with network parameters defined as in [53] (https://pypi.org/project/bctpy/) (see Fig. 1A). For both RSFC and SC, the focus was with nodal-level (1) within-network connectivity (400 features) defined as the sum of weights of one node attached to all nodes within its respective network divided by the total number of edges in the network, (2) inter-network connectivity (400 features) defined as the sum of weights from one node to all nodes outside its respective network divided by the number of edges in the network as well as (3) a ratio score (400 features) defined as within-network connectivity of a node in relation to its inter-network connectivity [12]. The total feature vector for each participant encompassed 2,800 features (1200 RSFC estimates + 1200 SC estimates + 400 region-wise GMV values). Two different feature sets were obtained from this and used in the ML framework explained below (Feature Set (FSet) A: 2 × 400 within- & inter-network connectivity for FC & SC + 400 region-wise GMV = 2000 features; Feature Set (FSet) B: 2 × 400 ratio-score for FC & SC + 400 region-wise GMV = 1200 features; see Fig. 1A).

Cognitive performance

All subjects took part in extensive neuropsychological assessment. For the current analyses, 14 cognitive tests spanning the cognitive domains attention, executive functions, episodic memory, working memory (WM) and language were selected (for details regarding test and variables chosen, see Suppl. Table S1) [40]. Due to the differential impact of aging on specific cognitive functions, we were interested in the examination of both global cognition and specific cognitive profiles in the prediction setting [1]. Therefore, we derived composite cognition scores following [24]. In summary, this included (1) replacement of missing values by the median for respective sex (males, females) and age groups (55 – 64 years, 65 – 74 years, 75 – 85 years), (2) conversion of raw scores into *z*-scores, (3) inversion of test scores with higher values meaning lower performance (i.e., time to complete the tasks or number of errors made), and (4) reduction of test performance to a global composite (one component solution) and distinct cognitive profiles (multicomponent solution based on eigenvalues > 1) using principal component analysis (PCA). Targets in ML prediction of cognitive performance constituted the individual global component and cognitive profile scores extracted from the PCA (see Fig. 1B). All cognitive analyses were performed using IBM SPSS Statistics 26 (https://www.ibm.com/de-de/analytics/spss-statistics-software) and custom Python (Version 3.7.6) code.

Machine learning framework

To answer the main question of this study, whether cognitive performance in healthy older adults can be predicted more accurately by multimodal information (region-wise GMV, RSFC & SC estimates) than by single modalities, a comprehensive ML framework approach was chosen. A schematic overview of the workflow can be found in Fig. 1D. Previous studies have shown that the use of a stacking approach in a multimodal context may be beneficial for prediction performance [54, 55]. To systematically examine a potential additional benefit of stacking for prediction accuracy, multimodal analyses were carried out both in a concatenation and stacking approach. In the concatenation approach, feature vectors in the multimodal settings were simply concatenated into one feature vector and entered into the ML pipeline. In contrast, stacking refers to an ensemble learning paradigm, which comprises two levels of learning [54, 55]. In the first layer, a machine learning (ML) model is obtained from each modality separately and each modality is in turn used to predict the cognitive variable of interest. The cross-validated predictions from the single-modality models are then used as the new feature vector for the second layer. In the second layer, the new input vector is used to train a meta-estimator and used for final predictions.

ML estimations were obtained for all single modalities, for pairwise combinations, and for a three-way combination (see Fig. 1C: Modality combinations as input features). Performance of different prediction algorithms were compared, which have been frequently applied in similar settings [32, 54–58]. These included Ridge regression, linear Support Vector Regression (linSVR), LASSO regression, Elastic Net (EN) regression, and Random Forest (RF) regression [32, 54–56, 59] (see Fig. 1D: Algorithms). The different algorithms were used in concatenation and in the first layer of the stacking approach. As the meta-estimator in stacking, a RF regressor was implemented according to recommendations in the literature [54–56, 58, 60, 61].

Following [62], ML model performance was evaluated using a repeated nested 10-fold cross-validation with 10 repeats (see Fig. 1D: ML approaches & cross-validation (CV) scheme). All hyperparameters were optimized in the inner folds to avoid data leakage (5-fold CV). In an initial step of the ML pipeline, all input features were scaled using the StandardScaler from scikit-learn within the cross-validation setup to ensure comparability in magnitudes of input features. In stacking, splits into training and test sets for single modalities were retained for training the second layer meta-estimator, i.e., RF regressor, to ensure separation of training and test set across layers and avoid data leakage [62]. To obtain the new input data for the second layer for each modality, predictions in the training set were obtained for each iteration of the repeated 10-fold CV based on the optimal hyperparameter configuration determined by an inner 5-fold CV. Those cross-validation predictions were then stacked for each iteration of the outer CV cycle and used as the new training set for the second layer. In turn, predictions on the test set for each iteration of the repeated tenfold CV were obtained, stacked and used as the new test set for the second layer. This procedure was performed to ensure that throughout all layers the training and test set were kept separate and that final stacked models were tested on previously unseen predictions [62]. Hyperparameters, i.e., number of trees and tree depth, of the meta-estimator were optimized in inner folds. The best parameter combination in terms of inner fold performance (i.e., MAE) was selected, applied to the outer fold training set and tested on the outer test set to evaluate ML performance. The following hyperparameters were tuned in both the concatenation and stacking approach: (i) regularization parameter C for linSVR (C: 10^{-4} to 10^{1}, 10 steps, logarithmic scale), (ii) regularization parameter lambda λ for Lasso (λ: 10^{-1} to 10^{2}, 10 steps) and Ridge (λ:10^{-3} to 10^{5}, 10 steps, logarithmic scale), (iii) regularization parameter lambda,λ, and alpha,α, for EN (λ: 10^{-1} to 10^{2}, 10 steps, logarithmic scale;α: 0.1 to 1, 10 steps), and (iv) number of trees and tree depth for RF (number of trees: 100 or 1000; tree depth: 4, 6, 8, 10, 20, 40, None). Mean absolute error (MAE) and coefficient of determination (R^2) were used to assess prediction performance. For completeness, the Pearson's correlation (r) between true and predicted targets was also calculated and reported in the Supplement. All machine learning analyses were performed using the scikit-learn library (version: 0.22.1) in Python [63] (https://scikit-learn.org/stable/index.html). Scripts for stacking were based on those from [62] (https://github.com/axifra/BrainAge_MRI-MEG) and adapted for the current study.

Confounder analyses

As ML performance may be extensively impacted by confounding variables, two different confounder analyses were carried out in the current study. First, we investigated prediction performance in conditions with different extents of deconfounding, i.e., without (no-deconf. condition) and with (deconf. condition) demographic confound regression (see Fig. 1C: Deconfounding). In both conditions, we controlled for the influence of estimated total intracranial volume (eTIV) by regressing it from the target [27, 55, 64]. In the deconf. condition, we additionally controlled for the demographic variables age, sex, and educational level in a similar fashion [55]. Confound regression was always performed within the ML pipeline to avoid data leakage [24, 55]. Second, prediction performance was examined in models using age, sex, and educational level as extra features (see Fig. 1C: Additional input features) [55]. ML estimations were obtained for demographic variables only and for all combinations with brain features.

Feature importance

Feature importance information was derived at two levels, i.e., feature and modality level, in the current study. For a more fine-grained anatomical exploration of the most relevant features (i.e., feature level), we decided to investigate results from the concatenation approach. To identify important features, mean coefficients were calculated by averaging coefficients across all CV folds for each ML model. For complexity reduction, we focused on the concatenation approach in the no-deconf. condition and models, in which all features were combined, to extract relevant features for prediction. The analyses of meaningful features were separately performed for models without and with extra features to gain a greater insight into the relevance of demographic features and the added benefit of using brain features for prediction. In an initial step, the 20 features with the highest coefficients were selected for each target in each algorithm (i.e., linSVR, Ridge, EN, Lasso, RF) and feature set (FSet A & FSet B). To ensure that features were consistently highly ranked across different analytic choices, only those features present in all algorithms and feature sets for each target were kept. Then, centroid coordinates of selected nodes in MNI space were retrieved from the 400-node Schaefer parcellation. Ultimately, an anatomical label using the cytoarchitectonically defined Julich-Brain atlas [65] implemented in the EBRAINS multilevel atlas framework (https://ebrains.eu/) was provided. In cases, in which a node was found within a gap map, the Desikan-Killiany atlas [66] implemented in FreeSurfer's freeview was additionally used.

For the closer examination at the modality level, feature importance information was derived from the second layer, i.e., meta-learner RF, of the stacking approach. Mean feature importances for each modality were calculated in the same way as in the feature level analysis. Again, to reduce complexity, focus was with the no-deconf. condition and models, in which all modalities, i.e., FC + SC + GMV, were combined. Feature importance analyses were performed for models without and with extra features. Each modality was ranked based on the feature importance results across analytic choices for each cognitive target. The most common ranking was reported in the Supplement.

ML validation analyses

We performed further analyses to validate our ML approach. Firstly, prediction performance was assessed for a theoretically defined composite (global) cognitive score to evaluate whether similar results are achieved as in our data-driven approach. To obtain a theoretically defined composite cognition score, test performance on the 14 cognitive tests (i.e., Z-scores) was averaged for each individual and used as targets in ML. Additionally, we chose to validate our findings by classifying extreme cognitive groups using a linear Support Vector Classifier (linSVC), Logistic Regression (Log), Ridge and Random Forest (RF) classifier. Extreme groups were defined as the top 25% (high cognitive performers) and lowest 25% (low cognitive performers) of individuals scoring on the global cognition component [31, 32]. Groups were matched for age, educational level, sex, and eTIV using propensity score matching ($N = 116$, 56 females, $M_{age} = 65.89$, $SD_{age} = 6.06$; see Suppl. Table S3-4). Moreover, we investigated the impact of including RSFC estimates derived from negative correlations on prediction performance exemplary for global cognition in the concatenation approach across analytic choices (FSet C: 2×400 within- & inter-network connectivity for

positive FC, 2×400 within- & inter-network connectivity for negative FC, 2×400 within- & inter-network connectivity for SC + 400 region-wise GMV = 2800 features). To validate our ML pipeline and to gain a greater insight into the confounding variables, we also performed age, educational level, and sex (matched for age, education & eTIV; $N = 340$, 170 females, $M_{age} = 66.57$, $SD_{age} = 6.77$; see Suppl. Table S2) predictions.

Model comparison and statistical analyses

Partial correlations between cognitive scores and age (corrected for education and sex) as well as education (corrected for age and sex) were computed to examine the link between potential confounders and cognitive performance, as summarised by the components derived from the PCA. A multivariate analysis of covariance (MANCOVA) was calculated to examine sex differences in cognitive variables (DV = cognitive scores, IV = sex, covariates = age and education).

ML performance was compared to estimations from a reference model, i.e., Dummy regressor [56]. In this case, the percentage of folds, for which the ML models were better than the reference model, was calculated. Further, two different types of multimodal bonus, B_{all} and B_{best}, were calculated for each multimodal combination according to [55]. B_{all} reflects the difference in performance between each multimodal model and the average of single modalities, while B_{best} constitutes the difference in performance between the multimodal model and the best single modality.

Results

Cognitive composite scores derived from principal component analysis

Principal component analysis (PCA) was used to derive cognitive composite scores, i.e., global cognition and specific cognitive profiles. First, the Kaiser-Meyer-Olkin (KMO) index was used to assess data suitability for PCA. The index was found to be satisfactory with a value of 0.91. Cognitive composite scores for each participant were defined as component scores derived from a one component solution. Cognitive profile scores for each individual were extracted from a solution based on the eigenvalue criterion > 1. In this context, two components could be identified by PCA (see Suppl. Tables S5-6 & Suppl. Fig. S7). The first component mostly related to (working) memory and executive functions, i.e., visual, visual spatial, and verbal WM, figural memory, problem solving, concept shifting, and susceptibility to interference (non-verbal memory & executive component; see Fig. 2 & Suppl. Table S6). The second component primarily pertained to verbal memory and language functions, i.e., semantic and phonemic verbal fluency, vocabulary, and verbal episodic memory (verbal memory & language component; see Fig. 2 & Suppl. Table S6).

All three cognitive scores were significantly negatively associated with age (cognitive composite: $r = -0.45$, $p < 0.001$, non-verbal memory & executive: $r = -0.41$, $p < 0.001$, verbal memory & language: $r = -0.16$, $p < 0.001$; adjusted for educational level and sex). Higher performance in all cognitive scores was significantly correlated with higher educational level (cognitive composite: $r = 0.43$, $p < 0.001$, non-verbal memory & executive: $r = 0.21$, $p < 0.001$, verbal memory & language: $r = 0.39$, $p < 0.001$). No sex differences were found for the global composite cognitive score using a MANCOVA with age and education as covariates (cognitive composite: $F(1,590) = 0.83$, $p = 0.36$, $\eta_p^2 = 0.001$). However, significant performance differences between males and females emerged for the two cognitive profiles (memory & executive: $F(1,590) = 16.52$, $p < 0.001$, $\eta_p^2 = 0.03$; verbal memory & language: $F(1,590) = 43.04$, $p < 0.001$, $\eta_p^2 = 0.07$).

ML results

Prediction results from unimodal and multimodal brain features for global cognition

Initially, ML was used to assess the prediction power of multimodal brain features, i.e., region-wise GMV, RSFC, and SC estimates, for global cognitive performance in older adults. Prediction performance across algorithms, feature sets, and ML approaches differed greatly between deconfounding strategies. Satisfactory prediction performance was only observed when no deconfounding was applied (Mean MAE: 0.74–0.79, Mean R^2: 0.02–0.14, in 65–100% of folds $R^2 >$ dummy regressor; see

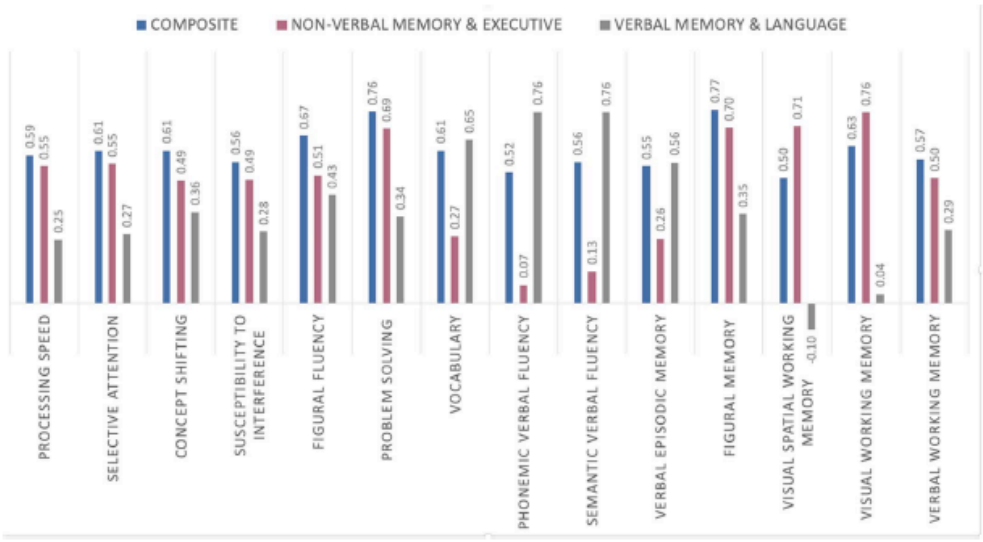


Fig. 2 Factor loadings of each cognitive function on the one component and multicomponent solution extracted from PCA analysis (after Varimax rotation)

Suppl. Tables S8-9, 11–16 & Suppl. Fig. S10). In this setting, multimodal models (Mean MAE: 0.74–0.78, Mean R^2: 0.03–0.14) tended to slightly better predict global cognitive performance than unimodal models (Mean MAE: 0.75–0.79, Mean R^2: 0.02–0.11) in different approaches, feature sets, and algorithms (see Figs. 3, 4 & Suppl. Tables S8-9, 11–16 & Suppl. Fig. S10). Across cognitive domains, a prediction performance gain in the best cases of up to 0.04 (best unimodal, B_{best}) to 0.06 (average unimodal, B_{all}) in R^2 could be observed in multimodal compared to unimodal models (see Suppl. Tables S17-20). Among single modalities, RSFC estimates (Mean MAE: 0.77–0.79, Mean R^2: 0.02–0.04) were found to be least predictive of global cognition across analytic choices (SC & GMV: Mean MAE: 0.75–0.78, Mean R^2: 0.05–0.11; see Figs. 3, 4 & Suppl. Tables S8-9, 11–16 Suppl. Fig. S10). Once we controlled for age, sex, and education, global cognition could no longer be successfully predicted and all previously reported differences between modalities disappeared (Mean MAE: 0.79–0.80, Mean R^2: –0.04–0.01, in 3–77% of folds R^2 > dummy regressor; Suppl. Tables S8-9, 11–16 & Suppl. Fig. S10). Thus, successful prediction of global cognition based on structural as well as structural and functional connectivity neuroimaging features along with a tendency for a multimodal benefit was only found in absence of confounder control.

Prediction results for global cognition using demographic features, i.e., age, sex, and education, and brain features plus extra demographic features

To get a better understanding of the impact of demographic feature on the cognitive performance prediction, prediction performance for global cognition was then investigated for models using only demographic features and models using brain features plus demographic features in absence of confounder control. Across approaches, algorithms, and feature sets, models including demographic features (i.e., age, sex, and education) could predict global cognition to a much greater degree than models solely based on brain features (Without extra features: Mean MAE: 0.74–0.79, Mean R^2: – 0.02–0.14, in 65–100% of folds R^2 > dummy regressor; With extra features: Mean MAE: 0.64–0.75, Mean R^2: 0.12–0.34, i.e., in 92–100% of folds R^2 > dummy regressor; see Fig. 4 & Suppl. Tables S21-24). Numerically, models with extra features could explain up to 20% more variance (R^2) in global cognition compared to those without.

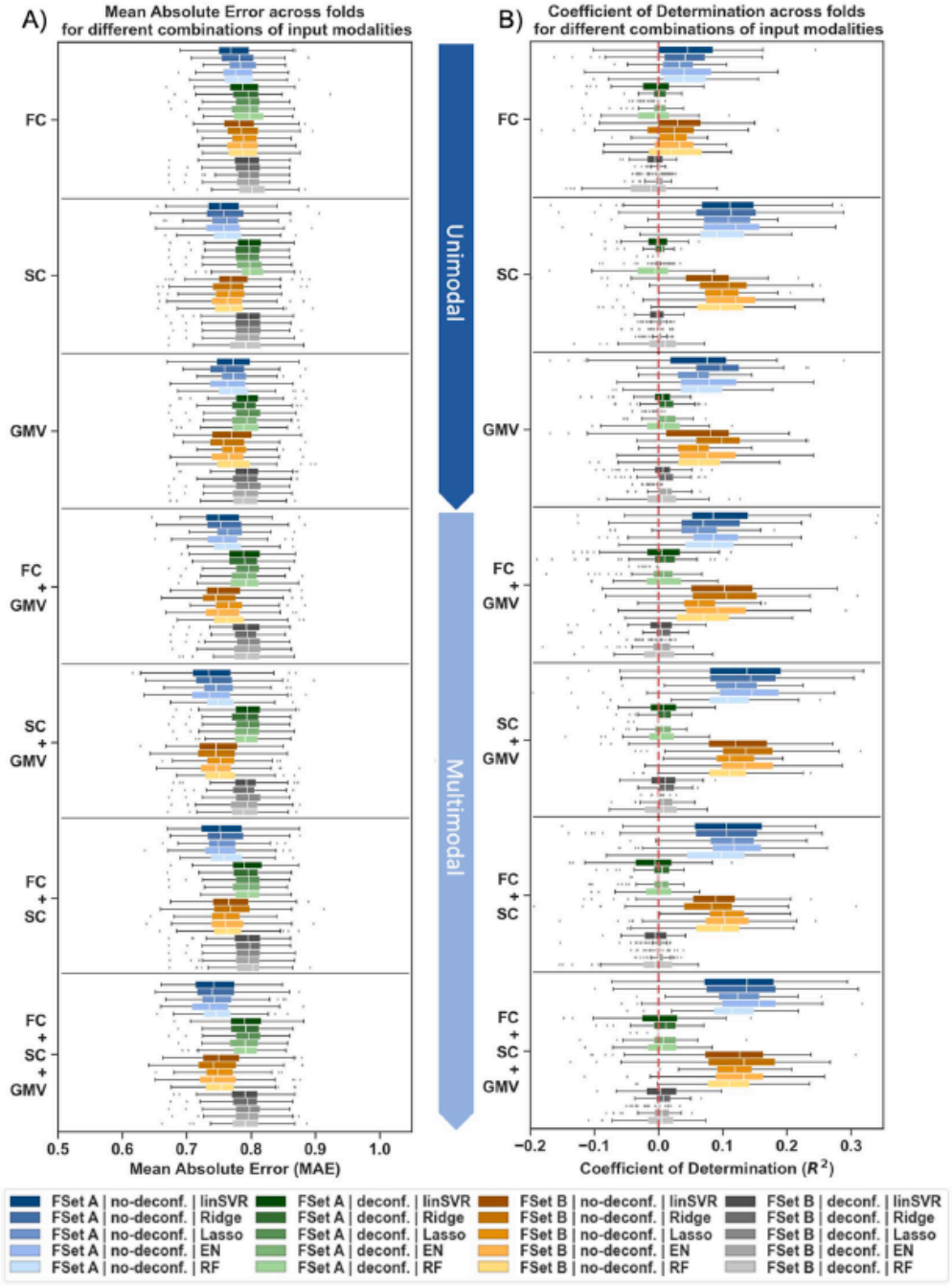
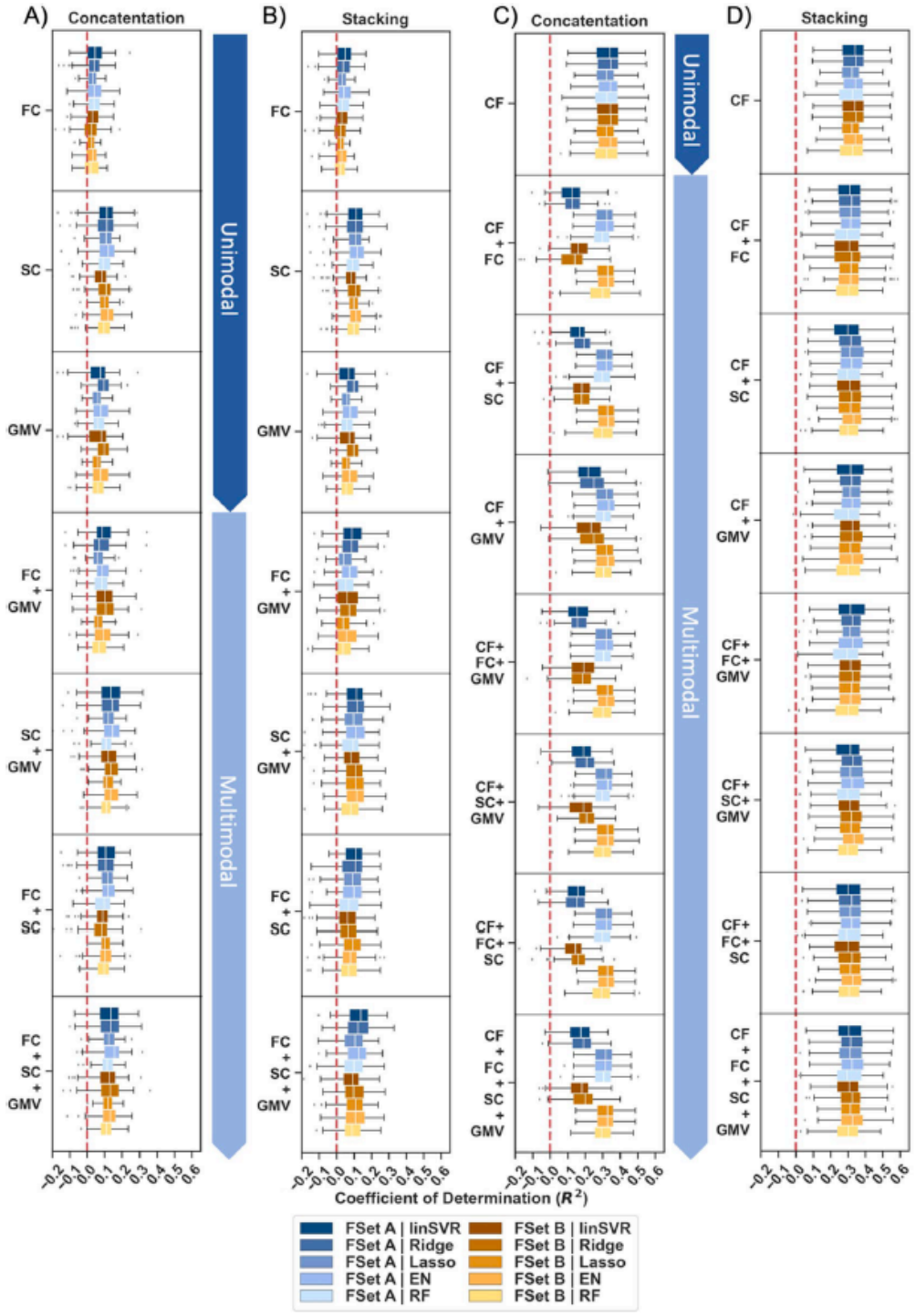


Fig. 3 Prediction performance for global cognition using unimodal and multimodal data across feature sets (FSet) A and B in the concatenation approach. **A** Mean absolute error (MAE) and **B** coefficient of determination (R^2) shown across folds for different algorithms (linear Support Vector Regression (linSVR), Ridge, Lasso, Elastic Net (EN) and Random Forest (RF) regression) and deconfounding strategies (no-deconf. = no deconfounding except for controlling for eTIV in target, deconf. = confound regression of age, sex, education, & eTIV)


A) Concatentation
B) Stacking
C) Concatentation
D) Stacking
Unimodal
Multimodal
FC
SC
GMV
FC + GMV
SC + GMV
FC + SC
FC + SC + GMV
CF
CF + FC
CF + SC
CF + GMV
CF+ FC+ GMV
CF+ SC+ GMV
CF+ FC+ SC
CF + FC + SC + GMV
-0.2 -0.1 0.0 0.1 0.2 0.3 0.4 0.5 0.6
Coefficient of Determination (R^2)
FSet A | linSVR
FSet A | Ridge
FSet A | Lasso
FSet A | EN
FSet A | RF
FSet B | linSVR
FSet B | Ridge
FSet B | Lasso
FSet B | EN
FSet B | RF

◂**Fig. 4** Prediction performance for global cognition using unimodal and multimodal data across feature sets (FSet) **A** and **B** in the concatenation and stacking approach with and without extra features. Coefficient of determination (R^2) displayed across folds for different algorithms (linear Support Vector Regression (linSVR), Ridge, Lasso, Elastic Net (EN) and Random Forest (RF) regression). Results shown for **A** the concatenation approach without extra features, **B** the stacking approach without extra features, **C** the concatenation approach with extra features, **D** the stacking approach with extra features. Only no-deconf. condition shown

Importantly, it should be highlighted that solely demographic features (Mean MAE: 0.64–0.65, Mean R^2: 0.32–0.34, in 100% of folds $R^2 >$ dummy regressor) predicted global cognition to a similar or even higher extent than brain features combined with demographic features (Mean MAE: 0.64–0.75, Mean R^2: 0.12–0.33; see Fig. 4 & Suppl. Tables S21-24). Thus, demographic information, i.e., age, sex, and education, were found to be highly predictive of global cognitive performance in older subjects (once these are not strictly controlled for by confound regression).

Prediction results for global cognition in the concatenation and stacking approach

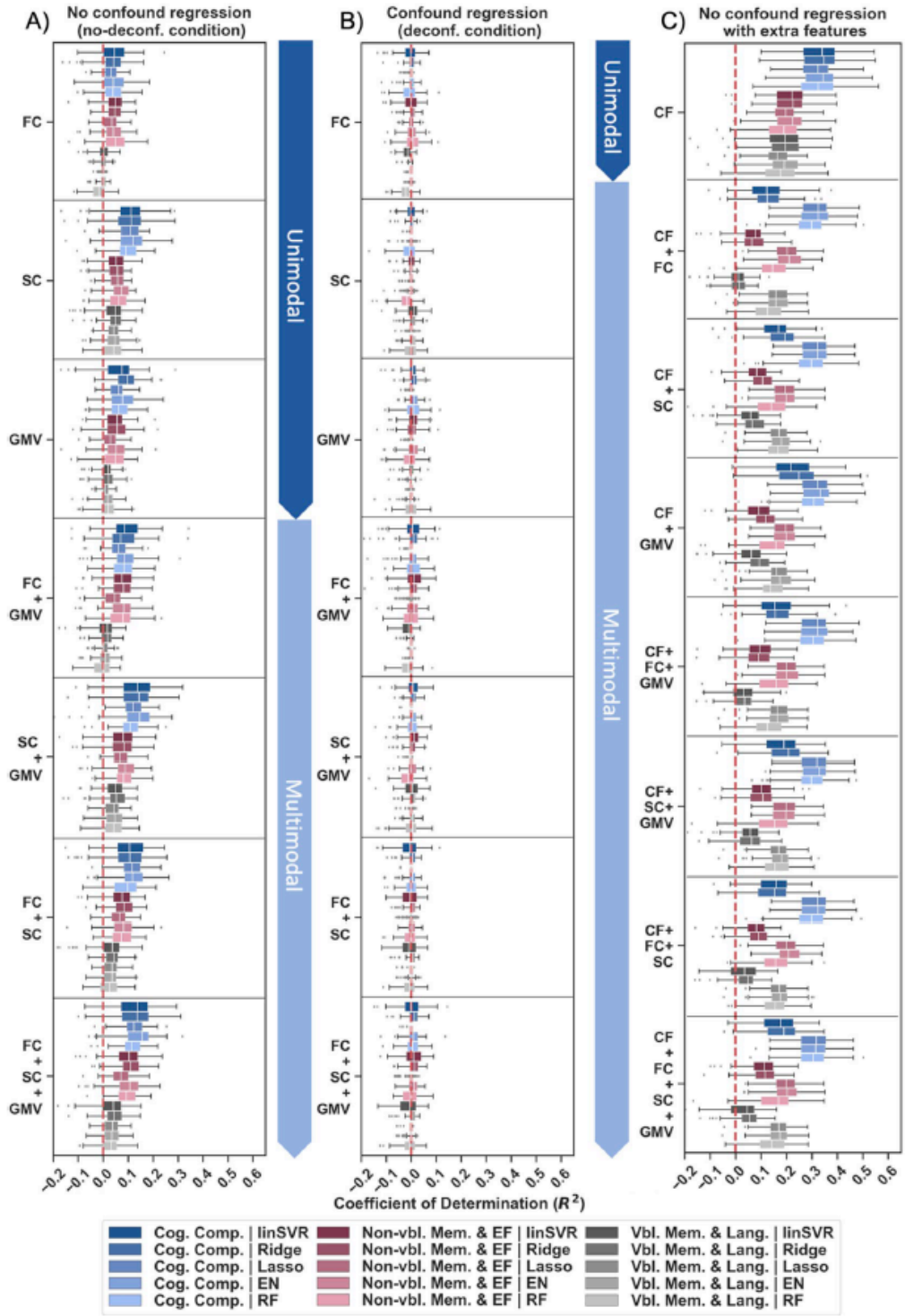
As previous studies have reported a benefit of stacking in terms of prediction accuracy, ML performance for global cognition was compared between a concatenation and stacking approach. In the current study, global cognition was predicted to a similar extent in the stacking (Mean MAE: 0.64–0.81, Mean R^2: − 0.03–0.34) and the concatenation (Mean MAE: 0.64–0.80, Mean R^2: − 0.04–0.34) approach (see Fig. 4 & Suppl. Tables S8-9, 11–16, 21–24). Only in models with extra features, differences between approaches emerged for two algorithms, i.e., linSVR and Ridge regression. Here, the prediction behaviour was found to be more stable in the stacking approach (see Fig. 4B, D). Nonetheless, the overall benefit of using a stacking approach remained marginal in the current investigation. Results for the two specific cognitive profiles are reported in the Supplement (see Suppl. Tables S25-48) and follow a similar pattern as global cognition.

Prediction results for global cognition and specific cognitive profiles

To address potential predictability differences across cognitive domains, prediction performance was further considered separately for global cognition and distinct cognitive profiles. Results revealed that global cognition and the two cognitive profiles may be predicted to different extents in absence of confounder control. Across modalities, pipeline configurations and algorithms, multimodal imaging data best predicted global cognition (Mean MAE: 0.74–0.79, Mean R^2: − 0.04–0.14) followed by the non-verbal memory & executive functions component (Mean MAE: 0.74–0.78, Mean R^2: − 0.03–0.11) and the verbal memory & language component (Mean MAE: 0.79–0.82, Mean R^2: − 0.03–0.05; see Fig. 5A & Suppl. Tables S8-9, 11–16, 21–48). It should be emphasized that while ML models could explain at least a moderate amount of variance in both global cognition and the non-verbal memory & executive functions component, this was not the case for the verbal memory & language component (see Fig. 5A). Despite an overall increase in prediction performance, predictability differences between targets were also found in models with extra features and disappeared altogether, when we controlled for age, sex, and education (see Fig. 5B, C). Hence, results hint at considerably lower predictability of language functions in older age based on currently employed multimodal input features.

Relevant features for the prediction of cognitive performance in older age

The analyses of important features were performed at both feature and modality level. In the feature level approach, analyses were separately carried out for models with and without extra features for the different cognitive targets and age in the concatenation approach. Across models without extra features, top ranked features for prediction of cognitive targets either belonged to the modality SC or GMV. In case of SC, inter-network connectivity features were more frequently found among the top ranked features than within-network features (see Fig. 6 & Table 2). For global cognition, nodes found in the rostral middle frontal gyrus (GMV; DMN) and the inferior temporal/parahippocampal gyrus (SC; limbic network) were


A) No confound regression (no-deconf. condition)
B) Confound regression (deconf. condition)
C) No confound regression with extra features
Unimodal
Multimodal
FC
SC
GMV
FC + GMV
SC + GMV
FC + SC
FC + SC + GMV
CF
CF + FC
CF + SC
CF + GMV
CF+ FC+ GMV
CF+ SC+ GMV
CF+ FC+ SC
CF + FC + SC + GMV
-0.2 -0.1 0.0 0.1 0.2 0.3 0.4 0.5 0.6
Coefficient of Determination (R^2)
Cog. Comp. | linSVR
Cog. Comp. | Ridge
Cog. Comp. | Lasso
Cog. Comp. | EN
Cog. Comp. | RF
Non-vbl. Mem. & EF | linSVR
Non-vbl. Mem. & EF | Ridge
Non-vbl. Mem. & EF | Lasso
Non-vbl. Mem. & EF | EN
Non-vbl. Mem. & EF | RF
Vbl. Mem. & Lang. | linSVR
Vbl. Mem. & Lang. | Ridge
Vbl. Mem. & Lang. | Lasso
Vbl. Mem. & Lang. | EN
Vbl. Mem. & Lang. | RF

◂**Fig. 5** Prediction performance for global cognition (Cog. Comp.) and specific cognitive profiles (Non-vbl. Mem. & EF, Vbl. Mem., & Lang.) using unimodal and multimodal data in feature set (FSet) **A** in the concatenation approach with and without extra features. Coefficient of Determination (R^2) displayed across folds for different algorithms (linear Support Vector Regression (linSVR), Ridge, Lasso, Elastic Net (EN) and Random Forest (RF) regression). Results shown for **A** no-deconf. condition without extra features, **B** deconf. condition without extra features, **C** no-deconf. condition with extra features

found to be important (see Fig. 6 & Table 2). In turn for the non-verbal memory & executive functions component, nodes in the parahippocampal / fusiform gyrus (SC; visual network) and temporal pole / entorhinal cortex (SC; limbic network) were relevant for prediction. For the verbal memory & language component, relevant nodes were found in the lingual / fusiform / parahippocampal gyrus (SC; visual network) and the angular gyrus (GMV; DMN) (see Fig. 6 & Table 2). For the age prediction, important nodes were found in the left and right parahippocampal gyrus (SC; visual and limbic network) and right fusiform / lingual gyrus (SC; visual network). Overlap was encountered in one feature with the non-verbal memory & executive functions component (see Fig. 6 & Table 2). In contrast, in models with extra features, the most relevant features constituted the demographic extra features and nearly no brain features reappeared among the top ranked features (see Table 2). For global cognition and the non-verbal memory & executive functions component, age and education were now found to be the most important features for prediction. A node in the temporal pole/entorhinal cortex (SC; limbic network) was additionally relevant for the prediction of the non-verbal memory & executive functions component (see Fig. 6 & Table 2). Interestingly, age seemed less important for the prediction of the verbal memory & language component. In this case, education appeared to be the sole feature with a consistently high mean coefficient across algorithms and feature sets. This also fits with our univariate results, which revealed a stronger correlation between the verbal memory & language component and education than with age.

Results from the feature level were complemented by those from the modality level. Across analytic choices and cognitive targets, SC and GMV were commonly ranked as the most important modalities in the second level of the stacking approach (see Suppl. Table S49). Along the lines, FC was ranked regularly as the least important modality in the current analyses for all cognitive targets. Once the extra features, i.e., age, sex, and education, were added to the models, these were found to be the most relevant modality in all models (see Suppl. Table S49). Nevertheless, the pattern of differences between brain modalities, i.e., FC, SC, and GMV, was mostly preserved. Thus, results from the modality level, further, supported those from the feature level and emphasized that brain structural features appear more important than brain functionally derived ones in predicting cognitive performance within in the current sample of healthy older adults from the 1000BRAINS study.

Validation results

Prediction performance was initially compared between the PCA-derived (used in the main analysis) and a theoretically defined global cognitive score (i.e., average test performance across 14 different cognitive tests). Across different options, prediction accuracies were found to be very similar for the two definitions of global cognition (PCA-defined: Mean R^2: – 0.04–0.14; theoretically defined: Mean R^2: – 0.04–0.14; see Suppl. Tables S50-57 & Suppl. Fig. S58). Additionally, we investigated the classification performance of extreme groups to further substantiate findings from the main analysis. Results suggested that the multimodal input data could not reliably distinguish between extreme cognitive groups with best performing models achieving only 65% accuracy (Mean accuracy: 45.5–65.4%; see Suppl. Tables S59 & Suppl. Fig. S60). As groups were matched for all confounders, these results further substantiated findings from our main analyses in the deconf. condition. Moreover, including RSFC estimates derived from negative correlations as additional input features (i.e., FSet C) revealed a relatively similar pattern of results as observed in the main analysis (FSet C: Without extra features: Mean R^2: 0.05–0.14 (no-deconf.)/-0.01–0.01 (deconf.); with extra features: Mean R^2: 0.10–0.34; FSet A&B: Without extra features: Mean R^2: 0.02–0.14 (no-deconf.) / – 0.02–0.01 (deconf.); with extra features: Mean R^2: 0.12–0.34; see Suppl. Tables S8, S13, S21, S23, S61-63 & Suppl. Fig. S64). Similarly as in the main analysis, FC estimates were found to lead to lowest

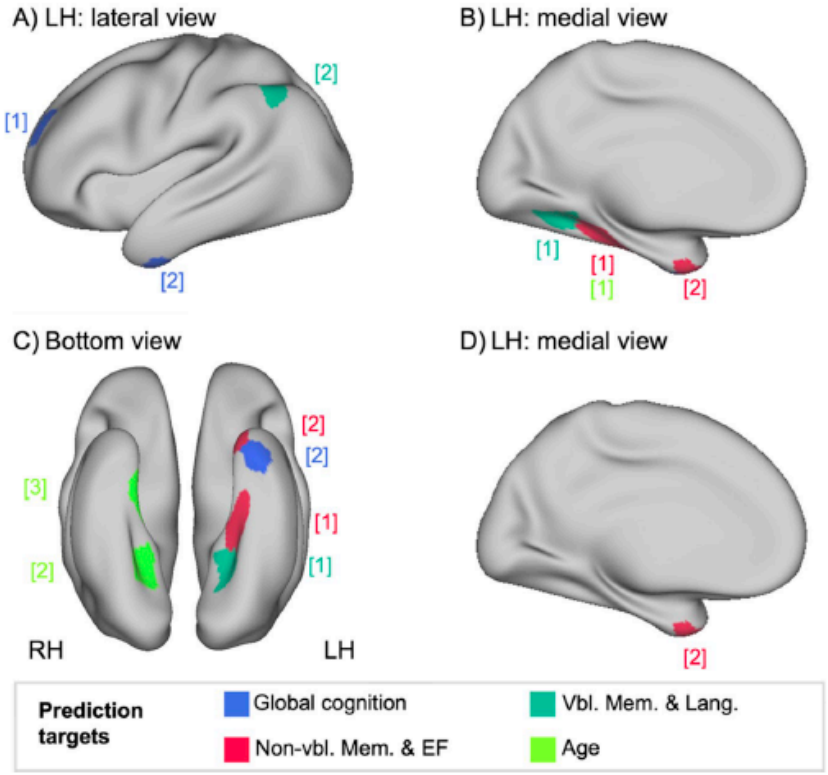


Fig. 6 Mapping of relevant features for the prediction of cognitive performance in older age to brain. **A–C** Nodes (in different colors labelled for different targets) relevant for prediction with no extra features, **D** node relevant for prediction with extra features.

prediction performance compared to SC estimates and region-wise GMV (see Suppl. Tables S61-63 & Suppl. Fig. S64). Thus, the inclusion of negative edge values in the estimation of RSFC estimates did not seem to boost signal for the ML models. Furthermore, to validate our ML pipeline and gain a greater insight into the confounding variables, we examined the predictability of age, sex, and educational level from our input features. Age (Mean R^2: 0.05–0.44; see Suppl. Tables S65-66 & Suppl. Fig. S67) and sex (Mean accuracy: 60.5–83.0%; see Suppl. Tables S68 & Suppl. Fig. S69) could be predicted with high accuracies. In contrast, educational level could be predicted less reliably from our features (Mean R^2: −0.45–0.04; see Suppl. Tables S70 & Suppl. Fig. S71).

Discussion

The aim of the current study was to investigate the general validity of the prediction of cognition from imaging data in healthy older adults. Thereby, we were specifically interested in whether (1) integrating information from a network perspective, i.e., RSFC and SC estimates, with morphological brain data, i.e., region-wise GMV, may lead to better prediction performance of different cognitive targets than unimodal models, (2) global cognition and distinct cognitive profiles differ in their predictability from imaging data, and (3) results generalize across different ML pipeline configurations and approaches, i.e., different modality combinations, algorithms, feature sets, deconfounding analyses and multimodal approaches, in a large sample of healthy older adults from the 1000BRAINS study. Across a variety of different analytic choices, moderate prediction performance of cognitive variables could solely be observed in absence of confounder control. In this context, we found only a slight trend for better predictability in multimodal than unimodal models, higher prediction accuracies for SC and GMV than RSFC and for global cognition compared to specific cognitive profiles. Noticeably, once age, sex, and education were controlled for, all previously reported

Table 2 Highly ranked features (according to mean coefficient) across algorithms and features sets in models with and without extra features in the concatenation approach

Model	Target		Feature	Centroid Coordinates			Desikan-Killiany Atlas | Julich-Brain Atlas
			Modality | Hemisphere | Network | Node	x	y	z	
−extra features	Global cognition	**1**	**GMV** LH | DMN | PFC 15	−22	50	32	Rostral middle frontal gyrus | Frontal-l (Gap Map)
		2	**SC: within** LH | Limbic | Node 6	−38	−6	−42	Inferior temporal & parahippocampal gyrus | Temporal-to-Parietal (Gap Map)
	Comp 1	**1**	**SC: inter** LH | Visual | Node 2	−30	−32	−18	Parahippocampal & fusiform gyrus | Temporal-to-Parietal (Gap Map)
		2	**SC: inter** LH | Limbic | Node 7	−24	6	−40	Temporal pole & entorhinal cortex | Temporal-to-Parietal (Gap Map)
	Comp 2	**1**	**SC: inter** LH | Visual | Node 4	−24	−54	−8	Fusiform & lingual gyrus | Ph1 (PhG)
		2	**GMV** LH | DMN | Par 7	−48	−60	46	Inferior parietal lobule & angular gyrus | PGa (IPL)
	Age	**1**	**SC: inter** LH | Visual | Node 2	−30	−32	−18	Parahippocampal gyrus | Temporal-to-Parietal (Gap Map)
		2	**SC: inter** RH | Visual | Node 36	26	−52	−8	Parahippocampal gyrus | Ph3 (PhG)
		3	**SC: inter** RH | Limbic | Node 26	22	−18	−28	Fusiform & lingual gyrus | Temporal-to-Parietal (Gap Map)
+extra features	Global cognition	**1**	**Age**	–	–	–	–
		2	**Education**	–	–	–	–
	Comp 1	**1**	**Age**	–	–	–	–
		2	**Education**	–	–	–	–
		3	**SC: inter** LH | Limbic | Node 7	-24	6	-40	Temporal pole & entorhinal cortex | Temporal-to-Parietal (Gap Map)
	Comp 2	**1**	**Education**	–	–	–	–

Comp 1 = non-verbal memory & executive functions component; Comp 2 = verbal memory & language component; LH = left hemisphere; RH = right hemisphere; DMN = default mode network; Visual = visual network; Limbic = limbic network; PFC = prefrontal cortex; Par = parietal

effects disappeared and rather low predictability was observed. Subsequent analyses showed that demographic variables alone already explained a substantial amount of variance in the target variables. Thus, results emphasize despite a small potential benefit of a multimodal approach, the considerable impact of factors such as age, sex, and education on the prediction of cognitive targets in healthy older adults.

Cognition emerges from the complex interaction of multiple organizational levels in the brain. As such, differences in structural and functional brain network architecture as well as in morphological brain features have been related to cognitive performance differences in older age [1, 3–13]. In terms of prediction, most prior studies have focused on the usage of single modalities to predict cognitive ability in healthy older adults. A multimodal approach, however, may allow for a more complete description of age-related cognitive decline than each single modality as aging has been found to affect the brain at all levels [67]. Initial encouraging results in different samples have demonstrated that the use of multimodal data may improve prediction performance for different cognitive abilities, e.g., fluid intelligence, global cognitive function, visual working memory, fluid reasoning, vocabulary [26, 31, 33, 55, 68]. For example, multimodal models, including information from structural and functional imaging, yielded improved

prediction accuracies of up to R^2 = 0.05 compared to R^2=0.02–0.04 in unimodal models for fluid intelligence in a large sample from the UK Biobank [31]. Similarly, in a longitudinal setting, changes in a clinical score, i.e., Clinical dementia rating (CDR), were found to be predicted with higher accuracies from different multimodal models (R^2 range=0.34–0.42), including non-brain information and brain features, than from single modalities (R^2 range=0.01–0.28) in a large sample from the OASIS-3 project [32]. Our findings extend prior research by revealing moderate prediction performance of different cognitive variables (global and domain-specific) across different analytic choices using combined parameters of brain structure and network architecture, i.e., region-wise GMV, RSFC, and SC estimates, and no demographic deconfounding. In the no deconfounding conditions, the best performing unimodal model (SC estimates) was found to explain up to 11% of variance (R^2) in our global cognitive target, while the best multimodal model (GMV+RSFC+SC) explained 14% of variance (R^2). In terms of magnitude of prediction performance, current results, thus, fall into the range of what has been reported in prior studies. Noticeably, this hints at a slight benefit of integrating information across different imaging modalities for the prediction of cognition in healthy aging.

Focusing on the single modalities, the lowest predictability was encountered for RSFC estimates. This further substantiates results from previous analyses of limited predictive potential of RSFC strength measures in different feature set combinations and hints at variations in prediction potential of RSFC for cognitive targets [24, 31, 54, 55, 67, 69]. For example, RSFC data led to lower prediction results (R^2=0.01) than anatomical markers (R^2 = 0.28), e.g., mean cortical thickness, cerebral GMV, and volumes of subcortical areas, in predicting cognitive decline (CDR change) in a sample of older adults from the OASIS-3 project [32]. Thus, it appears that cognitive performance differences in older age may be less clearly encoded in functional connectivity, especially in RSFC estimates, but more so in brain structural information. This may be due to the fact that brain function, i.e., RSFC and task-based FC, responds more adaptively to aging. Aging is accompanied by both increases and decreases in RSFC, which successively have been related to cognitive performance alterations [70]. Importantly, it has been postulated that the brain may engage into compensatory scaffolding and the recruitment of additional neural resources, e.g., connectivity, in an attempt to maintain cognitive function, when confronted with brain functional and structural decline [71, 72]. In this context, whether the additional neural response will lead to preserved cognition, will depend on the degree of scaffolding available and with it on the extent of neural insults that might have already taken place [71, 72]. Thus, it may be argued that age-related RSFC alterations and their relation to cognition are subject to high variability, which may complicate a clear mapping between RSFC patterns and cognitive performance in prediction. In contrast, age-related structural decline once having reached a sufficient degree typically results in cognitive performance decreases [73–76]. This clear correspondence may, in turn, be well captured by ML prediction models and may explain the moderate predictability based on SC estimates and region-wise GMV in the current study. Current results, in turn, emphasize that brain structural measures may be central to cognitive aging and suggest a prediction power advantage of brain structural information over RSFC patterns for cognitive abilities in older age [77].

Some cognitive functions are more strongly affected than others during the aging process, e.g., executive and memory functions [1]. This may also be expressed in different extents of predictability. To investigate this further, we considered different cognitive targets in our sample of older adults, i.e., global cognition and distinct cognitive profiles, in the present study. Results showed that global cognition was best predicted, followed by the non-verbal memory & executive functions component and finally the verbal memory & language component across analytic choices in the no-deconf. condition. One potential explanation for the performance benefit of global cognition over specific cognitive profiles may be related to cognitive aging being thought of as a largely domain-general process [78–81]. As such, it may be argued that general cognitive performance differences in older age may be much more prominent and in turn may also be more detectable at the whole-brain level than domain-specific alterations. In terms of relevant features for prediction, results revealed regions in the frontal and temporal lobe to be most predictive, which have been implicated in healthy and pathological aging as well as have been associated with age-related cognitive decline [82–86]. Specifically, our

results suggest that alterations in the communication within the limbic network and structural properties of the middle frontal gyrus in the DMN may be critical for identifying individual differences in global cognitive performance in older age.

The non-verbal memory & executive functions component was predicted second best. Highest loadings on this component were found for cognitive tests on problem-solving, figural memory as well as visual and visual-spatial WM. The structural wiring of the parahippocampal/fusiform gyrus (visual network) and temporal pole/entorhinal cortex (limbic network) to other networks throughout the brain were found to be important for prediction. Thus, predictive features spanned regions that are typically thought to be involved in cognitive tasks related to visual and memory-related processes [87–95]. Thus, global and domain-specific cognitive functions may not only be captured by distinct neural correlates, but may also differ in their most predictive features.

Interestingly, lowest prediction performance was observed for the verbal memory & language component in the current investigation. Results from prior prediction studies with older adults fit this account [26, 96, 97]. For example, language functions (HCP-A: $r=0.23$, BARBI: $r=0.12$) have been shown to lead to lower prediction performance than executive functions (HCP-A: $r=0.32$, BARBI: $r=0.28$) and attention (HCP-A: $r=0.37$, BARBI: $r=0.25$) in two independent samples based on SC data [96]. Thus, results are comparable to our SC results. Across algorithms, feature sets and multimodal approaches, we found correlation values between true and predicted scores to range from $r=0.19$ to 0.34 for global cognition and non-verbal memory & executive functions, while for the verbal memory & language component smaller correlation values in a range of $r=0.08$ to 0.23 were observed. Language functions, thus, not only appear to differ in aging trajectories (e.g., tend to remain more stable than for example executive and memory functions), but also in their predictability to other cognitive domains, e.g., processing speed, memory and executive functions, in older aged individuals [97]. A potential explanation may be that factors like education or occupational attainment may be highly relevant for the prediction of language-related cognitive performance overshadowing the predictive utility of brain features [26, 98]. This is also supported by the feature importance analyses in the current study. Without the addition of extra features, relevant regions for prediction included parts of the lingual/fusiform/parahippocampal gyrus (visual network) and the inferior parietal lobule/angular gyrus (DMN), which not only seem to be involved in different language-related functions, but also to be predictive of language abilities in older age [17, 99–102]. However, once added to the ML models, educational level appeared to be the most important feature for the prediction of verbal memory & language and with it to explain a large portion of variance in the target, which corresponds to prior research reporting strong associations between language measures and educational level [103, 104]. Current findings, thus, add to previous research by emphasizing the unique role of language functions in aging and stressing the intricate link to educational measures in older age.

Importantly, all previously described effects of successful prediction and emerging differences between modalities and cognitive targets were no longer encountered, once age, sex and education were controlled for. The significant drop in prediction performance after confounder control has to some degree also been reported in former studies [15, 18, 105]. For example, Kwak et al. reported a drop in mean prediction accuracy of neuropsychological test performance from RSFC in models adjusted for age (without confounder control: $r=0.253$, adjustment for age: $r=0.179$) [18]. Nevertheless, different cognitive targets could still be successfully predicted in healthy older adults after controlling for demographic factors across various studies. A potential explanation for divergent results in the current study compared to studies reporting successful prediction even after confounder control may be differences in samples, ML approaches, features, and targets used.

Therefore, to further evaluate the relevance of demographic variables in the prediction setting we investigated the individual contributions of age, sex, and education to the prediction by including these as extra features to the ML model. We found that the addition of age, sex, and education to our brain models drastically increased predictability of cognitive targets, in line with prior studies [31, 32, 55, 106, 107]. For example, Dadi et al. showed that fluid intelligence and neuroticism were more successfully predicted when sociodemographic information was included into the model in a large sample from the UK Biobank ($N=11{,}175$) [31]. Similarly, Rasero

et al. found that multimodal brain features together with age, sex, and education led to a prediction performance increase from median R^2=0.078 to median R^2=0.197 for global cognition [55]. Dadi et al. even reported fluid intelligence prediction based on all sociodemographic measures to perform slightly better without (R^2=0.17) than with brain imaging (R^2=0.16) [31]. The high relevance of demographic features for prediction was also mirrored in the current study. Present findings showed that joined models of brain features and demographic variables perform similar or even worse than models based only on the demographic features. Age, sex, and education were thereby found to reliably rank in the top features in joined models of brain and demographic features. Thus, it appears that the brain features, i.e., region-wise GMV, RSFC, and SC estimates, did not add substantial information to the prediction of cognitive performance in our older sample. Jointly, current results from the confounder analyses particularly accentuate the high impact of age, sex, and education and the limited informational value of currently employed brain features in the prediction of different cognitive variables in a large sample of healthy older adults. Given that age, sex, and education may have a substantial influence on prediction performance, it appears highly important to consider the influence of demographic features on results in future prediction studies in healthy aging. Along the lines, results from ML prediction without control for demographic factors should be considered with caution as results may not show the true predictive power of respective input features.

Methodological considerations and future outlook

In the current study, we employed both a concatenation and stacking approach to examine whether performance benefits may be observed for one over the other. Against initial predictions, the stacking approach did not reliably boost prediction accuracies [54–56, 58, 62]. Results from both approaches were found to be more or less comparable across a wide range of algorithms, feature sets, deconfounding strategies, and cognitive targets. Thus, current results provide further sustenance to prior work showing that a stacking benefit may not always be observed and different approaches should be compared to delineate, which one offers the best results for the question at stake [108].

Furthermore, it should be pointed out that a functionally derived cortical brain parcellation was used for all input modalities in the current study. The 400-nodes Schaefer parcellation was applied for RSFC, SC, and GMV to ensure comparability between modalities and to other prediction and lifespan studies [44, 50]. In future prediction studies, it might be valuable to explore the addition of subcortical regions, which are not covered by the current parcellation and have been shown to be highly relevant for distinct cognitive processes [109].

Another aspect to consider is that a significance-based threshold derived from null models based on randomization of time series information and permutation testing was included for resting-state connectivity matrices in the present study [11, 12, 51, 110]. While there are various studies that utilize resting-state connectivity matrices without a threshold, it was implemented here to reduce the amount of spurious correlations, which have been frequently encountered in RSFC [11, 12, 51, 53, 110–113]. Despite the potential of smaller correlations carrying meaningful information, no thresholding bears the risk of adding further noise into the analyses [11, 12]. As such, we have decided on a more conservative approach of using a threshold [53]. Furthermore, given that prediction performance appears generally low for FC based on the thresholded correlation matrices, we would anticipate that including those potentially smaller correlation values would not significantly impact ML prediction performance and boost the overall signal in the FC data, but rather add further noise to the ML models.

Additionally, it might become necessary in future studies to include other information about the aging process into prediction models for cognitive performance and prospective future cognitive decline. In the current study, we specifically investigated the use of RSFC and SC estimates due to the role of brain network patterns in aging and cognition. Nonetheless, their computation inherently includes a dimensionality reduction step and the loss of potentially relevant information. Similar to studies in younger cohorts, the use of raw connectivity measures (RSFC & SC) may be explored in future studies targeting the prediction of cognitive performance in older age. Moreover, one might consider adding FC dynamics and task-based

fMRI information to prediction models of cognitive variables in older age [114–117]. Beyond brain features, it may also be interesting to integrate non-brain information that may be relevant in terms of cognitive aging into ML models, such as genetic information, health or environmental features, to further improve and stabilize models [118].

In addition, newest studies have revealed that samples > 1000 or larger may be necessary to reliably detect brain-behavior relations with small effect sizes [68, 119, 120]. In this realm, our sample of $N = 594$ may not be large enough to obtain robust findings and higher prediction accuracies.

Moreover, the current study focused solely on a cross-sectional examination of prediction potential of cognitive performance in older age. To develop a marker for prospective cognitive decline in the future, it becomes necessary to shift attention to the investigation of longitudinal data and whether specific brain patterns may relate to later cognitive performance of an individual [121, 122].

Conclusions

The present study addressed the universality of cognitive performance prediction from imaging data in a large sample of healthy older adults using different ML approaches. Specifically, the benefit of integrating information across brain structure, i.e., region-wise GMV, and network organization, i.e., region-wise GMV, RSFC, and SC estimates, for the prediction of cognition compared to unimodal models as well as predictability differences between global cognition and two cognitive profiles were examined across a systematic analysis of different ML pipeline configurations. Present findings hint at moderate prediction performance of different cognitive targets from multimodal data in absence of confounder control. In this setting, we observed a small tendency for multimodal outperforming unimodal models in terms of prediction accuracy. Additionally, we observed higher predictability based on structural compared to functional brain features as well as better predictability of global cognition in comparison to distinct cognitive profiles. After controlling for age, sex, and education, previously described effects vanished stressing the intricate link between cognition and demographic factors at the brain level. Thus, present results emphasize the importance of considering these variables, i.e., age, sex, and education, in aging studies using a prediction framework. Furthermore, in future studies, it appears warranted to consider the usage of alternative input features in the search for a marker for age-related cognitive decline. Overall, present results suggest that although multimodal data may be beneficial for prediction of cognitive functioning in older cohorts, developing a marker for age-related cognitive decline may be aggravated by the influence of, e.g., demographic factors.

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Data availability Due to local regulations of data acquisition and usage, data of 1000BRAINS are available upon request from the responsible PI.

Declarations

Competing interests The authors declare no competing interests.

References

1. Hedden T, Gabrieli JDE. Insights into the ageing mind: a view from cognitive neuroscience. Nat Rev Neurosci. 2004;5:87–96. https://doi.org/10.1038/nrn1323.
2. Salthouse TA. What and When of Cognitive Aging. Curr Dir Psychol Sci. 2004;13:140–4. https://doi.org/10.1111/j.0963-7214.2004.00293.x.
3. Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, et al. Disruption of large-scale brain systems in advanced aging. Neuron. 2007;56:924–35. https://doi.org/10.1016/j.neuron.2007.10.038.
4. Chong JSX, Ng KK, Tandi J, Wang C, Poh J-H, Lo JC, et al. Longitudinal changes in the cerebral cortex functional organization of healthy elderly. J Neurosci. 2019;39:5534–50. https://doi.org/10.1523/JNEUROSCI.1451-18.2019.
5. Fjell AM, Sneve MH, Grydeland H, Storsve AB, de Lange A-MG, Amlien IK, et al. Functional connectivity change across multiple cortical networks relates to episodic memory changes in aging. Neurobiol Aging. 2015;36:3255–68. https://doi.org/10.1016/j.neurobiolaging.2015.08.020.
6. Grady C, Sarraf S, Saverino C, Campbell K. Age differences in the functional interactions among the default, frontoparietal control, and dorsal attention networks. Neurobiol Aging. 2016;41:159–72. https://doi.org/10.1016/j.neurobiolaging.2016.02.020.
7. Ng KK, Lo JC, Lim JKW, Chee MWL, Zhou J. Reduced functional segregation between the default mode network and the executive control network in healthy older adults: a longitudinal study. Neuroimage. 2016;133:321–30. https://doi.org/10.1016/j.neuroimage.2016.03.029.
8. Onoda K, Ishihara M, Yamaguchi S. Decreased Functional connectivity by aging is associated with cognitive decline. J Cogn Neurosci. 2012;24:2186–98. https://doi.org/10.1162/jocn_a_00269.
9. Raz N. Aging of the brain and its impact on cognitive performance: integration of structural and functional findings. Handb Aging Cogn 2nd Ed, Mahwah: Lawrence Erlbaum Associates Publishers; 2000, p. 1–90.
10. Rodrigue KM, Kennedy KM. The Cognitive consequences of structural changes to the aging brain. Handb Psychol Aging, Elsevier; 2011, p. 73–91. https://doi.org/10.1016/B978-0-12-380882-0.00005-X.
11. Stumme J, Jockwitz C, Hoffstaedter F, Amunts K, Caspers S. Functional network reorganization in older adults: graph-theoretical analyses of age, cognition and sex. NeuroImage. 2020;214:116756. https://doi.org/10.1016/j.neuroimage.2020.116756.
12. Stumme J, Krämer C, Miller T, Schreiber J, Caspers S, Jockwitz C. Interrelating differences in structural and functional connectivity in the older adult's brain. Hum Brain Mapp. 2022;43:5543–61. https://doi.org/10.1002/hbm.26030.
13. Wiseman SJ, Booth T, Ritchie SJ, Cox SR, Muñoz Maniega S, Valdés Hernández MDC, et al. Cognitive abilities, brain white matter hyperintensity volume, and structural network connectivity in older age. Hum Brain Mapp. 2018;39:622–32. https://doi.org/10.1002/hbm.23857.
14. Habib R, Nyberg L, Nilsson L-G. Cognitive and non-cognitive factors contributing to the longitudinal identification of successful older adults in the *Betula* Study. Aging Neuropsychol Cogn. 2007;14:257–73. https://doi.org/10.1080/13825580600582412.
15. Gao M, Wong CHY, Huang H, Shao R, Huang R, Chan CCH, et al. Connectome-based models can predict processing speed in older adults. NeuroImage. 2020;223:117290. https://doi.org/10.1016/j.neuroimage.2020.117290.
16. Jockwitz C, Bittner N, Caspers S, Amunts K. Deep characterization of individual brain-phenotype relations using a multilevel atlas. Curr Opin Behav Sci. 2021;40:153–60. https://doi.org/10.1016/j.cobeha.2021.04.016.
17. Jockwitz C, Krämer C, Stumme J, Dellani P, Moebus S, Bittner N, et al. Characterization of the angular gyrus in an older adult population: a multimodal multilevel approach. Brain Struct Funct. 2022. https://doi.org/10.1007/s00429-022-02529-3.
18. Kwak S, Kim H, Kim H, Youm Y, Chey J. Distributed functional connectivity predicts neuropsychological test performance among older adults. Hum Brain Mapp. 2021;42:3305–25. https://doi.org/10.1002/hbm.25436.
19. Pläschke RN, Patil KR, Cieslik EC, Nostro AD, Varikuti DP, Plachti A, et al. Age differences in predicting working memory performance from network-based functional connectivity. Cortex. 2020;132:441–59. https://doi.org/10.1016/j.cortex.2020.08.012.
20. Stites SD, Harkins K, Rubright JD, Karlawish J. Relationships between cognitive complaints and quality of life in older adults with mild cognitive impairment, mild alzheimer disease dementia, and normal cognition. Alzheimer Dis Assoc Disord. 2018;32:276–83. https://doi.org/10.1097/WAD.0000000000000262.
21. Orrù G, Pettersson-Yeo W, Marquand AF, Sartori G, Mechelli A. Using Support Vector Machine to identify imaging biomarkers of neurological and psychiatric disease: A critical review. Neurosci Biobehav Rev. 2012;36:1140–52. https://doi.org/10.1016/j.neubiorev.2012.01.004.
22. Avery EW, Yoo K, Rosenberg MD, Greene AS, Gao S, Na DL, et al. Distributed patterns of functional connectivity predict working memory performance in novel healthy and memory-impaired individuals. J Cogn Neurosci. 2020;32:241–55. https://doi.org/10.1162/jocn_a_01487.
23. He T, Kong R, Holmes AJ, Nguyen M, Sabuncu MR, Eickhoff SB, et al. Deep neural networks and kernel regression achieve comparable accuracies for functional connectivity prediction of behavior and demographics. NeuroImage. 2020;206:116276. https://doi.org/10.1016/j.neuroimage.2019.116276.
24. Krämer C, Stumme J, da Costa CL, Rubbert C, Caspers J, Caspers S, et al. Classification and prediction of cognitive performance differences in older age based on brain network patterns using a machine learning approach. Netw Neurosci. 2023;7:122–47. https://doi.org/10.1162/netn_a_00275.

25. Li X, Wang Y, Wang W, Huang W, Chen K, Xu K, et al. Age-Related decline in the topological efficiency of the brain structural connectome and cognitive aging. Cereb Cortex. 2020;30:4651–61. https://doi.org/10.1093/cercor/bhaa066.
26. Tsapanou A, Stern Y, Habeck C. Optimized prediction of cognition based on brain morphometry across the adult life span. Neurobiol Aging. 2020;93:16–24. https://doi.org/10.1016/j.neurobiolaging.2020.04.015.
27. Hilger K, Winter NR, Leenings R, Sassenhagen J, Hahn T, Basten U, et al. Predicting intelligence from brain gray matter volume. Brain Struct Funct. 2020;225:2111–29. https://doi.org/10.1007/s00429-020-02113-7.
28. Dyrba M, Grothe M, Kirste T, Teipel SJ. Multimodal analysis of functional and structural disconnection in Alzheimer's disease using multiple kernel SVM: Functional and Structural Disconnection in AD. Hum Brain Mapp. 2015;36:2118–31. https://doi.org/10.1002/hbm.22759.
29. Hojjati SH, Ebrahimzadeh A, Khazaee A, Babajani-Feremi A. Predicting conversion from MCI to AD by integrating rs-fMRI and structural MRI. Comput Biol Med. 2018;102:30–9. https://doi.org/10.1016/j.compbiomed.2018.09.004.
30. Hojjati SH, Ebrahimzadeh A, Babajani-Feremi A. Identification of the early stage of Alzheimer's disease using structural MRI and resting-state fMRI. Front Neurol. 2019;10:904. https://doi.org/10.3389/fneur.2019.00904.
31. Dadi K, Varoquaux G, Houenou J, Bzdok D, Thirion B, Engemann D. Population modeling with machine learning can enhance measures of mental health. GigaScience. 2021;10:giab071. https://doi.org/10.1093/gigascience/giab071.
32. Vieira BH, Liem F, Dadi K, Engemann DA, Gramfort A, Bellec P, et al. Predicting future cognitive decline from non-brain and multimodal brain imaging data in healthy and pathological aging. Neurobiol Aging. 2022;118:55–65. https://doi.org/10.1016/j.neurobiolaging.2022.06.008.
33. Xiao Y, Lin Y, Ma J, Qian J, Ke Z, Li L, et al. Predicting visual working memory with multimodal magnetic resonance imaging. Hum Brain Mapp. 2021;42:1446–62. https://doi.org/10.1002/hbm.25305.
34. Arbabshirani MR, Plis S, Sui J, Calhoun VD. Single subject prediction of brain disorders in neuroimaging: Promises and pitfalls. Neuroimage. 2017;145:137–65. https://doi.org/10.1016/j.neuroimage.2016.02.079.
35. Cui Z, Gong G. The effect of machine learning regression algorithms and sample size on individualized behavioral prediction with functional connectivity features. Neuroimage. 2018;178:622–37. https://doi.org/10.1016/j.neuroimage.2018.06.001.
36. Guyon I, Elisseeff A. An introduction to variable and feature selection. J Mach Learn Res. 2003;1157–82. https://www.jmlr.org/papers/volume3/guyon03a/guyon03a.pdf?ref=driverlayer.com/web.
37. Jollans L, Boyle R, Artiges E, Banaschewski T, Desrivières S, Grigis A, et al. Quantifying performance of machine learning methods for neuroimaging data. Neuroimage. 2019;199:351–65. https://doi.org/10.1016/j.neuroimage.2019.05.082.
38. Mwangi B, Tian TS, Soares JC. A review of feature reduction techniques in neuroimaging. Neuroinformatics. 2014;12:229–44. https://doi.org/10.1007/s12021-013-9204-3.
39. Paulus MP, Thompson WK. Computational approaches and machine learning for individual-level treatment predictions. Psychopharmacology. 2019. https://doi.org/10.1007/s00213-019-05282-4.
40. Caspers S, Moebus S, Lux S, Pundt N, Schütz H, Mühleisen TW, et al. Studying variability in human brain aging in a population-based German cohort-rationale and design of 1000BRAINS. Front Aging Neurosci. 2014;6:149. https://doi.org/10.3389/fnagi.2014.00149.
41. Schmermund A, Möhlenkamp S, Stang A, Grönemeyer D, Seibel R, Hirche H, et al. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: Rationale and design of the Heinz Nixdorf RECALL Study. Am Heart J. 2002;144:212–8. https://doi.org/10.1067/mhj.2002.123579.
42. Kalbe E, Kessler J, Calabrese P, Smith R, Passmore AP, Brand M, et al. DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. Int J Geriatr Psychiatry. 2004;19:136–43. https://doi.org/10.1002/gps.1042.
43. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. Neuroimage. 1999;9:179–94. https://doi.org/10.1006/nimg.1998.0395.
44. 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.
45. Pruim RHR, Mennes M, van Rooij D, Llera A, Buitelaar JK, Beckmann CF. ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. Neuroimage. 2015;112:267–77. https://doi.org/10.1016/j.neuroimage.2015.02.064.
46. Ashburner J, Friston KJ. Unified segmentation. Neuroimage. 2005;26:839–51. https://doi.org/10.1016/j.neuroimage.2005.02.018.
47. Gaser C, Dahnke R, Thompson PM, Kurth F, Luders E, Alzheimer's Disease Neuroimaging Initiative. CAT – a computational anatomy toolbox for the analysis of structural MRI data. bioRxiv. 2022. https://doi.org/10.1101/2022.06.11.495736.
48. Afyouni S, Nichols TE. Insight and inference for DVARS. Neuroimage. 2018;172:291–312. https://doi.org/10.1016/j.neuroimage.2017.12.098.
49. Jeurissen B, Tournier J-D, Dhollander T, Connelly A, Sijbers J. Multi-tissue constrained spherical deconvolution for improved analysis of multi-shell diffusion MRI data. Neuroimage. 2014;103:411–26. https://doi.org/10.1016/j.neuroimage.2014.07.061.
50. 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. https://doi.org/10.1152/jn.00338.2011.
51. Zalesky A, Fornito A, Bullmore E. On the use of correlation as a measure of network connectivity. Neuroimage. 2012;60:2096–106. https://doi.org/10.1016/j.neuroimage.2012.02.001.
52. Smith RE, Tournier J-D, Calamante F, Connelly A. SIFT2: Enabling dense quantitative assessment of brain white matter connectivity using streamlines tractography. Neuroimage. 2015;119:338–51. https://doi.org/10.1016/j.neuroimage.2015.06.092.
53. Rubinov M, Sporns O. Complex network measures of brain connectivity: Uses and interpretations. Neuroimage. 2010;52:1059–69. https://doi.org/10.1016/j.neuroimage.2009.10.003.
54. Liem F, Varoquaux G, Kynast J, Beyer F, Kharabian Masouleh S, Huntenburg JM, et al. Predicting brain-age from multimodal imaging data captures cognitive impairment. Neuroimage. 2017;148:179–88. https://doi.org/10.1016/j.neuroimage.2016.11.005.
55. Rasero J, Sentis AI, Yeh F-C, Verstynen T. Integrating across neuroimaging modalities boosts prediction accuracy of cognitive ability. PLOS Comput Biol. 2021;17:e1008347. https://doi.org/10.1371/journal.pcbi.1008347.
56. Engemann DA, Kozynets O, Sabbagh D, Lemaître G, Varoquaux G, Liem F, et al. Combining magnetoencephalography with magnetic resonance imaging enhances learning of surrogate-biomarkers. ELife. 2020;9:e54055. https://doi.org/10.7554/eLife.54055.
57. Qureshi MNI, Oh J, Cho D, Jo HJ, Lee B. Multimodal discrimination of schizophrenia using hybrid weighted feature concatenation of brain functional connectivity and anatomical features with an extreme learning machine. Front Neuroinformatics. 2017;11:59. https://doi.org/10.3389/fninf.2017.00059.
58. Rahim M, Thirion B, Comtat C, Varoquaux G. Transmodal Learning of functional networks for Alzheimer's disease prediction. IEEE J Sel Top Signal Process. 2016;10:1204–13. https://doi.org/10.1109/JSTSP.2016.2600400.
59. Rahim M, Thirion B, Bzdok D, Buvat I, Varoquaux G. Joint prediction of multiple scores captures better individual traits from brain images. Neuroimage. 2017;158:145–54. https://doi.org/10.1016/j.neuroimage.2017.06.072.
60. Karrer TM, Bassett DS, Derntl B, Gruber O, Aleman A, Jardri R, et al. Brain-based ranking of cognitive domains to predict schizophrenia. Hum Brain Mapp. 2019;40:4487–507. https://doi.org/10.1002/hbm.24716.
61. Wolpert DH. Stacked generalization. Neural Netw. 1992;5:241–59. https://doi.org/10.1016/S0893-6080(05)80023-1.
62. Xifra-Porxas A, Ghosh A, Mitsis GD, Boudrias M-H. Estimating brain age from structural MRI and MEG data: insights from dimensionality reduction techniques. NeuroImage. 2021;231:117822. https://doi.org/10.1016/j.neuroimage.2021.117822.
63. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O, et al. Scikit-learn: machine learning in python. J Mach Learn Res. 2011;12:2825–30.
64. Voevodskaya O, Simmons A, Nordenskjöld R, Kullberg J, Ahlström H, Lind L, et al. The effects of intracranial volume adjustment approaches on multiple regional MRI volumes in healthy aging and Alzheimer's disease. Front Aging Neurosci. 2014;6. https://doi.org/10.3389/fnagi.2014.00264.
65. Amunts K, Mohlberg H, Bludau S, Zilles K. Julich-Brain: A 3D probabilistic atlas of the human brain's cytoarchitecture. Science. 2020;369:988–92. https://doi.org/10.1126/science.abb4588.
66. 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. https://doi.org/10.1016/j.neuroimage.2006.01.021.
67. Dhamala E, Jamison KW, Jaywant A, Dennis S, Kuceyeski A. Distinct functional and structural connections predict crystallised and fluid cognition in healthy adults. Hum Brain Mapp. 2021;42:3102–18. https://doi.org/10.1002/hbm.25420.
68. Schulz M-A, Bzdok D, Haufe S, Haynes J-D, Ritter K. Performance reserves in brain-imaging-based phenotype prediction. Neuroscience. 2022. https://doi.org/10.1101/2022.02.23.481601.
69. Dubois J, Galdi P, Paul LK, Adolphs R. A distributed brain network predicts general intelligence from resting-state human neuroimaging data. Philos Trans R Soc B Biol Sci. 2018;373:20170284. https://doi.org/10.1098/rstb.2017.0284.
70. Ferreira LK, Busatto GF. Resting-state functional connectivity in normal brain aging. Neurosci Biobehav Rev. 2013;37:384–400. https://doi.org/10.1016/j.neubiorev.2013.01.017.
71. Park DC, Reuter-Lorenz P. The Adaptive brain: aging and neurocognitive scaffolding. Annu Rev Psychol. 2009;60:173–96. https://doi.org/10.1146/annurev.psych.59.103006.093656.
72. Reuter-Lorenz PA, Park DC. How does it STAC up? Revisiting the scaffolding theory of aging and cognition. Neuropsychol Rev. 2014;24:355–70. https://doi.org/10.1007/s11065-014-9270-9.
73. Fjell AM, Walhovd KB. Structural brain changes in aging: courses, causes and cognitive consequences. Rev Neurosci. 2010;21:187–221.
74. Kennedy KM, Raz N. Aging white matter and cognition: differential effects of regional variations in diffusion properties on memory, executive functions, and speed. Neuropsychologia. 2009;47:916–27. https://doi.org/10.1016/j.neuropsychologia.2009.01.001.
75. Persson J, Nyberg L, Lind J, Larsson A, Nilsson L-G, Ingvar M, et al. Structure-Function correlates of cognitive decline in aging. Cereb Cortex. 2006;16:907–15. https://doi.org/10.1093/cercor/bhj036.
76. Raz N, Rodrigue KM. Differential aging of the brain: patterns, cognitive correlates and modifiers. Neurosci Biobehav Rev. 2006;30:730–48. https://doi.org/10.1016/j.neubiorev.2006.07.001.

77. Lockhart SN, DeCarli C. Structural imaging measures of brain aging. Neuropsychol Rev. 2014;24:271–89. https://doi.org/10.1007/s11065-014-9268-3.
78. Tucker-Drob EM. Global and domain-specific changes in cognition throughout adulthood. Dev Psychol. 2011;47:331–43. https://doi.org/10.1037/a0021361.
79. Tucker-Drob EM, Reynolds CA, Finkel D, Pedersen NL. Shared and unique genetic and environmental influences on aging-related changes in multiple cognitive abilities. Dev Psychol. 2014;50:152–66. https://doi.org/10.1037/a0032468.
80. Tucker-Drob EM, Brandmaier AM, Lindenberger U. Coupled cognitive changes in adulthood: A meta-analysis. Psychol Bull. 2019;145:273–301. https://doi.org/10.1037/bul0000179.
81. Tucker-Drob EM, Salthouse TA. Individual differences in cognitive aging. In: Chamorro-Premuzic T, von Stumm S, Furnham A, editors. Wiley-Blackwell Handb. Individ. Differ., Oxford: Wiley-Blackwell; 2013, p. 242–67. https://doi.org/10.1002/9781444343120.ch9.
82. Armstrong NM, An Y, Shin JJ, Williams OA, Doshi J, Erus G, et al. Associations between cognitive and brain volume changes in cognitively normal older adults. NeuroImage. 2020;223:117289. https://doi.org/10.1016/j.neuroimage.2020.117289.
83. Kantarci K, Senjem ML, Avula R, Zhang B, Samikoglu AR, Weigand SD, et al. Diffusion tensor imaging and cognitive function in older adults with no dementia. Neurology. 2011;77:26–34. https://doi.org/10.1212/WNL.0b013e31822313dc.
84. Lemaitre H, Goldman AL, Sambataro F, Verchinski BA, Meyer-Lindenberg A, Weinberger DR, et al. Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and gray matter volume? Neurobiol Aging. 2012;33:617.e1-617.e9. https://doi.org/10.1016/j.neurobiolaging.2010.07.013.
85. McDonald CR, Gharapetian L, McEvoy LK, Fennema-Notestine C, Hagler DJ, Holland D, et al. Relationship between regional atrophy rates and cognitive decline in mild cognitive impairment. Neurobiol Aging. 2012;33:242–53. https://doi.org/10.1016/j.neurobiolaging.2010.03.015.
86. Sele S, Liem F, Mérillat S, Jäncke L. Decline variability of cortical and subcortical regions in aging: a longitudinal study. Front Hum Neurosci. 2020;14:363. https://doi.org/10.3389/fnhum.2020.00363.
87. Binney RJ, Parker GJM, Lambon Ralph MA. Convergent Connectivity and graded specialization in the rostral human temporal lobe as revealed by diffusion-weighted imaging probabilistic tractography. J Cogn Neurosci. 2012;24:1998–2014. https://doi.org/10.1162/jocn_a_00263.
88. Cai S, Chong T, Zhang Y, Li J, von Deneen KM, Ren J, et al. Altered Functional connectivity of fusiform gyrus in subjects with amnestic mild cognitive impairment: a resting-state fMRI study. Front Hum Neurosci. 2015;9. https://doi.org/10.3389/fnhum.2015.00471.
89. Diana RA, Yonelinas AP, Ranganath C. Medial temporal lobe activity during source retrieval reflects information type, not memory strength. J Cogn Neurosci. 2010;22:1808–18. https://doi.org/10.1162/jocn.2009.21335.
90. Mullally SL, Maguire EA. A new role for the parahippocampal cortex in representing space. J Neurosci. 2011;31:7441–9. https://doi.org/10.1523/JNEUROSCI.0267-11.2011.
91. Park S, Brady TF, Greene MR, Oliva A. Disentangling Scene content from spatial boundary: complementary roles for the parahippocampal place area and lateral occipital complex in representing real-world scenes. J Neurosci. 2011;31:1333–40. https://doi.org/10.1523/JNEUROSCI.3885-10.2011.
92. Pascual B, Masdeu JC, Hollenbeck M, Makris N, Insausti R, Ding S-L, et al. Large-scale brain networks of the human left temporal pole: a functional connectivity MRI study. Cereb Cortex. 2015;25:680–702. https://doi.org/10.1093/cercor/bht260.
93. Sele S, Liem F, Mérillat S, Jäncke L. Age-related decline in the brain: a longitudinal study on inter-individual variability of cortical thickness, area, volume, and cognition. NeuroImage. 2021;240:118370. https://doi.org/10.1016/j.neuroimage.2021.118370.
94. Stevens WD, Kahn I, Wig GS, Schacter DL. Hemispheric Asymmetry of visual scene Processing in the human brain: evidence from repetition priming and intrinsic activity. Cereb Cortex. 2012;22:1935–49. https://doi.org/10.1093/cercor/bhr273.
95. Van Petten C, Plante E, Davidson PSR, Kuo TY, Bajuscak L, Glisky EL. Memory and executive function in older adults: relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. Neuropsychologia. 2004;42:1313–35. https://doi.org/10.1016/j.neuropsychologia.2004.02.009.
96. Feng G, Wang Y, Huang W, Chen H, Dai Z, Ma G, et al. Methodological evaluation of individual cognitive prediction based on the brain white matter structural connectome. Hum Brain Mapp. 2022;hbm.25883. https://doi.org/10.1002/hbm.25883.
97. Shafto MA, Tyler LK. Language in the aging brain: the network dynamics of cognitive decline and preservation. Science. 2014;346:583–7. https://doi.org/10.1126/science.1254404.
98. Oschwald J, Guye S, Liem F, Rast P, Willis S, Röcke C, et al. Brain structure and cognitive ability in healthy aging: a review on longitudinal correlated change. Rev Neurosci. 2019;31:1–57. https://doi.org/10.1515/revneuro-2018-0096.
99. Damasio AR, Geschwind N. The neural basis of language. Annu Rev Neurosci. 1984;7:127–47. https://doi.org/10.1146/annurev.ne.07.030184.001015.
100. Heim S, Stumme J, Bittner N, Jockwitz C, Amunts K, Caspers S. Bilingualism and "brain reserve": a matter of age. Neurobiol Aging. 2019;81:157–65. https://doi.org/10.1016/j.neurobiolaging.2019.05.021.
101. Humphries C, Binder JR, Medler DA, Liebenthal E. Syntactic and semantic modulation of neural activity during auditory sentence comprehension. J Cogn Neurosci. 2006;18:665–79. https://doi.org/10.1162/jocn.2006.18.4.665.
102. Van Ettinger-Veenstra H, McAllister A, Lundberg P, Karlsson T, Engström M. Higher language ability is

related to angular gyrus activation increase during semantic processing, independent of sentence incongruency. Front Hum Neurosci. 2016;10:110. https://doi.org/10.3389/fnhum.2016.00110.
103. Jockwitz C, Mérillat S, Liem F, Oschwald J, Amunts K, Caspers S, et al. Generalizing age effects on brain structure and cognition: a two-study comparison approach. Hum Brain Mapp. 2019;40:2305–19. https://doi.org/10.1002/hbm.24524.
104. Opdebeeck C, Martyr A, Clare L. Cognitive reserve and cognitive function in healthy older people: a meta-analysis. Aging Neuropsychol Cogn. 2016;23:40–60. https://doi.org/10.1080/13825585.2015.1041450.
105. Gbadeyan O, Teng J, Prakash RS. Predicting response time variability from task and resting-state functional connectivity in the aging brain. NeuroImage. 2022;250:118890. https://doi.org/10.1016/j.neuroimage.2022.118890.
106. Yeung HW, Stolicyn A, Buchanan CR, Tucker-Drob EM, Bastin ME, Luz S, et al. Predicting sex, age, general cognition and mental health with machine learning on brain structural connectomes. Hum Brain Mapp. 2022;hbm.26182. https://doi.org/10.1002/hbm.26182.
107. Yu J, Rawtaer I, Fam J, Feng L, Kua E-H, Mahendran R. The individualized prediction of cognitive test scores in mild cognitive impairment using structural and functional connectivity features. NeuroImage. 2020;223:117310. https://doi.org/10.1016/j.neuroimage.2020.117310.
108. Dunås T, Wåhlin A, Nyberg L, Boraxbekk C-J. Multimodal image analysis of apparent brain age identifies physical fitness as predictor of brain maintenance. Cereb Cortex. 2021;bhab019. https://doi.org/10.1093/cercor/bhab019.
109. Weis S, Patil KR, Hoffstaedter F, Nostro A, Yeo BTT, Eickhoff SB. Sex classification by resting state brain connectivity. Cereb Cortex. 2020;30:824–35. https://doi.org/10.1093/cercor/bhz129.
110. Prichard D, Theiler J. Generating surrogate data for time series with several simultaneously measured variables. Phys Rev Lett. 1994;73:951–4. https://doi.org/10.1103/PhysRevLett.73.951.
111. Akiki TJ, Averill CL, Wrocklage KM, Scott JC, Averill LA, Schweinsburg B, et al. Topology of brain functional connectivity networks in posttraumatic stress disorder. Data Brief. 2018;20:1658–75. https://doi.org/10.1016/j.dib.2018.08.198.
112. Kruschwitz JD, List D, Waller L, Rubinov M, Walter H. GraphVar: A user-friendly toolbox for comprehensive graph analyses of functional brain connectivity. J Neurosci Methods. 2015;245:107–15. https://doi.org/10.1016/j.jneumeth.2015.02.021.
113. Váša F, Mišić B. Null models in network neuroscience. Nat Rev Neurosci. 2022;23:493–504. https://doi.org/10.1038/s41583-022-00601-9.
114. Feilong M, Guntupalli JS, Haxby JV. The neural basis of intelligence in fine-grained cortical topographies. ELife. 2021;10:e64058. https://doi.org/10.7554/eLife.64058.
115. Lavanga M, Stumme J, Yalcinkaya BH, Fousek J, Jockwitz C, Sheheitli H, et al. The virtual aging brain: a model-driven explanation for cognitive decline in older subjects. Neuroscience. 2022. https://doi.org/10.1101/2022.02.17.480902.
116. Soch J, Richter A, Kizilirmak JM, Schütze H, Feldhoff H, Fischer L, et al. Structural and functional mri data differentially predict chronological age and behavioral memory performance. eNeuro. 2022;9(6):ENEURO.0212-22.2022. https://doi.org/10.1523/ENEURO.0212-22.2022.
117. Sripada C, Angstadt M, Rutherford S, Taxali A, Shedden K. Toward a "treadmill test" for cognition: Improved prediction of general cognitive ability from the task activated brain. Hum Brain Mapp. 2020;41:3186–97. https://doi.org/10.1002/hbm.25007.
118. Murdaca G, Banchero S, Tonacci A, Nencioni A, Monacelli F, Gangemi S. Vitamin D and folate as predictors of MMSE in Alzheimer's disease: a machine learning analysis. Diagnostics. 2021;11:940. https://doi.org/10.3390/diagnostics11060940.
119. Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, Hatoum AS, et al. Reproducible brain-wide association studies require thousands of individuals. Nature. 2022;603:654–60. https://doi.org/10.1038/s41586-022-04492-9.
120. Masouleh SK, Eickhoff SB, Hoffstaedter F, Genon S, Alzheimer's Disease Neuroimaging Initiative. Empirical examination of the replicability of associations between brain structure and psychological variables. ELife. 2019;8:e43464. https://doi.org/10.7554/eLife.43464.
121. Damoiseaux JS. Effects of aging on functional and structural brain connectivity. Neuroimage. 2017;160:32–40. https://doi.org/10.1016/j.neuroimage.2017.01.077.
122. Salthouse TA. Cognitive correlates of cross-sectional differences and longitudinal changes in trail making performance. J Clin Exp Neuropsychol. 2011;33:242–8. https://doi.org/10.1080/13803395.2010.509922.

5 General Discussion

The current dissertation aimed at promoting the search for an imaging marker for age-related cognitive decline, providing a greater insight into the predictive power of imaging data for cognitive performance prediction in normal aging and advancing our understanding of the structure-function relationship in aging linked to cognition. In the first study, the biomarker potential of functional brain network information for age-related cognitive decline was addressed. In the second study, the age-characteristic interrelations between RSFC and SC patterns and cognitive performance were examined in older adults. In the third study, the potential benefit of using multimodal data, i.e. region-wise GMV, RSFC and SC estimates, for the prediction of cognitive performance in healthy aging was investigated.

The first study focussed on the classification and prediction of cognitive performance differences from RSFC estimates in healthy older adults. Across a systematic analysis of ML approaches, predictability of global and domain-specific cognition from RSFC estimates remained low with models failing to reliably outperform dummy models (Krämer et al., 2023). Thus, results hinted at limited utility of currently employed RSFC estimates as single biomarkers for age-related cognitive decline. The second study targeted the closer examination of structure-function relationships linked to cognition in aging and revealed the existence of three prominent aging profiles in older adults, which were associated with specific interrelations of RSFC, SC and cognitive performance (Stumme et al., 2022). In turn, the third study examined whether integrating information across modalities, i.e. region-wise GMV, RSFC and SC estimates, may boost the predictability of global and domain-specific cognitive performance in healthy older adults in a systematic evaluation of different ML approaches. Findings demonstrated moderate prediction performance across analytic choices in absence of confounder control (Krämer et al., 2024). In this context, a small trend for better prediction performance in multimodal compared to unimodal models and differences in prediction accuracies across modalities and cognitive targets were observed. These aforementioned effects could no longer be seen, once the effects of age, sex and education were controlled for. Results, thus, suggested the great impact of demographic factors, e.g. age, sex and education, despite a potential benefit of using multimodal data in the prediction of cognitive functioning in healthy older adults. Jointly, the results from this dissertation emphasize the challenges on the road to ultimately developing an imaging marker for age-related cognitive decline and the manifold insights that may be gained from a multimodal approach to study aging.

5.1 Effect sizes in brain-behaviour relationships in older age

In recent years, the number of studies in samples of younger adults and neurodegenerative patients reporting successful prediction and classification from imaging data in the realm of cognition has continuously increased (Cui and Gong, 2018; Dhamala et al., 2021; Dubois et al., 2018; Hojjati et al., 2017; Jiang et al., 2020; Khazaee et al., 2016; Sripada et al., 2020b). Nevertheless, these promising findings could not be translated to large samples of healthy older adults from the 1000BRAINS study in the current dissertation (Krämer et al., 2024, 2023). One potential explanation for this result may relate to small effect sizes in brain-cognition relationships encountered in older age. In comparison to younger cohorts, the heterogeneity of the aging process may pose unique obstacles to the identification of an accurate and reliable biomarker of cognitive abilities and thus, may attenuate effect sizes (Lin et al., 2018). The aging process is marked by brain structural and functional rearrangements and substantial inter-individual variability at the brain and cognitive level, which may lead to a convoluted link between cognition and brain in aging (Andrews-Hanna et al., 2007; Chan et al., 2014; Chong et al., 2019; Fjell et al., 2015; Grady et al., 2016; Habib et al., 2007; Hedden and Gabrieli, 2004; Jockwitz et al., 2019, 2017a, 2017b; Mowinckel et al., 2012; Ng et al., 2016; Onoda et al., 2012; Stumme et al., 2020). In turn, this may pose difficulties for identifying brain patterns linked to cognitive performance differences in healthy older adults, negatively impact on effect sizes and may explain the low discriminatory and predictive power across the first and third study of this dissertation (Scarpazza et al., 2020). This notion is further supported by a recent study by Kandaleft et al. (2022), which showed in a sample from the CamCAN study that fluid intelligence could only be predicted from RSFC in younger adults (18-40 years old), but not in middle aged (41-60 years old) or older adults (> 61 years old) (Kandaleft et al., 2022). Expanding on this, it has been shown that models derived from young adults using RSFC and SC information may not generalize well to older adults in the prediction of a variety of cognitive functions (Yu and Fischer, 2022). This, in turn, suggests age-specific brain-behaviour associations and profound differences between age groups. Thus, it appears that clear predictability differences between younger and older aged individuals may emerge and that increases in heterogeneity among individuals with advancing age may pose difficulties for accurate classification and prediction of cognitive abilities in older age.

Comparing the results to those extracted from patient samples, low classification and prediction performance may be linked to more pronounced differences between HC and patients (Amaefule et al., 2021; Kwak et al., 2021a). In this context, it has, for example, been shown that patients with MCI and AD display pronounced changes in brain structure,

e.g. extensive volume loss in medial temporal lobe structures, and function, i.e. shifts in network communication and the connectivity of central hub regions of the brain, compared to cognitively healthy older adults (Dai et al., 2015; Duara et al., 2008; Farahani et al., 2019; Lin et al., 2018; Sanz-Arigita et al., 2010; Supekar et al., 2008). ML classification and prediction studies on patient samples further support this argument. For instance, patients, i.e. MCI and AD, could be distinguished from HC based on RSFC graph metrics with high accuracies (maximum classification accuracy for three groups, i.e. HC, MCI and AD = 88.42%) as well as converters from MCI to AD from non-converters (maximum classification accuracy = 91.4%) (Hojjati et al., 2017; Khazaee et al., 2016). Similarly, a recent study has reported prediction accuracies of up to $R^2 = 0.55$ for memory performance based on morphometric information, e.g. grey matter density, demographic features and ApoE4 in a large sample (N=959) of HC, MCI and AD patients from the DZNE-longitudinal cognitive impairment and dementia study (Nemali et al., 2022). These magnitudes of effects may be more difficult to observe in a healthy population. This is supported by findings showing that training a model on data from healthy participants and neurodegenerative patients leads to higher prediction accuracies on different cognitive tests than when a model is trained solely on healthy participants (Kwak et al., 2021a). As such, ML models in healthy older adults may be hampered by smaller effect sizes (Krämer et al., 2023). In future studies, it might be valuable to investigate whether cognitive performance prediction in healthy older adults benefits from training on mixed populations and applying it in a second step to only healthy older adults.

Besides differences in samples, it is generally still unclear to what extent cognition and behaviour can be predicted based on brain imaging information (Easley et al., 2023; Genon et al., 2022; Schulz et al., 2022; Woo et al., 2017). Thus, the identification of neuroimaging markers for cognitive abilities or behavioural constructs has remained challenging similarly to developing diagnostic markers for diseases (Woo et al., 2017). It appears that only a small portion of variance in cognition and behaviour may be captured by brain features that have been investigated so far (Cui and Gong, 2018). This is represented in moderate prediction performance across a range of different studies and stands in contrast to prior and current results on the prediction of, for example, demographic factors, specifically age (Bittner et al., 2021; Cole, 2020; Krämer et al., 2024, 2023; Liem et al., 2017; Stumme et al., 2022). Even when attempts are being made to systematically increase effect sizes, e.g. extending fMRI features, averaging target phenotypes and using a more balanced sample, explained variance in cognitive targets was found to only increase marginally (Easley et al., 2023). As such, it has been shown that employing the aforementioned steps

might only increase explained variance (R^2) from 3% to 6% in fluid intelligence in a large sample of older adults from the UK Biobank based on fMRI information (Easley et al., 2023). Results from the current investigations further support this view and extend it to the use of brain network information, i.e. FC and SC estimates, and region-wise GMV. Across the first and third study, best models were based on multimodal brain information and did not explain more than 15% of variance in the different cognitive targets in absence of confounder control (Krämer et al., 2024, 2023). Thus, it may be argued that currently tested brain features may not be optimally suited to explain high amounts of variance in cognitive targets, but rather quickly reach a limit beyond which no increases in prediction performance are to be expected. Nevertheless, it should be pointed out that this may only apply to the types of features that have been tested so far and not necessarily extend to those developed in the future. Furthermore, to obtain a more realistic insight into brain-behaviour relationships and uncover potential replicability issues, even findings with moderate effect sizes or null results should be reported (Janssen et al., 2018). This may, in turn, also inform about possible new research avenues.

5.2 The role of RSFC for cognition prediction in healthy older adults

In recent years, a multitude of ML studies have been published on the use of RSFC information in the prediction of cognition and behaviour in different sample populations. This may be due to the ease of application of rsfMRI and the established link of RSFC to task performance (Nashiro et al., 2017). In this context, a majority of studies have reported successful prediction of cognitive variables, e.g. fluid intelligence, processing speed and working memory, based on RSFC information with high prediction accuracies in younger and older adults (Dhamala et al., 2021; Dubois et al., 2018; Gao et al., 2020; Pläschke et al., 2020). Until very recently, initial findings have been published revealing a more diverse picture in terms of the prediction potential of RSFC for cognitive variables (Dadi et al., 2021; Rasero et al., 2021; Vieira et al., 2022a). As such, several studies began to show reduced predictability of cognitive variables based on RSFC across datasets (Dadi et al., 2021; Heckner et al., 2023; Rasero et al., 2021; Tetereva et al., 2022; Vieira et al., 2022a). For example, RSFC patterns led to lower predictability of different cognitive measures, e.g. global cognition, fluid intelligence, and prospective global cognition and fluid intelligence, in large samples of young and older adults (i.e. from the HCP, UK Biobank and OASIS-3 project) compared to other imaging information, e.g. structural brain data (Dadi et al., 2021; de Dieu Uwisengeyimana et al., 2022; Rasero et al., 2021; Vieira et al., 2022a). Present findings add to this growing literature of limited predictability of cognitive and behavioural constructs based on RSFC, further expand it to RSFC estimates targeting

network integration and segregation and thus, stand in sharp contrast to earlier studies in the field. In the first study, it was shown that RSFC estimates led to low classifiability and predictability of cognitive performance across a wide range of analytic choices (Krämer et al., 2023). Results from the third study further corroborated initial findings and emphasized that among single modalities RSFC estimates led to the lowest prediction results compared to region-wise GMV and SC estimates (Krämer et al., 2024). Across analytic choices, mean prediction accuracies ranged between 2 to 4% explained variance for RSFC estimates compared to 5 to 11% explained variance in structural brain features for global cognition (Krämer et al., 2024). Overall, results suggest that functional connectivity, specifically RSFC estimates derived from graph-theoretical approaches, may capture cognitive performance differences in older age only to a limited extent (Krämer et al., 2024, 2023). In turn, current results emphasize that structural information may be more informative and predictive of these differences (Krämer et al., 2024). This is in line with prior studies showing high relevance of structural measures for cognitive aging and the successful prediction of cognitive abilities from SC features and structural information in health and disease (Feng et al., 2022; Li et al., 2020; Litwińczuk et al., 2022; Lockhart and DeCarli, 2014; Yu et al., 2020). In this context, it should be noted that one potential explanation for structural features outperforming functional ones may be related to the increased variability in brain function compared to structure in the aging process that may also complicate the link to cognition (Grady, 2012; Sala-Llonch et al., 2015). Both compensatory and dedifferentiation tendencies may be at work making a clear mapping between RSFC patterns and cognitive performance difficult for a ML model to establish in older adults (Goh, 2011; Reuter-Lorenz and Cappell, 2008; Sala-Llonch et al., 2015; Stumme et al., 2022). Along the lines, the low ML performance of RSFC for cognition prediction in older age observed in the first and third study of the present dissertation might have been further aggravated by the inherent dimensionality reduction of graph-theoretical approaches (Cui and Gong, 2018). This, in turn, might have caused relevant information for prediction to be lost ultimately resulting in low ML accuracies (Cui and Gong, 2018). Furthermore, only static RSFC has been examined in the current dissertation disregarding the time-varying nature of RSFC and richness in data across time (Petkoski et al., 2023). Given that age-related differences in the dynamic configuration of functional networks may be associated with cognitive performance, a shift in perspective to investigations of dynamic functional connectivity (dFC) in future studies may allow taking into consideration information beyond that of static RSFC, more fully capturing the variability in older age and with it enriching the information content to be used by a ML model (Battaglia et al., 2020; Viviano et al., 2017; Xia et al.,

2019; Yang et al., 2023). To sum up, results from this dissertation highlight that brain structural patterns may carry important information about cognitive performance differences in older age and in turn, question the usability of static RSFC measures, particularly graph-theoretically derived metrics, for cognitive performance prediction in older ages.

5.3 Multimodal aging profiles integrating SC, RSFC and cognition

Age-related cognitive decline is accompanied by macroscopic changes in brain structure, function and connectivity between brain regions. In this context, the usage of a multimodal approach is thought to allow for a more comprehensive description of cognitive aging and for the in-depth investigation of the relationship between brain structure, function and cognition in older age. Thus, supporting a more mechanistic understanding of age-related cognitive changes. In this context, recent research has embarked on examining the interrelation between RSFC and SC in aging and how it relates to cognition to foster a greater understanding for the causes of age-related functional network changes (Betzel et al., 2014; Fjell et al., 2017; Hirsiger et al., 2016; Madden et al., 2020; Straathof et al., 2019; Tsang et al., 2017; Zimmermann et al., 2016). Along the lines, prior studies have revealed mixed results. As such, some studies have suggested that RSFC and SC change independently across the life span and in higher ages (Fjell et al., 2017; Hirsiger et al., 2016; Tsang et al., 2017), while others have demonstrated SC to correlate with RSFC and to exert at least a partial influence on it (Betzel et al., 2014; Madden et al., 2020; Straathof et al., 2019; Zimmermann et al., 2016). Adding cognition to the equation, it also seems that no clear pattern may be observed. In this context, it has, for example, been found that only RSFC mediated the relationship between age and executive functions decline, but not SC (Madden et al., 2020). In contrast, Pur et al. (2022) showed in a longitudinal multivariate study that older adults with reduced processing speed capacity tended to show reduced SC primarily in frontal regions accompanied by decreases in FC in cingulo-opercular and DMN regions (Pur et al., 2022). Results from the second study of this dissertation add to the growing literature of structure-function relationships in the aging context and support previous results revealing joined patterns of RSFC and SC alterations in aging that may be related to cognitive performance differences. Along the lines, current findings demonstrated that three different aging profiles may be derived from multivariate analyses, i.e. partial least squares regression (PLSR), with distinct patterns of RSFC, SC and cognitive alterations, which may all be highly characteristic of the aging process (Stumme et al., 2022). Particulary, it was shown that the profiles may be distinguished by different acuteness of SC decline. Thereby, the first profile demonstrated a pattern of SC and RSFC alterations most commonly found in prior literature, i.e. declines in SC across the whole brain, lower

segregation of primary processing networks and higher integration of higher order networks in terms of RSFC and age-related impairments in cognitive performance (Betzel et al., 2014; Madden et al., 2020; Perry et al., 2017; Stumme et al., 2022; Zhao et al., 2015). Along the lines, the second profile revealed SC declines pertaining to the frontal lobe only and a strongly interconnected functional system, which was accompanied by the strongest age-related cognitive decline (Stumme et al., 2022). Lastly, the third profile exhibited rather preserved SC and comparably low overall RSFC, which was associated with similar cognitive performance declines as in the first profile (Stumme et al., 2022). Thus, current results suggest that the relationship between SC, RSFC and cognition during the aging process appears to be best captured by distinct patterns highlighting the complex interconnectedness of fuctional and structural systems supporting cognition in aging. Particularly, the severity of SC decline seems to play a fundamental role for age-related functional network reorganization and with it for cognition. Along the lines, current findings provide support for the dedifferentiation account in aging with the most strongly integrated functional system found to be associated with the greatest cognitive decline (Goh, 2011; Koen et al., 2020; Koen and Rugg, 2019). In this context, beginning SC decline was found to be related to increases in RSFC, although this additional recruitment did not appear to lead to higher cognitive maintenance. Thus, results from the second study emphasized that distinct patterns of interrelations between RSFC and SC changes during aging may be encountered, which may differentially relate to cognition (Stumme et al., 2022). In turn, these would have not been discovered by separate analysis of the two modalities and provide a framework for functional network shifts and related cognitive performance declines. Along the lines, multimodal analyses may offer new perspectives on the underlying root causes of age-related cognitive decline and support the view that they may more fully capture cognitive aging than single modalities on their own.

5.4 Potential benefits of multimodal data for cognition prediction in aging

Multimodal approaches may not only be informative in terms of a more detailed mechanistic understanding of the structure-function relationship in aging and its relation to cognition, but may also have a positive impact on predictability of cognitive performance in older age. Following this view, prediction performance should be boosted by including multimodal brain data as more information should be available characterising the relationship between brain and behaviour. This is indeed what has been reported in recent multimodal prediction studies on different cognitive functions cross-sectionally across the lifespan and in older cohorts as well as longitudinally (Cole, 2020; Dadi et al., 2021; Jiang et al., 2020; Rasero et al., 2021; Schulz et al., 2022; Tsapanou et al., 2020; Vieira et al.,

2022a; Xiao et al., 2021). Results from this dissertation extend prior findings by highlighting a similar tendency in multimodal models based on brain network information and region-wise GMV for the prediction of global and domain-specific cognitive performance in a large sample of healthy older adults in absence of confounder control, although only to a small extent (Krämer et al., 2024). While the first study was marked by low classification and prediction performance based on a single modality, i.e. RSFC estimates, the third study showed slightly improved prediction performance for multimodal models (Krämer et al., 2024, 2023). In this context, the best multimodal model (all brain features; mean $R^2 = 0.14$) outperformed the best single modality (SC estimates; mean $R^2 = 0.11$) by 3% more variance explained in the global cognitive target (Krämer et al., 2024). In terms of effect size, findings correspond to ranges reported in the literature (Dadi et al., 2021; Vieira et al., 2022a; Xiao et al., 2021). Overall, results from this dissertation suggest a small potential benefit of integrating information across modalities, i.e. region-wise GMV, RSFC and SC estimates, for cognitive performance prediction in healthy older adults by providing slightly more accurate approximations of cognition than single modalities.

5.5 Predictability differences among cognitive targets in older age

Distinct cognitive functions may be differentially affected by the aging process (e.g. processing speed, executive and memory functions tend to be more strongly impacted by aging than verbal abilities and semantic knowledge), which may result in predictability differences between them (Grady, 2012; Hedden and Gabrieli, 2004; Park and Reuter-Lorenz, 2009; Mather, 2010; Salthouse, 2004). This view is supported by present results pointing at considerable differences in prediction performance between different cognitive domains, i.e. global and domain-specific cognition, in healthy older adults (Krämer et al., 2024, 2023). In the first and third study, global cognition tended to be best predicted, followed by the non-verbal memory & executive component and the verbal memory & language component in absence of confounder control (Krämer et al., 2024, 2023). Superiority of global cognition in terms of predictability may be related to the fact that it may account for the greatest amount of variance in inter-individual differences in cognition and may, thus, be better predicted (Tucker-Drob, 2011; Tucker-Drob et al., 2014; Tucker-Drob and Salthouse, 2013). Further support for this stems from prior studies in primarily younger cohorts showing greater prediction accuracies for global compared to domain-specific cognition from imaging data (Sripada et al., 2020b; Vieira et al., 2022b). Current results expand on this and emphasize that a similar pattern may also emerge in healthy older adults.

By far, lowest prediction performance across the first and third study was observed for language functions (Krämer et al., 2024, 2023). Even when not controlling for demographic confounders, i.e. age, sex and education, language abilities failed to be successfully predicted in healthy older adults in this dissertation. These findings are in line with recent accounts in the literature across the lifespan and in older cohorts (Feng et al., 2022; Shafto and Tyler, 2014; Tsapanou et al., 2020). For instance, multimodal data could better predict fluid reasoning capabilities than vocabulary or language function in different large samples across the lifespan and in older adults (Tsapanou et al., 2020; Feng et al., 2022). A potential explanation may be that differences in language abilities are much more related to factors such as educational and occupational attainment and less so encountered in specific brain patterns, which was supported by the feature importance analysis in the third study (Krämer et al., 2024; Oschwald et al., 2019; Tsapanou et al., 2020). Findings from this dissertation, thus, hint at an exclusive role of language functions in aging and place emphasis on the link to measures such as educational attainment in older age. Overall, it appears that ML performance differences may partly be explained by differences in cognitive targets, with global cognition showing a predictability advantage compared to domain-specific constructs, when using a whole-brain approach. Whether these predictability differences in older adults also persist in, for example, a network-based approach (i.e. using features from only one specific network, e.g. FPN, as input to ML, which may be particularly important for a specific cognitive function, e.g. executive functions), remains to be investigated in future studies.

5.6 Relevance of demographic factors for cognition prediction in older adults

In ML classification and prediction studies, as in any other study, the variable of interest may not only be linked to the feature of choice, but also share relations with other factors, which may not be of principal interest and instead may overshadow or influence the examination of the link between feature and target (Boeke et al., 2020). These are often termed confounding variables or covariates to a study question. With the rise of ML studies in the neuroimaging field, also confounding variables have moved to the centre of attention with experiments showing their impact in various different ML settings and new methods being developed to control for these (Chyzhyk et al., 2022; Snoek et al., 2019). As prior studies have shown that the influence of covariates on ML performance may be substantial, different forms of confounder analyses were conducted in the studies of this dissertation (Omidvarnia et al., 2023; Rasero et al., 2021; Snoek et al., 2019). These included 1) varying degrees of deconfounding, i.e. controlling for age, sex and education (study 1 & 3), and 2) the usage of age, sex and education as extra features in the ML models (study 3) (Krämer

et al., 2024, 2023). Current results suggest a substantial impact of demographic factors on prediction performance and a strong link between those factors and cognition in healthy older adults (Krämer et al., 2024; Stumme et al., 2022). Particularly in the third study, controlling for age, sex and education caused prediction levels to drop to chance level, and with it, differences between modalities and cognitive targets to vanish (Krämer et al., 2024). In contrast, the addition of demographic factors to brain models led to drastic increases in prediction performance, similarly to findings reported in the literature (Dadi et al., 2021; Rasero et al., 2021; Vieira et al., 2022a; Yeung et al., 2022; Yu et al., 2020). Reconciling these two findings, it may be argued that confounder adjustment may have removed essential variance for the accurate prediction of cognition and that age, sex and education explain a substantial amount of variance in the cognitive targets. In the literature, findings regarding the loss of effects after confounder control remain relatively scarce. Nevertheless, there is initial evidence that controlling for demographic factors, e.g. age, may eliminate previous successful prediction results of cognitive targets in healthy older adults (Gbadeyan et al., 2022). Current results extend prior findings and suggest that age, sex and education appeared to have a particularly strong effect on cognition in the present samples (Krämer et al., 2024). Findings from this dissertation, thus, stress the importance of considering demographic factors in future prediction studies in the aging context and delineating their impact on prediction.

5.7 Systematic assessment of ML approaches

With the advance of ML techniques in recent years, a multitude of new approaches have entered the neuroimaging field. While there exist initial studies comparing the effect of different ML pipeline options and preprocessing steps on ML performance, there is currently no agreement on a standard ML pipeline to be used and substantial variability in pipelines tested (Arbabshirani et al., 2017; Dadi et al., 2019; Feng et al., 2022; Jollans et al., 2019; Pervaiz et al., 2020). Optimal choices may strongly depend on the dataset as one setup may simply not fit all (Dadi et al., 2019; Jollans et al., 2019; Paulus et al., 2019). Furthermore, currently limited insight is available regarding pipeline configurations for the use of graph-theoretically derived metrics (Dadi et al., 2019). Thus, different pipeline configurations were systematically evaluated across the first and third study in light of factors that have previously been shown to exert an influence on ML performance, e.g. algorithms, feature sets, sample size, feature selection/hyperparameter optimization steps and multimodal approaches (Krämer et al., 2024, 2023). Across analytic choices, current results were mostly consistent and did not differ substantially between pipeline options. This emphasizes a certain generalizability of the findings across analytic options

and thus, greater independence from analytic choices. In turn, this also means that there was not a single pipeline that was advantageous throughout. The exploration of different analytic choices inherently comes with exploiting researcher's degrees of freedom (Varoquaux et al., 2017). Keeping this in mind, for future studies it appears advisable to set up finely balanced analyses assessing, whether findings generalize across different ML pipeline configurations. In any case, it appears crucial to report variations in pipelines and corresponding results transparently and completely without the intentional leaving out of analytic choices that may be less favourable to provide a full account of the results (Janssen et al., 2018).

5.8 Limitations

One major methodological consideration relates to the choice of input features used across the three studies (Krämer et al., 2024, 2023; Stumme et al., 2022). Overall, prediction performance was limited (study 1 & 3) or explained less variance than prior studies (study 2) hinting at the fact that the selected features might have not been informative enough or at least possessed lower informational value compared to other input features. This appears to be especially true for the RSFC estimates. As already mentioned in paragraph 5.2, one potential explanation for current results pertains to the inherent dimensionality reduction step of graph-theoretical approaches potentially leading to the loss of relevant information (Cui and Gong, 2018). Additionally, only a limited range of graph-theoretical metrics were examined, which may be extended in future studies to include information on hubness, small-worldness and modularity (Betzel, 2022; Betzel et al., 2014; Sporns, 2011). Given that also the multimodal setup provided only limited prediction value, it might be further necessary to include other brain information into the models for accurate cognitive performance prediction in older age. Potential candidates based on initial promising findings in the literature in mostly younger cohorts are raw connectivity measures, task-based fMRI, dFC and edge time series information among others (Feilong et al., 2021; Sasse et al., 2022; Soch et al., 2022; Sripada et al., 2020a). In the future, it may also be valuable to look beyond brain information and integrate other factors that may be of importance in this context, i.e. genetic, health and environmental information, to obtain higher prediction performance and larger effect sizes (Murdaca et al., 2021).

Turning to the other part of the equation, also the target and its reliability may be reconsidered. For generalizable and reliable ML prediction, it is not only important to build models on input features that reliably carry sufficient signal for the task at hand, but also to provide a target variable that reliably measures and captures what it is intended to measure. As such, there is very recent evidence that a lack in reliability of a cognitive or behavioural

target variable may equally lead to poor prediction performance and potentially irreproducible effects (Gell et al., 2023; Nikolaidis et al., 2022). Potentially, providing an explanation for the low effect sizes encountered despite larger sample sizes (Nikolaidis et al., 2022). Additionally, the defined target may simply constitute a noisy representation of the underlying construct intended to be measured, which may provide an explanation for why targets such as age and sex yield consistently higher and more stable prediction results compared to cognitive factors and behavioural markers (Easley et al., 2023). An effect that was also observed across the three studies of this dissertation with cognition being far less reliably predicted from imaging data than age (Krämer et al., 2024, 2023; Stumme et al., 2022). In the future, it might, therefore, be advisable to pay more attention to the reliability of a measure, built on information from multiple time points and more rigorously address the construct validity of a given target variable.

Another point to consider is that solely cross-sectional data was used in this dissertation (Krämer et al., 2024, 2023; Stumme et al., 2022). Although interesting insights can be gained cross-sectionally and it offers the possibility to test different potential candidates as imaging marker for cognitive performance differences in older age, it only addresses the relation between cognition and brain at one time point (Damoiseaux, 2017; Salthouse, 2011). Aging is an inherently dynamic process and as such, brain and cognitive changes may evolve with time (Damoiseaux, 2017; Salthouse, 2011). Thus, a longitudinal perspective becomes essential, if we one day wish to develop a prospective marker for age-related cognitive decline and better understand the origins for the high inter-individual variability in aging.

Furthermore, it should be emphasized that ML may be complemented by other approaches that may lead to new and interesting insights beyond mere pattern recognition to characterize brain-behaviour relationships. Particularly, computational modelling approaches, such as for example The Virtual Brain (TVB) as a tool, may allow for causal discoveries and a deeper mechanistic understanding of the relation between brain structure, functional dynamics and observable behaviour, e.g. cognition (Falcon et al., 2016; Ritter et al., 2013). This may be achieved by the formulation and testing of distinct hypotheses within a brain network model driven by underlying biology (Falcon et al., 2016; Ritter et al., 2013). Fields of application vary from normal aging to neurodegenerative diseases (Falcon et al., 2016; Lavanga et al., 2022; Petkoski et al., 2023; Yalçınkaya et al., 2023). In turn, further insights from these approaches may not only potentially foster our knowledge on the underlying root causes for the high inter-individual variability in aging, but may also provide potential candidate biomarkers to be used in a ML predictive setting. Thus,

predictive analyses may in the future benefit from integrating information from computational models and from operating alongside these approaches, e.g. TVB, in the search for a reliable biomarker for age-related cognitive decline.

5.9 General Conclusion

This dissertation, particularly, investigated the biomarker potential of RSFC estimates targeting network integration and segregation, the age-characteristic interrelations between RSFC and SC patterns and cognitive performance and in turn, the benefit of using multimodal brain data, i.e. region-wise GMV, RSFC and SC estimates, for the prediction of cognitive performance differences in large (N>500) samples of healthy older adults from the 1000BRAINS cohort. Jointly, the three studies in this dissertation add to the literature by showing that currently employed RSFC estimates may only carry limited predictive value for cognitive performance differences in older age, that particular RSFC and SC patterns together with cognitive performance may be summarized in distinct aging profiles and that moderate prediction performance based on multimodal data may only be observed in absence of confounder control. Along the lines, results strongly emphasize the substantial impact demographic factors, i.e. age, sex and education, may have on ML performance and the criticality in considering these factors in prediction studies of cognition in healthy older age. Furthermore, current results highlight the various insights that may be gained by using a multimodal approach in different application contexts. In future studies, it might be worthwhile to investigate other input features including imaging and non-imaging data, to externally validate findings in larger cohorts of older adults and to move to a longitudinal setting. Furthermore, it should be stressed that while overall ML performance was limited in the first and third study of this dissertation, there is an intrinsic benefit in reporting null results and full accounts of ML pipelines tested to increase transparency throughout the field, to provide insight into potential future research avenues and draw a more realistic view of the state of the field. This dissertation can be viewed as a little puzzle piece that ties in with a growing number of ML studies in the neuroimaging field answering questions and at the same time raising new ones. There still remain many puzzle pieces to be solved in the coming years having the ultimate goal of developing a marker for prospective cognitive decline and providing early targeted interventions in mind.

6 References

Alfaro-Almagro, F., Jenkinson, M., Bangerter, N.K., Andersson, J.L.R., Griffanti, L., Douaud, G., Sotiropoulos, S.N., Jbabdi, S., Hernandez-Fernandez, M., Vallee, E., Vidaurre, D., Webster, M., McCarthy, P., Rorden, C., Daducci, A., Alexander, D.C., Zhang, H., Dragonu, I., Matthews, P.M., Miller, K.L., Smith, S.M., 2018. Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. NeuroImage 166, 400–424. https://doi.org/10.1016/j.neuroimage.2017.10.034

Alm, K.H., Soldan, A., Pettigrew, C., Faria, A.V., Hou, X., Lu, H., Moghekar, A., Mori, S., Albert, M., Bakker, A., 2022. Structural and Functional Brain Connectivity Uniquely Contribute to Episodic Memory Performance in Older Adults. Front. Aging Neurosci. 14, 951076. https://doi.org/10.3389/fnagi.2022.951076

Amaefule, C.O., Dyrba, M., Wolfsgruber, S., Polcher, A., Schneider, A., Fliessbach, K., Spottke, A., Meiberth, D., Preis, L., Peters, O., Incesoy, E.I., Spruth, E.J., Priller, J., Altenstein, S., Bartels, C., Wiltfang, J., Janowitz, D., Bürger, K., Laske, C., Munk, M., Rudolph, J., Glanz, W., Dobisch, L., Haynes, J.D., Dechent, P., Ertl-Wagner, B., Scheffler, K., Kilimann, I., Düzel, E., Metzger, C.D., Wagner, M., Jessen, F., Teipel, S.J., 2021. Association between composite scores of domain-specific cognitive functions and regional patterns of atrophy and functional connectivity in the Alzheimer's disease spectrum. NeuroImage: Clinical 29, 102533. https://doi.org/10.1016/j.nicl.2020.102533

Andrews-Hanna, J.R., Snyder, A.Z., Vincent, J.L., Lustig, C., Head, D., Raichle, M.E., Buckner, R.L., 2007. Disruption of Large-Scale Brain Systems in Advanced Aging. Neuron 56, 924–935. https://doi.org/10.1016/j.neuron.2007.10.038

Arbabshirani, M.R., Plis, S., Sui, J., Calhoun, V.D., 2017. Single subject prediction of brain disorders in neuroimaging: Promises and pitfalls. NeuroImage 145, 137–165. https://doi.org/10.1016/j.neuroimage.2016.02.079

Bagarinao, E., Watanabe, H., Maesawa, S., Mori, D., Hara, K., Kawabata, K., Yoneyama, N., Ohdake, R., Imai, K., Masuda, M., Yokoi, T., Ogura, A., Taoka, T., Koyama, S., Tanabe, H.C., Katsuno, M., Wakabayashi, T., Kuzuya, M., Ozaki, N., Hoshiyama, M., Isoda, H., Naganawa, S., Sobue, G., 2019. Reorganization of brain networks and its association with general cognitive performance over the adult lifespan. Sci Rep 9, 11352. https://doi.org/10.1038/s41598-019-47922-x

Battaglia, D., Boudou, T., Hansen, E.C.A., Lombardo, D., Chettouf, S., Daffertshofer, A., McIntosh, A.R., Zimmermann, J., Ritter, P., Jirsa, V., 2020. Dynamic Functional Connectivity between order and randomness and its evolution across the human adult lifespan. NeuroImage 222, 117156. https://doi.org/10.1016/j.neuroimage.2020.117156

Baum, G.L., Cui, Z., Roalf, D.R., Ciric, R., Betzel, R.F., Larsen, B., Cieslak, M., Cook, P.A., Xia, C.H., Moore, T.M., Ruparel, K., Oathes, D.J., Alexander-Bloch, A.F., Shinohara, R.T., Raznahan, A., Gur, R.E., Gur, R.C., Bassett, D.S., Satterthwaite, T.D., 2020. Development of structure–function coupling in human brain networks during youth. Proc. Natl. Acad. Sci. U.S.A. 117, 771–778. https://doi.org/10.1073/pnas.1912034117

Bayne, T., Brainard, D., Byrne, R.W., Chittka, L., Clayton, N., Heyes, C., Mather, J., Ölveczky, B., Shadlen, M., Suddendorf, T., Webb, B., 2019. What is cognition? Current Biology 29, R608–R615. https://doi.org/10.1016/j.cub.2019.05.044

Beard, J.R., Officer, A., de Carvalho, I.A., Sadana, R., Pot, A.M., Michel, J.-P., Lloyd-Sherlock, P., Epping-Jordan, J.E., Peeters, G.M.E.E. (Geeske), Mahanani, W.R., Thiyagarajan, J.A., Chatterji, S., 2016. The World report on ageing and health: a policy framework for healthy ageing. The Lancet 387, 2145–2154. https://doi.org/10.1016/S0140-6736(15)00516-4

Beaulieu, C., 2002. The basis of anisotropic water diffusion in the nervous system - a technical review. NMR Biomed. 15, 435–455. https://doi.org/10.1002/nbm.782

Behrens, T.E.J., Berg, H.J., Jbabdi, S., Rushworth, M.F.S., Woolrich, M.W., 2007. Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? NeuroImage 34, 144–155. https://doi.org/10.1016/j.neuroimage.2006.09.018

Bennett, I.J., Madden, D.J., 2014. Disconnected aging: Cerebral white matter integrity and age-related differences in cognition. Neuroscience 276, 187–205. https://doi.org/10.1016/j.neuroscience.2013.11.026

Bergstra, J., Yamins, D., Cox, D.D., 2013. Hyperopt: A python library for optimizing the hyperparameters of machine learning algorithms, in: Proceedings of the 12th Python in Science Conference. p. 20.

Betzel, R.F., 2022. Network neuroscience and the connectomics revolution, in: Connectomic Deep Brain Stimulation. Elsevier, pp. 25–58. https://doi.org/10.1016/B978-0-12-821861-7.00002-6

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

Biswal, B., Zerrin Yetkin, F., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar mri. Magn. Reson. Med. 34, 537–541. https://doi.org/10.1002/mrm.1910340409

Bittner, N., Jockwitz, C., Franke, K., Gaser, C., Moebus, S., Bayen, U.J., Amunts, K., Caspers, S., 2021. When your brain looks older than expected: combined lifestyle risk

and BrainAGE. Brain Struct Funct 226, 621–645. https://doi.org/10.1007/s00429-020-02184-6

Boeke, E.A., Holmes, A.J., Phelps, E.A., 2020. Toward Robust Anxiety Biomarkers: A Machine Learning Approach in a Large-Scale Sample. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 5, 799–807. https://doi.org/10.1016/j.bpsc.2019.05.018

Brickman, A.M., Meier, I.B., Korgaonkar, M.S., Provenzano, F.A., Grieve, S.M., Siedlecki, K.L., Wasserman, B.T., Williams, L.M., Zimmerman, M.E., 2012. Testing the white matter retrogenesis hypothesis of cognitive aging. Neurobiology of Aging 33, 1699–1715. https://doi.org/10.1016/j.neurobiolaging.2011.06.001

Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 10, 186–198. https://doi.org/10.1038/nrn2575

Bullmore, E.T., Bassett, D.S., 2011. Brain Graphs: Graphical Models of the Human Brain Connectome. Annu. Rev. Clin. Psychol. 7, 113–140. https://doi.org/10.1146/annurev-clinpsy-040510-143934

Cabeza, R., 2002. Hemispheric asymmetry reduction in older adults: The HAROLD model. Psychology and Aging 17, 85–100. https://doi.org/10.1037/0882-7974.17.1.85

Cabeza, R., 2001. Cognitive neuroscience of aging: Contributions of functional neuroimaging. Scandinavian Journal of Psychology 42, 277–286. https://doi.org/10.1111/1467-9450.00237

Cabeza, R., Albert, M., Belleville, S., Craik, F.I.M., Duarte, A., Grady, C.L., Lindenberger, U., Nyberg, L., Park, D.C., Reuter-Lorenz, P.A., Rugg, M.D., Steffener, J., Rajah, M.N., 2018. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. Nat Rev Neurosci 19, 701–710. https://doi.org/10.1038/s41583-018-0068-2

Cabral, J., Vidaurre, D., Marques, P., Magalhães, R., Silva Moreira, P., Miguel Soares, J., Deco, G., Sousa, N., Kringelbach, M.L., 2017. Cognitive performance in healthy older adults relates to spontaneous switching between states of functional connectivity during rest. Sci Rep 7, 5135. https://doi.org/10.1038/s41598-017-05425-7

Caspers, S., Moebus, S., Lux, S., Pundt, N., Schütz, H., Mühleisen, T.W., Gras, V., Eickhoff, S.B., Romanzetti, S., Stöcker, T., Stirnberg, R., Kirlangic, M.E., Minnerop, M., Pieperhoff, P., Mödder, U., Das, S., Evans, A.C., Jöckel, K.-H., Erbel, R., Cichon, S., Nöthen, M.M., Sturma, D., Bauer, A., Jon Shah, N., Zilles, K., Amunts, K., 2014. Studying variability in human brain aging in a population-based German cohort- rationale and design of 1000BRAINS. Front. Aging Neurosci. 6, 149. https://doi.org/10.3389/fnagi.2014.00149

Chan, M.Y., Alhazmi, F.H., Park, D.C., Savalia, N.K., Wig, G.S., 2017. Resting-State Network Topology Differentiates Task Signals across the Adult Life Span. J. Neurosci. 37, 2734–2745. https://doi.org/10.1523/JNEUROSCI.2406-16.2017

Chan, M.Y., Park, D.C., Savalia, N.K., Petersen, S.E., Wig, G.S., 2014. Decreased segregation of brain systems across the healthy adult lifespan. Proc Natl Acad Sci USA 111, E4997–E5006. https://doi.org/10.1073/pnas.1415122111

Chong, J.S.X., Ng, K.K., Tandi, J., Wang, C., Poh, J.-H., Lo, J.C., Chee, M.W.L., Zhou, J.H., 2019. Longitudinal Changes in the Cerebral Cortex Functional Organization of Healthy Elderly. J. Neurosci. 39, 5534–5550. https://doi.org/10.1523/JNEUROSCI.1451-18.2019

Chyzhyk, D., Varoquaux, G., Milham, M., Thirion, B., 2022. How to remove or control confounds in predictive models, with applications to brain biomarkers. GigaScience 11, giac014. https://doi.org/10.1093/gigascience/giac014

Cole, J.H., 2020. Multimodality neuroimaging brain-age in UK biobank: relationship to biomedical, lifestyle, and cognitive factors. Neurobiology of Aging 92, 34–42. https://doi.org/10.1016/j.neurobiolaging.2020.03.014

Colom, R., Karama, S., Jung, R.E., Haier, R.J., 2010. Human intelligence and brain networks. Dialogues in Clinical Neuroscience 12, 489–501. https://doi.org/10.31887/DCNS.2010.12.4/rcolom

Cox, S.R., Ritchie, S.J., Fawns-Ritchie, C., Tucker-Drob, E.M., Deary, I.J., 2019. Structural brain imaging correlates of general intelligence in UK Biobank. Intelligence 76, 101376. https://doi.org/10.1016/j.intell.2019.101376

Cui, Z., Gong, G., 2018. The effect of machine learning regression algorithms and sample size on individualized behavioral prediction with functional connectivity features. NeuroImage 178, 622–637. https://doi.org/10.1016/j.neuroimage.2018.06.001

Dadi, K., Rahim, M., Abraham, A., Chyzhyk, D., Milham, M., Thirion, B., Varoquaux, G., 2019. Benchmarking functional connectome-based predictive models for resting-state fMRI. NeuroImage 192, 115–134. https://doi.org/10.1016/j.neuroimage.2019.02.062

Dadi, K., Varoquaux, G., Houenou, J., Bzdok, D., Thirion, B., Engemann, D., 2021. Population modeling with machine learning can enhance measures of mental health. GigaScience 10, giab071. https://doi.org/10.1093/gigascience/giab071

Dai, Z., Yan, C., Li, K., Wang, Z., Wang, J., Cao, M., Lin, Q., Shu, N., Xia, M., Bi, Y., He, Y., 2015. Identifying and Mapping Connectivity Patterns of Brain Network Hubs in Alzheimer's Disease. Cereb. Cortex 25, 3723–3742. https://doi.org/10.1093/cercor/bhu246

Damoiseaux, J.S., 2017. Effects of aging on functional and structural brain connectivity.

NeuroImage 160, 32–40. https://doi.org/10.1016/j.neuroimage.2017.01.077

Damoiseaux, J.S., Beckmann, C.F., Arigita, E.J.S., Barkhof, F., Scheltens, Ph., Stam, C.J., Smith, S.M., Rombouts, S.A.R.B., 2008. Reduced resting-state brain activity in the "default network" in normal aging. Cerebral Cortex 18, 1856–1864. https://doi.org/10.1093/cercor/bhm207

Damoiseaux, J.S., Greicius, M.D., 2009. 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. https://doi.org/10.1007/s00429-009-0208-6

Davenport, T.H., Ronanki, R., 2018. Artificial intelligence for the real world. Harvard Business Review 96, 108–116.

de Dieu Uwisengeyimana, J., Nguchu, B.A., Wang, Y., Zhang, D., Liu, Y., Jiang, Z., Wang, X., Qiu, B., 2022. Longitudinal resting-state functional connectivity and regional brain atrophy-based biomarkers of preclinical cognitive impairment in healthy old adults. Aging Clin Exp Res. https://doi.org/10.1007/s40520-021-02067-8

Dhamala, E., Jamison, K.W., Jaywant, A., Dennis, S., Kuceyeski, A., 2021. Distinct functional and structural connections predict crystallised and fluid cognition in healthy adults. Hum Brain Mapp hbm.25420. https://doi.org/10.1002/hbm.25420

Dodge, H.H., Du, Y., Saxton, J.A., Ganguli, M., 2006. Cognitive Domains and Trajectories of Functional Independence in Nondemented Elderly Persons. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 61, 1330–1337. https://doi.org/10.1093/gerona/61.12.1330

Duara, R., Loewenstein, D.A., Potter, E., Appel, J., Greig, M.T., Urs, R., Shen, Q., Raj, A., Small, B., Barker, W., Schofield, E., Wu, Y., Potter, H., 2008. Medial temporal lobe atrophy on MRI scans and the diagnosis of Alzheimer disease. Neurology 71, 1986–1992. https://doi.org/10.1212/01.wnl.0000336925.79704.9f

Dubois, J., Galdi, P., Paul, L.K., Adolphs, R., 2018. A distributed brain network predicts general intelligence from resting-state human neuroimaging data. Phil. Trans. R. Soc. B 373, 20170284. https://doi.org/10.1098/rstb.2017.0284

Dyrba, M., Grothe, M., Kirste, T., Teipel, S.J., 2015. Multimodal analysis of functional and structural disconnection in Alzheimer's disease using multiple kernel SVM: Functional and Structural Disconnection in AD. Hum. Brain Mapp. 36, 2118–2131. https://doi.org/10.1002/hbm.22759

Easley, T., Chen, R., Hannon, K., Dutt, R., Bijsterbosch, J., 2023. Population modeling with machine learning can enhance measures of mental health - Open-data replication. Neuroimage: Reports 3, 100163. https://doi.org/10.1016/j.ynirp.2023.100163

Engemann, D.A., Kozynets, O., Sabbagh, D., Lemaître, G., Varoquaux, G., Liem, F., Gramfort, A., 2020. Combining magnetoencephalography with magnetic resonance imaging enhances learning of surrogate-biomarkers. eLife 9, e54055. https://doi.org/10.7554/eLife.54055

Ewers, M., Luan, Y., Frontzkowski, L., Neitzel, J., Rubinski, A., Dichgans, M., Hassenstab, J., Gordon, B.A., Chhatwal, J.P., Levin, J., Schofield, P., Benzinger, T.L.S., Morris, J.C., Goate, A., Karch, C.M., Fagan, A.M., McDade, E., Allegri, R., Berman, S., Chui, H., Cruchaga, C., Farlow, M., Graff-Radford, N., Jucker, M., Lee, J.-H., Martins, R.N., Mori, H., Perrin, R., Xiong, C., Rossor, M., Fox, N.C., O'Connor, A., Salloway, S., Danek, A., Buerger, K., Bateman, R.J., Habeck, C., Stern, Y., Franzmeier, N., for the Alzheimer's Disease Neuroimaging Initiative and the Dominantly Inherited Alzheimer Network, 2021. Segregation of functional networks is associated with cognitive resilience in Alzheimer's disease. Brain 144, 2176–2185. https://doi.org/10.1093/brain/awab112

Falcon, M.I., Jirsa, V., Solodkin, A., 2016. A new neuroinformatics approach to personalized medicine in neurology: The Virtual Brain. Current Opinion in Neurology 29, 429–436. https://doi.org/10.1097/WCO.0000000000000344

Farahani, F.V., Karwowski, W., Lighthall, N.R., 2019. Application of Graph Theory for Identifying Connectivity Patterns in Human Brain Networks: A Systematic Review. Front. Neurosci. 13, 585. https://doi.org/10.3389/fnins.2019.00585

Feilong, M., Guntupalli, J.S., Haxby, J.V., 2021. The neural basis of intelligence in fine-grained cortical topographies. eLife 10, e64058. https://doi.org/10.7554/eLife.64058

Feng, G., Wang, Y., Huang, W., Chen, H., Dai, Z., Ma, G., Li, X., Zhang, Z., Shu, N., 2022. Methodological evaluation of individual cognitive prediction based on the brain white matter structural connectome. Human Brain Mapping hbm.25883. https://doi.org/10.1002/hbm.25883

Ferreira, L.K., Busatto, G.F., 2013. Resting-state functional connectivity in normal brain aging. Neuroscience & Biobehavioral Reviews 37, 384–400. https://doi.org/10.1016/j.neubiorev.2013.01.017

Ferreira, L.K., Regina, A.C.B., Kovacevic, N., Martin, M. da G.M., Santos, P.P., Carneiro, C. de G., Kerr, D.S., Amaro, E., McIntosh, A.R., Busatto, G.F., 2016. Aging Effects on Whole-Brain Functional Connectivity in Adults Free of Cognitive and Psychiatric Disorders. Cereb. Cortex 26, 3851–3865. https://doi.org/10.1093/cercor/bhv190

Filzmoser, P., Liebmann, B., Varmuza, K., 2009. Repeated double cross validation. J. Chemometrics 23, 160–171. https://doi.org/10.1002/cem.1225

Fjell, A.M., Sneve, M.H., Grydeland, H., Storsve, A.B., Amlien, I.K., Yendiki, A., Walhovd,

K.B., 2017. Relationship between structural and functional connectivity change across the adult lifespan: A longitudinal investigation. Hum. Brain Mapp. 38, 561–573. https://doi.org/10.1002/hbm.23403

Fjell, A.M., Sneve, M.H., Grydeland, H., Storsve, A.B., de Lange, A.-M.G., Amlien, I.K., Røgeberg, O.J., Walhovd, K.B., 2015. Functional connectivity change across multiple cortical networks relates to episodic memory changes in aging. Neurobiology of Aging 36, 3255–3268. https://doi.org/10.1016/j.neurobiolaging.2015.08.020

Fjell, A.M., Sneve, M.H., Grydeland, H., Storsve, A.B., Walhovd, K.B., 2016. The Disconnected Brain and Executive Function Decline in Aging. Cereb. Cortex 27, 2303–2317. https://doi.org/10.1093/cercor/bhw082

Fjell, A.M., Walhovd, K.B., 2010. Structural Brain Changes in Aging: Courses, Causes and Cognitive Consequences. Reviews in the Neurosciences 21, 187–221. https://doi.org/10.1515/REVNEURO.2010.21.3.187

Fjell, A.M., Westlye, L.T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., Agartz, I., Salat, D.H., Greve, D.N., Fischl, B., Dale, A.M., Walhovd, K.B., 2009. High Consistency of Regional Cortical Thinning in Aging across Multiple Samples. Cerebral Cortex 19, 2001–2012. https://doi.org/10.1093/cercor/bhn232

Fornito, A., Zalesky, A., Breakspear, M., 2013. Graph analysis of the human connectome: Promise, progress, and pitfalls. NeuroImage 80, 426–444. https://doi.org/10.1016/j.neuroimage.2013.04.087

Franzmeier, N., Koutsouleris, N., Benzinger, T., Goate, A., Karch, C.M., Fagan, A.M., McDade, E., Duering, M., Dichgans, M., Levin, J., Gordon, B.A., Lim, Y.Y., Masters, C.L., Rossor, M., Fox, N.C., O'Connor, A., Chhatwal, J., Salloway, S., Danek, A., Hassenstab, J., Schofield, P.R., Morris, J.C., Bateman, R.J., the Alzheimer's disease neuroimaging initiative (ADNI), the Dominantly Inherited Alzheimer Network (DIAN), Ewers, M., 2020. Predicting sporadic Alzheimer's disease progression via inherited Alzheimer's disease-informed machine-learning. Alzheimers Dement. 16, 501–511. https://doi.org/10.1002/alz.12032

Gabrieli, J.D.E., Ghosh, S.S., Whitfield-Gabrieli, S., 2015. Prediction as a Humanitarian and Pragmatic Contribution from Human Cognitive Neuroscience. Neuron 85, 11–26. https://doi.org/10.1016/j.neuron.2014.10.047

Gao, M., Wong, C.H.Y., Huang, H., Shao, R., Huang, R., Chan, C.C.H., Lee, T.M.C., 2020. Connectome-based models can predict processing speed in older adults. NeuroImage 223, 117290. https://doi.org/10.1016/j.neuroimage.2020.117290

Gbadeyan, O., Teng, J., Prakash, R.S., 2022. Predicting response time variability from task

and resting-state functional connectivity in the aging brain. NeuroImage 250, 118890. https://doi.org/10.1016/j.neuroimage.2022.118890

Geerligs, L., Renken, R.J., Saliasi, E., Maurits, N.M., Lorist, M.M., 2015. A Brain-Wide Study of Age-Related Changes in Functional Connectivity. Cerebral Cortex 25, 1987–1999. https://doi.org/10.1093/cercor/bhu012

Gell, M., Eickhoff, S.B., Omidvarnia, A., Küppers, V., Patil, K.R., Satterthwaite, T.D., Müller, V.I., Langner, R., 2023. The Burden of Reliability: How Measurement Noise Limits Brain-Behaviour Predictions (preprint). Neuroscience. https://doi.org/10.1101/2023.02.09.527898

Genon, S., Eickhoff, S.B., Kharabian, S., 2022. Linking interindividual variability in brain structure to behaviour. Nat Rev Neurosci 23, 307–318. https://doi.org/10.1038/s41583-022-00584-7

Goh, J.O.S., 2011. Functional Dedifferentiation and Altered Connectivity in Older Adults: Neural Accounts of Cognitive Aging. Aging Dis 2, 30–48.

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

Grady, C., Sarraf, S., Saverino, C., Campbell, K., 2016. Age differences in the functional interactions among the default, frontoparietal control, and dorsal attention networks. Neurobiology of Aging 41, 159–172. https://doi.org/10.1016/j.neurobiolaging.2016.02.020

Guyon, I., Elisseeff, A., 2003. An Introduction to Variable and Feature Selection. Journal of machine learning research 1157–1182.

Habib, R., Nyberg, L., Nilsson, L.-G., 2007. Cognitive and Non-Cognitive Factors Contributing to the Longitudinal Identification of Successful Older Adults in the *Betula* Study. Aging, Neuropsychology, and Cognition 14, 257–273. https://doi.org/10.1080/13825580600582412

Harvey, P.D., 2019. Domains of cognition and their assessment. Dialogues in Clinical Neuroscience 21, 227–237. https://doi.org/10.31887/DCNS.2019.21.3/pharvey

Hastie, T., Tibshirani, R., Friedman, J.H., 2009. The elements of statistical learning: data mining, inference, and prediction, 2nd ed. ed, Springer series in statistics. Springer, New York, NY.

Hausman, H.K., O'Shea, A., Kraft, J.N., Boutzoukas, E.M., Evangelista, N.D., Van Etten, E.J., Bharadwaj, P.K., Smith, S.G., Porges, E., Hishaw, G.A., Wu, S., DeKosky, S., Alexander, G.E., Marsiske, M., Cohen, R., Woods, A.J., 2020. The Role of Resting-State Network Functional Connectivity in Cognitive Aging. Front. Aging Neurosci. 12, 177.

https://doi.org/10.3389/fnagi.2020.00177

He, T., Kong, R., Holmes, A.J., Nguyen, M., Sabuncu, M.R., Eickhoff, S.B., Bzdok, D., Feng, J., Yeo, B.T.T., 2020. Deep neural networks and kernel regression achieve comparable accuracies for functional connectivity prediction of behavior and demographics. NeuroImage 206, 116276. https://doi.org/10.1016/j.neuroimage.2019.116276

Heckner, M.K., Cieslik, E.C., Patil, K.R., Gell, M., Eickhoff, S.B., Hoffstädter, F., Langner, R., 2023. Predicting executive functioning from functional brain connectivity: network specificity and age effects. Cerebral Cortex 11, 6495–6507. https://doi.org/10.1093/cercor/bhac520

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

Hirsiger, S., Koppelmans, V., Mérillat, S., Liem, F., Erdeniz, B., Seidler, R.D., Jäncke, L., 2016. Structural and functional connectivity in healthy aging: Associations for cognition and motor behavior. Hum. Brain Mapp. 37, 855–867. https://doi.org/10.1002/hbm.23067

Hojjati, S.H., Ebrahimzadeh, A., Babajani-Feremi, A., 2019. Identification of the Early Stage of Alzheimer's Disease Using Structural MRI and Resting-State fMRI. Front. Neurol. 10, 904. https://doi.org/10.3389/fneur.2019.00904

Hojjati, S.H., Ebrahimzadeh, A., Khazaee, A., Babajani-Feremi, A., 2018. Predicting conversion from MCI to AD by integrating rs-fMRI and structural MRI. Computers in Biology and Medicine 102, 30–39. https://doi.org/10.1016/j.compbiomed.2018.09.004

Hojjati, S.H., Ebrahimzadeh, A., Khazaee, A., Babajani-Feremi, A., 2017. Predicting conversion from MCI to AD using resting-state fMRI, graph theoretical approach and SVM. Journal of Neuroscience Methods 282, 69–80. https://doi.org/10.1016/j.jneumeth.2017.03.006

Honey, C.J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J.P., Meuli, R., Hagmann, P., 2009. Predicting human resting-state functional connectivity from structural connectivity. PNAS 106, 2035–2040. https://doi.org/10.1073/pnas.0811168106

Hua, J., Tembe, W.D., Dougherty, E.R., 2009. Performance of feature-selection methods in the classification of high-dimension data. Pattern Recognition 42, 409–424. https://doi.org/10.1016/j.patcog.2008.08.001

Iordan, A.D., Cooke, K.A., Moored, K.D., Katz, B., Buschkuehl, M., Jaeggi, S.M., Jonides, J., Peltier, S.J., Polk, T.A., Reuter-Lorenz, P.A., 2018. Aging and Network Properties: Stability Over Time and Links with Learning during Working Memory Training. Front. Aging Neurosci. 9, 419. https://doi.org/10.3389/fnagi.2017.00419

Janssen, R.J., Mourão-Miranda, J., Schnack, H.G., 2018. Making Individual Prognoses in

Psychiatry Using Neuroimaging and Machine Learning. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 3, 798–808. https://doi.org/10.1016/j.bpsc.2018.04.004

Jbabdi, S., Johansen-Berg, H., 2011. Tractography: Where Do We Go from Here? Brain Connectivity 1, 169–183. https://doi.org/10.1089/brain.2011.0033

Jessen, F., Feyen, L., Freymann, K., Tepest, R., Maier, W., Heun, R., Schild, H.-H., Scheef, L., 2006. Volume reduction of the entorhinal cortex in subjective memory impairment. Neurobiology of Aging 27, 1751–1756. https://doi.org/10.1016/j.neurobiolaging.2005.10.010

Jiang, R., Calhoun, V.D., Fan, L., Zuo, N., Jung, R., Qi, S., Lin, D., Li, J., Zhuo, C., Song, M., Fu, Z., Jiang, T., Sui, J., 2020. Gender Differences in Connectome-based Predictions of Individualized Intelligence Quotient and Sub-domain Scores. Cerebral Cortex 30, 888–900. https://doi.org/10.1093/cercor/bhz134

Jiang, R., Scheinost, D., Zuo, N., Wu, J., Qi, S., Liang, Q., Zhi, D., Luo, N., Chung, Y., Liu, S., Xu, Y., Sui, J., Calhoun, V., 2022. A Neuroimaging Signature of Cognitive Aging from Whole-Brain Functional Connectivity. Advanced Science 9, 2201621. https://doi.org/10.1002/advs.202201621

Jockwitz, C., Caspers, S., 2021. Resting-state networks in the course of aging—differential insights from studies across the lifespan vs. amongst the old. Pflugers Arch - Eur J Physiol 473, 793–803. https://doi.org/10.1007/s00424-021-02520-7

Jockwitz, C., Caspers, S., Lux, S., Eickhoff, S.B., Jütten, K., Lenzen, S., Moebus, S., Pundt, N., Reid, A., Hoffstaedter, F., Jöckel, K.-H., Erbel, R., Cichon, S., Nöthen, M.M., Shah, N.J., Zilles, K., Amunts, K., 2017a. Influence of age and cognitive performance on resting-state brain networks of older adults in a population-based cohort. Cortex 89, 28–44. https://doi.org/10.1016/j.cortex.2017.01.008

Jockwitz, C., Caspers, S., Lux, S., Jütten, K., Schleicher, A., Eickhoff, S.B., Amunts, K., Zilles, K., 2017b. Age- and function-related regional changes in cortical folding of the default mode network in older adults. Brain Struct Funct 222, 83–99. https://doi.org/10.1007/s00429-016-1202-4

Jockwitz, C., Mérillat, S., Liem, F., Oschwald, J., Amunts, K., Caspers, S., Jäncke, L., 2019. Generalizing age effects on brain structure and cognition: A two-study comparison approach. Hum Brain Mapp 40, 2305–2319. https://doi.org/10.1002/hbm.24524

Jollans, L., Boyle, R., Artiges, E., Banaschewski, T., Desrivières, S., Grigis, A., Martinot, J.-L., Paus, T., Smolka, M.N., Walter, H., Schumann, G., Garavan, H., Whelan, R., 2019. Quantifying performance of machine learning methods for neuroimaging data.

NeuroImage 199, 351–365. https://doi.org/10.1016/j.neuroimage.2019.05.082

Kandaleft, D., Murayama, K., Roesch, E., Sakaki, M., 2022. Resting-state functional connectivity does not predict individual differences in the effects of emotion on memory. Sci Rep 12, 14481. https://doi.org/10.1038/s41598-022-18543-8

Kennedy, K.M., Raz, N., 2009. Aging white matter and cognition: Differential effects of regional variations in diffusion properties on memory, executive functions, and speed. Neuropsychologia 47, 916–927. https://doi.org/10.1016/j.neuropsychologia.2009.01.001

Khazaee, A., Ebrahimzadeh, A., Babajani-Feremi, A., 2016. Application of advanced machine learning methods on resting-state fMRI network for identification of mild cognitive impairment and Alzheimer's disease. Brain Imaging and Behavior 10, 799–817. https://doi.org/10.1007/s11682-015-9448-7

Khosla, M., Jamison, K., Ngo, G.H., Kuceyeski, A., Sabuncu, M.R., 2019. Machine learning in resting-state fMRI analysis. Magnetic Resonance Imaging 64, 101–121. https://doi.org/10.1016/j.mri.2019.05.031

Koen, J.D., Rugg, M.D., 2019. Neural Dedifferentiation in the Aging Brain. Trends in Cognitive Sciences 23, 547–559. https://doi.org/10.1016/j.tics.2019.04.012

Koen, J.D., Srokova, S., Rugg, M.D., 2020. Age-related neural dedifferentiation and cognition. Current Opinion in Behavioral Sciences 32, 7–14. https://doi.org/10.1016/j.cobeha.2020.01.006

Kong, R., Li, J., Orban, C., Sabuncu, M.R., Liu, H., Schaefer, A., Sun, N., Zuo, X.-N., Holmes, A.J., Eickhoff, S.B., Yeo, B.T.T., 2019. Spatial Topography of Individual-Specific Cortical Networks Predicts Human Cognition, Personality, and Emotion. Cerebral Cortex 29, 2533–2551. https://doi.org/10.1093/cercor/bhy123

Koutsouleris, N., Davatzikos, C., Borgwardt, S., Gaser, C., Bottlender, R., Frodl, T., Falkai, P., Riecher-Rossler, A., Moller, H.-J., Reiser, M., Pantelis, C., Meisenzahl, E., 2014. Accelerated Brain Aging in Schizophrenia and Beyond: A Neuroanatomical Marker of Psychiatric Disorders. Schizophrenia Bulletin 40, 1140–1153. https://doi.org/10.1093/schbul/sbt142

Koutsouleris, N., Gaser, C., Patschurek-Kliche, K., Scheuerecker, J., Bottlender, R., Decker, P., Schmitt, G., Reiser, M., Möller, H.-J., Meisenzahl, E.M., 2012. Multivariate patterns of brain–cognition associations relating to vulnerability and clinical outcome in the at-risk mental states for psychosis. Hum. Brain Mapp. 33, 2104–2124. https://doi.org/10.1002/hbm.21342

Koutsouleris, N., Kahn, R.S., Chekroud, A.M., Leucht, S., Falkai, P., Wobrock, T., Derks, E.M., Fleischhacker, W.W., Hasan, A., 2016. Multisite prediction of 4-week and 52-week

treatment outcomes in patients with first-episode psychosis: a machine learning approach. The Lancet Psychiatry 3, 935–946. https://doi.org/10.1016/S2215-0366(16)30171-7

Krämer, C., Stumme, J., Da Costa Campos, L., Dellani, P., Rubbert, C., Caspers, J., Caspers, S., Jockwitz, C., 2024. Prediction of cognitive performance differences in older age from multimodal neuroimaging data. GeroScience 46, 283–308. https://doi.org/10.1007/s11357-023-00831-4

Krämer, C., Stumme, J., da Costa Campos, L., Rubbert, C., Caspers, J., Caspers, S., Jockwitz, C., 2023. Classification and prediction of cognitive performance differences in older age based on brain network patterns using a machine learning approach. Network Neuroscience 7, 122–147. https://doi.org/10.1162/netn_a_00275

Kwak, S., Kim, Hairin, Kim, Hoyoung, Youm, Y., Chey, J., 2021a. Distributed functional connectivity predicts neuropsychological test performance among older adults. Hum Brain Mapp 42, 6495–6507. https://doi.org/10.1002/hbm.25436

Kwak, S., Park, S.M., Jeon, Y.-J., Ko, H., Oh, D.J., Lee, J.-Y., 2021b. Multiple Cognitive and Behavioral Factors Link Association Between Brain Structure and Functional Impairment of Daily Instrumental Activities in Older Adults. J Int Neuropsychol Soc 1–14. https://doi.org/10.1017/S1355617721000916

LaPlume, A.A., Anderson, N.D., McKetton, L., Levine, B., Troyer, A.K., 2022. When I'm 64: Age-Related Variability in Over 40,000 Online Cognitive Test Takers. The Journals of Gerontology: Series B 77, 104–117. https://doi.org/10.1093/geronb/gbab143

Lavanga, M., Stumme, J., Yalcinkaya, B.H., Fousek, J., Jockwitz, C., Sheheitli, H., Bittner, N., Hashemi, M., Petkoski, S., Caspers, S., Jirsa, V., 2022. The virtual aging brain: a model-driven explanation for cognitive decline in older subjects (preprint). Neuroscience. https://doi.org/10.1101/2022.02.17.480902

Lemaitre, H., Goldman, A.L., Sambataro, F., Verchinski, B.A., Meyer-Lindenberg, A., Weinberger, D.R., Mattay, V.S., 2012. Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and gray matter volume? Neurobiology of Aging 33, 617.e1-617.e9. https://doi.org/10.1016/j.neurobiolaging.2010.07.013

Lemm, S., Blankertz, B., Dickhaus, T., Müller, K.-R., 2011. Introduction to machine learning for brain imaging. NeuroImage 56, 387–399. https://doi.org/10.1016/j.neuroimage.2010.11.004

Li, X., Wang, Y., Wang, W., Huang, W., Chen, K., Xu, K., Zhang, J., Chen, Y., Li, H., Wei, D., Shu, N., Zhang, Z., 2020. Age-Related Decline in the Topological Efficiency of the

Brain Structural Connectome and Cognitive Aging. Cerebral Cortex 30, 4651–4661. https://doi.org/10.1093/cercor/bhaa066

Liem, F., Varoquaux, G., Kynast, J., Beyer, F., Kharabian Masouleh, S., Huntenburg, J.M., Lampe, L., Rahim, M., Abraham, A., Craddock, R.C., Riedel-Heller, S., Luck, T., Loeffler, M., Schroeter, M.L., Witte, A.V., Villringer, A., Margulies, D.S., 2017. Predicting brain-age from multimodal imaging data captures cognitive impairment. NeuroImage 148, 179–188. https://doi.org/10.1016/j.neuroimage.2016.11.005

Lin, Q., Rosenberg, M.D., Yoo, K., Hsu, T.W., O'Connell, T.P., Chun, M.M., 2018. Resting-State Functional Connectivity Predicts Cognitive Impairment Related to Alzheimer's Disease. Front. Aging Neurosci. 10, 94. https://doi.org/10.3389/fnagi.2018.00094

Litwińczuk, M.C., Muhlert, N., Cloutman, L., Trujillo-Barreto, N., Woollams, A., 2022. Combination of structural and functional connectivity explains unique variation in specific domains of cognitive function. NeuroImage 262, 119531. https://doi.org/10.1016/j.neuroimage.2022.119531

Lockhart, S.N., DeCarli, C., 2014. Structural Imaging Measures of Brain Aging. Neuropsychol Rev 24, 271–289. https://doi.org/10.1007/s11065-014-9268-3

Madden, D.J., Bennett, I.J., Burzynska, A., Potter, G.G., Chen, N., Song, A.W., 2012. Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 1822, 386–400. https://doi.org/10.1016/j.bbadis.2011.08.003

Madden, D.J., Bennett, I.J., Song, A.W., 2009. Cerebral White Matter Integrity and Cognitive Aging: Contributions from Diffusion Tensor Imaging. Neuropsychol Rev 19, 415–435. https://doi.org/10.1007/s11065-009-9113-2

Madden, D.J., Jain, S., Monge, Z.A., Cook, A.D., Lee, A., Huang, H., Howard, C.M., Cohen, J.R., 2020. Influence of structural and functional brain connectivity on age-related differences in fluid cognition. Neurobiology of Aging 96, 205–222. https://doi.org/10.1016/j.neurobiolaging.2020.09.010

Malagurski, B., Liem, F., Oschwald, J., Mérillat, S., Jäncke, L., 2020. Functional dedifferentiation of associative resting state networks in older adults – A longitudinal study. NeuroImage 214, 116680. https://doi.org/10.1016/j.neuroimage.2020.116680

Mather, M., 2010. Aging and cognition. WIREs Cogn Sci 1, 346–362. https://doi.org/10.1002/wcs.64

McConathy, J., Sheline, Y.I., 2015. Imaging Biomarkers Associated With Cognitive Decline: A Review. Biological Psychiatry 77, 685–692. https://doi.org/10.1016/j.biopsych.2014.08.024

Mowinckel, A.M., Espeseth, T., Westlye, L.T., 2012. Network-specific effects of age and in-scanner subject motion: A resting-state fMRI study of 238 healthy adults. NeuroImage 63, 1364–1373. https://doi.org/10.1016/j.neuroimage.2012.08.004

Murdaca, G., Banchero, S., Tonacci, A., Nencioni, A., Monacelli, F., Gangemi, S., 2021. Vitamin D and Folate as Predictors of MMSE in Alzheimer's Disease: A Machine Learning Analysis. Diagnostics 11, 940. https://doi.org/10.3390/diagnostics11060940

Mwangi, B., Tian, T.S., Soares, J.C., 2014. A Review of Feature Reduction Techniques in Neuroimaging. Neuroinform 12, 229–244. https://doi.org/10.1007/s12021-013-9204-3

Nashiro, K., Sakaki, M., Braskie, M.N., Mather, M., 2017. Resting-state networks associated with cognitive processing show more age-related decline than those associated with emotional processing. Neurobiology of Aging 54, 152–162. https://doi.org/10.1016/j.neurobiolaging.2017.03.003

Nemali, A., Vockert, N., Berron, D., Maas, A., Yakupov, R., Peters, O., Gref, D., Cosma, N., Preis, L., Priller, J., Spruth, E., Altenstein, S., Lohse, A., Fliessbach, K., Kimmich, O., Vogt, I., Wiltfang, J., Hansen, N., Bartels, C., Schott, B.H., Maier, F., Meiberth, D., Glanz, W., Incesoy, E., Butryn, M., Buerger, K., Janowitz, D., Ewers, M., Perneczhy, R., Rauchmann, B., Burow, L., Teipel, S., Kilimann, I., Göerß, D., Dyrba, M., Laske, C., Munk, M., Sanzenbacher, C., Müller, S., Spottke, A., Roy, N., Heneka, M., Brosseron, F., Roeske, S., Dobisch, L., Ramirez, A., Ewers, M., Dechent, P., Scheffler, K., Kleineidam, L., Wolfsgruber, S., Wagner, M., Jessen, F., Duzel, E., Ziegler, G., 2022. Individualized Gaussian Process-based Prediction of Memory Performance and Biomarker Status in Ageing and Alzheimer's disease (preprint). Neuroscience. https://doi.org/10.1101/2022.03.14.484226

Ng, K.K., Lo, J.C., Lim, J.K.W., Chee, M.W.L., 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. https://doi.org/10.1016/j.neuroimage.2016.03.029

Nikolaidis, A., Chen, A.A., He, X., Shinohara, R., Vogelstein, J., Milham, M., Shou, H., 2022. Suboptimal phenotypic reliability impedes reproducible human neuroscience (preprint). Neuroscience. https://doi.org/10.1101/2022.07.22.501193

Omidvarnia, A., Sasse, L., Larabi, D.I., Raimondo, F., Hoffstaedter, F., Kasper, J., Dukart, J., Petersen, M., Cheng, B., Thomalla, G., Eickhoff, S.B., Patil, K.R., 2023. Is resting state fMRI better than individual characteristics at predicting cognition? (preprint). Neuroscience. https://doi.org/10.1101/2023.02.18.529076

Onoda, K., Ishihara, M., Yamaguchi, S., 2012. Decreased Functional Connectivity by Aging

Is Associated with Cognitive Decline. Journal of Cognitive Neuroscience 24, 2186–2198. https://doi.org/10.1162/jocn_a_00269

O'Reilly, J.X., Croxson, P.L., Jbabdi, S., Sallet, J., Noonan, M.P., Mars, R.B., Browning, P.G.F., Wilson, C.R.E., Mitchell, A.S., Miller, K.L., Rushworth, M.F.S., Baxter, M.G., 2013. Causal effect of disconnection lesions on interhemispheric functional connectivity in rhesus monkeys. Proc. Natl. Acad. Sci. U.S.A. 110, 13982–13987. https://doi.org/10.1073/pnas.1305062110

Orrù, G., Pettersson-Yeo, W., Marquand, A.F., Sartori, G., Mechelli, A., 2012. Using Support Vector Machine to identify imaging biomarkers of neurological and psychiatric disease: A critical review. Neuroscience & Biobehavioral Reviews 36, 1140–1152. https://doi.org/10.1016/j.neubiorev.2012.01.004

Oschwald, J., Guye, S., Liem, F., Rast, P., Willis, S., Röcke, C., Jäncke, L., Martin, M., Mérillat, S., 2019. Brain structure and cognitive ability in healthy aging: a review on longitudinal correlated change. Reviews in the Neurosciences 31, 1–57. https://doi.org/10.1515/revneuro-2018-0096

Pacheco, J., Goh, J.O., Kraut, M.A., Ferrucci, L., Resnick, S.M., 2015. Greater cortical thinning in normal older adults predicts later cognitive impairment. Neurobiology of Aging 36, 903–908. https://doi.org/10.1016/j.neurobiolaging.2014.08.031

Park, D.C., Polk, T.A., Park, R., Minear, M., Savage, A., Smith, M.R., 2004. Aging reduces neural specialization in ventral visual cortex. Proc. Natl. Acad. Sci. U.S.A. 101, 13091–13095. https://doi.org/10.1073/pnas.0405148101

Park, D.C., Reuter-Lorenz, P., 2009. The Adaptive Brain: Aging and Neurocognitive Scaffolding. Annu. Rev. Psychol. 60, 173–196. https://doi.org/10.1146/annurev.psych.59.103006.093656

Patel, R., Mackay, C.E., Jansen, M.G., Devenyi, G.A., O'Donoghue, M.C., Kivimäki, M., Singh-Manoux, A., Zsoldos, E., Ebmeier, K.P., Chakravarty, M.M., Suri, S., 2022. Inter- and intra-individual variation in brain structural-cognition relationships in aging. NeuroImage 257, 119254. https://doi.org/10.1016/j.neuroimage.2022.119254

Paulus, M.P., Kuplicki, R., Yeh, H.-W., 2019. Machine Learning and Brain Imaging: Opportunities and Challenges. Trends in Neurosciences 42, 659–661. https://doi.org/10.1016/j.tins.2019.07.007

Paulus, M.P., Thompson, W.K., 2021. Computational approaches and machine learning for individual-level treatment predictions. Psychopharmacology 238, 1231–1239. https://doi.org/10.1007/s00213-019-05282-4

Perry, A., Wen, W., Kochan, N.A., Thalamuthu, A., Sachdev, P.S., Breakspear, M., 2017.

The independent influences of age and education on functional brain networks and cognition in healthy older adults. Hum. Brain Mapp. 38, 5094–5114. https://doi.org/10.1002/hbm.23717

Persson, J., Nyberg, L., Lind, J., Larsson, A., Nilsson, L.-G., Ingvar, M., Buckner, R.L., 2006. Structure–Function Correlates of Cognitive Decline in Aging. Cerebral Cortex 16, 907–915. https://doi.org/10.1093/cercor/bhj036

Pervaiz, U., Vidaurre, D., Woolrich, M.W., Smith, S.M., 2020. Optimising network modelling methods for fMRI. NeuroImage 211, 116604. https://doi.org/10.1016/j.neuroimage.2020.116604

Petkoski, S., Ritter, P., Jirsa, V.K., 2023. White-matter degradation and dynamical compensation support age-related functional alterations in human brain. Cerebral Cortex 33, 6241–6256. https://doi.org/10.1093/cercor/bhac500

Pläschke, R.N., Patil, K.R., Cieslik, E.C., Nostro, A.D., Varikuti, D.P., Plachti, A., Lösche, P., Hoffstaedter, F., Kalenscher, T., Langner, R., Eickhoff, S.B., 2020. Age differences in predicting working memory performance from network-based functional connectivity. Cortex 132, 441–459. https://doi.org/10.1016/j.cortex.2020.08.012

Pur, D.R., Preti, M.G., de Ribaupierre, A., Van De Ville, D., Eagleson, R., Mella, N., de Ribaupierre, S., 2022. Mapping of Structure-Function Age-Related Connectivity Changes on Cognition Using Multimodal MRI. Front. Aging Neurosci. 14, 757861. https://doi.org/10.3389/fnagi.2022.757861

Rahim, M., Thirion, B., Comtat, C., Varoquaux, G., 2016. Transmodal Learning of Functional Networks for Alzheimer's Disease Prediction. IEEE J. Sel. Top. Signal Process. 10, 1204–1213. https://doi.org/10.1109/JSTSP.2016.2600400

Rasero, J., Sentis, A.I., Yeh, F.-C., Verstynen, T., 2021. Integrating across neuroimaging modalities boosts prediction accuracy of cognitive ability. PLoS Comput Biol 17, e1008347. https://doi.org/10.1371/journal.pcbi.1008347

Raz, N., 2000. Aging of the brain and its impact on cognitive performance: Integration of structural and functional findings., in: The Handbook of Aging and Cognition, 2nd Ed. Lawrence Erlbaum Associates Publishers, Mahwah, NJ, US, pp. 1–90.

Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional Brain Changes in Aging Healthy Adults: General Trends, Individual Differences and Modifiers. Cereb Cortex 15, 1676–1689. https://doi.org/10.1093/cercor/bhi044

Raz, N., Rodrigue, K.M., 2006. Differential aging of the brain: Patterns, cognitive correlates and modifiers. Neuroscience & Biobehavioral Reviews 30, 730–748.

https://doi.org/10.1016/j.neubiorev.2006.07.001

Reuter-Lorenz, P.A., Cappell, K.A., 2008. Neurocognitive Aging and the Compensation Hypothesis. Curr Dir Psychol Sci 17, 177–182. https://doi.org/10.1111/j.1467-8721.2008.00570.x

Ritchie, S.J., Dickie, D.A., Cox, S.R., Valdes Hernandez, M. del C., Corley, J., Royle, N.A., Pattie, A., Aribisala, B.S., Redmond, P., Muñoz Maniega, S., Taylor, A.M., Sibbett, R., Gow, A.J., Starr, J.M., Bastin, M.E., Wardlaw, J.M., Deary, I.J., 2015. Brain volumetric changes and cognitive ageing during the eighth decade of life. Hum. Brain Mapp. 36, 4910–4925. https://doi.org/10.1002/hbm.22959

Ritter, P., Schirner, M., McIntosh, A.R., Jirsa, V.K., 2013. The Virtual Brain Integrates Computational Modeling and Multimodal Neuroimaging. Brain Connectivity 3, 121–145. https://doi.org/10.1089/brain.2012.0120

Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: Uses and interpretations. NeuroImage 52, 1059–1069. https://doi.org/10.1016/j.neuroimage.2009.10.003

Sala-Llonch, R., Bartrés-Faz, D., Junqué, C., 2015. Reorganization of brain networks in aging: a review of functional connectivity studies. Front. Psychol. 6, 663. https://doi.org/10.3389/fpsyg.2015.00663

Salami, A., Eriksson, J., Nilsson, L.-G., Nyberg, L., 2012. Age-related white matter microstructural differences partly mediate age-related decline in processing speed but not cognition. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 1822, 408–415. https://doi.org/10.1016/j.bbadis.2011.09.001

Salat, D.H., 2004. Thinning of the Cerebral Cortex in Aging. Cerebral Cortex 14, 721–730. https://doi.org/10.1093/cercor/bhh032

Salthouse, T.A., 2011. Cognitive correlates of cross-sectional differences and longitudinal changes in trail making performance. Journal of Clinical and Experimental Neuropsychology 33, 242–248. https://doi.org/10.1080/13803395.2010.509922

Salthouse, T.A., 2010. Selective review of cognitive aging. J Int Neuropsychol Soc 16, 754–760. https://doi.org/10.1017/S1355617710000706

Salthouse, T.A., 2009. When does age-related cognitive decline begin? Neurobiology of Aging 30, 507–514. https://doi.org/10.1016/j.neurobiolaging.2008.09.023

Salthouse, T.A., 2004. What and When of Cognitive Aging. Curr Dir Psychol Sci 13, 140–144. https://doi.org/10.1111/j.0963-7214.2004.00293.x

Sanz-Arigita, E.J., Schoonheim, M.M., Damoiseaux, J.S., Rombouts, S.A.R.B., Maris, E., Barkhof, F., Scheltens, P., Stam, C.J., 2010. Loss of 'Small-World' Networks in

Alzheimer's Disease: Graph Analysis of fMRI Resting-State Functional Connectivity. PLoS ONE 5, e13788. https://doi.org/10.1371/journal.pone.0013788

Sarwar, T., Ramamohanarao, K., Zalesky, A., 2019. Mapping connectomes with diffusion MRI: deterministic or probabilistic tractography? Magn Reson Med 81, 1368–1384. https://doi.org/10.1002/mrm.27471

Sasse, L., Larabi, D.I., Omidvarnia, A., Jung, K., Hoffstaedter, F., Jocham, G., Eickhoff, S.B., Patil, K.R., 2022. Intermediately Synchronised Brain States optimise trade-off between Subject Identifiability and Predictive Capacity (preprint). Neuroscience. https://doi.org/10.1101/2022.09.30.510304

Scarpazza, C., Ha, M., Baecker, L., Garcia-Dias, R., Pinaya, W.H.L., Vieira, S., Mechelli, A., 2020. Translating research findings into clinical practice: a systematic and critical review of neuroimaging-based clinical tools for brain disorders. Transl Psychiatry 10, 107. https://doi.org/10.1038/s41398-020-0798-6

Schulz, M.-A., Bzdok, D., Haufe, S., Haynes, J.-D., Ritter, K., 2022. Performance reserves in brain-imaging-based phenotype prediction (preprint). Neuroscience. https://doi.org/10.1101/2022.02.23.481601

Shafto, M.A., Tyler, L.K., 2014. Language in the aging brain: The network dynamics of cognitive decline and preservation. Science 346, 583–587. https://doi.org/10.1126/science.1254404

Sipper, M., 2022. High Per Parameter: A Large-Scale Study of Hyperparameter Tuning for Machine Learning Algorithms. Algorithms 15, 315. https://doi.org/10.3390/a15090315

Snoek, L., Miletić, S., Scholte, H.S., 2019. How to control for confounds in decoding analyses of neuroimaging data. NeuroImage 184, 741–760. https://doi.org/10.1016/j.neuroimage.2018.09.074

Soch, J., Richter, A., Kizilirmak, J.M., Schütze, H., Feldhoff, H., Fischer, L., Knopf, L., Raschick, M., Schult, A., Düzel, E., Schott, B.H., 2022. Structural and functional MRI data differentially predict chronological age and behavioral memory performance (preprint). Neuroscience. https://doi.org/10.1101/2022.03.24.485603

Sotiropoulos, S.N., Zalesky, A., 2019. Building connectomes using diffusion MRI: why, how and but. NMR in Biomedicine 32. https://doi.org/10.1002/nbm.3752

Sporns, O., 2011. The human connectome: a complex network: The human connectome. Annals of the New York Academy of Sciences 1224, 109–125. https://doi.org/10.1111/j.1749-6632.2010.05888.x

Sporns, O., Tononi, G., Kötter, R., 2005. The Human Connectome: A Structural Description of the Human Brain. PLoS Comp Biol 1, e42.

https://doi.org/10.1371/journal.pcbi.0010042

Spreng, R.N., Stevens, W.D., Viviano, J.D., Schacter, D.L., 2016. Attenuated anticorrelation between the default and dorsal attention networks with aging: evidence from task and rest. Neurobiology of Aging 45, 149–160. https://doi.org/10.1016/j.neurobiolaging.2016.05.020

Spreng, R.N., Turner, G.R., 2019. Structure and function of the aging brain., in: Samanez-Larkin, G.R. (Ed.), The Aging Brain: Functional Adaptation across Adulthood. American Psychological Association, Washington, pp. 9–43. https://doi.org/10.1037/0000143-002

Sripada, C., Angstadt, M., Rutherford, S., Taxali, A., Shedden, K., 2020a. Toward a "treadmill test" for cognition: Improved prediction of general cognitive ability from the task activated brain. Hum Brain Mapp 41, 3186–3197. https://doi.org/10.1002/hbm.25007

Sripada, C., Rutherford, S., Angstadt, M., Thompson, W.K., Luciana, M., Weigard, A., Hyde, L.H., Heitzeg, M., 2020b. Prediction of neurocognition in youth from resting state fMRI. Mol Psychiatry 25, 3413–3421. https://doi.org/10.1038/s41380-019-0481-6

Stanley, M.L., Moussa, M.N., Paolini, B.M., Lyday, R.G., Burdette, J.H., Laurienti, P.J., 2013. Defining nodes in complex brain networks. Front. Comput. Neurosci. 7. https://doi.org/10.3389/fncom.2013.00169

Stites, S.D., Harkins, K., Rubright, J.D., Karlawish, J., 2018. Relationships Between Cognitive Complaints and Quality of Life in Older Adults With Mild Cognitive Impairment, Mild Alzheimer Disease Dementia, and Normal Cognition. Alzheimer Disease & Associated Disorders 32, 276–283. https://doi.org/10.1097/WAD.0000000000000262

Straathof, M., Sinke, M.R., Dijkhuizen, R.M., Otte, W.M., 2019. A systematic review on the quantitative relationship between structural and functional network connectivity strength in mammalian brains. J Cereb Blood Flow Metab 39, 189–209. https://doi.org/10.1177/0271678X18809547

Stumme, J., Jockwitz, C., Hoffstaedter, F., Amunts, K., Caspers, S., 2020. Functional network reorganization in older adults: Graph-theoretical analyses of age, cognition and sex. NeuroImage 214, 116756. https://doi.org/10.1016/j.neuroimage.2020.116756

Stumme, J., Krämer, C., Miller, T., Schreiber, J., Caspers, S., Jockwitz, C., 2022. Interrelating differences in structural and functional connectivity in the older adult's brain. Human Brain Mapping 43, 5543–5561. https://doi.org/10.1002/hbm.26030

Suárez, L.E., Markello, R.D., Betzel, R.F., Misic, B., 2020. Linking Structure and Function in Macroscale Brain Networks. Trends in Cognitive Sciences 24, 302–315. https://doi.org/10.1016/j.tics.2020.01.008

Supekar, K., Menon, V., Rubin, D., Musen, M., Greicius, M.D., 2008. Network Analysis of

Intrinsic Functional Brain Connectivity in Alzheimer's Disease. PLoS Comput Biol 4, e1000100. https://doi.org/10.1371/journal.pcbi.1000100

Tetereva, A., Li, J., Deng, J.D., Stringaris, A., Pat, N., 2022. Capturing brain-cognition relationship: Integrating task-based fMRI across tasks markedly boosts prediction and test-retest reliability. NeuroImage 263, 119588. https://doi.org/10.1016/j.neuroimage.2022.119588

Tomasi, D., Volkow, N.D., 2012. Laterality patterns of brain functional connectivity: gender effects. Cereb. Cortex 22, 1455–1462. https://doi.org/10.1093/cercor/bhr230

Tomaszewski Farias, S., Cahn-Weiner, D.A., Harvey, D.J., Reed, B.R., Mungas, D., Kramer, J.H., Chui, H., 2009. Longitudinal Changes in Memory and Executive Functioning are Associated with longitudinal change in instrumental activities of daily living in older Adults. The Clinical Neuropsychologist 23, 446–461. https://doi.org/10.1080/13854040802360558

Tsang, A., Lebel, C.A., Bray, S.L., Goodyear, B.G., Hafeez, M., Sotero, R.C., McCreary, C.R., Frayne, R., 2017. White Matter Structural Connectivity Is Not Correlated to Cortical Resting-State Functional Connectivity over the Healthy Adult Lifespan. Front. Aging Neurosci. 9, 144. https://doi.org/10.3389/fnagi.2017.00144

Tsapanou, A., Stern, Y., Habeck, C., 2020. Optimized prediction of cognition based on brain morphometry across the adult life span. Neurobiology of Aging 93, 16–24. https://doi.org/10.1016/j.neurobiolaging.2020.04.015

Tucker-Drob, E.M., 2011. Global and domain-specific changes in cognition throughout adulthood. Developmental Psychology 47, 331–343. https://doi.org/10.1037/a0021361

Tucker-Drob, E.M., Reynolds, C.A., Finkel, D., Pedersen, N.L., 2014. Shared and unique genetic and environmental influences on aging-related changes in multiple cognitive abilities. Developmental Psychology 50, 152–166. https://doi.org/10.1037/a0032468

Tucker-Drob, E.M., Salthouse, T.A., 2013. Individual Differences in Cognitive Aging, in: Chamorro-Premuzic, T., von Stumm, S., Furnham, A. (Eds.), The Wiley-Blackwell Handbook of Individual Differences. Wiley-Blackwell, Oxford, UK, pp. 242–267. https://doi.org/10.1002/9781444343120.ch9

United Nations, Department of Economic and Social Affairs, Population Division, 2020. World population ageing, 2019 highlights.

Varoquaux, G., Raamana, P.R., Engemann, D., Hoyos-Idrobo, A., Schwartz, Y., Thirion, B., 2017. Assessing and tuning brain decoders: cross-validation, caveats, and guidelines. NeuroImage 145, 166–179. https://doi.org/10.1016/j.neuroimage.2016.10.038

Vieira, B.H., Liem, F., Dadi, K., Engemann, D.A., Gramfort, A., Bellec, P., Craddock, R.C.,

Damoiseaux, J.S., Steele, C.J., Yarkoni, T., Langer, N., Margulies, D.S., Varoquaux, G., 2022a. Predicting future cognitive decline from non-brain and multimodal brain imaging data in healthy and pathological aging. Neurobiology of Aging 118, 55–65. https://doi.org/10.1016/j.neurobiolaging.2022.06.008

Vieira, B.H., Pamplona, G.S.P., Fachinello, K., Silva, A.K., Foss, M.P., Salmon, C.E.G., 2022b. On the prediction of human intelligence from neuroimaging: A systematic review of methods and reporting. Intelligence 93, 101654. https://doi.org/10.1016/j.intell.2022.101654

Viviano, R.P., Raz, N., Yuan, P., Damoiseaux, J.S., 2017. Associations between dynamic functional connectivity and age, metabolic risk, and cognitive performance. Neurobiology of Aging 59, 135–143. https://doi.org/10.1016/j.neurobiolaging.2017.08.003

Voineskos, A.N., Rajji, T.K., Lobaugh, N.J., Miranda, D., Shenton, M.E., Kennedy, J.L., Pollock, B.G., Mulsant, B.H., 2012. Age-related decline in white matter tract integrity and cognitive performance: A DTI tractography and structural equation modeling study. Neurobiology of Aging 33, 21–34. https://doi.org/10.1016/j.neurobiolaging.2010.02.009

Voss, M.W., Wong, C.N., Baniqued, P.L., Burdette, J.H., Erickson, K.I., Prakash, R.S., McAuley, E., Laurienti, P.J., Kramer, A.F., 2013. Aging Brain from a Network Science Perspective: Something to Be Positive About? PLoS ONE 8, e78345. https://doi.org/10.1371/journal.pone.0078345

Wee, C.-Y., Yap, P.-T., Zhang, D., Denny, K., Browndyke, J.N., Potter, G.G., Welsh-Bohmer, K.A., Wang, L., Shen, D., 2012. Identification of MCI individuals using structural and functional connectivity networks. NeuroImage 59, 2045–2056. https://doi.org/10.1016/j.neuroimage.2011.10.015

Wen, W., Zhu, W., He, Y., Kochan, N.A., Reppermund, S., Slavin, M.J., Brodaty, H., Crawford, J., Xia, A., Sachdev, P., 2011. Discrete Neuroanatomical Networks Are Associated with Specific Cognitive Abilities in Old Age. Journal of Neuroscience 31, 1204–1212. https://doi.org/10.1523/JNEUROSCI.4085-10.2011

Whalley, L.J., Deary, I.J., Appleton, C.L., Starr, J.M., 2004. Cognitive reserve and the neurobiology of cognitive aging. Ageing Research Reviews 3, 369–382. https://doi.org/10.1016/j.arr.2004.05.001

Wig, G.S., Schlaggar, B.L., Petersen, S.E., 2011. Concepts and principles in the analysis of brain networks: Brain networks. Annals of the New York Academy of Sciences 1224, 126–146. https://doi.org/10.1111/j.1749-6632.2010.05947.x

Woo, C.-W., Chang, L.J., Lindquist, M.A., Wager, T.D., 2017. Building better biomarkers: brain models in translational neuroimaging. Nat Neurosci 20, 365–377.

https://doi.org/10.1038/nn.4478

World Health Organization, 2020. Decade of healthy ageing: baseline report. World Health Organization, Geneva.

Wu, J., Li, J., Eickhoff, S.B., Hoffstaedter, F., Hanke, M., Yeo, B.T.T., Genon, S., 2022. Cross-cohort replicability and generalizability of connectivity-based psychometric prediction patterns. NeuroImage 262, 119569. https://doi.org/10.1016/j.neuroimage.2022.119569

Xia, Y., Chen, Q., Shi, L., Li, M., Gong, W., Chen, H., Qiu, J., 2019. Tracking the dynamic functional connectivity structure of the human brain across the adult lifespan. Hum Brain Mapp 40, 717–728. https://doi.org/10.1002/hbm.24385

Xiao, Y., Lin, Y., Ma, J., Qian, J., Ke, Z., Li, L., Yi, Y., Zhang, J., Cam-CAN, Dai, Z., 2021. Predicting visual working memory with multimodal magnetic resonance imaging. Hum Brain Mapp 42, 1446–1462. https://doi.org/10.1002/hbm.25305

Xifra-Porxas, A., Ghosh, A., Mitsis, G.D., Boudrias, M.-H., 2021. Estimating brain age from structural MRI and MEG data: Insights from dimensionality reduction techniques. NeuroImage 231, 117822. https://doi.org/10.1016/j.neuroimage.2021.117822

Yalçınkaya, B.H., Ziaeemehr, A., Fousek, J., Hashemi, M., Lavanga, M., Solodkin, A., McIntosh, A.R., Jirsa, V.K., Petkoski, S., 2023. Personalized virtual brains of Alzheimer's Disease link dynamical biomarkers of fMRI with increased local excitability (preprint). Neurology. https://doi.org/10.1101/2023.01.11.23284438

Yang, X., Zhou, X., Xin, F., Becker, B., Linden, D., Hernaus, D., 2023. Age-dependent changes in the dynamic functional organization of the brain at rest: a cross-cultural replication approach. Cerebral Cortex 33, 6394–6406. https://doi.org/10.1093/cercor/bhac512

Yarkoni, T., Westfall, J., 2017. Choosing Prediction Over Explanation in Psychology: Lessons From Machine Learning. Perspect Psychol Sci 12, 1100–1122. https://doi.org/10.1177/1745691617693393

Yeh, C., Jones, D.K., Liang, X., Descoteaux, M., Connelly, A., 2021. Mapping Structural Connectivity Using Diffusion MRI : Challenges and Opportunities. Magnetic Resonance Imaging 53, 1666–1682. https://doi.org/10.1002/jmri.27188

Yeung, A.W.K., More, S., Wu, J., Eickhoff, S.B., 2022. Reporting details of neuroimaging studies on individual traits prediction: A literature survey. NeuroImage 256, 119275. https://doi.org/10.1016/j.neuroimage.2022.119275

Yu, J., Fischer, N.L., 2022. Age-specificity and generalization of behavior-associated structural and functional networks and their relevance to behavioral domains. Human

Brain Mapping 43, 2405–2418. https://doi.org/10.1002/hbm.25759

Yu, J., Rawtaer, I., Fam, J., Feng, L., Kua, E.-H., Mahendran, R., 2020. The individualized prediction of cognitive test scores in mild cognitive impairment using structural and functional connectivity features. NeuroImage 223, 117310. https://doi.org/10.1016/j.neuroimage.2020.117310

Zarogianni, E., Moorhead, T.W.J., Lawrie, S.M., 2013. Towards the identification of imaging biomarkers in schizophrenia, using multivariate pattern classification at a single-subject level. NeuroImage: Clinical 3, 279–289. https://doi.org/10.1016/j.nicl.2013.09.003

Zhao, T., Cao, M., Niu, H., Zuo, X.-N., Evans, A., He, Y., Dong, Q., Shu, N., 2015. Age-related changes in the topological organization of the white matter structural connectome across the human lifespan: Lifespan Trajectory of Human Structural Connectome. Hum. Brain Mapp. 36, 3777–3792. https://doi.org/10.1002/hbm.22877

Zimmermann, J., Ritter, P., Shen, K., Rothmeier, S., Schirner, M., McIntosh, A.R., 2016. Structural architecture supports functional organization in the human aging brain at a regionwise and network level: Structure Supports Function in Aging. Hum. Brain Mapp. 37, 2645–2661. https://doi.org/10.1002/hbm.23200

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