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Prediction of Cognitive Functioning across the Lifespan Using Structural and Functional Neuroimaging Data

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Zusammenfassung

Gesundes Altern geht mit strukturellen und funktionellen Veränderungen des Gehirns einher, die besonders bei komplexen kognitiven Leistungen, wie exekutiven Funktionen (EF), ausgeprägt sind. EF sind wichtig für Prozesse der Entscheidungsfindung und des Problemlösens sowie allgemein für adaptives Verhalten. Trotz Fortschritten in bildgebenden Verfahren sind die neuronalen Grundlagen von EF, insbesondere im Kontext kognitiver Alterungsprozesse, noch nicht vollständig verstanden. Angesichts des globalen demografischen Wandels hin zu einer älteren Bevölkerung gewinnt das Verständnis kognitiver Alterungsprozesse, insbesondere Veränderungen in EF, zunehmend an Bedeutung. Diese Dissertation zielt darauf ab, die neuronalen Grundlagen und Dynamiken altersbedingter Veränderungen in EF mittels verschiedener Methoden zu untersuchen, darunter Metaanalysen, Analysen funktioneller Konnektivität und Prädiktionsanalysen.

Die linke inferior frontale Übergangszone und der linke anteriore Cuneus/Precuneus wurden metaanalytisch als besonders alterssensitive Regionen identifiziert, deren Rekrutierungsmuster je nach Aufgabentyp und Alter variierten. Metaanalytisch wurde ein perzeptuo-motorisches Netzwerk aus visuellen, auditorischen und motorischen Regionen identifiziert, was eine Untersuchung von Altersunterschieden auf Ein- und Ausgabe-Ebene des Gehirns ermöglichte, die möglicherweise die Performanz auf höherer kognitiver Ebene beeinflussen. Prädiktionsanalysen ergaben insgesamt mäßig bis niedrige Vorhersagegenauigkeiten, wobei funktionelle intraindividuelle Variabilitätsmaße eine überlegene Vorhersageleistung für jüngere und strukturelle Maße für ältere Erwachsene lieferten. Überraschenderweise übertrafen über das gesamte Gehirn verteilte sowie zufällig generierte die EF-spezifischen Netzwerke bei der Vorhersage von EF-Fähigkeiten, was auf die Relevanz globalerer Netzwerkeigenschaften für individuelle Unterschiede in EF hindeutet.

Insgesamt betonen die Ergebnisse das komplexe Zusammenspiel struktureller sowie funktioneller Gehirnveränderungen und kognitivem Altern und zeigen eine altersabhängige Modalitätsspezifität in den neuronalen Prädiktoren von EF-Leistung. Die unterschiedliche Relevanz von randomisierten, globalen im Vergleich zu EF-spezifischen Netzwerken bei der Vorhersage von EF weist darauf hin, dass die Berücksichtigung globaler Gehirnmerkmale und die Kombination mehrerer Metriken die Vorhersagegenauigkeit verbessern könnten. Moderat bis niedrige Vorhersagegenauigkeiten unterstreichen die Notwendigkeit weiterer Forschung und Entwicklung effektiverer Biomarker für EF-Fähigkeiten, unter Berücksichtigung globaler Netzwerkdynamiken und der Anwendung adaptiver behavioraler Tests, die die Leistungsfähigkeit über das gesamte gesunde Altersspektrum sensitiv erfassen.

Summary

Healthy aging is associated with structural and functional changes in the brain. These changes are especially pronounced in complex cognitive tasks, like executive functioning (EF). EF is important for decision-making, problem-solving, and adaptive behavior. Advances in neuroimaging techniques have enabled a more detailed exploration of the neural substrates of cognitive aging, yet the neural underpinnings of EF, especially in the context of cognitive aging, remain incompletely understood. The global demographic shift towards an older population underscores the importance of understanding cognitive aging, particularly changes in EF.

This dissertation aimed to investigate the structural and functional neural substrates and dynamics of age-related differences in EF through a comprehensive methodological framework combining meta-analyses, functional connectivity analyses, and predictive modeling.

Meta-analyses highlighted left inferior frontal junction and left anterior cuneus/precuneus as regions significantly affected by aging, with recruitment patterns varying by task type and age. Subsequently, a meta-analytic synthesis identified a common perceptuo-motor network, comprising visual, auditory, and motor-related brain regions. This allows for the investigation of age differences already at the in- and output levels of the brain, which in turn could influence performance at higher cognitive levels. Prediction studies revealed moderate to low overall prediction accuracies, with measures of functional within-subject variability showing superior predictive performance for younger and structural measures for older adults. Surprisingly, whole-brain and random network approaches outperformed EF-specific networks in predicting EF abilities, suggesting that broader network properties may be more indicative of individual differences in EF than previously thought.

The findings highlight the complex interplay between structural and functional brain changes and cognitive aging, emphasizing an age-dependent modality specificity in the neural predictors of EF performance. The differential effectiveness of global versus EF-specific networks in predicting EF underscores the potential value of considering global brain characteristics and combining multiple metrics to enhance predictive accuracy. The modest to low prediction accuracies call for further research into developing more effective biomarkers for EF abilities, considering broader network dynamics, and adopting adaptive behavioral testing approaches to capture the full performance spectrum of healthy aging.

Abbreviations

aC/PrC	anterior cuneus/precuneus
aIns	anterior insula
ALE	activation likelihood estimation
ANOVA	analysis of variance
BOLD	blood-oxygen-level-dependent
CPM	Connectome-based Predictive Modeling
CRUNCH	Compensation-Related Utilization of Neural Circuits Hypothesis
DAN	dorsal attention network
DMN	Default-Mode Network
ECN	executive control network
EF	executive functioning
fALFF	fractional amplitude of low-frequency fluctuations
FDR	false discovery rate
FEF	frontal eye field
GMV	gray-matter volume
HAROLD	Hemispheric Asymmetry Reduction in Older Adults
IFG/J/S	inferior frontal gyrus/junction/sulcus
IPC/L	inferior parietal cortex/lobe
IPS	intraparietal sulcus
ITG	inferior temporal gyrus
MAE	mean absolute error
(a)MCC	(anterior) middle cingulate cortex
(e)MDN	(extended) Multiple-Demand Network
MFG	middle frontal gyrus
(f)MRI	(functional) magnetic resonance imaging
PASA	Posterior to Anterior Shift in Cognitive Aging
PCC	posterior cingulate cortex
PET	positron emission tomography
(DL)PFC	(dorsolateral) prefrontal cortex
ReHo	regional homogeneity
RMSE	root mean square error
ROI	region of interest
RSFC	resting-state functional connectivity
(pre)SMA	(pre-)supplementary motor area
STAC	Scaffolding Theory of Aging and Cognition
TMT	Trail Making Test
UN	United Nations
VBM	voxel-based morphometry
VLPFC	ventrolateral prefrontal cortex
WHO	World Health Organization

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1. Introduction

According to the World Health Organization (WHO) and the United Nations (UN), the age group of individuals aged 65 and above is experiencing unprecedented growth globally. As of 2018, older adults surpassed children under the age of five in terms of population, marking a historic demographic shift. Trends indicate that by 2050, older adults will outnumber adolescents and youth aged 15 to 24 (UN, 2023; WHO, 2023). In the context of this global demographic shift, understanding the dynamics of cognitive aging (i.e., age-related differences in cognitive processes) becomes increasingly important. Executive functioning (EF) plays a central role in various aspects of daily life, including decision-making, problem-solving, and goal-directed behavior. As older adults form a growing portion of the population, it becomes crucial to deepen our understanding of the multi-faceted changes in EF related to aging, focusing on declines in cognitive function. This understanding not only guides strategies to maintain cognitive functioning, reduce and/or slow down cognitive decline, and improve overall quality of live for older individuals but also guides the development of targeted interventions. Therefore, the insights derived from cognitive aging research play a central role in shaping healthcare practices and educational approaches tailored to meet the evolving needs of an aging society.

1.1 Healthy Aging

Healthy aging is associated with altered cognitive performance and brain activation patterns across various cognitive domains. Notably, these differences become especially pronounced in challenging, non-routine tasks that emphasize executive processes (Park et al., 2002; Drag and Bieliauskas, 2010; Stuss and Craik, 2019), while remaining relatively stable in other cognitive domains like vocabulary (Salthouse, 1996; Park et al., 2002), implicit memory, and knowledge storage (Park et al., 2002). Acquired knowledge, linked to crystallized intelligence, tends to remain stable or even improve with age, whereas EF, especially updating, is associated with fluid intelligence, which exhibits a decline with frontal lobe damage and age (Cattell, 1971; Friedman et al., 2006).

In recent decades, progress in neuroimaging techniques, including positron emission tomography (PET) and structural as well as functional magnetic resonance imaging (MRI), has substantially advanced our understanding of the neural correlates of cognitive aging. PET enables the observation and quantification of biological processes, such as changes in blood flow, metabolism, and neurotransmitter activity, by measuring the distribution and concentration of radiotracers. MRI employs strong magnetic fields and radiofrequency pulses to provide high-resolution images of brain structure. In addition, fMRI can detect changes in blood flow and oxygenation levels associated with neural activity, allowing for a real-time exploration of brain function. Despite these technological improvements, the underlying mechanisms of age-related differences remain incompletely understood (Cabeza et al., 2002; Davis et al., 2007). Certainly, the aging brain undergoes unfavorable changes, including a decline in dopaminergic receptors (Li, Lindenberger and Sikström, 2001; Yang et al., 2003), volumetric shrinkage of gray-matter structures (Resnick et al., 2003; Salat et al., 2004; Raz et al., 2005), and reduced white-matter density (Head et al., 2004; Wen and Sachdev, 2004). However, the brain also demonstrates a compensatory homeostatic response, indicating the dynamic and adaptive nature of neurobiological substrates of the cognitive system throughout the lifespan (Greenwood, 2007; Park & Reuter-Lorenz, 2008).

1.1.1 Theories of Cognitive Aging

In the pursuit of unraveling the neural dynamics underlying cognitive aging, prominent theories have emerged, offering partially comparable, complementary, but also conflicting perspectives on how the aging brain undergoes structural, functional, and adaptive transformations across different cognitive domains. Theories of cognitive aging highlight reduced lateralization or anteriorization of brain activation in older adults, often attributed to compensatory functions correlated with better performance. This includes HAROLD (Hemispheric Asymmetry Reduction in Older Adults; Cabeza, 2002) and PASA (Posterior to Anterior Shift in Cognitive Aging; Davis et al., 2007). The latter further suggests that well-practiced cognitive operations become less automatic with age, resulting in reduced activation of posterior regions and an increased reliance on frontal control regions (Grady et al. 1994; Madden et al. 1997; Madden et al. 2002; Madden et al. 2010; Schulte et al. 2011). Similarly, CRUNCH (Compensation-Related Utilization of Neural Circuits Hypothesis) proposes that increased modulation by the prefrontal cortex (PFC) compensates for less efficient neural circuits in older adults (Park and Reuter-Lorenz, 2008). STAC (Scaffolding Theory of Aging and Cognition), in turn, suggests that age-related structural and functional changes result in inefficient and/or noisy processing, leading to the development of scaffolds, or supportive frameworks, that maintain behavioral performance. These scaffolds involve strengthening of existing connections, developing new ones, and disusing fragile or deficient connections, resulting in increased bilateral activation and frontal hyperactivation in older adults (Park and Reuter-Lorenz, 2008). In 2002, Stern postulated two distinct mechanisms underlying cerebral reorganization in aging that closely align with STAC: neural reserve, where older adults exhibit increased recruitment of a specific brain region or network, and neural compensation, where older adults recruit alternative networks to compensate for the lost efficiency of specific brain regions. In contrast to Stern's proposal, STAC asserts that neural scaffolding is not exclusive to aging but is a normative process persisting throughout the lifespan.

1.2 Executive Functions

EF, also referred to as executive control, cognitive control, or higher-order cognitive abilities, is essential for a variety of daily activities. EF involves the management of attention, actions, and emotions to achieve overarching goals. Furthermore, these functions encompass the retention and manipulation of information, such as incorporating new knowledge into plans or considering alternatives as well as changing one's perspective. Although a formal definition remains elusive, EF can be conceptualized as a set of cognitive skills crucial for orchestrating goal-directed, complex thoughts, and behavior. While consensus exists on three core subcomponents – namely inhibitory control, working memory, and cognitive flexibility – (e.g., Lehto, 1996; Miyake et al., 2000; for reviews see: Alvarez & Emory, 2006; Diamond, 2013), debates persist regarding their distinctiveness (Baddeley & Hitch, 1974; Engle & Kane, 2004; Norman & Shallice, 1986; Stuss, 2006).

1.2.1 Neural Representation

Historically, EF were primarily associated with the frontal cortex, stemming from observations of patients with frontal lesions exhibiting deficits in EF (Shallice, Broadbent and Weiskrantz, 1982; Duncan, 1986; Owen et al., 1990). This association originated in the famous case of the 25-year-old construction worker Phineas Gage, who in 1848 survived an injury from a massive iron bar that passed through his left frontal lobe. After that, his behavior and personality changed, and he became irritable, aggressive, irresponsible, and distance reduced (Ratiu et al. 2004; Harlow, 1848). However, subsequent research challenged this exclusive frontal association, revealing that frontal lesions did not consistently impair EF (e.g., Eslinger and Damasio 1985; Shallice and Burgess 1991), and non-frontal lesions could lead to similar deficits (e.g., Anderson et al. 1991; Mountain and Snow 1993; Axelrod et al. 1996). This observation led to the recognition that EF relies on a widespread network, with no consensus of its precise neural substrate, due to its elusive nature (Collette et al., 2006).

While the PFC is widely acknowledged as a key area for EF (e.g., Buchsbaum et al. 2005; Alvarez and Emory 2006), posterior regions also contribute significantly (D'Esposito and Grossman, 1996; Duncan and Owen, 2000; Stuss and Levine, 2002; Langner et al., 2018). Some prefrontal areas, such as the dorsolateral prefrontal cortex (DLPFC), frontopolar PFC, and anterior middle cingulate cortex (aMCC), are consistently activated across diverse executive tasks, while other frontal and posterior areas are only activated in some tasks, emphasizing their task-specific function (Collette and Van der Linden, 2002; Wager and Smith, 2003).

Duncan's Multiple-Demand Network (MDN), proposed in 2010, highlighted a core network consistently recruited across tasks with varying cognitive demands (intraparietal sulcus [IPS], inferior frontal sulcus [IFS], DLPFC, anterior insula [aINS]/frontal operculum, pre-supplementary motor area [pre-SMA], aMCC). Building on this, Müller and colleagues (2015) integrated findings from meta-analyses on working memory (Rottschy et al., 2012), attention (Langner and Eickhoff, 2013), and inhibition (Cieslik et al., 2015), the most discussed subcomponents of EF (Miyake et al., 2000; Alvarez and Emory, 2006), to identify a common core network. They resulted in a network of seven regions (MCC/SMA, bilateral inferior frontal junction [IFJ] extending into inferior frontal gyrus [IFG], right middle frontal gyrus [MFG], bilateral aINS, right inferior parietal cortex [IPC], and IPS), which was very similar to Duncan's MDN. Camilleri and colleagues (2018) further expanded this and proposed an extended (e)MDN which is based on task-dependent and -independent functional connectivity analyses seeded from the regions of the meta-analytically defined MDN by Müller and colleagues. They found 17 regions (bilateral IFJ, aINS, SMA, pre-SMA, IPS, Putamen, Thalamus, right MFG extending into IFS, left dorsal pre-motor cortex, and inferior temporal gyrus) which they characterized, based on functional profiles, as the neurobiological substrate of EF. Based on consistent activation in executive control tasks and strong interconnectivity, they proposed a core network of the eMDN, consisting of bilateral IFJ extending into IFG, bilateral aIns, and bilateral pre-SMA extending into aMCC.

In light of these findings, the neural implementation of EF is considered distributed across the brain, relying on a core network, the so-called MDN, and additional task- and demand-dependent brain regions (Teuber, 1972; Duncan and Owen, 2000; Duncan, 2010; Miyake and Friedman, 2012; Camilleri et al., 2018). This distributed network model emphasizes the flexibility and adaptability of EF processes across various cognitive demands.

1.2.2 Assessment of Executive Functions

In both research and clinical settings, the assessment of EF often involves the use of comprehensive test batteries designed to measure various aspects of cognitive control. Examples of such test batteries include the Delis-Kaplan Executive Function System (Delis et al., 2004) and the Computerized Neurocognitive Battery (Gur et al., 2010). These tools provide a systematic and standardized approach to evaluating EF and its subcomponents in individuals.

An individual's ability to monitor and update information in working memory is commonly assessed using the n-back test. Here, participants are presented with a sequence of stimuli, often letters or numbers, and are required to respond when the current stimulus matches the one that appeared "n" steps back in the sequence. The level of difficulty can be adjusted by varying the value "n".

Inhibitory control is often measured through tests like Color-Word Interference. In this test, participants are presented with words written in colored ink and are required to name the ink color while inhibiting the automatic response to read the word itself. It includes conditions with congruent (i.e., matching color and word) and incongruent (i.e., mismatching color and word) stimuli, placing demands on the individual's ability to suppress interference from conflicting information. Another frequently used task is the flanker task or Attention Network Task (Fan et al., 2002). It typically involves the presentation of a central target stimulus (e.g., an arrow) flanked by distracting stimuli. For assessing sustained attention, Penn Continuous Performance Task can be used. Here, red vertical and horizontal lines flash within a digital numeric frame, resembling a digital clock. Participants are required to press the spacebar when these lines form complete numbers or letters.

Cognitive flexibility can be assessed with the Trail Making Test (TMT). The test consists of two parts. In the first part, participants are required to connect numbers in ascending order as quickly as possible. It primarily measures visual attention and processing speed. The second part involves alternating between numbers and letters in ascending order (1-A-2-B-3-C, and so on). Another commonly applied task is Wisconsin Card Sorting or Penn Conditional Exclusion Task. Participants are presented with four objects and must determine which one does not belong based on changing principles or criteria (e.g., line thickness, shape, and size). The participant receives feedback after each response, and the ruling principle changes after achieving ten consecutive correct answers for each criterion.

1.3 Healthy Aging and Executive Functioning

1.3.1 Neural Correlates

Findings from neuroimaging studies examining age-related differences in EF and its subcomponents – inhibitory control, working memory, cognitive flexibility – present a multifaceted and sometimes conflicting picture. A commonly observed pattern is an age-related increase in bilateral prefrontal activity (e.g., Madden et al., 1999; Morcom et al., 2003; Emery et al., 2008; Piefke, Onur and Fink, 2012), and a decrease in occipital activity (e.g., Madden et al., 2002, 2010; Schulte et al., 2011; Ansado et al., 2012). However, other studies (e.g., Zysset et al., 2007; Van Impe et al., 2011; Chmielewski, Yildiz and Beste, 2014; Bloemendaal et al., 2016), suggest an increase in occipital activity and a decline in frontal activity in older adults. Moreover, the age-related reduction in hemispheric asymmetry appears inconsistent across studies (e.g., Madden et al., 2002; Carp, Gmeindl and Reuter-Lorenz, 2010; Toepper et al., 2014). These diverse and sometimes contradictory findings underscore the need for quantitative data aggregation.

As of the time of this study, three meta-analyses have explored cognitive aging in association with EF. The initial meta-analysis by Spreng and colleagues (Spreng, Wojtowicz and Grady, 2010) comprehensively assessed all available experiments probing EF in aging, encompassing facets like working memory, task switching, and inhibitory control. Their findings unveiled a convergence of heightened age-related activation in bilateral DLPFC, right

MFG, left SMA, and left rostrolateral PFC. Notably, younger adults exhibited greater activation convergence in right ventrolateral PFC compared to older adults. Subsequently, Turner and Spreng (2012) conducted separate meta-analyses for working memory and inhibitory control, revealing distinct patterns of significantly convergent activation. The analysis on working memory resulted in convergence in lateral PFC regions in both hemispheres for both age groups, with older adults displaying increased convergence in anterior regions and younger adults in posterior regions of DLPFC. Additionally, an age-related increase in convergence was found in the bilateral SMA. Meanwhile, inhibition exhibited a "young-plus pattern", indicating shared recruitment of brain regions in both age groups, but with heightened activation in older adults in these regions (bilateral IFG, SMA, DLPFC, and right aINS). Contrary to the notion of a general compensatory increase in PFC activity, the authors argued that cognitive aging involves specific modifications in the neural networks engaged in the processing of a certain task or task component. In 2014, Di and colleagues conducted activation likelihood estimation (ALE) and voxel-based morphometry (VBM) meta-analyses, identifying increased age-related activation convergence in bilateral DLPFC, anterior cerebellum, and left IFG. Further conjunction analyses revealed an intriguing overlap between functional hyperactivation and gray-matter reduction in DLPFC, with these alterations correlating with task performance and suggesting that increased DLPFC activation is linked to better performance in older adults. While each meta-analysis demonstrated convergence in age-related lateral PFC activation, discrepancies emerged in additionally activated regions and activation patterns of EF subcomponents. Therefore, several open questions persist, including the consistency of findings across EF tasks, the specificity of subdomain-related activation patters, and the relationship between brain activation and performance. Furthermore, previous meta-analyses comprise methodological short-comings such as the inclusion of region of interest (ROI) experiments, the selection of tasks included, a small number of experiments ($n < 17$) as well as false discovery rate (FDR)-based correction for multiple comparisons. Meta-analyses with $n < 17$ experiments are prone to yield clusters of "convergence" driven by very few or even single experiments (Eickhoff et al., 2016). Applying voxel-level FDR-based correction has been shown to feature low sensitivity and a high susceptibility for false-positive findings in ALE meta-analysis (Eickhoff et al., 2016). To address these open questions and limitations, we conducted additional and more robust meta-analyses.

1.3.2 Brain Networks

To comprehend these age-related transformations, it is essential to consider the organizational structure of the human brain. The brain can be conceptualized as a complex and non-random network, referred to as the human connectome. Within this network, distinct subnetworks serve specialized mental functions, fostering both the segregation and integration of cognitive processes. Identifying these brain networks often involves studying their intrinsic functional connectivity, a method that has consistently identified resting-state networks aligning closely with task-related co-activation patterns (Damoiseaux et al. 2006; Smith et al. 2009). Notable among these networks is the Default-Mode Network (DMN; precuneus (PrC), posterior cingulate cortex (PCC), anterior medial PFC, lateral IPC), typically active during periods of rest as well as self-referential thinking and decreased in activity when engaging in externally focused tasks (Shulman et al., 1997; Raichle et al., 2001; for reviews see: Anticevic et al., 2012; Raichle, 2015). Concurrently, the executive control network (ECN) is associated with tasks demanding top-down cognitive control (bilateral DLPFC, ventrolateral (VL)PFC, DLPFC/frontal eye field (FEF), dorsomedial PFC, lateral parietal cortex, dorsal and ventromedial caudate, anterior thalamus, right frontal operculum, inferior temporal lobe, left aIns) (Seeley et al., 2007), while the salience network is involved in integrating sensory with visceral, autonomic, and hedonic signals (bilateral aIns, temporal pole, dorsal aMCC, SMA/pre-SMA, superior temporal lobe, parietal operculum, frontal pole, DLPFC, ventral striato-pallidum, dorsomedial thalamus, hypothalamus, sublenticular extended amygdala/paraolfactory, substantia nigra/ventral tegmental area, right VLPFC, left periaqueductal grey) (Seeley et al., 2007). Additionally, networks such as the dorsal attention network (DAN; bilateral FEF, IPS) and the ventral attention network (right temporoparietal junction, VLPFC) are important for top-down and bottom-up attentional processes, respectively (Corbetta and Shulman, 2002). Research has demonstrated that DMN deactivation tends to decrease with age, correlating with poorer performance in EF-related tasks (Persson et al., 2007; Prakash et al., 2012; Brown et al., 2019). Additionally, studies have proposed that the activation of the ECN and deactivation of the DMN may be more closely linked to EF performance than chronological age (Satterthwaite et al., 2013). Specifically, the Default-Executive Coupling Hypothesis of Aging proposes that the connectivity between the ECN and the DMN increases with age, a phenomenon associated with diminished performance in tasks that tax cognitive flexibility (Turner and Spreng, 2015; Kupis et al., 2021) and processing speed (Ng et al., 2016). Hence, healthy aging is accompanied not only by a decline in the performance of cognitively challenging tasks but also alterations in brain activity and connectivity patterns during both task and resting states (Park and Reuter-Lorenz, 2008).

1.3.3 Brain Metrics

In the exploration of the human brain, a variety of metrics have been developed to quantify its complex structure, function, and connectivity. These brain metrics, here derived from structural and functional MRI, serve as tools for investigating neural correlates and processes.

Resting-state functional connectivity (RSFC) has emerged as a pivotal metric in cognitive neuroscience, offering insights into the brain's intrinsic functional architecture by reflecting the temporal correlation of spontaneous blood-oxygen-level-dependent (BOLD) signal fluctuations between different brain regions at rest. It can be analyzed on a whole-brain scale to explore the global functional architecture or focused on specific, pre-defined networks or ROIs to understand their roles in cognitive processes and behaviors. Previous research has linked age-related differences in EF performance to alterations in RSFC within relevant networks (Steffener et al., 2009; Langner et al., 2015; Hausman et al., 2020). However, the significance of RSFC within EF-related networks as a reliable marker for individual EF performance remains an area of ongoing research. Additionally, the role of RSFC in age-related cognitive decline or improvement requires further exploration.

Another metric derived from resting-state fMRI, regional homogeneity (ReHo), has demonstrated sensitivity in detecting age differences during rest (Wu et al., 2007) and exhibited superior prediction accuracy for crystallized intelligence compared to RSFC (Larabi et al., 2021). ReHo assesses the local similarity of a voxel's time series to its neighboring voxels, based on the assumption that meaningful brain activity manifests in clusters of neighboring voxels rather than individual ones (Zang et al., 2004). It has been discussed as a measure of local connectivity, which is necessary for inducing global connectivity (Jiang and Zuo, 2016). Similarly, fractional amplitude of low-frequency fluctuations (fALFF), derived from resting-state fMRI, reflecting the relative contribution of low-frequency fluctuations within a specified frequency band to the entire frequency range (Zou et al., 2008), has shown a negative association with age and inhibitory control decline, suggesting its potential as an indicator of functional within-subject brain variability. These changes were linked to cortical atrophy, measured through cortical thickness or gray-matter volume (GMV), and a decline in inhibitory control (Hu et al., 2014; Vieira, Rondinoni and Garrido Salmon, 2020). GMV, a well-established and widely employed method for quantifying regional brain morphology, has been associated with cognitive aging, atrophy, and performance in tasks taxing EF (Good et al., 2001; Gunning-Dixon and Raz, 2003; Oh et al., 2014).

Several questions persist regarding the degree to which RSFC can predict individual differences in EF abilities, the specificity of these predictions across different EF components, and how changes in RSFC relate to age-related cognitive decline or improvement. And the application of ReHo and fALFF in predicting EF abilities is so far relatively underexplored compared to RSFC. Therefore, a multimodal approach, integrating these metrics, may offer a more comprehensive understanding of the neural correlates of EF and its changes throughout the lifespan, enhancing prediction accuracies and elucidating underlying mechanisms.

1.4 Aims of Thesis

This dissertation integrates findings from four publications, each contributing a unique perspective to our understanding of EF, through diverse neuroscientific methodologies. The overarching goal was to advance a comprehensive understanding of EF, its neural underpinnings, network interactions, and changes with age.

In Study 1, we examined age-related differences in EF-related brain activity through within- and between-group meta-analyses. This included identifying consistent EF-related brain regions sensitive to aging, investigating their connectivity profiles, and assessing the association between whole-brain functional connectivity, age, and EF scores.

As age-related differences in EF performance may extend beyond exclusive involvement in EF-related or higher-order cognitive brain regions, Study 2 aimed to establish a robust functional definition of brain correlates of in- and output-related processing, in particular perceptuo-motor processes. This involved conducting coordinate-based meta-analyses on basic visual, auditory, and motor-related processing, creating separate as well as a combined perceptuo-motor network. Additionally, we compared our meta-analytically derived task-based networks to three RSFC-based data-driven network definitions from the literature. Lastly, we computed the minimum z-statistic of our three meta-analytically derived brain networks to investigate common, domain-general brain regions across these networks.

In Study 3, we investigated the predictability of EF abilities in young and old adults based on network type and EF demand level (high-demand vs. low-demand). An EF network was defined from large-scale neuroimaging meta-analyses capturing diverse EF facets. We explored whether and how RSFC within this network predicts individual abilities in three major EF subcomponents (i.e., inhibitory control, cognitive flexibility, working memory), comparing its predictive power with EF-unspecific networks (i.e., perceptuo-motor, whole-brain, and ten randomly sampled networks).While we focused on the linear regression algorithm partial least squares, for conceptual replication and robustness, we additionally applied a non-linear prediction algorithm (random forest) as well as a data-driven feature selection approach (Finn et al., 2015; Shen et al., 2017).

Finally, Study 4 explored the predictive capacities of structural and functional metrics (GMV, RSFC, ReHo, fALFF) on EF across age groups and task-demand levels. Utilizing a linear regression approach, we assessed the degree to which these metrics within an EF-related, a perceptuo-motor, and a whole-brain network predicted individual EF subcomponents, examining potential variations based on network, metric, task-demand level, and age group.

1.5 Methodological Framework

To thoroughly investigate the multi-faceted neural basis of EF and its changes throughout the lifespan, we employed a range of methodological approaches. This strategy allowed us to explore EF's age-related dynamics and brain correlates from multiple perspectives, aiming to achieve a more comprehensive understanding.

1.5.1 Activation Likelihood Estimation Meta-Analysis

Employing coordinate-based ALE meta-analyses (Turkeltaub et al., 2002, 2012; Eickhoff et al., 2009, 2012) offers several advantages when aggregating and interpreting data from neuroimaging studies on EF across different age groups. This method is particularly beneficial as it overcomes the common obstacles of individual neuroimaging experiments, such as reduced reliability from small sample sizes (Button et al., 2013) and the variability in experimental design, data processing, and analysis criteria (Carp, 2012). Furthermore, ALE meta-analyses counteract the effects of publication bias (i.e., adjusting data analysis, inference, and thresholds until desired or significant result is found), a major issue in neuroimaging studies due to its analytical flexibility, by converging findings across studies to identify consistent patterns of brain activity (Carp, 2012; Müller et al., 2017). By synthesizing data across different experiments, ALE meta-analyses provide a statistically robust and objective assessment of the brain regions consistently associated with EF across the lifespan. Given the not fully understood neural correlates and mechanisms of EF, this approach not only enhances the reliability of findings by pooling data, but also offers a comprehensive synthesis of age-sensitive neural correlates of EF, establishing a solid foundation for further exploring the neural mechanisms underlying cognitive aging.

1.5.2 Exploration of Resting-State Networks Involving Age-Sensitive Regions

To deepen our understanding about the intrinsic functional architecture that supports EF in young and old individuals, we analyzed the task-independent whole-brain functional connectivity patterns of the identified age-sensitive brain regions. Such analyses may offer insights into the intrinsic brain networks relevant for individual differences in EF performance, their within- and between-network dynamics as well as their changes with age.

1.5.3 Prediction Analyses

Finally, multivariate analysis, particularly machine learning, enabled us to further investigate connectivity patterns and interindividual differences in EF performance. In contrast to traditional univariate (or rather bivariate) approaches, which typically involve correlations between a single brain metric and EF performance, multivariate analysis allows for the detection of complex patterns indicative of EF performance. Therefore, these models increase the sensitivity to detect interindividual differences in cognitive performance (Marek et al. 2022; Pat et al. 2022). Furthermore, multivariate analysis enhances validity by resulting in patterns of connectivity (vs. individual connections), reducing the likelihood of spurious associations. Additionally, multivariate prediction models demonstrated superior test-retest reliability compared to single imaging features (Taxali et al., 2021), overcoming concerns about the reliability of edge-level RSFC (Noble, Scheinost and Constable, 2019). Multivariate models should therefore offer robust analyses of brain–behavior associations.

Machine learning, in particular, has shown great promise in identifying trait markers of EF performance by analyzing RSFC patterns (Reineberg et al., 2015; He et al., 2021). Therefore, adding this approach to our analysis framework allows us to analyze interindividual differences in brain–behavior associations.

1.6 Ethics Vote

Data were obtained from the publicly available enhanced Nathan Kline Institute - Rockland Sample (Nooner et al., 2012). Analysis of the data was approved by the local ethics committee of the Medical Faculty of the Heinrich Heine University Düsseldorf (study number: 4039).

2. Heckner, M.K., Cieslik, E.C., Eickhoff, S.B., Camilleri, J.A., Hoffstaedter, F., & Langner, R. (2021). The Aging Brain and Executive Functions Revisited: Implications from Meta-analytic and Functional-Connectivity Evidence. *Journal of Cognitive Neurosci*ence 33(9):1716–1752. https://doi.org/10.1162/jocn_a_01616

3. Heckner, M.K., Cieslik, E.C., Küppers, V., Fox, P.T., Eickhoff, S.B., & Langner, R. (2021). Delineating visual, auditory and motor regions in the human brain with functional neuroimaging: a Brain-Map-based meta-analytic synthesis. *Scientific Reports* 11:9942. https://doi.org/10.1038/s41598-021-88773-9

4. 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* 33(11):6495-6507. https://doi.org/10.1093/cercor/bhac520

5. Heckner, M.K., Cieslik, E.C., Paas Oliveros, L.K., Eickhoff, S.B., Patil, K.R., & Langner, R. (2023). Predicting executive functioning from brain networks: modality specificity and age effects. *Cerebral Cortex* 33(22):10997-11009. https://doi.org/10.1093/cercor/bhad338

6. Discussion

This dissertation aimed to investigate the structural as well as functional neural substrates and dynamics of age-related differences in EF performance. Initially, meta-analyses were employed to examine age-related alterations in EF-related brain activity, highlighting age-dependent activation patterns in left IFJ and left anterior cuneus/precuneus (aC/PrC). Subsequently, a meta-analytic synthesis identified a common perceptuo-motor network, enabling the exploration of potential age-related differences in brain input and output regions. The investigation extended to RSFC within EF-specific and EF-unspecific networks (i.e., perceptuo-motor, whole-brain, random networks), with surprising findings revealing the superior predictive capability of EF-unspecific networks over EF-specific ones. Overall low prediction accuracies challenged RSFC's biomarker potential for individual EF abilities. We next explored whether different structural (i.e., GMV) as well as functional (i.e., ReHo, fALFF) metrics might offer better predictions. Although overall prediction accuracies remained modest, intriguingly, fALFF showed superior predictive performance for younger adults, while GMV was most accurate when predicting performance for older adults. Collectively, our findings provide multi-faceted insights into age-related alterations in EF-related brain activity and its organizational patterns. They show modality- as well as age-specificity of brain–behavior associations, but also obstacles in association with prediction results as well as measurement uncertainties associated with RSFC.

6.1 Age-Related Differences in Executive Functioning: Insights from Meta-Analyses and Functional Connectivity

We meta-analytically identified two brain regions, left IFJ and left aC/PrC, being particularly sensitive to cognitive aging. By examining their meta-analytical contributions, including the experiments shaping their clusters of convergence, along with analyzing their RSFC profiles and the association of these profiles with age and EF, we gained valuable insights into the neural substrates and dynamics of EF and cognitive aging.

6.1.1 Left Inferior Frontal Junction

The pooled meta-analysis of age differences in EF-related brain activity yielded convergence in left IFJ. Furthermore, our results indicate varying recruitment patterns in left IFJ between younger and older adults depending on the type of task. Task-dependent findings suggest an age-related decrease in IFJ activation for working memory tasks (e.g., Bäckman et al., 2011; Podell et al., 2012; Prakash et al., 2012). This is in line with the dedifferentiation hypothesis of cognitive aging, stating that brain regions showing specialized responses to specific cognitive tasks become less specialized with increasing age (Baltes and Lindenberger, 1997; Park et al., 2001, 2004; Li and Sikström, 2002; Goh, 2011). Conversely, inhibitory control and attention shifting tasks suggest an age-related increase in left IFJ activity (e.g., Townsend, Adamo and Haist, 2006; Zysset et al., 2007; Korsch, Frühholz and Herrmann, 2014), possibly due to compensatory neural recruitment caused by the attempt to increase relevant and decrease irrelevant information processing (Townsend, Adamo and Haist, 2006; Korsch, Frühholz and Herrmann, 2014). Looking at individual study contributions of our analysis, the convergence in left IFJ for experiments on inhibitory control and cognitive flexibility was mainly driven by the activation contrast old > young (rather than young > old). Conversely, for experiments on working memory, convergence was mainly driven by the contrast young > old (rather than old > young). These findings, although purely descriptive, suggest a common cognitive mechanism underlying inhibitory control and cognitive flexibility, as reflected in the convergent activation of IFJ activity.

Research frequently associates left IFJ with cognitive flexibility processes (Brass and Cramon, 2004; Derrfuss et al., 2005; Worringer et al., 2019). This notion is also supported by repetitive transcranial magnetic stimulation studies (Higo et al., 2011; Zanto et al., 2011), indicating IFJ's causal involvement in updating task representations and regulating neural excitability in visual areas according to the task goal. Derrfuss et al. (2004) found significant overlap in IFJ activity across experiments probing working memory, task switching, and inhibitory control, suggesting its broad role in EF. Additional indirect support comes from the anatomical position of left IFJ, situated at the junction of the inferior frontal and inferior precentral sulci, and thus at the intersection of three functional neuroanatomical domains: premotor, language, and working memory. While our study cannot clarify the precise functional role of left IFJ, existing literature suggests that this region may integrate information from these three domains (Brass et al., 2005). In particular, it is proposed to (re)activate and implement relevant stimulus–response mappings, connecting stimulus information with motor output aligned with behavioral goals (Hartstra, Waszak and Brass, 2012; Worringer et al., 2019).

Our findings from RSFC underscore the significant role of left IFJ in EF. The RSFC map of left IFJ strongly aligns with Camilleri et al.'s (2018) proposed neural correlate of EF, known as the eMDN, and the ECN. The observed negative association between the RSFC of left IFJ and age indicates that age-related connectivity changes are not regionally specific (e.g., prefrontal) but rather widespread, including the DAN, the ECN, and the eMDN. Prior research has documented an age-related decline in RSFC within these networks (Campbell et al., 2012; He et al., 2014). This decline may be linked to the frequently reported age-related deterioration in EF performance, indicating reduced FC between regions and networks crucial for EF. With its pivotal functional role in stimulus–response mapping and its importance for all EF subcomponents, left IFJ appears to function as a key node for EF. This role involves both broad domain-general recruitment as well as intrinsic correlations with multiple task-positive networks.

In summary, our combined meta-analytic and connectivity results highlight the pivotal role of left IFJ in EF. While its involvement in EF tends to be mostly domain-general, its recruitment appears to shift with age, depending on the specific cognitive task. Notably, older adults exhibit a heightened reliance on left IFJ during tasks taxing cognitive flexibility and inhibition, whereas younger adults demonstrate a stronger recruitment during working memory tasks. The age-related decline in RSFC of left IFJ and its connections to diverse task-positive networks suggest (i) generalized changes throughout the brain rather than isolated degradation in a specific region as well as (ii) a potential neural correlate underlying the decline in EF performance with age.

6.1.2 Left anterior Cuneus/Precuneus

Convergence in left aC/PrC was found by the meta-analyses EF pooled and EF old > young. Convergence in the pooled meta-analysis was mainly driven by the contrast old > young, indicating increased activation in older compared to younger adults. The aC/PrC has been linked to initiating shifts of attentional focus (Langner and Eickhoff, 2013; Bzdok et al., 2015; Worringer et al., 2019). This is in accordance with our finding of activity convergence in left aC/PrC being driven by tasks taxing inhibition and cognitive flexibility, where shifting the attentional focus and thus inhibiting irrelevant input plays a key role. Previous studies (DiGirolamo et al., 2001; Townsend, Adamo and Haist, 2006; Kuptsova et al., 2016) exploring age-related differences in attention shifting indicate that both younger and older adults utilize the same regions, namely frontoparietal regions including PrC, during shift conditions. Notably, older adults additionally recruited these regions during the control condition (i.e., attentional focusing). The authors suggested that older adults depend more on executive networks, even in non-shift task conditions, to compensate for reduced efficiency of sensory and cognitive processing. An alternative explanation could be that older adults have difficulties inhibiting the alternate task even during the non-shift condition. Upon inspecting the study contributions to the left aC/PrC cluster in the pooled EF meta-analysis, 92% of the studies contributing to the convergence in left aC/PrC result from the contrast old > young. 83% of these studies did not report inclusive masking with a task-positive effect, and 68% compared against an active control condition rather than rest. Although we did not directly investigate deactivations due to a lack of studies meeting our inclusion criteria, one could argue, based on these statistics, that the convergence in left aC/PrC might be predominantly driven by consistently greater aC/PrC deactivation in older adults during the control (vs. task) condition and/or consistently greater deactivation in younger adults during the experimental (vs. control) task, rather than a higher task-induced aC/PrC activation in older adults. This potential age-related deactivation during control (vs. task) and deactivation difficulties (compared to younger adults) in task (vs. control) could contribute to inefficiencies in attentional switching in older adults. Together with PCC, PrC is considered one of the central and specialized hubs of the DMN, intrinsically connected to the DMN and attentional networks, in line with our RSFC findings. Its role may involve controlling the dynamic interaction between these networks for an efficient distribution of attention (Leech et al., 2011). Furthermore, PrC occupies a special position within the DMN, being coupled with the DMN at rest and with task-positive networks during task performance (Leech et al., 2011; Utevsky, Smith and Huettel, 2014). Its widespread FC pattern, encompassing higher association regions, supports its crucial role in integrating internally and externally driven stimulus processing (Cavanna and Trimble, 2006).

The RSFC of PrC with sensorimotor regions decreased in older adults, while its RSFC with regions linked to the DMN and DAN increased with age. Previous studies have found that older adults failed to deactivate the DMN during various cognitive tasks (Lustig et al., 2003; Grady et al., 2006; Persson et al., 2007; Park et al., 2010). Spreng and Schacter (2011) suggested that this difficulty arises from a decrease in large-scale network flexibility in response to changing task demands. These differences might also be attributed to variations during fixation, as older adults exhibit reduced susceptibility to mind wandering (Giambra, 1989; Jackson and Balota, 2012). Furthermore, older adults may find it more challenging to maintain fixation on the cross, potentially explaining the age-related RSFC increase of left PrC with the DAN. Additionally, it has been proposed that functional networks become less specific with age (Geerligs, Maurits, et al., 2014; Geerligs, Renken, et al., 2014). Consequently, there could be a dedifferentiation in activation patterns, aligning with the dedifferentiation hypothesis of neural aging, and a compensatory recruitment of additional brain regions. This idea is also supported by the cognitive aging theories CRUNCH (Reuter-Lorenz and Cappell, 2008) and STAC (Park and Reuter-Lorenz, 2008), which posit that, in older adults, maintaining cognitive and behavioral performance involves weakening connections that have become fragile or deficient, strengthening existing connections, and developing new connections.

We observed a positive correlation of RSFC between left aC/PrC and bilateral visual cortices with the total EF and cognitive flexibility score. Conversely, negative associations with cognitive flexibility were observed for RSFC between left aC/PrC and both bilateral inferior parietal lobe and right middle temporal gyrus. While enhanced RSFC of PrC with visual areas seems supportive of cognitive flexibility, the connectivity of PrC with regions linked to the DMN and DAN is associated with poorer performance in tasks taxing cognitive flexibility. Taking our previous findings into account, a similar RSFC map was positively linked to age, possibly indicating dedifferentiation in activation patterns as proposed in the dedifferentiation theory of neural aging (Baltes and Lindenberger, 1997; Park et al., 2001, 2004; Li and Sikström, 2002; Goh, 2011), or compensatory activations as postulated in CRUNCH (Reuter-Lorenz and Cappell, 2008) and STAC (Park and Reuter-Lorenz, 2008). However, the limitations of the available data and methods employed do not allow for more definitive and theory-specific conclusions.

In summary, our findings suggest that older adults specifically recruit left aC/PrC, potentially to compensate for attentional and focus-shifting difficulties. Conversely, our results suggest an age-related increase in relative aC/PrC deactivation during the control task and/or an age-related activation decrease during the experimental task, proposing an alternative hypothesis for higher task-induced aC/PrC activation in older adults. The intrinsic coupling of left aC/PrC's with the DMN and DAN supports its proposed role as a specialized hub in both internal and external information processing. The age-related decrease in RSFC between aC/PrC and sensorimotor networks suggests some decoupling issues detrimental to action-related, externally oriented processing. Simultaneously, the increase in RSFC between DMN and DAN suggests age-related difficulties in decoupling aC/PrC from the DMN during task states and from DAN-related regions during rest. Considering left aC/PrC's often reported covariation with left IFJ during rest, which was, however, not found in the current study, our findings may reflect a dedifferentiation in functional network patterns in older adults, potentially undermining the special role this region plays in shifting between internally and externally directed attention.

6.1.3 Perceptuo-Motor Networks

Age-related differences in EF performance might occur at a brain-wide level, extending beyond exclusive involvement in EF-related or higher-order cognitive brain regions. Brain regions associated with in- and output-related processing, particularly those linked to visual, auditory, and motor functions, could already be influenced by aging (Barsalou, 2003; Ionescu, 2012). Consequently, we meta-analytically defined a perceptuo-motor network to ensure a comprehensive examination of the neural correlates of age-related differences in EF.

Comparing our meta-analytic findings with data-driven RSFC-based network definitions, we observed a large degree of overlap in expected areas associated with basic visual, auditory, or motor processing. This alignment supports the idea that brain networks are rather consistently organized across both task and resting states (Smith et al., 2009; James, Hazaroglu and Bush, 2016; Tavor et al., 2016; Parker Jones et al., 2017). However, in contrast to RSFC-derived networks, our task-based results display a higher specificity, including additional, domain-unspecific regions (e.g., IFJ, preSMA, aIns) associated with higher-order cognitive functions. This suggests that, during tasks, perceptuo-motor networks are recruited alongside supramodal, integrative regions linked to cognitive control. One potential explanation is an adaptive functional brain organization that adjusts network topology depending on task demands.

For instance, Di et al. (2013) reported more between-network than within-network connections during task performance (vs. resting-state), along with a hub shift (i.e., redistribution of activity within key brain regions) during task states. Similar to our results and the comparison with RSFC-based network definitions, these authors specifically identified the thalamus as having a stronger coactivation profile throughout the brain (i.e., a higher number of coactivations with other brain regions) during task than during rest. The authors concluded that the thalamus mediates cortico-cortical communication during tasks, but that this mediation is weakened at rest. Left aIns and preSMA, consistently implicated in our perceptuo-motor networks, may play a similar role in mediating cortico-cortical communication during task states. aIns is thought to have a pivotal role in monitoring and implementing relevant task sets (Dosenbach et al., 2006, 2007; Sridharan, Levitin and Menon, 2008; Cieslik et al., 2015), while preSMA has been linked to cognitive action control and motor preparation (Mostofsky and Simmonds, 2008; Sharp et al., 2010; Barber et al., 2013). These regions are part the MDN (Duncan and Owen, 2000; Duncan, 2010; Fedorenko, Duncan and Kanwisher, 2013), consistently recruited during various cognitively demanding tasks. Additionally, task context effects, such as the way how instructions are presented, must be considered. Collectively, these findings support the view of brain networks as entities that are not strictly separate but can be (partly) combined, disconnected, and recombined to generate the neural circuitry that subserves specific cognitive functions.

6.2 Prediction of EF Abilities

6.2.1 Methodological Considerations

Pearson's correlation coefficient (*r*) is a common measure in neuroscience for evaluating predictive analyses, providing information about the strength and direction of linear relationships between observed and predicted scores. While useful, it does not directly measure the accuracy of a model (Li, 2017) or magnitude of errors. In contrast, root mean square error (RMSE) and mean absolute error (MAE) quantify prediction accuracy by assessing the magnitude of errors. RMSE calculates the average squared differences between observed and predicted scores, amplifying large errors and thus being more sensitive towards outliers, while MAE computes the average absolute differences between observed and predicted scores. While Pearson's *r* is influenced by the variance of the outcome variable, meaning its value can be affected by the spread of data points around the regression line, both RMSE and MAE are independent of outcome variable variance, allowing for meaningful comparisons across different datasets. However, it is important to note that RMSE and MAE are scale-dependent, meaning comparisons across datasets require identical scaling of the outcome variable. Another measure for evaluating predictive analyses is prediction R^2. It is calculated by comparing the MSE of the predicted values to the MSE of the observed values and subtracting it from 1. This yields a value that ranges from negative to positive, where a negative value indicates that the predictive model performs worse than simply guessing the mean of the observed data, while a positive value indicates the model's ability to outperform this baseline (Scheinost et al., 2019).

Consequently, Pearson's *r*, RMSE, MAE, and prediction R^2 offer distinct yet complementary information. Poldrack et al. (2020) discuss best practices for evaluating prediction and advocate for the inclusion of multiple accuracy measures, particularly RMSE, MAE, and R^2, since high correlation coefficients may mask significant discrepancies between predicted and observed data, such as those resulting from outliers or highly heterogeneous groups. Therefore, we chose to calculate multiple measures to ensure a thorough assessment of prediction accuracy.

6.2.2 Prediction Accuracies

Primarily, we assessed the accuracy of predicting EF abilities from within-network GMV, RSFC, ReHo, and fALFF using RMSE ($< .8$) and the respective correlation coefficient (*r*; performance was z-scored). Consequently, the interpretation focuses on the correlation coefficient of successful/meaningful predictions. Prediction accuracies were generally relatively low across different modalities, networks, and age groups. In both of our studies, the explained variance (R^2) (Scheinost et al., 2019) did not exceed 6%, suggesting that while RSFC, GMV, ReHo, and fALFF are somewhat associated with EF abilities, their capacity to predict individual performance is limited. From a translational perspective, when aiming to discover biomarkers for individual-level prediction, these results are rather unsatisfactory.

It is surprising to note that, while prediction from within-network fALFF resulted in the best overall prediction accuracy (i.e., RMSE), the correlation coefficient was quite low and only very little variance in EF performance could be eventually explained (R^2). GMV resulted in greater associations and was able to explain variance in more tasks and conditions. This raises the question of how to reconcile the discrepancy between enhanced prediction accuracies (i.e., RMSE) and the relatively weak brain–behavior associations (i.e., Pearson's *r*) observed in fALFF-derived features. It is possible that variability in brain function within individuals is highly important, even necessary, for EF, but that interindividual differences in this variability, as reflected by fALFF, might not correspond effectively with individual EF abilities, at least not within the typical performance range. Further research is needed to understand the neural mechanisms and the functional meaning of fALFF.

In summary, brain–behavior associations were overall rather modest to weak, yet they were more pronounced when derived from structural rather than functional brain features. This raises doubts about the practicality of using functional brain metrics at rest for predicting individual EF abilities. Although the brain–behavior associations in our study are rather low, they align with findings from other research in the field (e.g., Ferguson et al. 2017; Greene et al. 2018; He et al. 2021). This consistency calls for the development of more informative measures or methods and a critical re-evaluation of the predictive and explanatory value of the examined models.

6.2.3 Network Specificity

The analysis of variance (ANOVA) revealed a main effect of network on prediction accuracy. Post-hoc pairwise comparisons showed significant differences among all networks. Surprisingly, the highest prediction accuracy was achieved using the whole-brain connectome, surpassing random networks, the perceptuo-motor network, and, unexpectedly, the executive function-related network. Power et al.'s (2011) connectome version might excel due to its larger feature space, offering 34,716 connections compared to only 1,225 in the executive function-related network. However, control analyses with randomly selected networks of the same size as the executive function-related network still significantly outperformed the latter as well as the perceptuo-motor network, indicating that the number of features alone does not drive the prediction outcomes. This raises questions about what variance is being explained, especially when whole-brain or random networks outperform those specifically linked to EF.

Moreover, our findings suggest that inter-individual differences in EF might be more related to global brain organization rather than specific networks (also see Pläschke et al., 2020). Brain regions important but not specific to EF, possibly modulating between-network communication, might be absent in meta-analytically derived networks but included in whole-brain approaches. For instance, our prediction analysis using the data-driven approach for feature selection Connectome-based Predictive Modeling (CPM; i.e., RSFC edges that were significantly associated with the EF target variables) (Finn et al., 2015; Shen et al., 2017) revealed that predictive connections were spread across various brain regions and multiple intrinsic networks. This pattern supports the notion that inter-network connectivity could offer more insights into individual EF performance than intra-network connectivity. Research has consistently demonstrated that the ability to dynamically reconfigure connections between frontoparietal and frontotemporal networks (i.e., network flexibility) can predict individual performance levels in working memory tasks (Braun et al., 2015).

Furthermore, our replication analyses using a data-driven feature selection (CPM) and a non-linear prediction algorithm (random forest) indicate that neither selected, relevant features from the whole brain nor the assumption of non-linear relationships meaningfully improve prediction accuracy over a linear algorithm and pre-defined networks. Importantly, these results speak against the idea that between-network connectivity contained more information than within-network connectivity, as prediction accuracy of the data-driven feature-selection approach across the whole-brain did not outperform predictions limited to pre-defined functional networks.

The lack of visible interindividual differences in EF performance when predicting from meta-analytically defined brain networks might stem from the fact that meta-analyses are based on consistent activation across subjects, potentially overlooking brain regions more strongly associated with individual differences. This limitation could similarly affect RSFC derived from within these networks. However, RSFC, whether derived from the whole-brain or random network approaches, also fails to accurately predict performance, suggesting a weak overall association with individual performance levels.

Moreover, high variability in brain anatomy and functional organization among individuals could cause individual differences to not be visible when predicting from pre-defined brain networks derived from group-average maps (Wang and Liu, 2014). Thus, predictions based on individualized brain networks, recognizing differences in region size, location, and connectivity, could be more effective. For example, a study demonstrated that RSFC among individualized regions better predicted fluid intelligence than connectivity from group-level brain atlases (Li et al., 2019). This points to the potential of tailored approaches in understanding and predicting EF performance.

In conclusion, our findings show that a well-defined executive function-related network does not outperform a perceptuo-motor network, random networks, or the full connectome in predicting EF abilities. Surprisingly, the latter did – irrespective of task demand level, age, or modality. This indicates that the whole-brain connectome and even random networks, which are structurally akin to the executive function-related network, proved to be more informative about individual EF abilities. This suggests that broader network approaches, as well as individualized brain networks, could potentially yield more accurate EF predictions. Importantly, replicating these findings across modalities in Study 4 highlights the critical need for using brain measures that go beyond mere association with EF, but rather possess the capability to meaningfully explain variance in individual EF abilities.

6.2.4 Modality Specificity and Age Effects

Our ANOVA results revealed significant differences in prediction accuracy across modalities, with notable distinctions between age groups. For younger adults, the highest prediction accuracy was found with fALFF, followed by GMV, RSFC, and ReHo. Conversely, older adults showed the best results with GMV, then RSFC, fALFF, and ReHo. This pattern suggests an age-dependent modality specificity, with GMV and fALFF being particularly informative for older and younger adults, respectively.

RSFC's better prediction accuracies can be explained by the modality × network interaction, with the whole-brain approach showing the best results. However, Study 3's finding that random networks significantly exceeded the predictiveness of the EF-specific and perceptuo-motor networks, counters the idea that a larger feature space inherently leads to better predictions.

Task demand levels also played a role, with all metrics better predicting high-demand conditions, especially for features extracted from GMV and fALFF. Age-related effects further qualified these results, with older adults showing better accuracy in low-demand conditions and younger adults in high-demand ones. This suggests that the cognitive demands of a task interact with age-related neural changes, impacting predictive accuracy.

GMV's relevance in older adults aligns with previous research linking regional GMV to global atrophy, particularly in EF-associated fronto-parietal areas (Taki et al., 2004; Chee et al., 2006; Hu et al., 2014). In contrast, in younger adults, fALFF achieved the highest prediction accuracy for EF performance. fALFF, indicating spontaneous low-frequency fluctuations in the BOLD signal, has been suggested to reflect the brain's intrinsic connectivity (Biswal et al., 1995; Fox and Raichle, 2007) and is considered a measure of functional variability within subjects. This variability is thought to represent cognitive adaptability, particularly in adjusting mental states to meet task demands (Bolt, Anderson and Uddin, 2018; Uddin, 2020). In young adults, fALFF patterns are more closely associated with behavior compared to older adults, where fALFF seems less informative for individual EF performance.

Research indicates an age-related decrease in fALFF and GMV in key prefrontal regions such as the pre-SMA, SMA, and DLPFC, which are vital for EF (Hu et al., 2014). These findings suggest that prefrontal brain areas undergo simultaneous age-related structural and functional changes. Younger (and faster) adults typically exhibit higher variability in brain activity across different tasks and greater regional dedifferentiation in signal variability compared to older (slower) adults (Garrett et al., 2011). This greater variability might enable younger brains to more flexibly and efficiently configure optimal neural networks for processing inputs and achieving behavioral objectives, as variability is believed to fuel the exploration of potential functional architectures in brain networks (Garrett et al., 2011, McIntosh et al., 2010; Deco et al., 2011).

The modest association between brain activity and behavior observed with within-network RSFC may stem from its unregulated nature. Recent studies suggest that predicting behavior based on brain connectivity during tasks (or movie watching) may be more effective than during rest (Greene et al., 2018; Sripada et al., 2020; Finn and Bandettini, 2021; Kraljević et al., 2023). Tasks influence the brain's functional state, potentially offering valuable insights into individual differences in functional brain organization and their behavioral implications (Greene et al., 2018). In contrast, resting-state lacks specific influences, leading to high interindividual variability (Buckner, Krienen and Yeo, 2013; Tailby et al., 2015) and providing no certainty about the recorded mental state or control over participants' mental processes (Finn and Bandettini, 2021). Measurement conditions involving movie watching, on the other hand, have been associated with the selection of specific pathways, including higher-level brain regions integrating sensory information and increased interhemispheric exchange through global reorganization of functional communities (Gilson et al., 2018). In this context, a recent paper titled "Is it time to put rest to rest?" questioned whether cognitive neuroscience using resting-state fMRI data has plateaued and suggested transitioning to integrated designs that combine the advantages of both rest (i.e., self-generated activity) and task (i.e., control and interpretability) (Finn, 2021).

Examples for integrated designs include task-signature echoes, where task paradigms are used to learn signatures of brain activity that correspond to particular task conditions, followed by searching for these signatures (an echo) in resting-state data; annotated rest, where introspection data is acquired about the subjective mental experience during or after the scan; state-informed approaches, where the brain state is monitored, for example through real-time neuroimaging, and tasks are given at certain intervals to causally test the influence of ongoing activity; or naturalistic designs such as movie watching. It has been shown that between-network communication increases during movie watching compared to within-network communication (i.e., network integration), while within-network communication increases during rest compared to between-network communication (i.e., network segregation) (Betzel et al., 2020). Higher network integration has been associated with the transfer of intermodular information, while higher network segregation has been linked to processing local, specialized information (Shine et al., 2016; Fukushima et al., 2018). In the context of EF, higher network integration might explain why the whole-brain approach and even random networks outperformed the specific executive function-related network in the current study, as these approaches may include important hubs of other relevant brain networks.

High expression of ReHo, a measure of local brain connectivity, is thought to be indicative of global connectivity (i.e., RSFC; Jiang and Zuo, 2016). Therefore, it would not be surprising if both local and global connectivity measures are affected by variations caused by mental states such as task-focused thinking or mind wandering during rest periods (Gregory et al., 2016). This susceptibility to state effects could explain their lower predictive accuracies in resting-state studies.

fALFF, in contrast, primarily captures the local variability reflecting spontaneous, intrinsic brain connectivity and might therefore be less susceptible to these transient mental states during rest making it a more stable predictor of brain function, particularly in contexts lacking external tasks.

In the context of age-related differences, GMV emerged as a key predictor for older adults, and it also showed decent prediction accuracies for younger adults. The structural nature of GMV, as opposed to the more dynamic functional measures like RSFC and ReHo, lends it greater reliability for capturing consistent, trait-level brain activity. However, it is crucial to note that RSFC and ReHo should not be prematurely labeled as weak indicators of individual performance differences. Their dynamic nature inherently poses challenges in reliably measuring them as trait markers, which may impact their qualification as stable predictors. Their lower prediction accuracies should be understood more as a reflection of the complex interplay between state (transient conditions) and trait (enduring characteristics) interactions, rather than a straightforward measure of cognitive abilities.

Our results align with previous research (Pläschke et al., 2020) indicating tighter brain–behavior associations in older adults – across all structural and functional modalities – possibly due to age-related global neural changes such as brain atrophy or white-matter degeneration, influencing network integrity (Cabeza, Nyberg and Park, 2016) and segregation (Chan et al., 2017; Varangis et al., 2019) that is linked to EF performance. These associations, however, vary depending on the cognitive demand of tasks. Prediction for younger adults was better for high-demand conditions, while for older adults it was more accurate for low-demand conditions. These observed age-related differences might be explained by how aging affects neural networks. In low-demand conditions, older adults can often compensate for age-related decline using alternative neural mechanisms such as the additional recruitment of domain-general resources (Carp, Gmeindl and Reuter-Lorenz, 2010). This aligns with CRUNCH (Reuter-Lorenz and Cappell, 2008), which postulates that the aging brain adapts by engaging additional neural resources or networks to support declining cognitive functions. These compensatory mechanisms, however, may have limitations, particularly in high-demand conditions that challenge EF more intensely. Beyond a certain level of task complexity, the ability of older adults to increase neural activation or recruit extra resources may not suffice, leading to diminished cognitive performance despite compensatory efforts. Alterations in BOLD responsivity during tasks, which reflect changes in neural activity, can influence the brain's ability to respond effectively to higher cognitive demands (Nagel et al., 2011). These alterations may manifest as shifts in activation patterns or efficiency in neural processing, impacting cognitive performance, particularly in tasks requiring more complex EF. Such findings underscore the importance of adaptive behavioral testing methods. To effectively capture the range of cognitive abilities and account for the extent of compensatory strategies employed by different age groups, tests need to be sensitive to variations in task difficulty and individuals' adaptive responses. Adaptive testing approaches should primarily involve adjusting the difficulty level to match individual ability levels, especially considering dimensions beyond the target construct that may affect task performance. For example, perceptual demands may require adjustments to account for impaired perception and its impact on cognitive resource recruitment. This nuanced approach to adaptive testing is crucial for a comprehensive understanding of cognitive aging and for developing interventions tailored to the needs of older adults. Furthermore, it should be noted that in all behavioral tasks except the n-back, older adults exhibited greater variability in performance. This increased variability could potentially contribute to enhanced prediction accuracies.

Interestingly, our analyses indicate that the TMT demonstrates better prediction accuracies as well as brain–behavior associations across different demand levels, networks, and age groups. This suggests that the TMT is particularly sensitive in detecting variations in EF performance. The likely reason for this heightened sensitivity is that the TMT assesses multiple facets and stages of cognitive processing, making it responsive to a wide range of cognitive changes. This aspect becomes particularly relevant when examining low-demand and high-demand conditions independently, rather than as a subtractive measure (i.e., high-demand - low-demand). By separately analyzing these conditions, the TMT can provide nuanced insights into how individuals manage and adapt to varying levels of cognitive challenge, thereby offering a more detailed understanding of their EF performance.

In summary, our results highlight the distinct advantages of GMV and fALFF in predicting EF, with these effects being notably age-dependent. GMV's predictive strength is more evident in older adults, likely due to broader neural changes such as atrophy, while fALFF appears to be a key predictor in younger adults, reflecting their brain's adaptive capabilities. Moreover, our findings emphasize the importance of selecting appropriate tests and utilizing adaptive testing methods to uncover meaningful associations between brain function and behavior.

6.3 Conclusion

The meta-analytic approach highlighted left IFJ's and left aC/PrC's important roles in age-related differences in EF. Although RSFC analyses point towards a domain-general role of left IFJ in EF, the pattern of contributions to the meta-analytic results also suggests process-specific modulations by age. In particular, older adults appear to rely more on left IFJ in the context of cognitive flexibility and inhibition, whereas younger adults recruit it more strongly in the context of working memory. Our findings further suggest that older adults specifically recruit left aC/PrC during EF tasks to compensate for attentional difficulties, while also experiencing age-related changes in deactivation patterns during cognitive tasks. Furthermore, alterations in RSFC involving aC/PrC, DMN, and DAN indicate potential challenges in decoupling between internal and external attentional processes, potentially leading to a dedifferentiation of functional patterns in older adults.

Our prediction studies revealed overall moderate to low prediction accuracies and brain–behavior associations with the explained variance in target variables not exceeding 6%, which is in line with findings from other research in the field. These outcomes raise important questions about the utility of the brain metrics examined for predicting individual differences in EF abilities. While GMV and fALFF showed superiority over ReHo and RSFC in predicting individual EF performance, the results overall challenge the potential of these single metrics to serve as useful biomarkers for individual EF levels. It appears that individual differences in EF abilities may be more significantly influenced by global brain characteristics, such as overall atrophy or neural variability, which are better captured by structural and functional measures, respectively.

Interestingly, we observed an age-related modality specificity, suggesting that structural measures like GMV, indicative of overall atrophy, provide more meaningful insights for older adults, whereas functional measures like fALFF, reflecting brain variability, are more informative for younger adults. This underscores the need for considering age-specific neural changes in EF prediction models. Additionally, the lack of network specificity and the overall moderate prediction accuracies emphasize the importance of exploring more global properties of the brain, potentially by combining different structural and functional metrics, to enhance the sensitivity of predictors for both young and older adults.

Our findings also highlight the necessity of adaptive behavioral testing, particularly given the better prediction accuracies in low-demand task conditions for older adults and high-demand conditions for younger adults. Future research could benefit from replication with larger and more diverse samples, various cognitive states such as task performance or movie watching, and continuous age distributions, to enable deeper insights into the brain's capacity to predict individual mental abilities.

Moreover, given the increasing reliance on machine learning in behavioral neuroscience, there is a pressing need for developing robust methods to compare outcomes of different models, taking into account cross-validation schemes. This would enable a more accurate interpretation and application of machine learning outputs in understanding and predicting cognitive abilities across the lifespan.

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