# Altered Functional Brain Networks in Schizophrenia, Parkinson's Disease and Advanced Age: Insights from Applying Machine Learning for Connectivity-based Predictions

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## Zusammenfassung

Die Anwendung der Magnetresonanztomographie zur Untersuchung von Zusammenhängen zwischen Gehirn und Verhalten hat unser Verständnis von Schizophrenie (SCZ), Morbus Parkinson (MP) und des normalen Alterns (NA) in Bezug auf Veränderungen in funktionellen Gehirnnetzwerken, einschließlich Veränderungen in der funktionellen Kommunikation des Gehirns im "Ruhezustand" (d.h. in aufgabenfreien Zuständen), erheblich verbessert. Diese Ergebnisse basieren jedoch auf traditionellen massen-univariaten Gruppenaggregaten innerhalb der Stichprobe und beziehen sich daher meist auf Veränderungen in verschiedenen Verbindungen über das gesamte Gehirn oder in Ruhezustandsnetzwerken.

Erst in den letzten Jahren, hat das maschinelle Lernen (ML) in der Neurobildgebungsforschung beträchtliche Aufmerksamkeit erhalten, um relevante, auf Neurobildgebung-basierende Biomarker auf der Ebene einzelner Individuen zu erfassen. Bisher wurde ML in erster Linie eingesetzt, um die bestmöglichen Vorhersagen zu erreichen, um in der Zukunft für automatisierte Bildgebungsmarker-basierte Entscheidungen in der klinischen Routine für die personalisierte Medizin integriert zu werden. Im Gegenzug untersuchte diese Dissertation, ob ML genutzt werden kann, um Erkenntnisse über Erkrankungen und das Altern zu gewinnen.

Die beiden Dissertationsstudien zielten darauf ab, das Verständnis von Netzwerkveränderungen im Zusammenhang mit SCZ, MP und NA sowie der kognitiven Leistung im Alter durch die Anwendung modernster ML- und Kreuzvalidierungsschemata zu verbessern. Dafür wurde die funktionelle Konnektivität im Ruhezustand (FRK) in verschiedenen funktionellen Gehirnnetzwerken untersucht, die aus aufgabenbasierten Meta-Analysen abgeleitet wurden und mit kognitiven, sozial-affektiven, motivationalen und motorisch-sensorischen Funktionen assoziiert sind. Es wurden Support-Vektor-Maschinen Klassifikationen und Relevanz-Vektor-Maschinen Regressionen durchgeführt, um zu untersuchen, ob die FRK-Muster innerhalb verschiedener funktioneller Netzwerke mit SCZ, MP und NA sowie der kognitiven Leistung assoziiert sind und somit Vorhersagen auf der Basis einzelner Individuen erlauben.

In der ersten Dissertationsstudie wurde untersucht, ob die bekannten Beeinträchtigungen verschiedener Funktionen in SCZ, MP und NA sich gleichermaßen in der jeweiligen Gruppe in einer hohen Klassifikationsgenauigkeit eines funktionsentsprechenden Netzwerks widerspiegeln würden. Des Weiteren wurde evaluiert, ob die jeweiligen Netzwerke differentielle Informationen bezüglich der unterschiedlichen Erkrankungen und das Altern enthalten. Die Ergebnisse zeigten, dass sowohl SCZ als auch MP durch unterschiedliche Netzwerke, die gut mit bekannten klinischen und pathophysiologischen Merkmalen resonieren, spezifisch gut vorhergesagt werden konnten. Bei SCZ unterschieden die Netzwerke für Belohnungsverarbeitung, Empathie, kognitive Emotionsregulation

und emotionale Verarbeitung die Patienten am genauesten von den Kontrollen. Bei MP ergaben Netzwerke, die mit dem autobiographischen Gedächtnis, der motorische Ausführung und der Theory-of-Mind Kognition assoziiert sind, die genauesten Klassifikationen. Im Gegensatz dazu klassifizierten alle Netzwerke ältere von jungen Erwachsenen mit hoher Genauigkeit und übertrafen beide klinischen Klassifikationen.

Die zweite Dissertationsstudie untersuchte altersbedingte Unterschiede in der Vorhersagbarkeit der individuellen Arbeitsgedächtniskapazität (AGK) aus funktionalen Netzwerken, die mit dem AG assoziiert sind, und Netzwerken, die in unterschiedlichem Ausmaß mit dem AG verbunden sind. Dabei wurde untersucht, ob und inwieweit die verschiedenen Netzwerke bei jungen und älteren Erwachsenen prädiktiv sind. Es zeigte sich, dass nur bei älteren Erwachsenen AGK aus dem AG-Netzwerk, AG-entfernteren Netzwerken, die mit exekutiven Funktionen und Kognition höherer Ordnung assoziiert sind, einem aufgaben-negativen Netzwerk sowie AG-unabhängigen motorisch-sensorischen Systemen vorhergesagt werden konnte. Ein ähnliches Maß an Vorhersagekraft über die verschiedenen Netzwerke hinweg ist vorrangig mit einer niedrigeren AGK assoziiert. Diese Ergebnisse unterstützen die Annahme einer verringerten Segregation funktioneller Gehirnnetzwerke, einer Verschlechterung der Netzwerkintegrität innerhalb der verschiedenen Netzwerke und/oder einer Kompensation durch Reorganisation als Faktoren, die Assoziationen zwischen niedriger und hoher AGK und netzwerkinterner FRK bei älteren Erwachsenen bewirken.

Diese Studien deuten darauf hin, dass die FRK ein Marker für funktionelle Netzwerkdysregulierungen bei SCZ und MP ist sowie für eine Reorganisation auf neuronaler Ebene, die mit veränderter Netzwerkintegrität im fortgeschrittenen Alter in einer globaleren Weise verbunden ist. Zusammen verbessern die Ergebnisse das neurobiologische Verständnis von SCZ, MP und NA, das auf dem FRK-Muster der funktionellen Netzwerke und auf der Ebene des einzelnen Individuums beruht, was die Ergebnisse früherer univariater Ansätze erweitert. Daher können ML-Ansätze als leistungsfähige Methoden zur Untersuchung von Zusammenhängen zwischen Gehirn und Verhalten dienen. Die Ergebnisse könnten auf das Potenzial der Untersuchung von Theranostik-Markern hinweisen, d.h. Netzwerkmarker, die über die Diagnose von Patienten und der Vorhersage des Krankheitsverlaufs hinaus helfen, indem sie auch als Ziel für therapeutische Anwendungen relevant sind. Theranostik-Marker können zu einem anderen Zweig der personalisierten Medizin mit einem Schwerpunkt auf individualisierten netzwerkbasierten therapeutischen Interventionen führen.

## Abstract

The application of magnetic resonance imaging to investigate brain-behavior relationships has greatly enhanced our understanding of schizophrenia (SCZ), Parkinson's disease (PD), and normal aging (NA) with respect to changes in functional brain networks, including alterations in the functional communication of the brain at ‘’rest” (i.e., in task-free states). These findings are, however, based on traditional mass-univariate within-sample group-aggregates and are thus mostly related to changes in various connections across the whole-brain or within common resting-state networks.

In more recent years, the rise of machine learning (ML) in neuroimaging research has received considerable attention with regards to its ability to detect relevant neuroimaging-based biomarkers on the single-subject level. So far, ML has primarily been used to achieve the best possible predictions for the future implementation of automated neuroimaging-based decision-making in clinical routine for personalized medicine. In turn, the thesis investigated whether ML can be utilized to gain knowledge about diseases and aging.

The two studies in this dissertation aimed to improve the understanding of network changes related to SCZ, PD, and NA, as well as cognitive performance in advanced age by applying state-of-the-art ML and cross-validation schemes. To this end, resting-state functional connectivity (RSFC) was investigated in various functional brain networks derived from task-based meta-analyses associated with cognitive, social-affective, motivational, motor-sensory functions. Support vector machine classifications and relevance vector machine regression were performed to investigate whether RSFC patterns within different functional networks are associated with SCZ, PD, and NA, as well as cognitive performance, and thus, allow predictions based on single-subjects.

The first study of the thesis investigated whether the known impairments of different functions in SCZ, PD, or NA, would equally translate into a high classification accuracy for a given network in the respective group. Additionally, the study evaluated whether the respective networks contain differential information related to the different conditions. The results showed that both SCZ and PD were specifically well predicted by distinct networks that resonate well with known clinical and pathophysiological features. For SCZ, the reward, empathy, cognitive emotion regulation, and emotional processing networks distinguished patients most accurately from controls. For PD, networks subserving autobiographical memory, motor execution, and theory-of-mind cognition yielded the most accurate classifications. In contrast, all networks discriminated older from young adults with high accuracies and outperformed both clinical classifications.

The second study examined age-related differences in the predictability of individual working memory capacity (WMC) from functional networks associated with WM and networks linked to WM to different degrees. Thereby, the study investigated whether and to which degree the different networks were

predictive in young and older adults. It was found that only in older adults WMC could be predicted from the WM network, WM-related networks associated with executive functions and higher-order cognition, and a task-negative network as well as WM-unrelated motor-sensory systems. A similar degree of predictive power across the diverse networks was primarily associated with low WMC. These results support the notion of a decreased segregation of functional brain networks, deterioration of network integrity within different networks, and/or compensation by reorganization as factors driving associations between low and high WMC and within-network RSFC in older adults.

These studies suggest RSFC as a marker of functional network dysregulations in SCZ and PD as well as neural-level reorganization associated with altered network integrity in advanced age in a more global way. Together, the results improve the neurobiological understanding of SCZ, PD, and NA that is grounded in the RSFC pattern of functional networks on a single-subject level, which extends the results of previous univariate approaches. Hence, ML approaches can serve as powerful tools for the investigation of brain-behavior relationships. The findings of this thesis may point to the potential of investigating theranostic markers, i.e., network makers that aid beyond the diagnosis of patients and predicting disease progression by also being relevant as therapeutic targets. Theranostic markers may lead to another branch of personalized medicine with a focus on individualized network-based therapeutic interventions.

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# Table of Content

# 1 GENERAL INTRODUCTION

The following introduction provides additional background information on the two studies. The first section describes the clinical picture of schizophrenia (SCZ) and Parkinson's disease (PD) as well as the characteristics of normal aging (NA). In connection with the latter, different cognitive, motivational, social-affective, and motor-related functions are introduced, which are linked to the brain networks that play an important role in the studies. Furthermore, parallels between the diseases and developmental conditions are defined. The second section provides an outline of brain network-based functional connectivity, which provided the data basis of the analyses in both studies. Specifically, the section first explains how functional magnetic resonance imaging (fMRI) can be used to detect networks of brain regions for certain mental functions and how the disadvantages of individual studies in their inaccuracy in the localization of core networks can be overcome with meta-analyses. Subsequently, the RSFC and its advantages as well as open research questions, will be introduced. This section also outlines an overview of some of the previous findings related to SCZ, PD, NA, and cognitive performance associated with the research topic. The third section introduces ML and the two specific ML algorithms used in the studies. Moreover, it presents the selection of ML input features and the assessment of predictive power using cross-validations as used in the thesis studies.

## 1.1 Introduction to Clinical and Developmental Conditions

Psychiatric and neurodegenerative disorders are widespread and are expected to increase over the next decades (Jacobi et al., 2014; Jellinger, 2014). SCZ is still one of the most mysterious and devastating mental diseases. Although the way one perceives the environment is definitively quite subjective, it is still fascinating how the human brain is capable of creating such an escapistic state of hallucinations and delusional thinking (Chadwick, 1993; Weiner, 2003). PD, as one of the most dreaded neurodegenerative diagnoses with its apparent severe movement disturbances, is known for its enormous physical and emotional challenges (Baittie, 2014). The prevalence of developing a psychiatric disorder or neurodegenerative condition across the lifespan contrasts with the pathway of normal healthy aging. Given the growing elderly population and the increase in human life expectancy (Bongaarts, 2009; Sinclair & LaPlante, 2019) but also the endeavors towards immortality (Google's Calico Project), the focus on healthy aging has become as present as it has ever been. Successful aging is defined as aging in the absence of disease and disabilities as well as with the maintenance of physical and cognitive functions, social engagement, and productivity (J. W. Rowe & Kahn, 1997). The tremendous societal interest in healthy aging is reflected in increasing awareness and associated

efforts to optimize the personal lifestyle to maintain psychological well-being and life quality until advanced age.

### 1.1.1 Schizophrenia

SCZ is characterized by a heterogeneous representation of psychological dysfunctions causing a lost touch with reality in the acute psychotic state. Internal experiences of the characteristic perceptual and thought disturbances such as hallucinations and delusions affect the patients, for instance, by hearing commanding or offensive voices and the obsession of being persecuted or controlled (Rey, 2011). Delusions and the common formal thought alterations are signs of affected thinking in these patients. The latter potentially manifests itself in missing associations between different thoughts resulting in conversations that seem odd and distorted (Hart & Lewine, 2017). Broadly, the symptom spectrum is clustered into positive and negative symptom dimensions. The positive dimension is expressed as distortions or exaggerations of ''normal'' psychological functioning and encompasses delusions, hallucinations, and formal thought disorder. In contrast, the negative dimension is represented by an attenuation or a lack of ''normal'' functioning, including symptoms such as avolition, blunted affect, and social withdrawal (Eaton et al., 1995; van Os & Kapur, 2009). Well-established prominent impairments further include cognitive deficits in attention, memory, and executive functions (Salva et al., 2008; Vahia & Cohen, 2008). Moreover, patients suffer from social-affective alterations such as dysfunctional emotion regulation and show impairments in the interaction with their social environment. Furthermore, a core feature of the disease is an aberrant learning of reward- and aversion-predicting stimuli (Murray, Cheng, et al., 2008; Murray, Corlett, et al., 2008; Ochsner, 2008).

### 1.1.2 Parkinson's Disease

PD is a severe progressive neurodegenerative disorder manifesting itself in a characteristic appearance. An unstable upright standing caused by a loss of reflexes accompanied by stiffness and inflexibility of the limb, neck, and trunk leads to a reduced range of motion in patients. Furthermore, the typical shaking movements during rest ("tremor") are a defining feature of PD, which discontinues with action and mostly affects the hands but potentially also legs, jaw, and chin. Facial expressions can be extremely reduced, and walking might involve less arm swinging. These external expressions of the cardinal PD symptoms, as listed above, are summarized into the predominant motor symptoms: tremor at rest, bradykinesia, rigidity, and postural instability (Jankovic, 2008).

Although motor symptoms are the clinical hallmarks of PD, the non-motor symptom spectrum has received increasing importance for understanding the complexity and course of PD as a progressive

disorder (Kalia & Lang, 2015). Non-motor symptoms include autonomic dysfunctions (e.g., hypotension and/or constipation), cognitive impairments (e.g., mild cognitive impairment (MCI), dementia), psychiatric symptoms (depression, anxiety, delusions), sleep disorders (e.g., rapid eye movement sleep behavior disorder, insomnia, hypersomnia) and sensory abnormalities (e.g., olfactory dysfunction, pain) (Mahlknecht et al., 2015; Poewe et al., 2017).

### 1.1.3 Normal Aging

Normal healthy aging represents aging in the absence of a neurodegenerative or psychiatric disease and affects people with large inter-individual variability (Glisky, 2007). Even in the absence of MCI or dementia, cognitive changes are frequent and the most intensively studied domain in human aging research (Craik & Salthouse, 2011a; Hartshorne & Germine, 2015). One of the most frequent reasons for complaints from the elderly is related to memory problems. A variety of studies have demonstrated that new information is deficiently encoded, stored, and retrieved and affects autobiographic and semantic memory content (Park & Festini, 2017a). Memory deterioration with advanced age is also linked to working memory (WM), the capability to temporarily maintain, update, and manipulate information (Braver & West, 2008), which is considered as an important executive function (Miyake et al., 2000). Apart from WM, a similar decline in executive functions affects cognitive action control, the ability to suppress a prepotent response in favor of a contextually more appropriate action (Braver & West, 2008) as well as attention (Nobre et al., 2014). In particular, aging is associated with aberrant vigilant attention, the ability to maintain the focus of cognitive activity on a particular task at hand over a more extended period (Staub et al., 2013). All three executive functions, WM, cognitive action control, and attention, are essential for the effective functioning of higher-order cognition and the implementation of complex goal-directed behavior (Satpute et al., 2012).

Compared to diffuse cognitive deterioration in older adults, social-affective functioning, as well as the intersection of these domains, have been rarely investigated. However, increasingly recognized and examined are age differences related to, e.g., theory-of-mind cognition, emotional processing, or emotion regulation (Kensinger & Gutchess, 2017; Mather, 2016). In particular, difficulties have been demonstrated in reasoning about the beliefs of other individuals, intentions, or goals, known as theory-of-mind cognition (Henry et al., 2013), and dedifferentiated emotional processing patterns during affective picture viewing. Thereby, negative affective pictures were perceived as more negative and arousing, whereas positive pictures were perceived as more positive and less arousing in older (vs. younger) adults (Grühn & Scheibe, 2008). Moreover, when negative emotions are triggered, emotion regulation is less efficient in decreasing unpleasant emotions when older adults are instructed to

employ cognitively demanding strategies. For instance such as reappraisal, referring to cognitively change the meaning of a situation, to alter the negative emotional response (Urry & Gross, 2010).

In addition to cognitive and social-affective alterations with advanced age, reward-based decision-making and motor-execution, have been even more rarely investigated. Nevertheless, impairments in both domains are part of the multifaceted deteriorations in NA. These impairments impact tasks which require the adaptation to external feedback of right or wrong, or task-switching to pursue rewarding feedback. Together, these have been particularly linked to reward-related decision-making deficits in learning and reversing a specific reward contingency (Marschner et al., 2005). Additionally, physical activities of daily living are affected by coordination difficulties when the elderly are asked for bi-manually and multi-jointly coordinated movements. Moreover, a general slowing of movements has been observed in the elderly and is linked to impaired motor performance (Hunter et al., 2016; Seidler et al., 2010).

These specific diseases were chosen as model examples in combination with NA as they share certain essential parallels. Firstly, both diseases can be linked to age. Particularly, age is a critical factor that is relevant to the onset and clinical course of both diseases and is related to NA. The SCZ onset is rather early in life and typically occurs during adolescence and early adulthood (Häfner et al., 2013). In contrast, the onset of PD is in late adulthood, i.e., age is the most significant risk factor for the development of PD, therefore, it is one of the best examples of an age-related disease (Hindle, 2010; Poewe et al., 2017). Furthermore, SCZ (Shahab et al., 2019; Sheffield et al., 2016, 2019) and PD (Beheshti et al., 2020; Rodriguez et al., 2015) have been associated with premature brain aging, that is, accelerated neurodegeneration compared to NA. Additionally, SCZ has also been linked to developmental disorders as being in part associated with neural and environmental events occurring early in development (Gupta & Kulhara, 2010; M. J. Owen et al., 2011). On the other hand, age contributes to the clinical progression and outcome of both diseases. Usually, for SCZ an earlier, whereas, for PD a later age at onset is associated with more severe symptoms, greater cognitive impairments, and a worse progression (Diederich et al., 2003; Hindle, 2010; Immonen et al., 2017; Kao & Liu, 2010; Levy, 2007; Pagano et al., 2016). Secondly, both diseases and NA are related to dopaminergic alterations. SCZ and PD are characterized by disease-specific changes of the dopaminergic system [Jankovic, 2008; Toda and Abi-Dargham, 2007] linked to the core clinical features of both diseases (Cassidy et al., 2018; Heinz & Schlagenhauf, 2010; Kalia & Lang, 2015). In contrast, NA is linked to a more global dopamine decline that resonates with the broader deteriorations in various cognitive functions (Bäckman et al., 2006, 2010; Berry et al., 2016; MacDonald et al., 2012). Moreover, the possible treatment-related complications such as Parkinsonian symptoms in SCZ and psychoses in PD, further emphasizing the link between both diseases, symptoms, and affected dopaminergic brain

circuits (Forsaa et al., 2010; Mathews et al., 2005). Together, these findings demonstrate that age and dopamine play a substantial role that link all three conditions but also express different phenotypic characteristics in SCZ, PD, and NA.

## 1.2 Brain Network-based Functional Connectivity

### 1.2.1 Functional Brain Networks

The human brain operates in flexible and specialized network configurations (Yeo et al., 2015). Brain networks are composed of spatially distributed but functionally linked brain regions that are conjointly recruited to implement flexible, adaptive behavior (Pessoa, 2014). The view that the brain is organized in various networks has emerged in recent decades by the rapid growth of knowledge from fMRI studies on brain-behavior relationships (van den Heuvel & Hulshoff Pol, 2010). By utilizing changes in blood oxygen level-dependent (BOLD) signal, fMRI allows the localization of brain areas of increased or decreased neuronal activity linked to the processing of various sensory stimuli or the performance of different cognitive, social-affective or motor tasks (Glover, 2011; Huettel et al., 2009) associated with healthy or disordered brain states. To reveal the neural correlates linked to a particular cognitive process, such as WM, researchers set up task-based fMRI studies to induce two or more different cognitive states. The induced states target the process of interest and a baseline condition while acquiring MRI brain volumes. To investigate the neural basis of WM, the n-back task has been one of the most established experimental paradigm in fMRI studies (A. M. Owen et al., 2005). This task requires the participants to monitor a sequence of verbal or non-verbal stimuli and to identify when the currently presented stimulus is the same as the one presented preceding n trials. The n is usually set to 1, 2, or 3 (e.g., within a 2-back task of the following letter sequence: A–B–A–C, the response target would be the second A as A is preceding two trials). Continuous WM processes are required during the n-back task, such as online monitoring and updating, to respond accurately to the target stimuli that recur at the specified interval. In contrast, the usually employed 0-back control condition does not place demands on WM. For detecting significant activation clusters of the network of brain areas associated with WM functioning, a fundamental statistical fMRI analysis aims to compare the BOLD signal differences between the induced cognitive conditions by employing the subtraction principle, e.g., 2-back – 0-back effect (Huettel et al., 2009; Ragland et al., 2002). Similarly, fMRI studies have revealed networks linked to a plethora of different mental processes, such as motor execution (Gerardin et al., 2000), autobiographical memory (Denkova et al., 2006), cognitive action control (Leung et al., 2000), vigilant attention (Langner et al., 2012), cognitive emotion regulation (McRae et al., 2010) and theory-of-mind cognition (Gallagher et al., 2000).

fMRI has provided enormous knowledge of brain-behavior localization in the healthy brain. Furthermore, the application to neurodegenerative and psychiatric diseases, as well as NA, have elucidated aberrant regional brain activity of such functional brain networks associated with altered behavioral performance of underlying mental tasks (Gur & Gur, 2010; Hedden, 2007; J. B. Rowe & Siebner, 2012). In addition to the salient disease symptoms such as delusions and hallucinations in SCZ or motor dysfunctions in PD, both disorders exhibit disease-characteristic features in further mental functions of various behavioral domains. For SCZ, apart from the well-established alterations within the reward network that are linked to positive and negative symptoms (Deserno et al., 2013; Heinz & Schlagenhauf, 2010; Radua et al., 2015), disturbances in cognitive and social-affective brain-behavior relationships are among the representative characteristics of psychopathological diversity (Barch, 2005; Gur & Gur, 2010; Ochsner, 2008). In turn, the complexity of PD comprises, apart from the prominent motor features and abnormalities of the motor network (Herz et al., 2014), cognitive and social-affective brain-behavior dysfunctions (Bodden et al., 2010; Dirnberger & Jahanshahi, 2013; G. W. Duncan et al., 2013), and an increased risk for dementia (Aarsland et al., 2001; Aarsland et al., 2003).

Contrary to disease-specific brain-behavior dysfunctions, NA impacts various cognitive, social-affective, reward, and motor-related networks (Hedden, 2007; Mather, 2016; Seidler et al., 2010; Vink et al., 2015). Most compelling, however, is the inter-individual variability of aging (Nyberg et al., 2012). Notably, there is considerable heterogeneity in cognitive functioning, although the overall picture of NA is one of cognitive decline, some older adults maintain their cognitive performance. Several fMRI studies demonstrated that this variability of declined and maintained cognitive performance depends on neuro-functional reorganization associated with different patterns of regional network activation (Grady, 2012). These different patterns have been characterized as either dedifferentiation, denoted as a loss in the distinctiveness of neural activation across a variety of cognitive processes, or compensation, defined as additional neural recruitment associated with maintained cognitive performance in advanced age (Cabeza et al., 2018; Rajah & D'Esposito, 2005; Spreng et al., 2010).

Overall, as outlined above, previous research found that with diseases (SCZ, PD) and healthy aging, functional networks are affected differently. However, some common changes across these conditions may affect networks related to cognitive functions, such as memory, attention, cognitive control (SCZ, PD, NA) and reward-related decision making (SCZ, NA), or motor control (PD, NA).

### 1.2.2 Coordinate-based Meta-analysis

A vast amount of task-based neuroimaging studies provided a multitude of neural networks associated with different mental processes (e.g., working memory, cognitive emotion regulation, etc.) of various

behavioral domains (e.g., cognition, social and emotional functioning, etc.). To probe the same mental process, a variety of studies have been carried out by using a heterogeneity of paradigms on rather small samples. Consequently, studies produced highly variable results and uncertainty of the ''true'' core neural correlates of the target mental process (Eickhoff et al., 2016; Müller et al., 2018). In particular, and to continue with the example of working memory, numerous studies have investigated the neural underpinnings of working memory by employing several paradigms, e.g., the n-back task, the Sternberg task, delayed simple matching task or delayed matching to sample task (A. M. Owen et al., 2005; Rottschy et al., 2012). Moreover, these studies not only differed in the type of paradigm used but also in the kind of stimuli applied (e.g., letters, numbers, words, abstract symbols, pictures). Additionally, there are dissimilarities in experimental manipulations, including variations in WM load, storage time interval, or distraction components across studies, and results vary considerably depending on the contrast performed. Hence, inconsistent results of brain-behavior relationships of the same mental process are limitations of single studies and have raised the need to consolidate neuroimaging results quantitatively. To elucidate which brain network is consistently associated with a specific mental process across a large number of individual studies, a widely used and well-established technique is the coordinate-based meta-analysis using the activation likelihood estimation (ALE) algorithm (Eickhoff et al., 2009, 2012; Turkeltaub et al., 2002). ALE is a powerful approach that identifies significantly overlapping clusters of neural activation across individual experiments of published neuroimaging studies in an unbiased manner. To quantify the consistency (i.e., spatial convergence) of WM-related neural activation across selected studies, ALE models each activation foci as 3D Gaussian distributions centered at the reported coordinates from fMRI studies to account for spatial uncertainty associated with each focus. The Gaussian distribution width is estimated concerning the between-subject and between-template spatial normalization variance based on the collected data. Importantly, the ALE algorithm weights the between-subject variance by the number of subjects included per study accommodating the notion that larger samples should provide a higher probability of the ''true'' localization. Hence, the Gaussian distributions are modeled as ''tighter'' to reflect the smaller spatial uncertainty (Eickhoff et al., 2009). For each experiment, the probabilities of all activation foci for each voxel are combined. Subsequently, the voxel-wise ALE scores defined by the union across all combined activation probabilities are calculated to quantify the convergence across experiments at each location in the brain (Turkeltaub et al., 2012). To distinguish ''real'' from random convergence, the ALE results are tested against an empirical null-distribution of ALE scores obtained under conditions of random spatial association across experiments derived from permutation procedures (Eickhoff et al., 2012).

Coordinate-based ALE meta-analysis has been applied by numerous studies to synthesize task-based fMRI data from hundreds of participants and several modifications in experimental design to define core regions of functional brain networks robustly. These networks pertain to particular mental functions and comprise networks related to, e.g., WM (Rottschy et al., 2012), autobiographical memory (Spreng et al., 2009), vigilant attention (Langner & Eickhoff, 2013), emotion processing and regulation (Buhle et al., 2014; Sabatinelli et al., 2011), reward-related decision making (Liu et al., 2011), or motor execution (Witt et al., 2008).

### 1.2.3 Resting-State Functional Connectivity

More recently, resting-state fMRI (RS-fMRI) has gained popularity in neuroimaging research. Compared to task-based fMRI, RS-fMRI enables the examination of the brain at "rest" (i.e., without an externally structured task) (Biswal, 2012). Similar to task-based fMRI, RS-fMRI studies have revealed evidence of altered brain networks associated with behavioral deficits in clinical and developmental conditions. However, the latter operates at the level of intrinsic functional communication between network regions in task-free states (Azeez & Biswal, 2017; M. H. Lee et al., 2013). RS-fMRI captures low-frequency fluctuations in the BOLD signal that provides a measure of network's resting-state functional connectivity (RSFC) within networks by computing the temporal correlation of spontaneous BOLD signal time courses between spatially distributed brain regions (Fox & Raichle, 2007). Functionally related brain regions exhibit increased temporal coherence in spontaneous brain activity at ''rest'' (Fox et al., 2007; Fox & Raichle, 2007) that converge with task-related fMRI network activations (Smith et al., 2009). Thus, investigating variations in interregional RSFC strength has evolved as a promising marker for network disturbances in disease and developmental conditions as well as for cognitive functions (van den Heuvel & Hulshoff Pol, 2010; Dongyang Zhang & Raichle, 2010). In contrast to task-based neuroimaging, examining RSFC in patients and adults of advanced age offers three crucial advantages. Firstly, it may circumvent task-specific confounds associated with task activation differences due to differences in task performance, strategy, or motivation. Secondly, RS studies can be also used to examine patients with cognitive or physical dysfunctions that are incapable of performing fMRI tasks, thus allowing the assessment of a broader patient sample. Thirdly, the ease of acquiring RS data while the subject lies quietly, mind-wandering in the scanner for 5 to 13 minutes provides an immense practical advantage over longer and demanding task-based fMRI studies (Birn et al., 2013; Fox & Greicius, 2010).

Intriguingly, since the rise of RS-fMRI, a vast number of studies delineated a wealth of alterations in whole-brain RSFC and well-established resting-state networks (RSNs) associated with SCZ, PD, or NA (Damoiseaux, 2017; Gao & Wu, 2016; Greicius, 2008; Karbasforoushan & Woodward, 2012; Prodoehl

et al., 2014; Sala-Llonch et al., 2015; Q. Yu et al., 2012). Furthermore, it was demonstrated that differences in RSFC could provide a reliable neural substrate of inter-individual cognitive performance (Hampson et al., 2006; Mueller et al., 2013; Smith et al., 2015) and this brain-behavior association can be affected by NA (Li et al., 2017; H. Zhang et al., 2018). However, these previous findings of RSFC studies in disease and developmental conditions are limited in the following three aspects:

(1) These studies do not offer insight into connectivity alterations in well-circumscribed functional networks recruited during a specific mental process, and that are known to be affected in clinical and developmental conditions (cf. Schilbach et al., 2014). Contrary to the investigation of network-based RSFC alterations, the majority of previous studies used data-driven independent component analysis to enable a robust definition of separate RSN of covariant activity (Damoiseaux et al., 2006; Smith et al., 2009). However, these studies are limited in their reliability as they depend on the current sample data (Cole et al., 2010). In turn, with seed-based approaches, the RSFC structure may be potentially biased depending on the selected seed region, especially by using regions from a single previous study (Eickhoff et al., 2009; Turkeltaub et al., 2002). In the former data-driven approach, the functional meaning associated with the derived networks is usually post-hoc assigned by using reverse inference, i.e., inferring the existence of particular mental functions based on the involvement of certain brain regions, as these results initially lack any direct relationship to mental functions (Poldrack, 2011). Hence, neither approach allows the investigation of altered functional connectivity (FC) in SCZ, PD, or NA in a priori robustly defined brain networks that are linked to potentially affected mental functions of interest (Figure 1 depicts a schematic principle of a network-based RSFC).

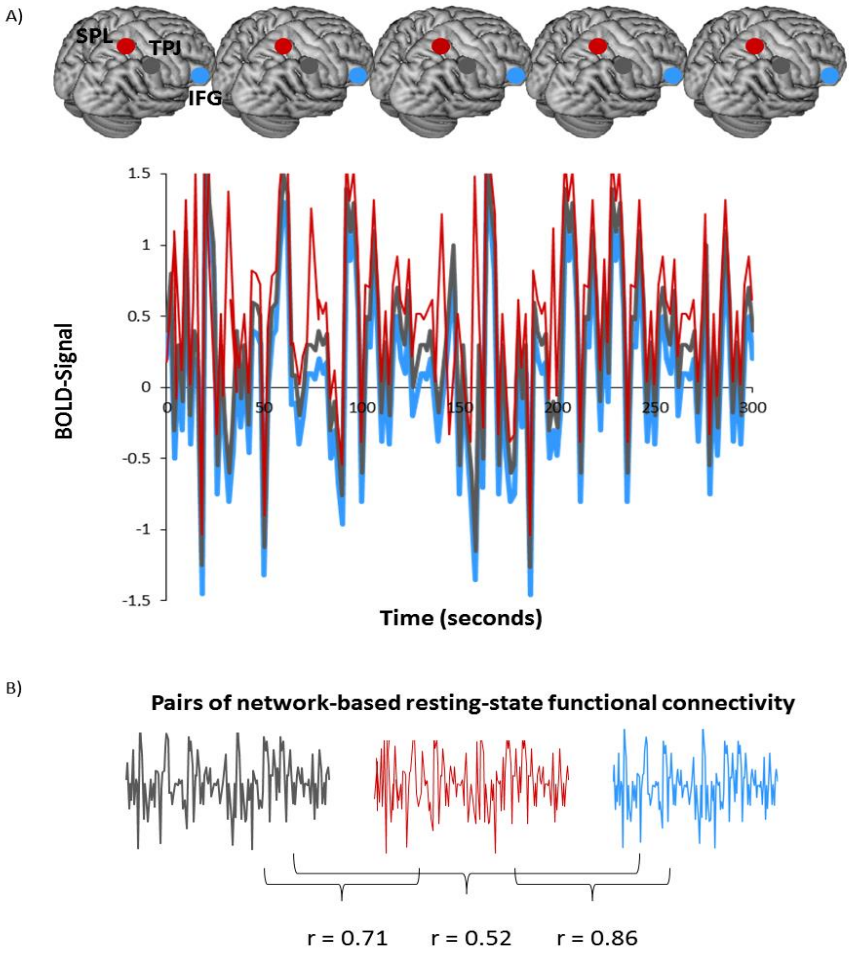


**Figure 1**: Schematic Principle of a Network-based Resting-State Functional Connectivity

A) The eigenvariates of the BOLD-signal time series of seed regions within a network are extracted from a series of RS-fMRI Echo-Planar Imaging images. For the right superior parietal lobule (SPL) depicted in red, the right inferior frontal gyrus (IFG) in blue and for the temporo-parietal junction (TPJ) in grey. B) The correlation coefficients (r) between the signal time course of each pair of network regions reflects the network-based FC.

(2) Previous RS-fMRI studies neglected subtle disease- and age-related effects as well as information on inter-individual cognitive performance that are manifested in spatially distributed patterns across the multiple interconnectivities of a given functional brain network (Orrù et al., 2012). This negligence relates to the conventional approach to perform RSFC data analysis with univariate statistics to identify significantly altered RSFC of single connections based on average between-group differences (e.g., SCZ vs. HC, PD vs. HC, or young vs. old; Bzdok, 2017). By far the majority of RS-fMRI studies of inter-individual differences in advanced age used correlation analysis to establish a relationship between age-related RSFC alterations of single connections and cognitive performance (Andrews-Hanna et al., 2007; Jockwitz et al., 2017; Mevel et al., 2013; L. Wang et al., 2010).

(3) Most RSFC studies did not exploit the potential to associate the unique pattern of functional brain network connectivity of an individual as a feature for a clinical diagnosis, developmental stage, or cognitive performance. Moreover, the generalizability of findings on such a brain-behavior relationships in terms of making predictions about an unknown subject was most often not assessed (Dubois & Adolphs, 2016).

## 1.3. Machine Learning in Neuroimaging

ML techniques have recently received substantial attention in the field of neuroimaging (Lemm et al., 2011). The combination of ML-based methods and neuroimaging offers the possibility of making inferences about the status of an individual subject from the multivariate patterns in neuroimaging data. Providing information at the single-subject level is particularly interesting for clinical decision-making (Arbabshirani et al., 2017; Orrù et al., 2012; Zarogianni et al., 2013) but ML methods are also promising tools to advance and strengthen the current knowledge about the neurobiological alterations of diseases and developmental conditions.

Supervised ML refers to multivariate decoding techniques where an algorithm is provided with neuroimaging data represented as input features X (n subjects x m variables) and corresponding outcome as either discrete or continuous target variables Y (one value per subject) (Bishop, 2006; Bzdok & Meyer-Lindenberg, 2018). Input features can comprise brain imaging data, such as RSFC from RS-fMRI. Depending on whether the learning task is a classification or regression problem, different algorithms are applied. Given the input features, in classification problems the aim is to predict a discrete variable (label), e.g., in binary classification: 1= patient and 0 = healthy control (HC), whereas in regression problems the aim is to predict a continuous variable, e.g., a cognitive performance score 2.8, 9, or 13.6, etc. In supervised ML, an algorithm is trained on these known data pairs by optimizing the model parameter to map the relationship between features and targets. The trained model is then applied to predict the discrete outcome (e.g., 1 = patient) or continuous outcome (e.g., cognitive performance score = 9) from previously unseen features of an individual (Arbabshirani et al., 2017; Orrù et al., 2012). Most importantly, this approach allows generating useful predictions in new subjects from unseen out-of-sample data (i.e., data not used for training the model). For example, the study by Tang et al. (2012) classified SCZ patients (vs. HC) based on whole-brain RSFC with an accuracy of 93.2% and found that most discriminative connections were located within the visual, cortical, default-mode, and sensorimotor networks.

Different ML algorithms are available for solving classification and regression tasks. For instance, support vector machine and relevance vector machine can both be applied to classify subjects as well as to predict a particular cognitive performance score from individual patterns in neuroimaging data.

### 1.3.1 Support Vector Machine

For pattern-classification, the support vector machine (SVM) has emerged as a powerful algorithm that allows to capture diagnostically relevant key differences contained in the features between groups of individuals (disease group vs. healthy controls) to predict the group membership of a new test subject (C.-C. Chang & Lin, 2001, 2011; P.-H. Chen et al., 2005; see Figure 2A). The non-sparse two-class $\nu$-SVM is trained to optimize the hyperplane function that separates the individual subjects input features according to the target group labels (e.g. patient vs. healthy controls). To map non-linear relationships, SVM uses the kernel trick in which the input features are transformed into a higher dimensional feature space via kernel function in order to model a linear separator to divide the data. To find the optimal hyperplane that separates both groups, the margin, i.e., the distance between the hyperplane and the two groups need to be maximized by incorporating the location of support vectors. These are the important data points belonging to one of the groups but lying closest to the other group, hence these are the most difficult cases to classify. During the training different soft-margin regularization parameters $\nu$ are iteratively tested to attain the optimal weight parameters w for the hyperplane function by solving a primal and dual optimization problem. Thereby the regularization parameter $\nu$ controls the minimal and maximal fraction of training errors (misclassifications/margin errors, i.e., slack variables $\xi_i$) and the number of support vectors (i.e., controlling model complexity and overfitting). After solving the dual optimization problem, the optimal weights are assigned to only a subset of training data points, the support vectors. The resulting optimized model for separating the groups is then applied to classify features of a new subject into one of the two groups in relation to the support vectors (for more details, please see Bishop, 2006; C.-C. Chang & Lin, 2001; P.-H. Chen et al., 2005; Hastie et al., 2009c).

### 1.3.2 Relevance Vector Machine

The relevance vector machine (RVM) is a well-established ML algorithm used for pattern-regression (see Figure 2B). Set in Bayesian formulations, RVM provides posterior probability outputs as well as allows obtaining sparse solutions (Tipping, 2001; Tipping & Faul, 2003). RVM for pattern-regression tasks is applied to map the relationship between input features and a pre-defined corresponding target variable by weighting the importance of single features within the complex feature pattern in determining the specific continuous target value. Thereby, RVM utilizes zero-mean Gaussian prior

distributions with variance σ2 over the model weights w governed by one hyperparameter α associated with each weight. Each hyperparameter and variance is iteratively optimized during the training phase by maximizing the marginal likelihood function to compute the posterior distribution over the weights associated with the corresponding data. As a result of the optimization process, the posterior probability for many weight parameters peak around zero, and these parameters are pruned out from the model. Most importantly, this leads to sparsity as the final model solely contains the parameters associated with the relevant vectors, i.e., the ''relevant'' subset of specific features to predict the target variable in the most representative subjects. The trained RVM model is then utilized in the test phase to predict the target value from the feature pattern of a new subject in relation to the relevance vectors (for more details, please see Bishop, 2006; Tipping, 2001; Valente, De Martino, Esposito, Goebel, & Formisano, 2011).

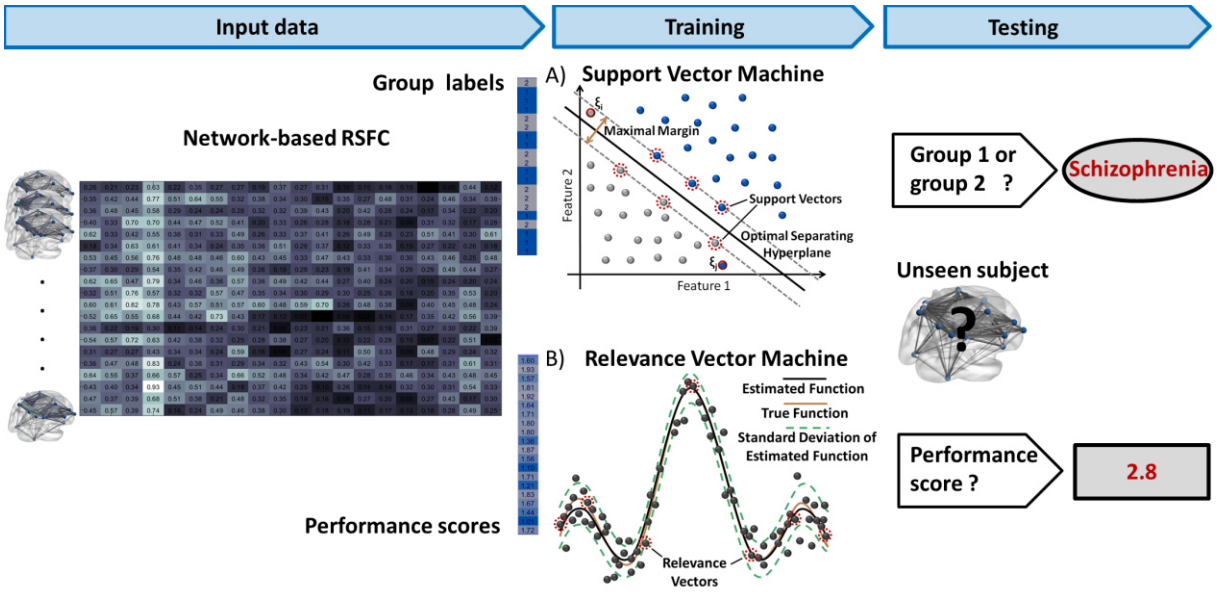


**Figure 2**: Machine Learning Analysis Workflow for Classifications and Performance Predictions based on Network-based Resting-State Functional Connectivity

### 1.3.3 Feature Reduction

ML-based neuroimaging studies have been challenged by a phenomenon referred to as the ''curse of dimensionality''. This challenge relates to the large number of brain features, such as connections of the entire brain, that greatly outnumber the amount of observations usually determined by small sample sizes (Arbabshirani et al., 2017; Domingos, 2012). In cases of whole-brain connectivity, features can comprise 264 functional regions resulting in up to 34.716 connections (Power et al., 2011). Thus,

feature reduction has been increasingly used to tackle this disequilibrium. One essential step involves feature selection, the selection of a subset of features, expected to facilitate the training of the ML model by removing redundant predictor features, experimental noise. The reduction aims to avoid ML model overfitting, resulting in improved prediction accuracy and generalizability (Mwangi et al., 2014). On the contrary, a high number of features or utilizing only a small subset of features may lead to underfitting and, consequently, poor prediction accuracy and generalizability. Thus, the number of informative features is crucial for ML applications to capture relevant underlying information. Over- and under-fitting can be counteracted by adapting the model complexity (Domingos, 2012; Janssen et al., 2018).

For RSFC data, the selection approach can consist of selecting regions of interest based on previous literature on differences in FC between groups or cognitive performance. Accordingly, the selection can be performed in an objective manner by using, e.g., functionally meaningful features such as brain networks derived from a coordinate-based meta-analysis (Mwangi et al., 2014) and are based on prior knowledge regarding affected functional brain systems in different phenotypical conditions (Chu et al., 2012). Consequently, potentially relevant features are selected in a hypothesis-driven manner while at the same time decreasing computational load and time of the ML analysis (Orrù et al., 2012). Importantly, this approach also leads to results with superior interpretability as the predictive models are based on well-circumscribed brain systems.

### 1.3.4 Assessment of Predictive Power

The generalization performance of an ML model refers to its prediction capacity on new unseen test subjects, i.e., subjects not involved in training the model. The evaluation of model performance provides the quality measure of the finally chosen model (Hastie et al., 2009b). A standard procedure to train the model and to empirically evaluate its predictive power to extrapolate to unseen test subjects is the implementation of a two-step cross-validation (CV) scheme. Firstly, the model algorithm is fitted on training data based on pairs of features-target and, secondly, its generalization performance is evaluated on the hold-out unseen test data, i.e., based on out-of-sample prediction.

Yet, neuroimaging studies have mostly used a ‘’leave-one-out’’ CV scheme, which involves the exclusion of a single-subject as the test set while the model is trained on the remaining sample. Although this results in a desirably large training set, it also leads to unstable predictive performance and overly optimistic results due to increased test set variance. For controlling both drawbacks, repeated random split strategies have been implemented for the studies of this thesis. In particular, a 10-fold CV has evolved as a superior scheme for the estimation of predictive accuracy (Hastie et al., 2009a; Varoquaux et al., 2016). This procedure involves randomly splitting the entire data set into ten

equally sized subsamples. The model is then trained on nine subsamples, and the testing is performed on the subjects of the one left-out unseen subsample. By leaving out each of the subsamples one at a time, the CV process is then repeated ten times. The advantage of this method is a superior training-test-set data balance in which it matters less how the data is divided, and usually lower variance in model performance is achieved. Subsequently, the prediction performance is averaged across the ten different data splits.

In cases where the model parameters are tuned on the data (for example, the regularization parameter v of the SVM), the most reliable way of attaining the highest accuracy and generalizability to the test data is by implementing a nested CV scheme (Lemm et al., 2011; Varoquaux et al., 2016). This scheme ensures that model parameter optimization and evaluation are performed independently of each other, hence, avoiding a circularity bias and invalidated results given by overestimates of the generalization performance of the model (Kriegeskorte et al., 2009). In a nested CV scheme, an inner ‘‘nested" CV loop is first implemented to optimize the regularization parameters through grid-search to achieve the most accurate model fit. Secondly, an outer CV loop is used to evaluate the generalizability of the inner loop selected model to new subjects that have not been part of the model optimization process. On both loop levels, the data is randomly split into training and test splits. In either CV scheme, more stable estimates of the performance of a model can be attained, incorporating the broad spectrum of sample heterogeneity of the disease or aging population, by performing multiple repetitions of a 10-fold CV scheme. Thereby, in each repetition, the data are shuffled and randomly split so that different distributions of sample subjects are assigned to the folds in each repetition (Varoquaux et al., 2016).

Supervised ML allows the association of patterns of RSFC with disease or developmental conditions and cognitive performance. Most importantly, the identification of disease, aging, or cognitive characteristic in RSFC patterns across the whole-brain or specific brain networks can then be generalized to make predictions based on new single-subjects outside the model training procedure. So far, several studies that deployed RSFC for predictions, have demonstrated the importance of RSFC as a neural marker to predict (Arbabshirani et al., 2017; Du et al., 2018; Kambeitz et al., 2015; Orrù et al., 2012; Wolfers et al., 2015; Zarogianni et al., 2013), PD (Y. Chen et al., 2015; Long et al., 2012), and NA (Billings et al., 2017; Meier et al., 2012; Vergun et al., 2013) as well as inter-individual differences in cognition (Finn et al., 2015; Rosenberg et al., 2016; Shen et al., 2017). Thereby, the major aim of previous studies was preferably determined by extracting RSFC-based biomarkers linked to the most accurate predictions in classifying disease from healthy conditions for clinical application and personalized medicine. The precise method of how these models were generated and whether they contained disease- or aging-related insight was rather of secondary importance. Thus, the identified

regions that played the most crucial role for the predictions were often barely discussed in the context of neurobiological, behavioral, and/or the psychopathological insights.

# 2 RATIONALE OF THE THESIS

Given the outlined theoretical background and presented limitations, leveraging the advantages of different approaches to a unique methodological combination applied in the thesis studies shall provide novel insights into brain-behavior relationships in SCZ, PD, and NA. Meta-analytical networks are reflections of robustly and objectively defined, circumscribed functional brain systems. Moreover, RSFC is an easily accessible, informative neural marker associated with SCZ, PD, NA, and inter-individual differences in cognitive performance. In summary, examining RSFC within a priori meta-analytically derived brain networks pertaining to a specific mental function constitutes a functionally meaningful selection of brain features for the application of ML algorithms. Meaningful dimensionality reduction results in increased interpretability of RSFC changes related to well-defined brain systems. The combination with ML algorithms offers the potential to investigate whether complex and distributed patterns in RSFC within functional brain networks are associated with SCZ, PD, NA, and inter-individual differences in cognitive performance. Moreover, ML enables predictions at the level of new subjects on their phenotypic status.

ML holds excellent promises for personalized medicine as a diagnostic tool for individual patient-level classification of disease and the prognosis of disease progression or treatment response. However, this method has been rarely used to address its impact on gaining novel insight into classical brain-behavior relationships and such questions have been primarily investigated with traditional univariate analysis approaches. Hence, it remains largely unexplored whether connectivity patterns within functional networks during task-free states are associated with a specific disease or developmental condition or inter-individual performance differences at the single-subject level. Therefore, this lack of knowledge raises the questions of whether ML can aid in gaining insights into pathological changes in SCZ and PD as well as developmental alterations in NA linked to RSFC patterns in functional brain networks. Importantly, this approach allows one to address open questions about how the commonalities and phenotypical differences of these conditions manifest themselves in different functional brain systems. For this purpose, ML-based predictions offer to interpret prediction capacity as a measure of the amount of information about the diseases, NA, and cognitive performance that is contained in different networks. Conversely, it allows one to interpret how much information is contained in networks with regard to the different conditions. The amount of information also serves as an indicator of the degree of change in the integrity of the networks with respect to the different phenotypical conditions. Thus, the motivation behind the approach aims to enhance our understanding of the

relationships between SCZ, PD, NA, as well as cognitive performance and functional brain networks. As a result, this thesis, therefore, aims to address the following central research questions:

**Study 1: On the Integrity of Functional Brain Networks in Schizophrenia, Parkinson's Disease, and Advanced Age: Evidence from Connectivity-based Single-Subject Classification**

Do known impairments in different functions in SCZ, PD, or NA, respectively, manifest in the connectivity patterns within networks that subserve these affected mental functions, and hence, translate into high classification accuracy for a given network in the respective group?

This study aimed to investigate in a "proof-of-principle'', explorative, and comparative manner whether networks pertaining to functions known to be affected by SCZ, PD, and NA carry differential information related to these conditions. Thereby, it was examined whether single-subjects can be differently classified based on a variety of different functional networks with respect to their condition. Comparisons were performed to evaluate the single-subject classification accuracies within and between the three conditions and across the various networks.

**Study 2: Age differences in predicting working memory performance from network-based functional connectivity**

Do neuro-behavioral features of aging manifest in inter-individual differences in behavioral measures of WM capacity (WMC) associated with variations in connectivity patterns at rest within the WM network and different cognitive networks, either closely or distantly related to WM?

This study aimed to examine whether age-related differences in RSFC patterns within functional brain networks related to WM to different degrees are associated with individual WMC. Thereby it was investigated whether and to which degree individual WMC can be predicted from different cognitive networks in young and old participants. By comparing prediction performance across networks and between the two age groups, it was evaluated whether aging affects the neural-level organization at rest related to inter-individual WM task demands outside the scanner.

Furthermore, for NA, the results from both studies allowed one to assess which networks that performed well in distinguishing young and old participants also contained relevant behavioral information on age-related inter-individual cognitive performance. Additionally, the specificity of brain-behavior relationships in young and older adults was examined to evaluate if distinct networks carry information on cognitive performance to different degrees.

# 3 STUDIES OF THE THESIS

## STUDY 1:

## ON THE INTEGRITY OF FUNCTIONAL BRAIN NETWORKS IN SCHIZOPHRENIA, PARKINSON'S DISEASE, AND ADVANCED AGE: EVIDENCE FROM CONNECTIVITY-BASED SINGLE-SUBJECT CLASSIFICATION

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## Abstract

Previous whole-brain functional connectivity studies achieved successful classifications of patients and healthy controls but only offered limited specificity as to affected brain systems. Here, we examined whether the connectivity patterns of functional systems affected in schizophrenia (SCZ), Parkinson's disease (PD), or normal aging equally translate into high classification accuracies for these conditions. We compared classification performance between pre-defined networks for each group and, for any given network, between groups. Separate support vector machine classifications of 86 SCZ patients, 80 PD patients, and 95 older adults relative to their matched healthy/young controls, respectively, were performed on functional connectivity in 12 task-based, meta-analytically defined networks using 25 replications of a nested 10-fold cross-validation scheme. Classification performance of the various networks clearly differed between conditions, as those networks that best classified one disease were usually non- informative for the other. For SCZ, but not PD, reward, empathy, emotion regulation, and emotion-processing networks distinguished patients most accurately from controls. For PD, but not SCZ, networks subserving autobiographical memory, motor execution, and theory-of-mind cognition yielded the best classifications. In contrast, young–old classification was excellent based on all networks and outperformed both clinical classifications. Our pattern-classification approach captured associations between clinical and developmental conditions and functional network integrity with a higher level of specificity than did previous whole-brain analyses. Taken together, our results support resting-state connectivity as a marker of functional dysregulation in specific networks known to be affected by SCZ and PD, while suggesting that aging affects network integrity in a more global way.


**Keywords:** schizophrenia; Parkinson's disease; normal aging; support vector machine; resting-state fMRI; functional connectivity; brain networks; machine learning

## Introduction

Schizophrenia (SCZ) and Parkinson's disease (PD) are two of the most prevalent and socioeconomically relevant brain diseases (Andlin-Sobocki et al., 2005). Although SCZ onset typically emerges during adolescence and early adulthood (Häfner et al., 2013), PD is characterized by an onset during late adulthood (Hughes et al., 1992; Poewe et al., 2017) and has been associated with premature aging, that is, earlier and more rapid neurodegeneration as compared to the course of normal aging (NA) (Rodriguez et al., 2015). Both SCZ and PD are characterized by disease-specific pathophysiological changes of the dopaminergic system (Jankovic, 2008; Toda & Abi-Dargham, 2007), contrasting with a more global dopamine decline in NA (Bäckman et al., 2006). However, it has been proposed that dopaminergic dysfunction in SCZ arises as a secondary effect due to alterations of the glutaminergic system (Laruelle et al., 2003). In contrast, in PD dopaminergic deficiency represents the primary cause leading to pathophysiological upstream dysregulations of different neural systems (Obeso et al., 2008). These neurobiological features of SCZ, PD, and NA (Bäckman et al., 2006; Jankovic, 2008; Laruelle et al., 2003; Obeso et al., 2008; Rodriguez et al., 2015; Toda & Abi-Dargham, 2007) may manifest themselves in functional connectivity alterations at the level of large-scale brain networks (Cole et al., 2013; Kelly et al., 2009; Narr & Leaver, 2015; Prodoehl et al., 2014; Sala-Llonch et al., 2015). However, some putative commonalities (neurodegeneration, dopaminergic dysregulations, and altered connectivity) need to be juxtaposed with the prominent phenotypical differences between SCZ, PD, and NA (Bäckman et al., 2006; Jankovic, 2008; Narr & Leaver, 2015; Prodoehl et al., 2014; Sala-Llonch et al., 2015; Toda & Abi-Dargham, 2007) and the fact that the clinical presentations of SCZ and PD are very different (Eaton et al., 1995; Jankovic, 2008; Kalia & Lang, 2015; van Os & Kapur, 2009), raising the question whether various functional systems are differentially affected in the three conditions. Rather than assessing altered activations in different functional systems by conducting task-based functional magnetic resonance imaging (fMRI) studies, we examined altered functional connectivity within various functional networks robustly defined by meta-analyses of task-based neuroimaging studies in a comparative fashion (cf. New et al., 2015; Schilbach et al., 2016). This has the practicable advantage of using easily accessible, short, and standardized resting-state (RS) data while at the same time incorporating the consolidated knowledge based on task-based imaging into the analysis. We argue that such an approach is particularly relevant, given that in contrast to RS imaging, task-based assessments will rarely be feasible in a routine clinical setting.

Alterations in functional network integrity patterns in SCZ, PD, or older adults (compared to respective healthy/young controls) can be captured by using machine learning-based classification. For extracting a diagnostically relevant marker that allows the classification of individual subjects based on the connectivity in functional brain networks, multivariate decoding algorithms like support vector

machine (SVM) should provide the most appropriate approach for this endeavor. Rather than testing each connection independently for group differences, SVMs are trained on part of the data by weighting all connections in order to separate the known clinical status from healthy controls (HCs). Classification accuracy can then be determined by assessing the ability to predict group membership of previously unseen subjects. Applied to (whole-brain) connectivity data, this approach has previously been found to distinguish SCZ patients (cf. Arbabshirani, Plis, Sui, & Calhoun, 2017; Kambeitz et al., 2015; Wolfers, Buitelaar, Beckmann, Franke, & Marquand, 2015) or PD patients (cf. Y. Chen et al., 2015; Long et al., 2012) from healthy controls (HC), as well as aged from young subjects (NA) (cf. Meier et al., 2012; Vergun et al., 2013).

Previous pattern-classification studies aimed at providing the best possible classification performance on whole-brain connectivity. In contrast, the aim of this work was to assess whether specific functionally defined networks are altered in SCZ, PD, and NA. Although previous studies mainly used independent component analysis (ICA) based data-driven methods to extract major RS networks (Damoiseaux et al., 2006; Smith et al., 2009), our work is based on a priori meta-analytically defined networks associated with specific sets of behavioral functions, such as working memory (Rottschy et al., 2012) or emotional processing (Sabatinelli et al., 2011). In contrast to well-established RS networks, these networks represent the consolidated information from hundreds of task-based fMRI studies and hence those locations in the brain that are reliably activated when subjects perform tasks pertaining to a particular mental function. We thus argue that these nodes define robust functional networks in the brain related to specific mental domains. In turn, the functions associated with RS networks are usually derived from a reverse inference approach, as these lack any direct relationship to mental functions (Poldrack, 2011). We suggest that this more direct relationship between the network-nodes and actual task-demands is an important advantage of our approach. Moreover, the employed strategy results in an a priori, unbiased definition of the respective networks, whereas ICA-based networks are usually defined from the current data (Cole et al., 2010). Our meta-analytically derived network model approach, thus, offers the potential to investigate functional connectivity within robust a priori brain networks that are implicated in processing a specific mental process.

Therefore, this study aimed to examine whether the known impairment of different functions in SCZ, PD, or aging, respectively, would equally translate into a high classification accuracy for a given network in the respective group, based on the connectivity pattern within this network. As a "proof-of-principle" approach, we, therefore, intended to investigate whether various a priori networks based on task-activation findings carry differential disease-related information assessable by RS imaging. To this end, we examined two diseases which are clinically very disparate but well studied in the previous neuroimaging literature. The findings were then juxtaposed to findings on age-related effects in the

same networks. Thereby, we could evaluate whether the respective networks carry differential information related to the different conditions or, conversely, whether the different networks carry differential information related to a particular condition. Given some putative commonalities and especially phenotypical differences, the aim was to examine the possibility for differential classification of SCZ, PD und age, rather than to primarily study the specific diseases and their clinical separation from each other or aging per se. In our investigation, these three groups thereby serve as examples to evaluate this approach. For example, we assume that connectivity in the reward (Rew) network will be potent in differentiating SCZ patients from matched HCs, as several studies have shown impairments related to reward learning in SCZ, and the neurobiology of this network has been linked to psychosis (Deserno et al., 2013; Heinz & Schlagenhauf, 2010; Radua et al., 2015). Likewise, we would expect a good classification accuracy for PD patients based on FC in the motor network, given that motor impairments represent the core feature of this disease (Jankovic, 2008), and motor circuits in the brains of PD patients are altered during motor tasks and at rest (Herz et al., 2014; Prodoehl et al., 2014; Tessitore et al., 2014). Finally, NA is accompanied by cognitive decline in various domains (Glisky, 2007), such as deterioration in working-memory function (Braver & West, 2008). For the latter, age-related neural changes have repeatedly been shown at task (Dennis & Cabeza, 2008; Rajah & D'Esposito, 2005) and rest (Keller et al., 2015). Accordingly, we assume that the working memory (WM) network allows a clear distinction between old and young adults.

In an explorative manner, we furthermore assessed a broad set of networks associated with different behavioral domains (cognitive, social-affective, motivational and motor-related) since all three conditions (PD, SCZ, and NA) show alterations in various functional domains on the behavioral and neural level (Barch, 2005; G. W. Duncan et al., 2013; Seidler et al., 2010). Importantly, in our approach, we reasoned that classification performance may be interpreted as an indication for the amount of information contained in a given network regarding a particular disease or age status, and thus, of the degree of change observed in the integrity of particular networks under these conditions.

We assume that classification performance will be best for connectivity in those networks that subserve mental functions known to be affected in SCZ and PD. SCZ is characterized by prominent social-affective/motivational alterations (Brunet-Gouet & Decety, 2006; Deserno et al., 2013; Heinz & Schlagenhauf, 2010; Kring & Elis, 2013; Radua et al., 2015), whereas in PD motor impairments are most affected (Herz et al., 2014; J. B. Rowe & Siebner, 2012; Tessitore et al., 2014). We, therefore, hypothesized that social-affective/motivational and motor-related networks provide a superior classification of SCZ and PD patients, respectively. As both diseases are accompanied by cognitive impairments as well, we assumed that cognitive networks may also be predictive to some degree (Barch, 2005; G. W. Duncan et al., 2013; Elgh et al., 2009; Nieoullon, 2002). As NA is associated with a

broad spectrum of decline affecting various functional systems (albeit to a varying degree) (Hedden, 2007; Mather, 2016; Seidler et al., 2010), we expected that most networks allowed for an accurate discrimination of old from young adults.

## Materials and Methods

### Samples

#### *Schizophrenia*

RS fMRI data and phenotypical information of 86 SCZ patients and 84 HCs obtained from the COBRE sample (http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html) and the University Hospital of Göttingen, Germany, were included in the analysis. SCZ diagnosis was assigned as assessed by the DSM-IV-TR based on the structured clinical interview (SCID-P) and the International Classification of Diseases (ICD-10), respectively. SCZ symptom severity was assessed using the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987) evaluating the severity of positive and negative symptoms as well as the general psychopathology. Patients received their regular medication therapy with considerable variability in the exact compounds used and a high prevalence of combination drug therapy (medicated patients but exact medication and dose unknown for Olanzapine equivalent dose (Gardner et al., 2010): COBRE: 50.9%; Göttingen: 25.8%; medication status unknown: COBRE: 1 SCZ patient; Göttingen: 2 SCZ patients).

#### *Parkinson's disease*

RS fMRI data of 80 PD patients and 84 HCs obtained from the RWTH Aachen University Hospital and the University Hospital Düsseldorf, Germany, were included in the analysis. Diagnosis of PD was assigned by consultant neurologists with longstanding expertise in movement disorders based on clinical examination and review of the medical history. Included PD patients fulfilled the standard UK Brain Bank criteria for PD and had on average a mild cognitive impairment as confirmed by the Montreal Cognitive Assessment (MoCA) but no major depression symptoms (Hoops et al., 2009; Hughes et al., 1992; Nasreddine et al., 2005). To assess PD symptom severity and evaluate motor impairments the Unified Parkinson's disease Rating Scale Part III ( UPDRS; Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003) and Hoehn and Yahr Scale ( H & Y Scale; Hoehn & Yahr, 1967) were applied. All patients were medicated with their regular individual PD-related treatment [medication and dose unknown for Levodopa equivalent daily dose (Tomlinson et al., 2010): Aachen: 28.1%; Düsseldorf: 12.5%].

### *Healthy controls*

RS fMRI data of HC ($HC_{SCZ}$ and $HC_{PD}$) were obtained from the four different sites as respective clinical subjects (SCZ and PD) and were without any record of neurological or psychiatric disorders as confirmed via structured clinical screening.

### *Normal Aging*

RS fMRI data of 95 old (age range: 55 – 70 years) and 93 young (age range: 20 – 35 years) participants with an age range of 15 years in each group were obtained from the population-based 1000BRAINS study (Caspers et al., 2014) and another separate study at the Research Centre Jülich, Germany. This relatively small age-range aims to enhance the subsample homogeneity. "NA" in old participants refers to the absence of neurodegenerative diseases. Older adults showed cognitive performance adequate for their age as assessed by the Mild Cognitive Impairment and Early Dementia Detection assessment (DemTect > 13; Kalbe et al., 2004) and all participants did not exhibit clinically relevant symptoms for depression as evaluated via the Beck Depression Inventory-II ( BDI-II < 13; Beck, Steer, & Brown, 1996). Importantly, target and control groups (i.e., patients vs. HC, old vs. young adults) of all three samples (PD, SCZ, NA) represent subsamples from larger samples that were post-hoc matched for gender, within-scanner movement and (only for the clinical samples) age (cf. S1 Table 1 for sample and group matching characteristics). Written informed consent from all subjects and approval by the local ethics committees was obtained from all sites. Joint reanalysis of the anonymized data was approved by the ethics committee of the Heinrich Heine University Düsseldorf.

**S1 Table 1**: Sample and Group Matching Characteristics

| Sample | n (males) | Age (years) | Head movement (DVARS) | Age at onset (years) | Illness duration (years) | Antipsychotic/ dopaminergic medication | Neuropsychology and Psychopathology | | |
|---|---|---|---|---|---|---|---|---|---|
| **SCZ sample** | | | | | | **OZP-equivalent** | **PANSS: Total / PS / NS / GEN** | | |
| **COBRE** | | | | | | | | | |
| SCZ patients | 55 (46) | 38 ± 14 | 1.66 ± 0.55* | 20 ± 8 | 17 ± 14 | 13 ± 8 | 58 ± 14 / 14 ± 5 / 14 ± 5 / 29 ± 8 | | |
| $HC_{scz}$ | 55 (42) | 38 ± 12 | 1.44 ± 0.41 | | | | | | |
| **Göttingen** | | | | | | | | | |
| SCZ patients | 31 (25) | 32 ± 10 | 1.47 ± 0.30* | 25 ± 8 | 7 ± 8 | 14 ± 9 | 52 ± 11 / 12 ± 3 / 13 ± 4 / 28 ± 6 | | |
| $HC_{scz}$ | 29 (22) | 32 ± 9 | 1.31 ± 0.23 | | | | | | |
| **Total** | | | | | | | | | |
| SCZ patients | 86 (71) | 36 ± 13 | 1.59 ± 0.48* | | | | | | |
| $HC_{scz}$ | 84 (64) | 36 ± 11 | 1.39 ± 0.36 | | | | | | |
| **PD Sample** | | | | | | **LEDD** | **H & Y Scale** | **UPDRS-III** | **MoCA** |
| **Aachen** | | | | | | | | | |
| PD patients | 32 (21) | 64 ± 9 | 0.51 ± 0.16 | 59 ± 8 | 6 ± 5 | 449 ± 238 | 2 ± 1 | 23 ± 12 | 27 ± 2 |
| $HC_{PD}$ | 33 (20) | 63 ± 6 | 0.62 ± 0.29 | | | | | | |
| **Düsseldorf** | | | | | | | | | |
| PD patients | 48 (30) | 59 ± 9 | 0.69 ± 0.26 | 51 ± 9 | 8 ± 6 | 1029 ± 416 | 2.5 ± 1 | 16 ± 8 | 24 ± 4 |
| $HC_{PD}$ | 51 (30) | 57 ± 9 | 0.68 ± 0.22 | | | | | | |
| **Total** | | | | | | | | | |
| PD patients | 80 (51) | 61 ± 9 | 0.62 ± 0.24 | | | | | | |
| $HC_{PD}$ | 84 (50) | 59 ± 8 | 0.66 ± 0.25 | | | | | | |
| **NA sample** | | | | | | | **DemTect** | | **BDI-II** |
| **Jülich** | | | | | | | | | |
| Old | 48 (26) | 61 ± 5 | 1.58 ± 0.41* | | | | 16 ± 2 | | 5 ± 5 |
| Young | 52 (26) | 26 ± 3 | 1.24 ± 0.24 | | | | | | 5 ± 4 |
| **1000BRAINS Jülich** | | | | | | | | | |
| Old | 47 (25) | 64 ± 4 | 1.79 ± 0.43* | | | | 15 ± 2 | | 6 ± 5 |
| Young | 41 (23) | 28 ± 4 | 1.28 ± 0.26 | | | | | | 4 ± 4 |
| **Total** | | | | | | | | | |
| Old | 95 (51) | 63 ± 5 | 1.68 ± 0.43* | | | | | | |
| Young | 93 (49) | 27 ± 4 | 1.26 ± 0.25 | | | | | | |

SCZ, schizophrenia; $HC_{SCZ}$, matched healthy controls (HCs) of SCZ sample; PD, Parkinson's disease; $HC_{PD}$, matched HCs of PD sample; NA, normal aging; characteristic values in mean±standard deviation; DVARS, derivative of root mean squared variance over voxels (head movement parameter) (Power et al., 2012); significant difference in age (clinical samples), gender and movement are marked with * for p <0.05; SCZ: OZP-equivalent (Gardner et al., 2010), Olanzapine equivalent dose; PANSS, Positive and Negative Symptom Scale, (PS, Positive Symptoms Scale/NS, Negative Symptoms Scale/GEN, General Psychopathology Scale); PD: LEDD **(Tomlinson et al., 2010)**, Levodopa equivalent daily dose; H & Y Scale, Hoehn and Yahr Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; MoCA, Montreal Cognitive Assessment; NA: DemTect, Mild Cognitive Impairment and Early Dementia Detection, BDI-II, Beck Depression Inventory II.

## Resting-state fMRI data acquisition, preprocessing, and analysis

During image acquisition (see Supplement S1 Table SI for fMRI parameters), participants were instructed to lie still, let their mind wander, and not fall asleep (confirmed at debriefing). SPM8 (www.fil.ion.ucl.ac.uk/spm) was used for image realignment, spatial normalization to the MNI-152 template using the unified segmentation approach (Ashburner & Friston, 2005), and smoothing ''5-mm full width at half-maximum Gaussian kernel''.

We investigated 12 functional networks, robustly defined by previous quantitative meta-analyses, to reflect neural correlates of a broad set of cognitive, social-affective/motivational, and motor functions (see S1 Table 2 for an overview and S1 Table SII for detailed network coordinates and corresponding brain regions). Only meta-analytic networks with a minimum of 10 nodes were included, since a lower

number of features are uninformative for robust classification. RS functional connectivity (RSFC) within each network was computed per subject by first extracting the time-series for each node within 6 mm of the meta-analytic peaks. To reduce spurious correlations, variance explained by the six movement parameters and their derivatives (modeled as first and second order effects) as well as the mean white-matter and cerebrospinal fluid signal time-courses was removed from the time series (Satterthwaite et al., 2013; Varikuti et al., 2017). Subsequently, time series were high-pass filtered retaining frequencies above 0.01 Hz. Connectivity was computed as the Fisher's Z-transformed Pearson correlation between the time series of each network's nodes; connectivity values were adjusted for effects of acquisition site, gender, movement, total brain volume, and (only for the clinical samples) age (cf. Schilbach et al., 2016, 2014) to avoid classification based on spurious between-subject effects.

**S1 Table 2**: Network Overview

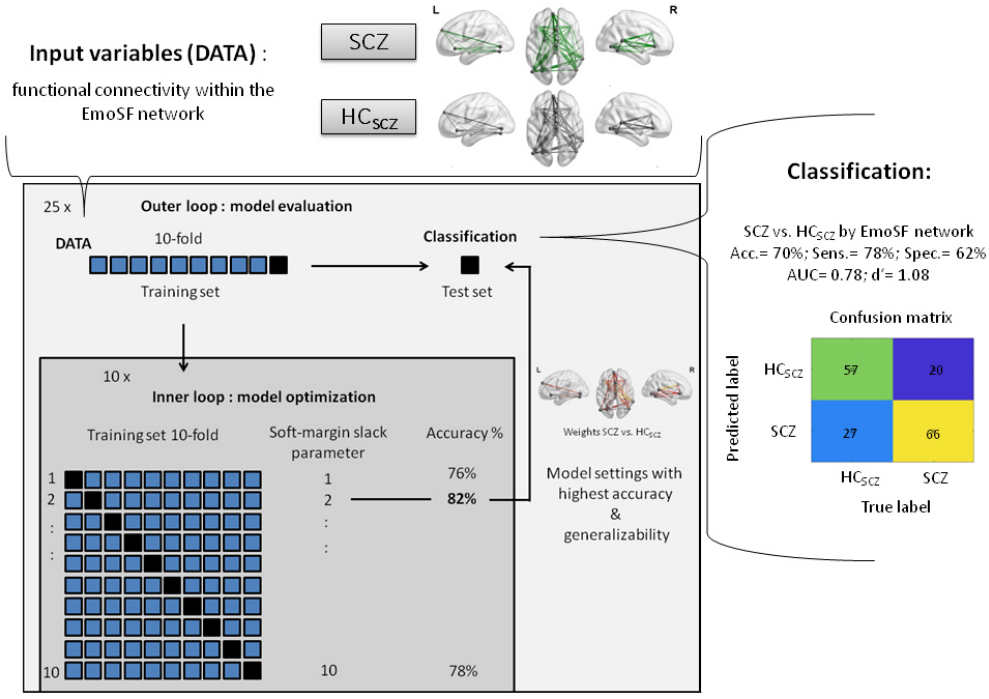
| Network (Abbr.) | Network | Contrast | Nodes | Publication |
|---|---|---|---|---|
| **EmoSF** | emotional scene and face processing | emotional scene > neutral scene and emotional face>neutral face | 24 | (Sabatinelli et al., 2011) |
| **ER** | cognitive emotion regulation | reappraise > naturalistic emotional responses | 14 | (Buhle et al., 2014) |
| **ToM** | theory-of-mind cognition | Theory-of-mind > non-social baseline | 15 | (Bzdok et al., 2012) |
| **Empathy** | empathic processing | ''feel into'' affect-laden social situations > watched or listened passively | 19 | (Bzdok et al., 2012) |
| **Rew** | reward-related decision making | ME: reward valence and decision stages | 25 | (Liu et al., 2011) |
| **AM** | autobiographical memory | autobiographical memory > non-autobiographical baseline | 22 | (Spreng et al., 2009) |
| **SM** | semantic memory | access to word meaning > processing word structure | 23 | (Binder et al., 2009) |
| **WM** | working memory | ME: n-back, Sternberg, delayed matching to sample and delayed simple matching tasks | 23 | (Rottschy et al., 2012) |
| **CogAC** | cognitive action control | ME: stroop-task, spatial interference task, stop-signal task and go/no-go task | 19 | (Cieslik et al., 2015) |
| **VigAtt** | vigilant attention | ME: detection task, discrimination task | 16 | (Langner & Eickhoff, 2013) |
| **MNS** | mirror neuron system | action observation ∩ action imitation | 11 | (Caspers et al., 2010) |
| **Motor** | motor execution | finger tapping > baseline; excl. regions associated with visually paced finger-tapping tasks | 10 | (Witt et al., 2008) |

ME, main effect.

### Support Vector Machine Features and Classification

To examine whether the RSFC pattern of a network contains predictive information on the respective groups (SCZ vs. $HC_{SCZ}$, PD vs. $HC_{PD}$, old vs. young) non-sparse linear two-class SVMs were computed using LibSVM (Chang & Lin, 2011) (https://www.csie.ntu.edu.tw/~cjlin/libsvm). SVMs were trained separately for each of all three analyses (PD, SCZ, NA) and each of the functional networks. Of note, we did not attempt between-patient classification (i.e., PD vs. SCZ), as the different groups were closely matched to their respective controls but substantially different from each other with respect to age, gender, and movement. The input variables (features) to the SVM consisted of edge-wise RSFC between all nodes of a given network. Each SVM was trained and tested by a nested 10-fold cross-validation scheme for each individual group [see example S1 Figure 1 (Xia et al., 2013)] (cf. Lemm, Blankertz, Dickhaus, & Müller, 2011). The inner loop used a 10-fold cross-validation within the training group to optimize the soft-margin slack parameter. For each fold of the outer loop, the left-out (unseen) 10% were then classified using the SVM trained on the (entire) training-set using the optimized parameter. This nested scheme ensured that classifier optimization and evaluation were performed independently of each other (Kriegeskorte et al., 2009). Classification performance was evaluated based on accuracy (Acc.), balanced accuracy (bAcc.), sensitivity (Sens.), and specificity (Spec.) as well as two measures derived from signal-detection theory: the area under the receiver operating characteristics (ROC) curve (AUC) (Fawcett, 2004) and d'. Acc. denotes the overall proportion of subjects correctly classified as patients (PD, SCZ) or advanced age versus healthy or younger age, respectively. The bAcc. is calculated as the average proportion of subjects correctly classified as patients (PD, SCZ) or advanced age versus healthy or younger age, respectively. Sens. indicates the percentage of patients (SCZ or PD) correctly classified as ill or subjects correctly classified as old in the aging sample (true positives). Spec., in turn, represents the fraction of HCs correctly classified as healthy or subjects correctly identified as young in the aging sample (true negatives). AUC refers to the area under the ROC curve. A ROC curve depicts the relationship between true positive rate and false positive rate, and its AUC value indicates the sensitivity of the diagnostic process independent of any specific decision criterion. Finally, we assessed d', an alternative index of diagnostic sensitivity independent of the decision criterion, calculated as z(true positive rate) – z(false positive rate). To increase robustness, the entire procedure was repeated 25 times, and each performance measures was averaged across repetitions. To examine significant differences in classification performance between networks within each group, pairwise t-tests were performed for each of the 12 networks based on the accuracies obtained from the 25 cross-validation outer loop replications of the separate SVMs (significance threshold of $p < 0.05$, Bonferroni-corrected for the number of pairwise network comparisons).

To compare the separately conducted classifications for SCZ versus $HC_{SCZ}$ and PD versus $HC_{PD}$ subgroups, accuracies obtained for each individual analysis for every network were converted to standardized z-scores by reference to the binomial distribution reflecting chance level and corrected for multiple comparisons by the amount of networks-based classifications. Log-likelihood ratios were estimated to identify networks showing better classification performance for one patient group than the other. To investigate significant differences in classification performance between the groups, t-tests were calculated based on the 25 accuracies obtained from the cross-validation outer loop replications of the separate SVMs performed in each group (SCZ, PD, NA) for each of the 12 networks (significance threshold of $p < 0.05$, Bonferroni-corrected for the number of groups and networks).

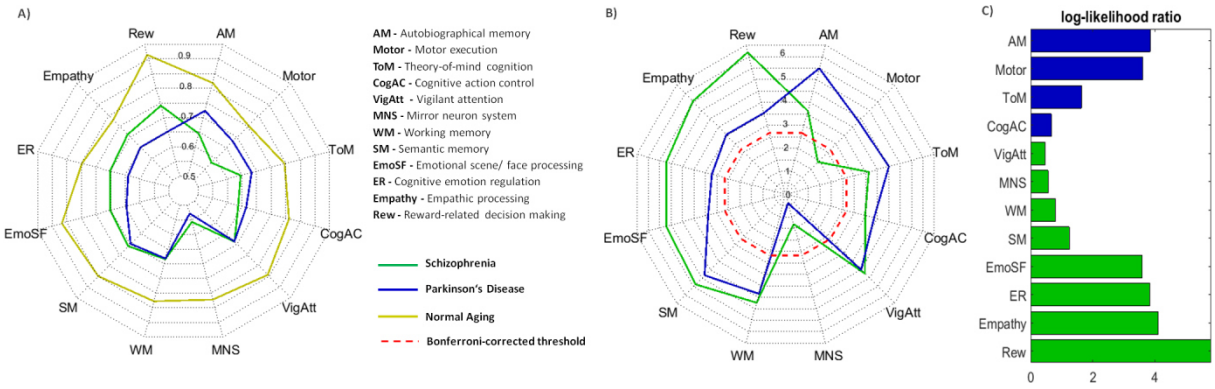



**S1 Figure 1**: Linear Two-class SVM Nested 10-Fold Cross-validation Scheme

Illustration of an SVM example for classification of the SCZ sample based on the EmoSF network. As input variables (DATA) (= features) served the subjects' RSFCs of all edges of every network. The inner loop was performed in a 10-fold manner with 10 repetitions conducted as parameter setting optimization on a training sample. The outer loop was performed in a 10-fold manner with 25 repetitions conducted as classification accuracy testing on an unseen test set. Classification performance measures are computed based on the confusion matrix. Acc., accuracy; Sens., sensitivity; Spec., specificity; AUC, area under the ROC curve and d'.

## Results

As expected, SCZ patients could be distinguished above chance even with the highest accuracy from matched HCs based on RSFC in the reward network (Rew; Acc. = 74%; AUC =0.80). In turn, PD patients were distinguished above chance from their matched HCs based on RSFC in the motor network (Motor; Acc. = 68%; AUC = 0.77). Finally, old and young subjects were differentiated very well from each other based on RSFC in the working memory network (WM; Acc. = 83%; AUC = 0.90). Results are summarized as follows: S1 Figure 2A for the polar plot of group classification accuracies, S1 Table 3 for Acc., Sens., Spec. and AUC, S1 Table SIII for bACC., S1 Table SIV for d', S1 Figure SI for z-standardized accuracies of all groups, and S1 Figure SII for variance of accuracies.




**S1 Figure 2**: Group Classification Results of the SVM

(A) Polar plot of group classification accuracies based on all 12 networks for SCZ (in green), PD (in blue) and NA (in yellow). Accuracy refers to the proportion of subjects correctly classified as patients (PD, SCZ) or older age and subjects correctly classified as being HCs or younger age. (B) Polar plot of z-standardized accuracies (corrected for multiple comparisons) of patients classification for SCZ (in green) and PD (in blue). (C) Log-likelihood ratios of classification performance for networks showing higher classification for one patient group vs. the other.

Considering the performance of all functional networks in distinguishing SCZ and PD patients from their respective HCs, a clear differentiation between networks becomes evident, even though only 2 (SCZ) and 1 (PD) out of 12 networks, respectively, did not significantly exceed chance accuracy (S1 Figure 2B). The following results and discussion are focused on networks with superior classification performance for the respective disorders. In this context, we would like to re-iterate that we did not attempt to train any classifier to distinguish SCZ from PD patients, since the two samples differed substantially from each other in various confounding factors such as age, gender distribution, and within-scanner movement.

**S1 Table 3**: Classification Results of the Support Vector Machine of all Groups based on Specific Networks

| Network (Abbr.) | SCZ vs. $HC_{SCZ}$ **Acc.** (Sens. / Spec.) **AUC** | PD vs. $HC_{PD}$ **Acc.** (Sens. / Spec.) **AUC** | Old vs. Young **Acc.** (Sens. / Spec.) **AUC** |
|---|---|---|---|
| **EmoSF** | **70%** (78% / 62%) **0.78** | **65%** (65% / 64%) **0.71** | **87%** (88% / 85%) **0.95** |
| **ER** | **70%** (80% / 60%) **0.77** | **64%** (67% / 62%) **0.70** | **80%** (82% / 78%) **0.87** |
| **ToM** | **65%** (76% / 53%) **0.70** | **68%** (74% / 63%) **0.74** | **80%** (80% / 79%) **0.88** |
| **Empathy** | **71%** (71% / 71%) **0.80** | **65%** (66% / 64%) **0.74** | **78%** (78% / 78%) **0.86** |
| **Rew** | **74%** (74% / 74%) **0.80** | **65%** (64% / 66%) **0.75** | **91%** (91% / 92%) **0.96** |
| **AM** | **64%** (70% / 59%) **0.72** | **72%** (74% / 70%) **0.77** | **82%** (83% / 81%) **0.90** |
| **SM** | **71%** (76% / 66%) **0.77** | **70%** (67% / 72%) **0.81** | **85%** (86% / 83%) **0.92** |
| **WM** | **68%** (69% / 67%) **0.77** | **68%** (67% / 70%) **0.75** | **83%** (83% / 83%) **0.90** |
| **CogAC** | **64%** (70% / 58%) **0.67** | **66%** (64% / 69%) **0.75** | **81%** (82% / 80%) **0.92** |
| **VigAtt** | **69%** (73% / 64%) **0.73** | **69%** (69% / 68%) **0.74** | **84%** (84% / 85%) **0.92** |
| **MNS** | **56%** (65% / 46%) **0.56**[#] | **53%** (53% / 52%) **0.46**[#] | **82%** (83% / 81%) **0.88** |
| **Motor** | **58%** (69% / 47%) **0.51**[#] | **68%** (66% / 70%) **0.77** | **75%** (76% / 75%) **0.87** |

Abbreviations: Acc., Accuracy (in %)/Sens., sensitivity (in %)/Spec., specificity (in %)/AUC, area under the ROC curve.

EmoSF, emotional scene/ face processing, ER, cognitive emotion regulation, ToM, theory-of-mind cognition, Empathy, empathic processing, Rew, reward-related decision making, AM, autobiographical memory, SM, semantic memory, WM, working memory, CogAC, cognitive action control, VigAtt, vigilant attention, MNS, mirror neuron system, Motor, motor execution.

[#]Network with no significant classification result.

Acc. refers to the proportion of subjects correctly classified as patients (PD, SCZ) or older age and subjects correctly classified as being healthy or younger age (mean of sensitivity and specificity). Sensitivity relates to the percentage of patients (SCZ or PD) correctly classified as being ill or else subjects correctly identified as old in the aging sample (true positives). Specificity relates to the percentage of healthy subjects correctly classified as being healthy or else subjects correctly identified as young in the aging sample (true negatives). AUC refers to the area under the ROCs curve. The ROC curve depicts the relationship between true positive rate and false positive rate.

For SCZ, the reward (Rew; Acc. = 0.74%; AUC = 80), the empathic processing (Empathy; Acc. = 71%; AUC = 0.80), cognitive emotion regulation (ER; Acc. =70%; AUC = 0.77) as well as the emotional scene and face processing networks (EmoSF; Acc. = 70%; AUC = 0.78) distinguished patients most accurately from their HCs. Hence these networks' connectivity patterns may be considered to contain the highest level of information with respect to SCZ. The Rew network was significantly better in the SCZ classification compared to all other networks ($p$< 0.001). For PD, the networks subserving autobiographical memory (AM; Acc. = 72%; AUC = 0.77), motor execution (Motor; Acc. = 68%; AUC = 0.77) and theory-of-mind cognition (ToM; Acc. = 68%; AUC = 0.74) yielded the highest classification accuracies, that is, contained the most informative PD-related differences in RSFC. The AM network

was significantly better in the PD classification compared to all other networks ($p < 0.001$). All network comparison results within the patient groups are summarized in S1 Table SV and SVI.

The between-network comparison of classification performance with respect to SCZ and PD revealed that the networks discriminating either disorder from their respective controls were highly specific (S1 Figure 2B, C), indicating that these networks carry differential amounts of information regarding SCZ and PD, respectively. In particular, the Rew network showed the best performance at distinguishing SCZ patients from HCs (Rew: z = 6.2) but were notably worse at discriminating PD patients from their HCs (Rew: z = 3.5). Similarly, the Empathy, ER and EmoSF networks exhibited high accuracies at classifying SCZ patients and their respective HCs (Empathy: z = 5.5; ER: z = 5.2 and EmoSF: z = 5.2) but inferior performance at distinguishing PD patients from their HCs (Empathy: z = 3.5; ER: z = 3.2 and EmoSF: z = 3.4). In turn, the motor network very well classified PD patients and their HCs (z = 4.3) but was remarkably ineffective at classifying SCZ patients and their HCs (z = 1.9). Likewise, the AM and ToM networks achieved high accuracies in classifying PD patients and controls (AM: z = 5.5; ToM: z = 4.5) but performed much less well when classifying SCZ patients and controls (AM: z = 3.6; ToM: z = 3.6). Networks which were most accurate in distinguishing SCZ from HCs (Rew, Empathy, ER and EmoSF) exhibited significant better classification performance in the SCZ group compared to the PD group (Rew: $p < 0.001$; Empathy: $p < 0.001$; ER: $p < 0.001$; EmoSF: $p < 0.001$; S1 Table SVII). Likewise, networks which performed best at discriminating PD patients from HCs (AM, Motor and ToM) showed significant better classification performance in the PD group compared to the SCZ group (AM: $p < 0.001$; Motor: $p < 0.001$; ToM: $p < 0.001$; S1 Table SVII). This differential picture markedly contrasted with the results obtained for the classification between old and young subjects. In the aging sample, each network yielded accuracies ≥ 75% (see S1 Table SVIII for network comparison results within NA), significantly outperforming every classification obtained in the SCZ or PD samples ($p < 0.001$; see S1 Figure 2A, S1 Figure SI, S1 Table 3, S1 Table SIX and S1 Table SX). In particular, for each network, the accuracy for classifying a previously unseen participant as young or old was about 10% higher than any clinical classification based on the same network. Only the reward processing network yielded the highest accuracy (Acc. = 91%; AUC = 0.96) and was also significantly better at classifying young vs. old subjects than any of the other networks ($p < 0.001$; S1 Table SVIII). Additionally, the comparison of all three separate group classifications revealed that the variance of the classification accuracies over the 25 replications of the outer loop was distinctively lower for the classification of age, as compared with classifying the clinical status. (S1 Figure SII).

## Discussion

We assessed whether RSFC patterns in a diverse set of functionally defined brain networks allowed for a classification of patients with SCZ or PD or healthy older adults on the one hand, and their respective healthy or young controls on the other. Thereby, we evaluated which functional system was most informative for a given condition (i.e., SCZ, PD, or higher age). Conversely, our analysis also assessed the amount of information on each condition found in a given network. Our results show in a proof-of-principle manner that networks pertaining to functions known to be affected by SCZ, PD, or aging indeed exhibited good classification performance for the respective condition. Furthermore, each network's young-old classification outperformed any disease-related classification. This indicates that specific networks are affected by and associated with the diseases, whereas for healthy older adults, RSFC appears to be altered rather globally.

### Conceptual Considerations

Our study demonstrates that machine-learning techniques can be successfully used to assess whether RSFC in functional systems known to be affected in SCZ, PD, or advanced age exhibits high classification capacity for the respective condition. Further, our approach compared the classification capacity of RSFC patterns between different functional networks and between several clinical and physiological states. Of note, for each classification, target and control groups (i.e., SCZ vs. HCscz, PD vs. $HC_{PD}$, old vs. young) were well matched with respect to gender and (for the clinical samples) age. In addition, RSFC variance attributable to these confounding factors or within-scanner movement were regressed out of the data before the SVM analyses. Therefore, these confounds were evidently heterogeneous across the three groups (SCZ, PD, NA) but should not have influenced classification accuracy within each condition. In spite of proper matching and state-of-the-art removal of variance related to motion (cf. Power et al., 2012; Satterthwaite et al., 2013), residual effects that only manifest in the multivariate pattern cannot be fully ruled out. However, one factor worth noting is that, for example, we observed differential classification performance across networks in the SCZ sample, largely ruling out a dominant general effect of head motion.

Given that both groups were assessed under their regular medication, differences in classification performance may be influenced by pharmacological treatment. In particular, we cannot exclude that classification results of networks modulated via dopaminergic transmission (e.g., reward or motor system) might originate from interactions between disease condition and medication. Unfortunately, however, we could not perform a more detailed assessment of the influence of medication, as the compounds, duration of treatment, and doses varied considerably between subjects, with many receiving a combination of drugs.

When comparing classification performance to previous work based on whole-brain functional connectomes (cf. Y. Chen et al., 2015; Long et al., 2012; Meier et al., 2012; Su et al., 2013; Tang et al., 2012; Vergun et al., 2013; Y. Yu et al., 2013), we note that our approach yielded higher functional specificity, allowing inference on the amount of disease-specific information in well-defined functional systems. We acknowledge the fact that even though most of the classifications well-exceeded chance level, the achieved network-based classification accuracies are not strong enough for successful connectivity-based single-subject disease diagnosis. Still, our "sparse" approach achieved classification accuracies comparable to those reported in previous whole-brain studies, whose feature space obviously was substantially larger than ours. This is particularly noteworthy given that two further aspects besides feature space could be expected to decrease classifier performance in our study (Arbabshirani et al., 2017; Haller et al., 2014; Kambeitz et al., 2015; Schnack & Kahn, 2016; Varoquaux et al., 2016): First, all of our three groups were based on relatively large samples that were combined from two different measurement sites and hence should be more heterogeneous than usual. Second, we used replicated 10-fold cross-validation, rather than the more optimistic leave-one-out approach (Varoquaux et al., 2016). We thus argue that the chosen combination of examining robustly defined functional networks and optimized analysis through replicated and nested 10-fold cross-validation may provide valuable new insights into the pathophysiology of brain disorders that is not attainable through global analyses of the entire functional connectome.

### Classification of Schizophrenia patients and controls

We found that the networks subserving reward-related decision making, empathic processing, cognitive emotion regulation as well as emotional scene and face processing yielded the best performance. Given the prominent role of the dysfunctional reward system associated with dopaminergic alteration in SCZ (Toda & Abi-Dargham, 2007) and aberrant salience processing in psychosis (Heinz & Schlagenhauf, 2010; Radua et al., 2015), it very much corroborates with the Rew network showing the best result in differentiating SCZ from HCs (Acc. = 74% AUC = 0.80). Impaired abilities to relate to others' affective states (Benedetti et al., 2009; Derntl et al., 2012; Harvey et al., 2012), dysfunctional emotion regulation (Khoury & Lecomte, 2012; van der Meer et al., 2014) as well as aberrant processing of emotional stimuli (Takahashi et al., 2004) are features of SCZ and mirrored in the degree of SCZ-related information that is contained in the Empathy (AUC = 0.80), ER (AUC = 0.77) and EmoSF (AUC = 0.78) networks.

### Classification of Parkinson's disease patients and controls

The superior classification performance observed for the motor execution network (AUC = 0.77) is hardly surprising, since motor impairments represent a key clinical feature of PD, and differences in action-related brain circuitry are well established in this disorder (Herz et al., 2014; J. B. Rowe & Siebner, 2012; Tessitore et al., 2014). The finding that the AM (AUC = 0.77) network also achieved a very good differentiation of PD patients from HCs was rather surprising, though. While PD is a neurodegenerative disorder and dementia is common in PD patients (Aarsland et al., 2001, 2003), several patients showed evidence for mild cognitive impairment, using the Montreal Cognitive Assessment for screening. We can hence only speculate that the RSFC differences in the AM network may pick up these deficits as revealed by standard behavioral screening instruments. Finally, the good classification performance achieved by the ToM network (AUC = 0.74) was unexpected but matches a growing literature of impaired social cognition in PD patients (Bora et al., 2015; Díez-Cirarda et al., 2015; Poletti et al., 2011).

### Age Group Classification

One of the most striking observations from this study was that every single network achieved a better classification with respect to age group than with respect to SCZ or PD. While we hypothesized that the broad spectrum of age-related changes in various mental functions (Craik & Salthouse, 2011; Glisky, 2007; Seidler et al., 2010) would be reflected by changes in several networks (Craik & Salthouse, 2011; Hedden, 2007; Mather, 2016; Seidler et al., 2010; Vink et al., 2015), the consistency (across both networks and replications) of high classification accuracies is intriguing. It stands to reason that the mechanisms underlying the discriminative changes in functional connectivity patterns may be diverse. In particular, they should include neurodegeneration [cognitive networks (Hedden, 2007)], neurochemical changes [Rew network (Bäckman et al., 2006)], altered affective processing [socialaffective networks (Mather, 2016)] and use-dependent plasticity [motor networks (Demirakca et al., 2016)]. Moreover, the Rew network showed outstanding performance in the young vs. old classification. The fact that this network even outperformed the SCZ and PD classifications indicates the relevance of age-related changes associated with the reward system (Vink et al., 2015) as a marker for age group classification. In addition, it may be argued that in spite of all inter-individual variability, age-related changes represent a more homogeneous change of the neuro-functional architecture (Ferreira et al., 2016; Meier et al., 2012) relative to the inevitable heterogeneity among clinical populations.

Given that connectivity patterns of all systems differentiated very well between young and old participants, we acknowledge the possibility that the relevant drivers may be of non-neural origin. In

particular, despite of our optimized confound removal (Power et al., 2012; Satterthwaite et al., 2013; Varikuti et al., 2017), we cannot exclude that residual effects related to motion or brain atrophy as well as physiological effects such as macro- and microvascular changes and their cumulative impact on hemodynamic signals (D'Esposito et al., 2003) may have contributed to our findings.

Although the contributions of neural and non-neural effects outlined in this section certainly warrant further investigation, one of the most critical conclusions that should be taken from the high classification accuracy between younger and older participants is the danger of obtaining spuriously high accuracies in clinical classification studies if patients and HCs are not carefully matched for age.

## Conclusions and Outlook

We investigated the potential of RS connectivity patterns in a wide variety of functional networks to distinguish SCZ and PD patients from matched HCs as well as old from young adults. We showed that networks defined by robust activation due to mental operations known to be affected in the respective condition indeed contained information on the respective condition that is captured by our pattern-classification approach and translates into good classification accuracies. Classification accuracies obtained through replicated, nested 10-fold cross-validation were not only generally comparable to those obtained from whole-brain analyses but also revealed a differentiated picture for both disorders in comparisons. Both SCZ and PD were specifically well predicted by distinct networks that resonate well with known clinical and pathophysiological features. The presented approach, thus, opens an avenue toward robust and more specific assessments of clinical and developmental differences in functional systems than previous whole-brain analyses. One of the most striking findings of this work was the fact that integrity in all networks was much better at identifying participants with advanced age than with any of the two disorders. While the most likely heterogeneous mechanisms behind this phenomenon certainly need to be addressed in more detail, the current findings highlight the importance of considering age-related effects as a potential source of bias in clinical classification studies.

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## Supplement

**S1 Table SI**: Functional Magnetic Resonance Imaging Parameters

| **Acquisition Site** | **Measurement Parameters:** Scanner/volumes/TR/TE/FA/voxel size |
|---|---|
| **Schizophrenia Sample** | |
| Mind Research Network, Center for Biomedical Research Excellence (COBRE), The University of New Mexico, Albuquerque, NM, USA | 3 T/300/2000/29/75°/3 x 3 x 4 $mm^3$ |
| University Hospital Göttingen, Germany | 3 T/156/2000/30/70°/3 x 3 x 3 $mm^3$ |
| **Parkinson's Disease Sample** | |
| RWTH, University Hospital Aachen, Germany | 3 T/165/2200/30/90°/3.1 x 3.1 x 3.1 $mm^3$ |
| HHU, University Hospital Düsseldorf, Germany | 3 T/300/2200/30/90°/3.1 x 3.1 x 3.1 $mm^3$ |
| **Normal Aging Sample** | |
| Research Centre Jülich, Germany | 3 T/200/2200/30/80°/3.1 x 3.1 x 3.1 $mm^3$ |
| 1000BRAINS **(Caspers et al., 2014)**, Research Centre Jülich, Germany | 3 T/300/2200/30/90°/3.1 x 3.1 x 3.1 $mm^3$ |

Measurement parameters: Scanner: magnetic field strength of the scanner/ number of acquired volumes/TR: repetition time (in ms)/TE: echo time (in ms)/ FA: flip angle/ voxel size.

**S1 Table SII**: Network Coordinates and Corresponding Brain Regions

| **Emotional Scene / Face Processing (EmoSF)** (Sabatinelli et al., 2011) | | | |
|---|---|---|---|
| **x** | **y** | **z** | **Macroanatomical Region** |
| 4 | 47 | 7 | R Anterior Cingulate Cortex |
| 42 | 25 | 3 | R Inferior Frontal Gyrus (p. Triangularis) |
| -42 | 25 | 3 | L Inferior Frontal Gyrus (p. Triangularis) |
| 48 | 17 | 29 | R Inferior Frontal Gyrus (p. Opercularis) |
| -42 | 13 | 27 | L Inferior Frontal Gyrus (p. Triangularis) |
| -2 | 8 | 59 | L Posterior Medial Frontal |
| 20 | -4 | -15 | R Amygdala |
| -20 | -6 | -15 | L Amygdala |
| -20 | -33 | -4 | L Hippocampus |
| 14 | -33 | -7 | R Lingual Gyrus |
| 53 | -50 | 4 | R Middle Temporal Gyrus |
| 38 | -55 | -20 | R Anterior Fusiform Gyrus |
| -40 | -55 | -22 | L Anterior Fusiform Gyrus |
| 38 | -76 | -16 | R Posterior Fusiform Gyrus |
| -40 | -78 | -21 | L Cerebellum |
| -4 | 52 | 31 | L Superior Medial Gyrus |
| 36 | 25 | -3 | R Anterior Insula |
| -38 | 25 | -8 | L Inferior Frontal Gyrus (p. Orbitalis) |
| 2 | 19 | 25 | R Anterior Cingulate Cortex |
| 0 | -15 | 10 | Thalamus |
| -2 | -31 | -7 | Superior Colliculus |
| -28 | -70 | -14 | L Fusiform Gyrus |
| 46 | -68 | -4 | R Inferior Temporal Gyrus |
| -48 | -72 | -4 | L Inferior Occipital Gyrus |

| **Cognitive Emotion Regulation (ER)** (Buhle et al., 2014) | | | |
|---|---|---|---|
| **x** | **y** | **z** | **Macroanatomical Region** |
| 48 | 24 | 9 | R Inferior Frontal Gyrus (p. Triangularis) |
| 42 | 21 | 45 | R Middle Frontal Gyrus |
| 9 | 30 | 39 | R Superior Medial Gyrus |
| 0 | -9 | 63 | L Posterior Medial Frontal |
| -3 | 24 | 30 | L Anterior Cingulate Cortex |
| -33 | 3 | 54 | L Middle Frontal Gyrus |
| -36 | 21 | -3 | L Anterior Insula |
| -42 | 45 | -6 | L Inferior Frontal Gyrus (p. Orbitalis) |
| 63 | -51 | 39 | R Inferior Parietal Lobule |
| -42 | -66 | 42 | L Angular Gyrus |
| -63 | -51 | -21 | L Inferior Temporal Gyrus |
| -51 | -39 | 3 | L Middle Temporal Gyrus |
| 30 | -3 | -15 | R Amygdala |
| -18 | -3 | -15 | L Amygdala |

**Theory-of-Mind Cognition (ToM)**
(Bzdok et al., 2012)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| 0 | 52 | -12 | R Mid Orbital Gyrus |
| 2 | 58 | 12 | R Superior Medial Gyrus |
| -8 | 56 | 30 | L Superior Medial Gyrus |
| 2 | -56 | 30 | L Precuneus |
| 56 | -50 | 18 | R Superior Temporal Gyrus |
| -48 | -56 | 24 | L Angular Gyrus |
| 54 | -2 | -20 | R Anterior Middle Temporal Gyrus |
| -54 | -2 | -24 | L Anterior Middle Temporal Gyrus |
| 52 | -18 | -12 | R Middle Temporal Gyrus |
| -54 | -28 | -4 | L Middle Temporal Gyrus |
| 50 | -34 | 0 | R Posterior Superior Temporal Sulcus |
| -58 | -44 | 4 | L Posterior Superior Temporal Sulcus |
| 54 | 28 | 6 | R Inferior Frontal Gyrus (p. Triangularis) |
| -48 | 30 | -12 | L Inferior Frontal Gyrus (p. Orbitalis) |
| 48 | -72 | 8 | R Occipital Lobe (V5/MT) |

**Empathic Processing (Empathy)**
(Bzdok et al., 2012)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| 2 | 56 | 18 | L Superior Medial Gyrus |
| 36 | 22 | -8 | R Inferior Frontal Gyrus (p. Orbitalis) |
| -30 | 20 | 4 | L Anterior Insula |
| 50 | 12 | -8 | R Anterior Insula |
| -44 | 24 | -6 | L Inferior Frontal Gyrus (p. Orbitalis) |
| -4 | 18 | 50 | L Posterior Medial Frontal |
| -2 | 28 | 20 | L Anterior Cingulate Cortex |
| -4 | 42 | 18 | L Anterior Cingulate Cortex |
| -2 | -32 | 28 | Posterior Cingulate Cortex |
| 52 | -58 | 22 | R Posterior Superior Temporal Gyrus |
| -56 | -58 | 22 | L Posterior Superior Temporal Gyrus |
| 22 | -2 | -16 | R Amygdala |
| 54 | -8 | -16 | R Middle Temporal Gyrus |
| 52 | -36 | 2 | R Posterior Superior Temporal Sulcus |
| -12 | -4 | 12 | L Anterior Thalamus |
| 6 | -32 | 2 | R Posterior Thalamus |
| 26 | -26 | -12 | R Hippocampus |
| 2 | -20 | -12 | Midbrain |
| 14 | 4 | 0 | R Globus Pallidum |

**Reward-related Decision Making (Rew)**
(Liu et al., 2011)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| 12 | 10 | -6 | R Nucleus Caudate |
| -10 | 8 | -4 | L Pallidum |
| 36 | 20 | -6 | R Anterior Insula |
| -32 | 20 | -4 | L Anterior Insula |
| 0 | 24 | 40 | L Superior Medial Gyrus |
| 0 | 54 | -8 | L Mid Orbital Gyrus |
| 24 | -2 | -16 | R Amygdala |
| 6 | -14 | 8 | R Thalamus |
| -6 | -16 | 8 | L Thalamus |
| 0 | 8 | 48 | L Posterior Medial Frontal Gyrus |
| 8 | -18 | -10 | R Brainstem |
| -6 | -18 | -10 | L Brainstem |
| 2 | 44 | 20 | L Anterior Cingulate Cortex |
| -24 | 2 | 52 | L Middle Frontal Gyrus |
| -38 | -4 | 6 | L Insula |
| 24 | 40 | -14 | R Superior Orbital Gyrus |
| -16 | 42 | -14 | L Superior Orbital Gyrus |
| 40 | 32 | 32 | R Middle Frontal Gyrus |
| -28 | -56 | 48 | L Inferior Parietal Lobule |
| 28 | -58 | 50 | R Superior Parietal Lobule |
| 0 | -32 | 32 | L Posterior Cingulate Cortex |
| -36 | 50 | 10 | L Middle Frontal Gyrus |
| -46 | 42 | -4 | L Inferior Frontal Gyrus (p. Orbitalis) |
| 30 | 4 | 50 | R Middle Frontal Gyrus |
| -22 | 30 | 48 | L Superior Frontal Gyrus |

**Autobiographical Memory (AM)**
(Spreng et al., 2009)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| -1 | -53 | 21 | L Precuneus |
| -26 | -28 | -17 | L Parahippocampal Gyrus |
| -49 | -61 | 31 | L Angular Gyrus |
| -2 | 51 | -11 | L Mid Orbital Gyrus |
| -60 | -9 | -18 | L Middle Temporal Gyrus |
| -50 | 27 | -12 | L Inferior Frontal Gyrus (p. Orbitalis) |
| 26 | -33 | -15 | R Fusiform Gyrus |
| -1 | 20 | 57 | L Posterior Medial Frontal |
| 55 | -58 | 30 | R Angular Gyrus |
| -47 | 9 | 46 | L Precentral Gyrus |
| -42 | 53 | 7 | L Middle Frontal Gyrus |
| 26 | -14 | -23 | R Parahippocampal Gyrus |
| 54 | -5 | -20 | R Middle Temporal Gyrus |
| -39 | 13 | -41 | L Inferior Temporal Gyrus |
| -38 | -82 | 38 | L Middle Occipital Gyrus |
| -48 | 29 | 17 | L Inferior Frontal Gyrus (p. Triangularis) |

| | | | |
|---|---|---|---|
| -11 | 62 | 9 | L Superior Medial Gyrus |
| 4 | -8 | 2 | Thalamus |
| -4 | 39 | 16 | L Anterior Cingulate Cortex |
| -5 | -34 | 36 | L Midcingulate Cortex |
| -29 | 16 | 51 | L Middle Frontal Gyrus |
| 31 | 1 | -26 | R Amygdala |

**Semantic Memory (SM)**
(Binder et al., 2009)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| -46 | -69 | 28 | L Angular Gyrus |
| -50 | -56 | 31 | L Angular Gyrus |
| -64 | -44 | -4 | L Posterior Middle Temporal Gyrus |
| -47 | -24 | -17 | L Middle Temporal Gyrus |
| -40 | -12 | -30 | L Inferior Temporal Gyrus |
| -8 | -57 | 17 | L Precuneus |
| -20 | 36 | 44 | L Superior Frontal Gyrus |
| -53 | 27 | -4 | L Inferior Frontal Gyrus (p. Orbitalis) |
| 54 | -59 | 30 | R Angular Gyrus |
| 43 | -72 | 31 | R Middle Occipital Gyrus |
| -1 | 51 | -7 | L Mid Orbital Gyrus |
| -5 | 56 | 24 | L Superior Medial Gyrus |
| -31 | -34 | -16 | L Fusiform Gyrus |
| -8 | 29 | -10 | L Anterior Cingulate Cortex |
| -46 | 25 | 23 | L Inferior Frontal Gyrus (p. Triangularis) |
| 64 | -41 | -2 | R Posterior Middle Temporal Gyrus |
| -43 | -53 | 55 | L Inferior Parietal Lobule |
| -1 | -18 | 40 | L Midcingulate Cortex |
| -2 | -56 | 46 | L Precuneus |
| 51 | 20 | 26 | R Inferior Frontal Gyrus (p. Triangularis) |
| 64 | -38 | 32 | R Supramarginal Gyrus |
| -23 | 26 | -16 | L Inferior Frontal Gyrus (p. Orbitalis) |
| -5 | -39 | 40 | L Midcingulate Cortex |

**Working Memory (WM)**
(Rottschy et al., 2012)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| -32 | 22 | -2 | L Anterior Insula |
| -48 | 10 | 26 | L Inferior Frontal Gyrus (p. Opercularis) |
| -46 | 26 | 24 | L Inferior Frontal Gyrus (p. Triangularis) |
| -38 | 50 | 10 | L Anterior Middle Frontal Gyrus |
| 36 | 22 | -6 | R Anterior Insula |
| 50 | 14 | 24 | R Inferior Frontal Gyrus (p. Triangularis) |
| 44 | 34 | 32 | R Middle Frontal Gyrus |
| 38 | 54 | 6 | R Anterior Middle Frontal Gyrus |
| 2 | 18 | 48 | L Posterior Medial Frontal |
| -28 | 0 | 56 | L Posterior Middle Frontal Gyrus |

| | | | |
|---|---|---|---|
| 30 | 2 | 56 | R Posterior Middle Frontal Gyrus |
| -42 | -42 | 46 | L Inferior Parietal Lobule/Intraparietal Sulcus |
| -34 | -52 | 48 | L Inferior Parietal Lobule/Intraparietal Sulcus |
| -24 | -66 | 54 | L Superior Parietal Lobule |
| 42 | -44 | 44 | R Inferior Parietal Lobule/Intraparietal Sulcus |
| 32 | -58 | 48 | R Angular Gyrus/Intraparietal Sulcus |
| 16 | -66 | 56 | R Superior Parietal Lobule |
| -12 | -12 | 12 | L Thalamus |
| -16 | 2 | 14 | L Nucleus Caudate |
| -16 | 0 | 2 | L Globus Pallidum |
| 12 | -10 | 10 | R Thalamus |
| -34 | -66 | -20 | L Cerebelum/Fusiform Gyrus |
| 32 | -64 | -18 | R Cerebelum/Fusiform Gyrus |

**Cognitive Action Control (CogAC)**
(Cieslik et al., 2015)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| 36 | 22 | -4 | R Anterior Insula |
| 2 | 16 | 48 | L Posterior Medial Frontal |
| 48 | 12 | 30 | R Inferior Frontal Gyrus (p. Opercularis) |
| 36 | 2 | 54 | R Middle Frontal Gyrus |
| 48 | 30 | 24 | R Inferior Frontal Gyrus (p. Triangularis) |
| -38 | -44 | 46 | L Inferior Parietal Lobule/Intraparietal Sulcus |
| -24 | -66 | 48 | L Superior Parietal Lobule |
| 40 | -46 | 46 | R Inferior Parietal Lobule/Intraparietal Sulcus |
| 60 | -44 | 24 | R Supramarginal Gyrus |
| 30 | -62 | 52 | R Superior Parietal Lobule |
| -44 | 10 | 30 | L Precentral Gyrus |
| -34 | 20 | -4 | L Anterior Insula |
| -26 | 2 | 52 | L Middle Frontal Gyrus |
| 6 | -18 | -2 | R Thalamus |
| -40 | -66 | -10 | L Inferior Occipital Gyrus |
| 48 | 19 | 6 | R Inferior Frontal Gyrus (p. Opercularis) |
| 8 | 29 | 30 | R Midcingulate Cortex |
| -45 | 27 | 30 | L Inferior Frontal Gyrus (p. Triangularis) |
| 11 | 7 | 7 | R Nucleus Caudate |

**Vigilant Attention (VigAtt)**
(Langner & Eickhoff, 2013)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| -2 | 8 | 50 | L Posterior Medial Frontal |
| 8 | 32 | 46 | R Superior Medial Gyrus |
| 0 | 26 | 34 | L Midcingulate Cortex |
| 50 | 8 | 32 | R Precentral Gyrus |
| 40 | 22 | -4 | R Anterior Insula |
| 46 | 36 | 20 | R Anterior Middle Frontal Gyrus |
| -40 | -12 | 60 | L Precentral Gyrus |

| | | | |
|---|---|---|---|
| -46 | -68 | -6 | L Inferior Occipital Gyrus |
| -48 | 8 | 30 | L Precentral Gyrus |
| 62 | -38 | 17 | R Inferior Parietal Lobe |
| 8 | -12 | 6 | R Thalamus |
| 32 | -90 | 4 | R Middle Occipital Gyrus |
| -42 | 12 | -2 | L Anterior Insula |
| -10 | -14 | 6 | L Thalamus |
| 6 | -58 | -18 | Cerebellar Vermis |
| 44 | -44 | 46 | R Inferior Parietal Lobule |

**Mirror Neuron System (MNS)**
(Caspers et al., 2010)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| -56 | 8 | 28 | L Precentral Gyrus |
| -54 | 6 | 40 | L Precentral Gyrus |
| 58 | 16 | 10 | R Inferior Frontal Gyrus (p. Opercularis) |
| 44 | -54 | -20 | R Fusiform Gyrus |
| -38 | -40 | 50 | L Inferior Parietal Lobule/Intraparietal Sulcus |
| 51 | -36 | 50 | R Inferior Parietal Lobule/Intraparietal Sulcus |
| -1 | 16 | 52 | L Posterior Medial Frontal |
| -54 | -50 | 10 | L Posterior Middle Temporal Gyrus |
| -52 | -70 | 6 | L Occipital Lobe (V5) |
| 54 | -64 | 4 | R Occipital Lobe (V5) |
| 30 | -62 | 63 | R Superior Parietal Lobule |

**Motor Execution (Motor)**
(Witt et al., 2008)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| -39 | -21 | 54 | L Postcentral Gyrus |
| 41 | -16 | 57 | R Precentral Gyrus |
| -3 | -2 | 54 | L Posterior Medial Frontal |
| -57 | 2 | 32 | L Precentral Gyrus |
| -53 | -24 | 21 | L Supramarginal Gyrus |
| 45 | -38 | 48 | R Inferior Parietal Lobule |
| -23 | -7 | 1 | L Globus Pallidum |
| 25 | -8 | 3 | R Globus Pallidum |
| -22 | -52 | 26 | L Cerebellum |
| 18 | -54 | -22 | R Cerebellum |

R= right; L = left; for consistency coordinates (MNI-space) are assigned to the most probable brain areas as revealed by the SPM Anatomy Toolbox (Version 2.1) (Eickhoff et al., 2005, 2006, 2007).

**S1 Table SIII**: Classification Results of the Support Vector Machine of all Groups based on Specific Networks (balanced accuracy)

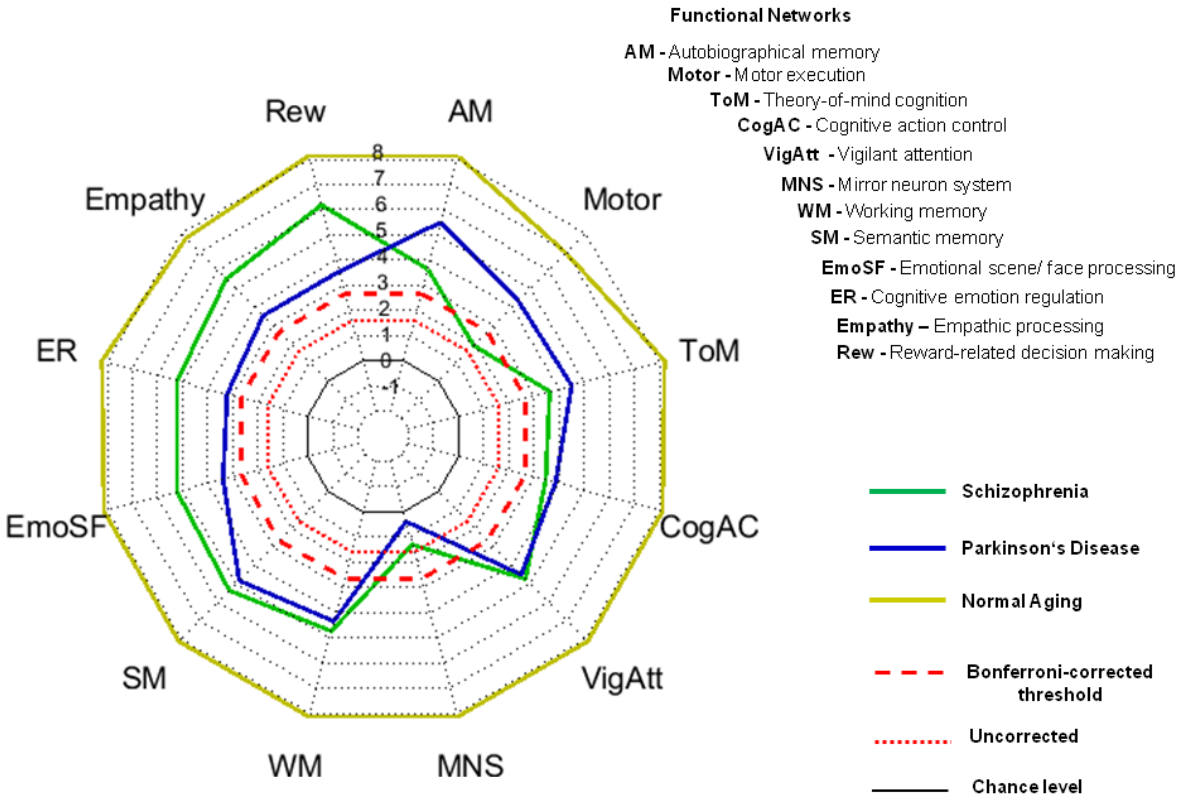
| Network (abbr.) | SCZ vs. $HC_{SCZ}$ | PD vs. $HC_{PD}$ | Old vs. Young |
|---|---|---|---|
| **EmoSF** | 70% | 65% | 87% |
| **ER** | 70% | 64% | 80% |
| **ToM** | 64% | 68% | 80% |
| **Empathy** | 71% | 65% | 78% |
| **Rew** | 74% | 65% | 91% |
| **AM** | 64% | 72% | 82% |
| **SM** | 71% | 70% | 85% |
| **WM** | 68% | 68% | 83% |
| **CogAC** | 64% | 66% | 81% |
| **VigAtt** | 69% | 69% | 84% |
| **MNS** | 56% | 53% | 82% |
| **Motor** | 58% | 68% | 75% |

Balanced accuracy is calculated as the average proportion of subjects correctly classified as patients (PD, SCZ) or advanced age versus healthy or younger age, respectively.

**S1 Table SIV**: Classification Results of the Support Vector Machine of all Groups based on Specific Networks (d')

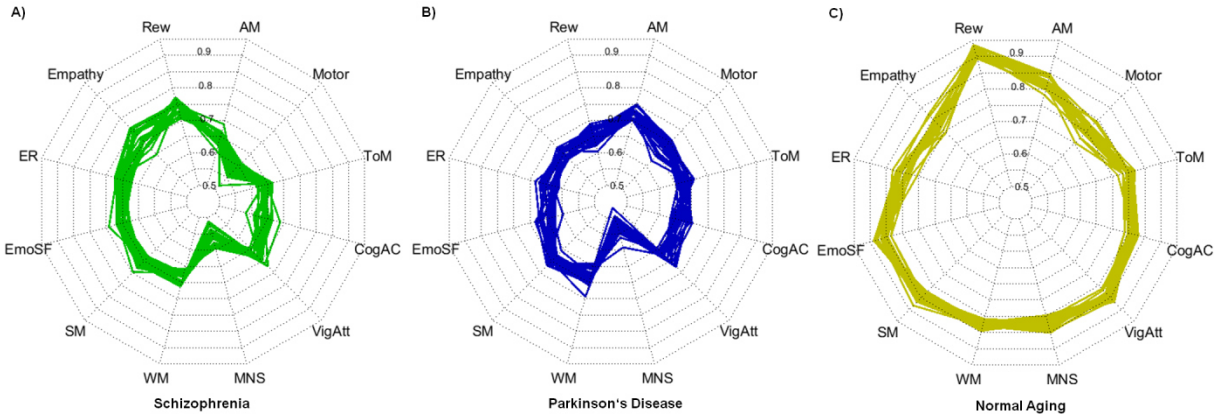
| Network (abbr.) | SCZ vs. $HC_{SCZ}$ | PD vs. $HC_{PD}$ | Old vs. Young |
|---|---|---|---|
| **EmoSF** | 1.08 | 0.75 | 2.24 |
| **ER** | 1.10 | 0.72 | 1.68 |
| **ToM** | 0.77 | 0.97 | 1.66 |
| **Empathy** | 1.12 | 0.79 | 1.55 |
| **Rew** | 1.29 | 0.78 | 2.75 |
| **AM** | 0.75 | 1.19 | 1.83 |
| **SM** | 1.11 | 1.04 | 2.07 |
| **WM** | 0.96 | 0.95 | 1.90 |
| **CogAC** | 0.71 | 0.85 | 1.77 |
| **VigAtt** | 0.99 | 0.98 | 2.02 |
| **MNS** | 0.29 | 0.14 | 1.86 |
| **Motor** | 0.42 | 0.94 | 1.38 |

**d'**: sensitivity index calculated as z (true positive rate) – z (false positive rate).




**S1 Figure SI**: Group Classification Results of the Support Vector Machine (z-values)

Polar plot of z-standardized accuracies (corrected for multiple comparisons) of group classification based on all 12 networks for schizophrenia (in green), Parkinson's disease (in blue) and normal aging (in yellow).




**S1 Figure SII**: Variance of Group Classification Results of the Support Vector Machine (accuracies)

Polar plot of variance for group classification accuracies over all 25 repetitions in the outer loop based on all 12 networks for A) schizophrenia (in green), B) Parkinson's disease (in blue) and C) normal aging (in yellow).

**S1 Table SV**: Differences in Classification Performance between Networks within Schizophrenia

| Network (abbr.) comparison | Mean difference (Acc.) | T | *P* |
|---|---|---|---|
| **EmoSF - ER** | -0.04 | -0.10 | 0.92 |
| **EmoSF - ToM** | **5.64** | **15.10** | **<**0.001 |
| **EmoSF - Empathy** | -1.24 | -2.21 | 0.037 |
| **EmoSF - Rew** | -3.88 | -9.77 | <0.001 |
| **EmoSF - AM** | **5.56** | **14.51** | **<0.001** |
| **EmoSF - SM** | **-0.88** | **-2.11** | **0.046** |
| **EmoSF - WM** | **1.76** | **3.89** | **<0.001** |
| **EmoSF - CogAC** | **6.32** | **12.26** | **<0.001** |
| **EmoSF - VigAtt** | **1.40** | **3.50** | **0.002** |
| **EmoSF - MNS** | **14.44** | **24.06** | **<0.001** |
| **EmoSF - Motor** | **12.00** | **20.79** | **<0.001** |
| **ER - ToM** | **5.68** | **11.96** | **<0.001** |
| **ER - Empathy** | -1.20 | -1.75 | 0.093 |
| **ER - Rew** | -3.84 | -9.00 | <0.001 |
| **ER - AM** | **5.60** | **11.85** | **<0.001** |
| **ER - SM** | **-0.84** | **-2.11** | **0.046** |
| **ER - WM** | **1.80** | **4.06** | **0.001** |
| **ER - CogAC** | **6.36** | **10.15** | **<0.001** |
| **ER - VigAtt** | **1.44** | **3.00** | **0.006** |
| **ER - MNS** | **14.48** | **28.56** | **<0.001** |
| **ER - Motor** | **12.04** | **21.69** | **<0.001** |
| **ToM - Empathy** | **-6.88** | **-11.50** | **<0.001** |
| **ToM - Rew** | **-9.52** | **-26.03** | **<0.001** |
| **ToM - AM** | -0.08 | -0.21 | 0.834 |
| **ToM - SM** | -6.52 | -16.45 | <0.001 |
| **ToM - WM** | -3.88 | -9.04 | <0.001 |
| **ToM - CogAC** | 0.68 | 1.46 | 0.156 |
| **ToM - VigAtt** | -4.24 | -10.26 | <0.001 |
| **ToM - MNS** | 8.80 | 16.73 | <0.001 |

| | | | |
|---|---|---|---|
| **ToM - Motor** | 6.36 | 10.86 | <0.001 |
| **Empathy - Rew** | -2.64 | -4.21 | 0.001 |
| **Empathy - AM** | **6.80** | **12.63** | **<0.001** |
| **Empathy - SM** | **0.36** | **0.53** | **0.604** |
| **Empathy - WM** | **3.00** | **4.33** | **<0.001** |
| **Empathy - CogAC** | **7.56** | **10.65** | **<0.001** |
| **Empathy - VigAtt** | **2.64** | **4.18** | **<0.001** |
| **Empathy - MNS** | **15.68** | **25.03** | **<0.001** |
| **Empathy - Motor** | **13.24** | **16.80** | **<0.001** |
| **Rew - AM** | **9.44** | **22.44** | **<0.001** |
| **Rew - SM** | **3.000** | **8.54** | **<0.001** |
| **Rew - WM** | **5.640** | **10.67** | **<0.001** |
| **Rew - CogAC** | **10.20** | **17.67** | **<0.001** |
| **Rew - VigAtt** | **5.28** | **11.96** | **<0.001** |
| **Rew - MNS** | **18.32** | **38.85** | **<0.001** |
| **Rew - Motor** | **15.88** | **32.57** | **<0.001** |
| **AM - SM** | -6.44 | -14.51 | <0.001 |
| **AM - WM** | -3.80 | -9.81 | <0.001 |
| **AM - CogAC** | 0.76 | 1.88 | 0.073 |
| **AM - VigAtt** | -4.16 | -11.03 | <0.001 |
| **AM - MNS** | 8.88 | 17.72 | <0.001 |
| **AM - Motor** | 6.44 | 12.62 | <0.001 |
| **SM - WM** | 2.64 | 6.01 | <0.001 |
| **SM - CogAC** | 7.20 | 13.37 | <0.001 |
| **SM - VigAtt** | 2.280 | 5.12 | <0.001 |
| **SM - MNS** | 15.32 | 29.18 | <0.001 |
| **SM - Motor** | 12.88 | 30.84 | <0.001 |
| **WM - CogAC** | 4.56 | 9.79 | <0.001 |
| **WM - VigAtt** | -0.36 | -0.73 | 0.475 |
| **WM - MNS** | 12.68 | 21.78 | <0.001 |
| **WM - Motor** | 10.24 | 17.05 | <0.001 |
| **CogAC - VigAtt** | -4.92 | -9.91 | <0.001 |
| **CogAC - MNS** | 8.12 | 11.43 | <0.001 |
| **CogAC - Motor** | 5.68 | 9.23 | <0.001 |

| | | | |
|---|---|---|---|
| **VigAtt - MNS** | 13.04 | 23.74 | <0.001 |
| **VigAtt - Motor** | 10.60 | 19.57 | <0.001 |
| **MNS - Motor** | -2.44 | -4.14 | <0.001 |

Comparison between networks with highest classification performance and all other networks in schizophrenia (in bold); significance threshold $p_{corr} < 0.001$.

**S1 Table SVI**: Differences in Classification Performance between Networks within Parkinson's Disease

| Network (abbr.) comparison | Mean difference (Acc.) | T | *P* |
|---|---|---|---|
| **EmoSF - ER** | 0.52 | 0.97 | 0.344 |
| **EmoSF - ToM** | **-3.84** | **-7.41** | **<0.001** |
| **EmoSF - Empathy** | -0.64 | -1.76 | 0.092 |
| **EmoSF - Rew** | -0.64 | -1.15 | 0.261 |
| **EmoSF - AM** | **-7.80** | **-14.92** | **<0.001** |
| **EmoSF - SM** | -5.32 | -11.54 | <0.001 |
| **EmoSF - WM** | -3.72 | -5.46 | <0.001 |
| **EmoSF - CogAC** | -1.84 | -3.35 | 0.003 |
| **EmoSF - VigAtt** | -4.24 | -7.23 | <0.001 |
| **EmoSF - MNS** | 11.72 | 17.77 | <0.001 |
| **EmoSF - Motor** | **-3.52** | **-5.73** | **<0.001** |
| **ER - ToM** | **-4.36** | **-8.25** | **<0.001** |
| **ER - Empathy** | -1.16 | -2.29 | 0.031 |
| **ER - Rew** | -1.16 | -1.88 | 0.073 |
| **ER - AM** | **-8.32** | **-19.48** | **<0.001** |
| **ER - SM** | -5.84 | -11.12 | <0.001 |
| **ER - WM** | -4.24 | -9.31 | <0.001 |
| **ER - CogAC** | -2.36 | -4.60 | 0.001 |
| **ER - VigAtt** | -4.76 | -12.25 | <0.001 |
| **ER - MNS** | 11.20 | 14.66 | <0.001 |
| **ER - Motor** | **-4.04** | **-6.51** | **<0.001** |
| **ToM - Empathy** | **3.20** | **6.77** | **<0.001** |
| **ToM - Rew** | **3.20** | **7.04** | **<0.001** |
| **ToM - AM** | -3.96 | -9.13 | <0.001 |
| **ToM - SM** | **-1.48** | **-3.20** | **0.004** |
| **ToM - WM** | **0.12** | **0.22** | **0.825** |

| | | | |
|---|---|---|---|
| **ToM - CogAC** | **2.00** | **3.67** | **0.001** |
| **ToM - VigAtt** | **-0.40** | **-0.75** | **0.460** |
| **ToM - MNS** | **15.56** | **26.81** | **<0.001** |
| **ToM - Motor** | 0.32 | 0.49 | 0.626 |
| **Empathy - Rew** | 0.00 | 0.00 | 1.000 |
| **Empathy - AM** | **-7.16** | **-18.76** | **<0.001** |
| **Empathy - SM** | -4.68 | -13.03 | <0.001 |
| **Empathy - WM** | -3.08 | -5.02 | <0.001 |
| **Empathy - CogAC** | -1.20 | -2.40 | 0.025 |
| **Empathy - VigAtt** | -3.60 | -6.47 | <0.001 |
| **Empathy - MNS** | 12.36 | 21.21 | <0.001 |
| **Empathy - Motor** | **-2.88** | **-5.28** | **<0.001** |
| **Rew - AM** | **-7.16** | **-13.48** | **<0.001** |
| **Rew - SM** | -4.68 | -10.67 | <0.001 |
| **Rew - WM** | -3.08 | -4.96 | <0.001 |
| **Rew - CogAC** | -1.20 | -2.35 | 0.027 |
| **Rew - VigAtt** | -3.60 | -7.06 | <0.001 |
| **Rew - MNS** | 12.36 | 17.43 | <0.001 |
| **Rew - Motor** | **-2.88** | **-4.61** | **0.001** |
| **AM - SM** | **2.48** | **6.40** | **<0.001** |
| **AM - WM** | **4.08** | **9.05** | **<0.001** |
| **AM - CogAC** | **5.96** | **13.39** | **<0.001** |
| **AM - VigAtt** | **3.56** | **7.07** | **<0.001** |
| **AM - MNS** | **19.52** | **31.65** | **<0.001** |
| **AM - Motor** | 4.28 | 9.30 | <0.001 |
| **SM - WM** | 1.60 | 2.80 | 0.010 |
| **SM - CogAC** | 3.48 | 8.05 | <0.001 |
| **SM - VigAtt** | 1.080 | 1.900 | 0.070 |
| **SM - MNS** | 17.04 | 26.78 | <0.001 |
| **SM - Motor** | **1.80** | **3.46** | **0.002** |
| **WM - CogAC** | 1.88 | 2.96 | 0.007 |
| **WM - VigAtt** | -0.52 | -0.94 | 0.357 |
| **WM - MNS** | 15.44 | 20.15 | <0.001 |
| **WM - Motor** | **0.20** | **0.27** | **0.790** |

| | | | |
|---|---|---|---|
| **CogAC - VigAtt** | -2.40 | -4.59 | 0.001 |
| **CogAC - MNS** | 13.56 | 18.80 | <0.001 |
| **Cog AC- Motor** | **-1.68** | **-3.26** | **0.003** |
| **VigAtt - MNS** | 15.96 | 21.69 | <0.001 |
| **VigAtt - Motor** | **0.72** | **1.20** | **0.243** |
| **MNS - Motor** | **-15.24** | **-21.46** | **<0.001** |

Comparison between networks with highest classification performance and all other networks in Parkinson's disease (in bold); significance threshold $p_{corr} < 0.001$.

**S1 Table SVII**: Group Differences between Schizophrenia and Parkinson's Disease Classification based on Specific Networks

| Network (abbr.) | Mean difference (Acc.) | T | *P* |
|---|---|---|---|
| **EmoSF** | 5.60 | 10.88 | <0.001 |
| **ER** | 6.16 | 11.46 | <0.001 |
| **ToM** | -3.88 | -9.41 | <0.001 |
| **Empathy** | 6.20 | 9.36 | <0.001 |
| **Rew** | 8.84 | 16.94 | <0.001 |
| **AM** | -7.76 | -19.24 | <0.001 |
| **SM** | 1.16 | 2.69 | 0.010 |
| **WM** | 0.12 | 0.22 | 0.827 |
| **CogAC** | -2.56 | -4.37 | <0.001 |
| **VigAtt** | -0.04 | -0.07 | 0.942 |
| **MNS** | 2.88 | 4.43 | <0.001 |
| **Motor** | -9.92 | -15.08 | <0.001 |

Networks with highest classification performance in schizophrenia (in green); networks with highest classification performance in Parkinson's disease (in blue); significance threshold $p_{corr} < 0.001$.

**S1 Table SVIII**: Differences in Classification Performance between Networks within Normal Aging

| Network (abbr.) comparison | Mean difference (Acc.) | T | *P* |
|---|---|---|---|
| **EmoSF - ER** | 7.08 | 18.30 | <0.001 |
| **EmoSF - ToM** | 7.40 | 19.55 | <0.001 |
| **EmoSF - Empathy** | 8.76 | 17.97 | <0.001 |
| **EmoSF - Rew** | **-4.52** | **-12.85** | **<0.001** |
| **EmoSF - AM** | 4.96 | 10.23 | <0.001 |

| | | | |
|---|---|---|---|
| **EmoSF - SM** | 1.72 | 4.04 | <0.001 |
| **EmoSF - WM** | 3.96 | 8.97 | <0.001 |
| **EmoSF - CogAC** | 5.80 | 14.81 | <0.001 |
| **EmoSF - VigAtt** | 2.32 | 5.70 | <0.001 |
| **EmoSF - MNS** | 4.60 | 10.55 | <0.001 |
| **EmoSF - Motor** | 11.48 | 20.83 | <0.001 |
| **ER - ToM** | 0.32 | 0.74 | 0.465 |
| **ER - Empathy** | 1.68 | 3.83 | 0.001 |
| **ER - Rew** | **-11.60** | **-29.62** | **<0.001** |
| **ER - AM** | -2.12 | -5.23 | <0.001 |
| **ER - SM** | -5.36 | -13.71 | <0.001 |
| **ER - WM** | -3.12 | -7.94 | <0.001 |
| **ER - CogAC** | -1.28 | -3.22 | 0.004 |
| **ER - VigAtt** | -4.76 | -13.69 | <0.001 |
| **ER - MNS** | -2.48 | -6.13 | <0.001 |
| **ER - Motor** | 4.40 | 6.96 | <0.001 |
| **ToM - Empathy** | 1.36 | 3.73 | 0.001 |
| **ToM - Rew** | **-11.92** | **-33.53** | **<0.001** |
| **ToM - AM** | -2.44 | -5.55 | <0.001 |
| **ToM - SM** | -5.68 | -16.02 | <0.001 |
| **ToM - WM** | -3.44 | -9.19 | <0.001 |
| **ToM - CogAC** | -1.60 | -6.05 | <0.001 |
| **ToM - VigAtt** | -5.08 | -15.12 | <0.001 |
| **ToM - MNS** | -2.80 | -8.08 | <0.001 |
| **ToM - Motor** | 4.08 | 10.32 | <0.001 |
| **Empathy - Rew** | **-13.28** | **-28.64** | **<0.001** |
| **Empathy - AM** | -3.80 | -8.36 | <0.001 |
| **Empathy - SM** | -7.04 | -14.63 | <0.001 |
| **Empathy - WM** | -4.80 | -11.31 | <0.001 |
| **Empathy - CogAC** | -2.96 | -6.88 | <0.001 |
| **Empathy - VigAtt** | -6.44 | -16.09 | <0.001 |
| **Empathy - MNS** | -4.16 | -8.69 | <0.001 |
| **Empathy - Motor** | 2.72 | 5.46 | <0.001 |
| **Rew - AM** | **9.48** | **23.19** | **<0.001** |

| | | | |
|---|---|---|---|
| **Rew - SM** | **6.24** | **17.03** | **<0.001** |
| **Rew - WM** | **8.48** | **20.54** | **<0.001** |
| **Rew - CogAC** | **10.32** | **28.36** | **<0.001** |
| **Rew - VigAtt** | **6.84** | **20.41** | **<0.001** |
| **Rew - MNS** | **9.12** | **29.68** | **<0.001** |
| **Rew - Motor** | **16.00** | **30.60** | **<0.001** |
| **AM - SM** | -3.24 | -6.74 | <0.001 |
| **AM - WM** | -1.00 | -2.22 | 0.036 |
| **AM - CogAC** | 0.84 | 1.80 | 0.085 |
| **AM - VigAtt** | -2.64 | -6.83 | <0.001 |
| **AM - MNS** | -0.36 | -0.85 | 0.404 |
| **AM - Motor** | 6.52 | 12.10 | <0.001 |
| **SM - WM** | 2.24 | 6.19 | <0.001 |
| **SM - CogAC** | 4.08 | 12.92 | <0.001 |
| **SM - VigAtt** | 0.60 | 1.90 | 0.070 |
| **SM - MNS** | 2.88 | 5.91 | <0.001 |
| **SM - Motor** | 9.76 | 17.41 | <0.001 |
| **WM - CogAC** | 1.84 | 5.66 | <0.001 |
| **WM - VigAtt** | -1.64 | -4.24 | <0.001 |
| **WM - MNS** | 0.64 | 1.48 | 0.151 |
| **WM - Motor** | 7.52 | 18.04 | <0.001 |
| **CogAC - VigAtt** | -3.48 | -12.03 | <0.001 |
| **CogAC - MNS** | -1.20 | -2.80 | 0.010 |
| **CogAC - Motor** | 5.68 | 11.46 | <0.001 |
| **VigAtt - MNS** | 2.28 | 5.35 | <0.001 |
| **VigAtt - Motor** | 9.16 | 15.73 | <0.001 |
| **MNS - Motor** | 6.88 | 14.31 | <0.001 |

Significance threshold $p_{corr} < 0.001$.

**S1 Table SIX**: Group Differences between Schizophrenia and Normal Aging Classifications based on Specific Networks

| Network (abbr.) | Mean difference (Acc.) | T | *P* |
|---|---|---|---|
| **EmoSF** | -16.68 | -38.84 | < 0.001 |
| **ER** | -9.56 | -19.91 | < 0.001 |
| **ToM** | -14.92 | -44.24 | < 0.001 |
| **Empathy** | -6.68 | -9.73 | < 0.001 |
| **Rew** | -17.32 | -42.98 | < 0.001 |
| **AM** | -17.28 | -36.36 | < 0.001 |
| **SM** | -14.08 | -34.52 | < 0.001 |
| **WM** | -14.48 | -36.37 | < 0.001 |
| **CogAC** | -17.20 | -35.61 | < 0.001 |
| **VigAtt** | -15.76 | -36.60 | < 0.001 |
| **MNS** | -26.52 | -50.20 | < 0.001 |
| **Motor** | -17.20 | -27.42 | < 0.001 |

Significance threshold $p_{corr} < 0.001$.

**S1 Table SX**: Group Differences between Parkinson's Disease and Normal Aging Classifications based on Specific Networks

| Network (abbr.) | Mean difference (Acc.) | T | *P* |
|---|---|---|---|
| **EmoSF** | -22.28 | -43.66 | < 0.001 |
| **ER** | -15.72 | -30.34 | < 0.001 |
| **ToM** | -11.04 | -27.35 | < 0.001 |
| **Empathy** | -12.88 | -26.08 | < 0.001 |
| **Rew** | -26.16 | -53.25 | < 0.001 |
| **AM** | -9.52 | -20.87 | < 0.001 |
| **SM** | -15.24 | -39.09 | < 0.001 |
| **WM** | -14.60 | -28.46 | < 0.001 |
| **CogAC** | -14.64 | -32.50 | < 0.001 |
| **VigAtt** | -15.72 | -31.78 | < 0.001 |
| **MNS** | -29.40 | -50.67 | < 0.001 |
| **Motor** | -7.28 | -11.55 | < 0.001 |

Significance threshold $p_{corr} < 0.001$.

## STUDY 2:

# AGE DIFFERENCES IN PREDICTING WORKING MEMORY PERFORMANCE FROM NETWORK-BASED FUNCTIONAL CONNECTIVITY

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Total: 70%

## Abstract

Deterioration in working memory capacity (WMC) has been associated with normal aging but it remains unknown how age affects the relationship between WMC and connectivity within functional brain networks. We therefore examined the predictability of WMC from fMRI-based resting-state functional connectivity (RSFC) within eight meta-analytically defined functional brain networks and the connectome in young and old adults using relevance vector machine in a robust cross-validation scheme. Particular brain networks have been associated with mental functions linked to WMC to a varying degree and are associated with age-related differences in performance. Comparing prediction performance between the young and old sample revealed age-specific effects: In young adults, we found a general unpredictability of WMC from RSFC in networks subserving WM, cognitive action control, vigilant attention, theory-of-mind cognition, and semantic memory, whereas in old adults each network significantly predicted WMC. Moreover, both WM-related and -unrelated networks were differently predictive in older adults with low versus high WMC. These results indicate that the within-network functional coupling during task-free states is specifically related to individual task performance in advanced age, suggesting neural-level reorganization. In particular, our findings support the notion of a decreased segregation of functional brain networks, deterioration of network integrity within different networks and/or compensation by reorganization as factors driving associations between individual WMC and within-network RSFC in older adults. Thus, using multivariate pattern regression provided novel insights into age-related brain reorganization by linking cognitive capacity to brain network integrity.


**Keywords:** working memory; brain networks; aging; resting-state functional magnetic resonance imaging; machine learning; relevance vector machine, performance prediction

## Introduction

Decline in various cognitive and executive functions has been recognized as a part of normal aging (Glisky, 2007; Salthouse et al., 2003). In particular, age-related deterioration in working memory (WM) functionality, that is, the capability to temporarily maintain, update, and manipulate information, has received increased attention (Braver & West, 2008). WM decline has been addressed in a majority of cognitive aging theories (Park & Festini, 2017b) and is considered a source of age-related deficits in a wide range of cognitive tasks (Gazzaley et al., 2005; Park et al., 1996; Salthouse, 1991) and social-affective behaviors (Moran, 2013; Opitz et al., 2012).

While the neural underpinnings of age-related deficits in cognitive functions were found to be associated with activation differences in task-related brain networks (Cabeza et al., 2016a; Hedden, 2007; Nielson et al., 2006), several findings have demonstrated that age-related WM decline may in part be accounted for by changes in resting-state functional connectivity (RSFC) architecture of the brain (Charroud et al., 2016; Jockwitz et al., 2017; Sala-Llonch, Arenaza-Urquijo, et al., 2012). It remains unclear, however, to which extent neuro-behavioral features of aging manifest in individual differences in WM capacity (WMC) associated with variations in interregional coupling at rest across different cognitive networks. To investigate how WM performance relates to other cognitive systems in an aging population prone to WM decline is particularly interesting as it has been shown that WMC is strongly associated with variations among other executive functions (Courtney, 2004; Miyake et al., 2000) as well as constitutes an underlying executive function in a broad range of higher-order cognitions including language comprehension and reasoning (Kane, Conway, Hambrick, et al., 2007). Hence, shared neuro-behavioral variance can be expected among executive and higher-order cognitive functions that are regulated by the degree these functions depend on WMC. This interplay may potentially be affected by variation in WMC in older adults that associate with neural-level reorganization as previously reported for age-related brain-behavior relationships (Grady, 2012; Sala-Llonch et al., 2015). It is, however, still unclear which role RSFC within brain networks related to different aspects of cognitive function may play as a marker of individual WMC, raising the question whether RSFC within these networks can be considered (equally) informative about individual WMC and how this relationship may change with age.

Here we addressed this question by taking a novel approach leveraging the power of coordinate-based meta-analyses (Eickhoff et al., 2016; Müller et al., 2018) to robustly define regions of the brain that are consistently recruited across dozens to hundreds of neuroimaging studies examining a particular mental function. In turn, in the commonly used data-driven approach to define networks from whole-brain RSFC data by means of independent component analysis (ICA), the mental functions associated

with these networks are usually derived via reverse inference, as there is no a priori knowledge about the mental functions these networks subserve (Poldrack, 2011). Although the ICA-based approach has yielded stable and reproducible resting-state networks, the networks are usually defined from the same data set as used for the subsequent analysis (Cole et al., 2010). In contrast, our meta-analytically derived network model approach offers an a priori, unbiased definition of nodes forming a functional network, among which RSFC may then be computed for individual participants (cf. Pläschke et al., 2017; Schilbach et al., 2014; Varikuti et al., 2017). That is, meta-analyses provide robust information on the most likely location of the brain network subserving a task by integrating over task-activation findings based on hundreds of participants. Such a network can then be used to study individual RSFC connectivity profiles, which in turn can be linked to specific cognitive processes. Given that mental functions should best relate to interactions between multiple regions (Genon et al., 2018), we assume that the pattern of within-network connectivity may capture a substantial degree of inter-individual differences in cognitive performance. Using machine learning (ML)-based regression methods, previous studies have successfully predicted cognitive performance from RSFC distributed across the brain (Rosenberg et al., 2016) and revealed age effects in the prediction of executive functions from connectivity profiles between specific resting-state networks (La Corte et al., 2016). In the current work we employed the relevance vector machine (RVM; Tipping, 2001) in order to identify the relationship between input features (here: RSFC within a pre-defined functional network) and a continuous target variable (here: WMC score). The capability of such an approach to predict individual WMC in previously unseen subjects was evaluated using a repeated cross-validation scheme, yielding a scalar measure of average prediction performance for each network. To investigate the relationship between functional network integrity and WM performance and resolve the above-mention question about network specificity (see also Pläschke et al., 2017), we here examined five different meta-analytically defined networks. To examine how these relationships were affected by age, we compared prediction performance in young and old samples. The five networks comprised: WM (Rottschy et al., 2012), cognitive action control (CogAC; Cieslik, Mueller, Eickhoff, Langner, & Eickhoff, 2015), vigilant attention (VigAtt; Langner & Eickhoff, 2013), theory-of-mind cognition (ToM; Bzdok et al., 2012), and semantic memory (SM; Binder, Desai, Graves, & Conant, 2009). Importantly, the WM network reflects consistent neural recruitment during WM tasks that primarily demand recognition-related processes, such as the n-back paradigm, rather than tapping free retrieval-under-interference processes as examined via complex WM span tasks (Kane, Conway, Miura, et al., 2007).

The choice of these networks was based on our intent to cover a range of functional systems that are functionally (and neurally) either closely or only distantly related to WM (Chun, 2011; Diamond, 2013; Mutter et al., 2006; Nyberg et al., 2003; Unsworth et al., 2014). WM, CogAC, and VigAtt networks are

representatives of executive function networks closely related to WM, whereas ToM and SM networks are linked to higher-order cognitive processes involving reasoning and language comprehension (i.e., more distantly associated with WM). Thereby, the ToM network is linked to social reasoning, and the SM network is linked to semantic memory/processing and associated with language comprehension (Martin & Chao, 2001; Van Overwalle, 2009). Given that several lower-level sub-processes contribute to higher-level executive functioning (Miyake et al., 2000; Müller et al., 2015), it may be argued that networks associated with the former may predict WMC better than do higher-order networks.

In addition, three WM-unrelated (''control'') meta-analytic networks were included to assess whether WMC predictability is specifically associated with the above-mentioned cognitive networks closely or distantly related to WM. These control networks were linked to task-negative, social-affective and introspective processes, as well as motor and sensory processes. In particular, the three networks comprised (i) the extended social-affective default network (eSAD; Amft et al., 2015), (ii) a combined motor network associated with finger tapping and prosaccade eye movements (Motor+PS; Cieslik, Seidler, Laird, Fox, & Eickhoff, 2016; Witt, Meyerand, & Laird, 2008), and (iii) a combined motor-sensory network linked to finger tapping and hand stimulation/somatosensory processing (Motor+SS; Lamp et al., 2019; Witt et al., 2008). These motor-sensory systems are strongly interconnected compared to large-scale cognitive networks with transitions between network boundaries, and converge less with fronto-parietal cognitive areas (Cieslik et al., 2016; Fox & Raichle, 2007; Yeo et al., 2011). While the coupling between the default-mode and WM networks has been associated with WM performance (Keller et al., 2015; Piccoli et al., 2015), the eSAD network is strongly involved in social-affective and introspective processes (Amft et al., 2015). Hence, it may be positioned between (broadly) WM-linked networks and WM-unrelated control networks. For all three ''control'' networks, age-related functional connectivity changes have been reported (Chan et al., 2014a, 2017; Roski et al., 2013; L. Wang et al., 2010). Furthermore, we combined all individually investigated networks (related to cognitive action control, vigilant attention, theory-of-mind cognition, and semantic memory as well as eSAD) with the WM network to assess the predictability of intra- and inter-network connectivity. To further expand on this, we also examined predictability based on a connectome-wide network of 264 functional areas (Power et al., 2011), in order to compare the performance of the whole-brain connectome with that of our "sparse" functional networks and network combinations.

Previous findings and theories strongly suggest a general factor involved in age-related cognitive decline across several domains (Gazzaley et al., 2005; Mather, 2016; Moran, 2013; Park et al., 1996; Salthouse, 1991), which can partly be attributed to a general slowing in information processing (Salthouse, 1996; Salthouse, 1994). This, in turn, may possibly be related to a dedifferentiation/decreased segregation of functional networks (Chan et al., 2014a, 2017; Goh, 2011;

Roski et al., 2013; Sala-Llonch et al., 2015). Alternatively, performance decline with age might reflect a global age-related deterioration in network integrity, observable across various functional networks throughout the brain (Varangis et al., 2019; Zonneveld et al., 2019). Either or both of these network-related changes should result in less specific associations between performance and RSFC within any given network in advanced age. We therefore hypothesized similar predictive power across different networks with advanced age, as compared to greater network specificity in young adults, for whom we expected to find better prediction performance in networks more closely related to WM processing. Such an age-related "broadening" (i.e., network non-specificity) of WMC predictability should not only apply to distinct though related brain systems but might as well extend to WM-unrelated networks.

## Materials and Methods

### Sample

In the following we report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. Resting-state functional magnetic resonance imaging (fMRI) data of 50 young (age range: 20 – 34 years) and 45 old (age range: 51 – 71 years) participants were acquired at the Research Centre Jülich, Germany. For this explorative study, we did not estimate predictability effect sizes a priori for determining sample size. Participants did not report any present or past psychiatric or neurological disorders (including dementia), as assessed in a structured interview. Older adults' cognitive performance was age-adequate as evaluated by the Mild Cognitive Impairment and Early Dementia Detection assessment (DemTect; Kalbe et al., 2004; scores 13-18: age-adequate cognitive performance). None of the participants showed clinically relevant symptoms of depression as evaluated via the Beck Depression Inventory-II (all BDI-II scores < 13; Beck, Steer, & Brown, 1996). For further sample characteristics, please see S2 Table 1. Written informed consent was obtained from all participants before entering the study, which was approved by the ethics committee of the RWTH Aachen University Hospital, Aachen, Germany.

**S2 Table 1**: Sample Characteristics

| Normal Aging Sample | *N* (males) | Age (years) | Head Movement (DVARS) | DemTect | BDI-II | WMC |
|---|---|---|---|---|---|---|
| Young | 50 (27) | 26 ± 3 | 1.25 ± 0.25 | - | 6 ± 5 | 1.93 ± 0.24 |
| Old | 45 (24) | 62 ± 5 | 1.57 ± 0.41* | 16 ± 2 | 5 ± 5 | 1.60 ± 0.29* |
| WMC Low | 24 (9) | 61 ± 5 | 1.51 ± 0.46 | 16 ± 2 | 6 ± 5 | 1.40 ± 0.26 |
| WMC High | 21 (15) | 62 ± 6 | 1.63 ± 0.34 | 17 ± 2 | 4 ± 5 | 1. 82 ± 0.09* |

*Note.* All values (except *n*) represent mean ± standard deviation;

DVARS, derivative of root mean squared variance over voxels (head movement parameter);

DemTect, Mild Cognitive Impairment and Early Dementia Detection; BDI-II, Beck Depression Inventory II;

WMC, working memory capacity score;

* Significantly different between groups at $p < 0.05$

## Performance Measures

### *Working Memory Span Tasks: Corsi Block-Tapping*

Visuo-spatial WMC was assessed by the computerized version of the Corsi block-tapping task (forward and backward versions) from the Schuhfried Test System (https://www.schuhfried.com/test/CORSI; test forms S1 and S5). Here, participants were presented with a spatial array of nine irregularly arranged cubes on the monitor and observed a cursor that tapped a sequence of cubes. After an acoustic signal, participants were asked to re-tap the sequence either in the same (forward) or reverse (backward) order. Starting with three block taps, sequence length increased after three runs of a given length up to a maximum of 9 taps. The visuo-spatial WM span scores (forward and backward) correspond to the longest sequence correctly reproduced twice in a row.

### *Complex Working Memory Span Tasks: Operation and Reading Span*

Complex verbal WMC was assessed by a shortened version of the "operation and reading span tasks" (Oswald et al., 2015). For each trial in the operation span task, participants were first presented with an arithmetic equation, then had to decide whether a presented answer is true or false. After each trial, a letter was presented to remember for later recall. After 3 to 7 trials, a 4 × 3 letter matrix was presented, and participants were asked to recall the letter sequence by clicking on the letters in the correct order. The reading span task was similarly structured except for the distractor task presented between letters, which consisted of sentences (approximately 10–15 words) for which participants had to decide whether or not they made sense. In total, each of the five sequence lengths (3-7 trials) was

presented once in a pseudo-randomized order per subtests. The verbal WM complex span was then calculated by the average number of letters recalled in the correct order across all trials of each subtest.

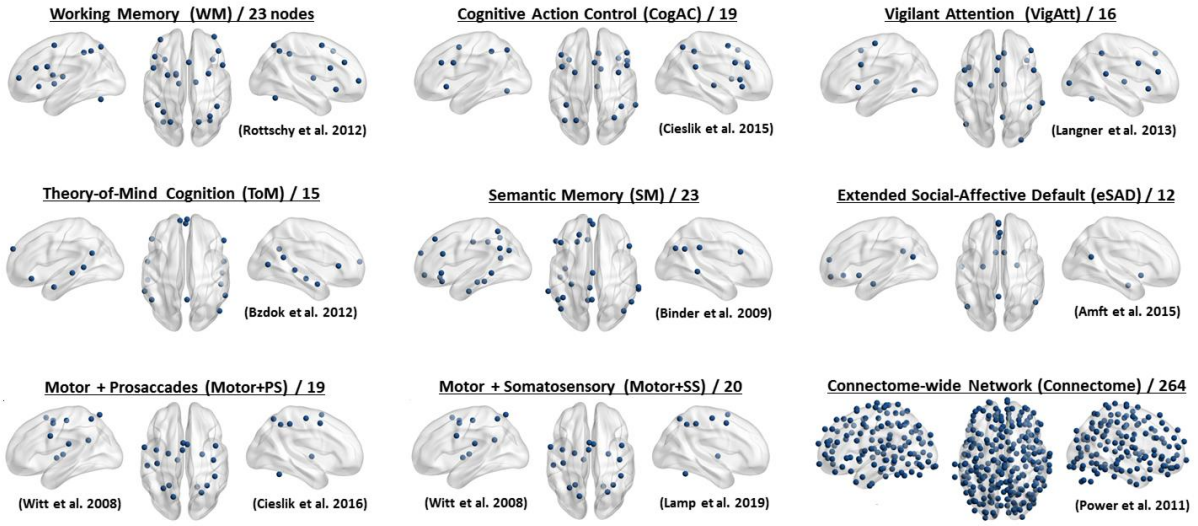
### *Composite Working Memory Capacity Score*

As we aimed to assess global WMC, we aggregated all three test scores (Corsi forward and backward scores, complex span score) into a composite WMC score per subject by expressing individual performance per test as a fraction of the theoretically maximal score for this test and summing these values. The intercorrelations and age-controlled partial correlation between the single WMC subscores were calculated. Differences in WMC scores between young and old adults were assessed by the independent sample t-test, the relationship between WMC and age by a Pearson correlation analysis.

## fMRI Data Acquisition and Processing

Whole-brain fMRI data were collected using a 3-T MR scanner (Tim-TRIO, Siemens Medical Systems) with a T2*-weighted echo-planar imaging (EPI) sequence (200 volumes; TR: 2200 ms; TE: 30 ms; flip angle: 80°; voxel size: 3.1 x 3.1 x 3.1 $mm^3$; 36 axial slices; inter-slice gap: 0.47 mm). During fMRI data acquisition, participants were instructed to lie still, close their eyes, let their mind wander, and not fall asleep (confirmed at debriefing). After discarding initial four EPI volumes to allow for field saturation, images were processed using SPM12 (www.fil.ion.ucl.ac.uk/spm) involving EPI unwarping (using additionally acquired field maps), two-pass affine realignment for motion correction, spatial normalization to the MNI-152 template brain provided by SPM12 using the “unified segmentation” approach (Ashburner & Friston, 2005), as well as spatial smoothing with a 5-mm FWHM Gaussian kernel.

The above-mentioned five cognitive brain networks examined here comprised, to varying degrees, common and distinct brain regions. For instance, the WM, CogAC, VigAtt, und SM networks included peak coordinates in the inferior frontal gyrus, parietal regions, and midline structures. All but the SM and ToM networks included the anterior insula, while the SM and ToM networks were the only ones to include temporal regions and the mid-orbital gyrus. Moreover, only the SM network exhibited a strong left lateralization, presumably due to its involvement in language. In contrast, the ToM network uniquely included the right posterior temporo-parietal junction. Subcortical structures were only part of the WM, CogAC, and VigAtt networks (see S2 Figure. 1, S2 Table SI for an overview, and S2 Table SII for detailed network coordinates and corresponding brain regions).




**S2 Figure 1**: Nodes of Meta-analytically defined Networks

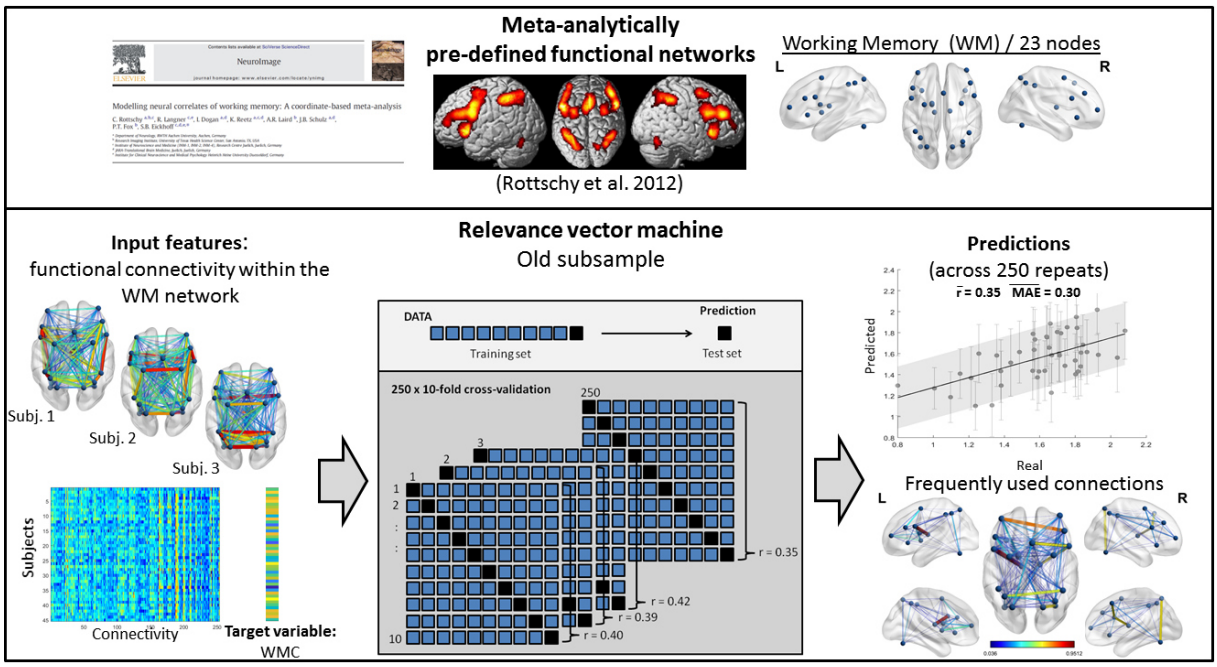
RSFC within each of the meta-analytically defined networks were computed by first extracting the BOLD-signal time course of each node as the first eigenvariate of all voxels located within a 6-mm sphere around the meta-analytic peak voxel and conforming to the CanLab gray-matter mask (https://canlabweb.colorado.edu). In order to reduce spurious correlations, variance explained by (i) the six movement parameters obtained during preprocessing, (ii) their derivatives (each modeled as first- and second-order effects), as well as (iii) the mean white-matter and cerebrospinal-fluid signal time courses were statistically removed from each node's time series (Ciric et al., 2017; Satterthwaite et al., 2013), which has been shown to yield reliable estimates of within- and between-network connectivity (Varikuti et al., 2017). Moreover, this approach ensures that less gray-matter-specific, motion-unrelated variance of BOLD-signal fluctuations of neural origin will be removed from the data (G. Chen et al., 2012), as compared to global signal regression. Subsequently, time series were high-pass filtered retaining frequencies above 0.01 Hz.

Although we regressed out motion-related variance such that afterwards the correlation between RSFC and motion was near zero, we conducted further analyses to follow up on this important issue, given that motion-related artifacts in resting-state fMRI data can lead to spurious functional connectivity. In particular, two additional RSFC denoising procedures were separately applied: First, global signal regression was performed (Ciric et al., 2017; Power et al., 2018; Satterthwaite et al., 2013). Second, data censoring was applied to remove data points in each time series that were contaminated by motion (using the method proposed by Afyouni & Nichols, 2018) and to account for spuriously inflated RSFC of short-distance connections and spuriously decreased RSFC of long-distance ones (Ciric et al., 2018).

Pair-wise functional connectivity was computed as Fisher's Z-transformed Pearson correlation between the first eigenvariate of the time series of each network's nodes. Connectivity values were then adjusted (via linear regression) for effects of age, gender and movement based on the derivative of root mean squared variance over voxels (DVARS) within each age group to avoid predictions based on spurious between-subject differences (N. W. Duncan & Northoff, 2013; Power et al., 2012; Satterthwaite et al., 2013). Analogously, WMC scores were adjusted for effects of age and gender within each age group.

### RVM Features and Prediction

RSFC values for all connections within a given network and subject represent individual features from which the individual WMC score were predicted using RVM (Tipping, 2001; Tipping & Faul, 2003) as implemented in the SparseBayes package *(*version 2.0 Matlab R2017b; http://www.relevancevector.com). To estimate the generalizability of the RVM models, a 10-fold cross-validation scheme was employed (see S2 Figure 2 for a schematic analysis workflow). The available data (subjects) were randomly split into 10 equally sized subgroups. In each cross-validation fold, an RVM was trained on 9 of these and then used to predict the WMC score of the left-out split (i.e., the subjects not used during training). Input features (= all RSFC values of a given network) and target variables were scaled to zero mean and unit standard deviation based only on the training sample as to avoid any leakage. Deconfounding of input features and targets (as described above) was done once outside the cross-validation as recently proposed as the optimal strategy for prediction studies on individual phenotypes from RSFC (Pervaiz et al., 2020). To ensure the robustness of performance evaluation against the initial folds, the cross-validation procedure was repeated 250 times using independent splitting. These analyses were performed for each network separately in young (n = 50) and old (n = 45) adults to investigate age-related differences in predictive performance. To examine whether residual movement-related effects may be a relevant contributor to WMC predictability, additional analyses were conducted with including DVARS as a predictor in the models (see supplementary method section for details).




**S2 Figure 2**: Schematic Exemplary Analysis Workflow: Working Memory Capacity (WMC) is Predicted from Resting-state Functional Connectivity in the WM Network in the Old Sample

$\bar{r}$ / $\overline{MAE}$: mean Pearson correlation coefficient / mean absolute error between real and predicted scores across 250 cross-validation repeats.

Prediction accuracy (i.e., the ability of a given network's RSFC pattern to predict individual WMC scores) was indicated by the mean Pearson's correlation ($\bar{r}$) and mean absolute error ($\overline{MAE}$) between the real and predicted WMC scores computed first within each of the 10-folds and subsequently across all 250 cross-validation replications. To test whether performance was significantly different from zero, one-sample *t*-tests were performed on the 250 correlation coefficients, correcting for multiple comparisons over the assessed networks using Bonferroni's method. In addition, we only considered those predictions relevant that were at least of a medium effect size (i.e., $\bar{r} \geq 0.24$, corresponding to Cohen's d ≥ 0.5). When WMC predictability was significant in either the young or old group, group differences were calculated using independent sample *t*-tests (Bonferroni-corrected for the number of networks). To evaluate effect sizes of group differences, Fisher's Z-transformed mean correlation coefficients of the young and old groups were subtracted from each other. Subsequently, Cohen's *q* served for effect size interpretation (Cohen, 1988).

Moreover, to statistically examine differences in prediction performance between significantly predictive networks within each group, paired-sample *t*-tests were performed on prediction accuracies obtained from the 250 cross-validation replications of the RVMs (significance threshold: $p < 0.05$, Bonferroni-corrected for the number of comparisons). For a given network to be considered notably

different, its prediction accuracy needed to differ to an at least small degree (Cohen's q) from most of the other networks (i.e., from at least 6 out of 8 networks).

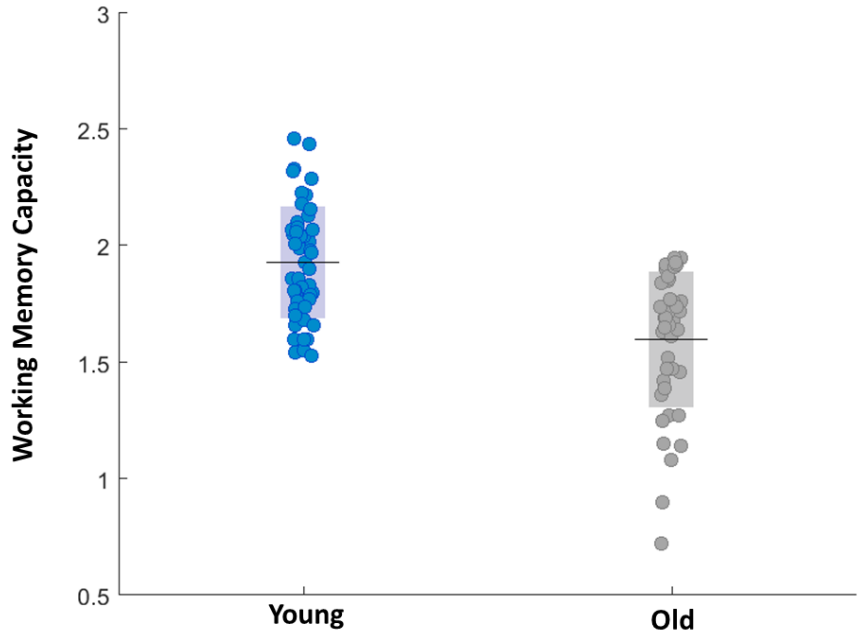
To examine a potential performance dependence of WMC predictability from network-based RSFC in advanced age, the older sample was median-split into high- and low-WMC subgroups (post-hoc to the prediction analyses). The prediction accuracies ($\bar{r}$) were calculated within each subgroup, and significance tests were conducted as described above.

Given the inherent sparsity of RVM prediction models, induced by forcing feature weights to be zero to indicate irrelevant network connections, the remaining non-zero (i.e., contributing) connections in each RVM model were inspected to determine which connections of a given network were predictive of individual WMC scores. Connections used in at least 90% of the total 2500 predictive models per network are reported as the most frequently used and, therefore, most consistently predictive connections and are visualized with the BrainNet Viewer (Xia et al., 2013).

## Results

### Working Memory Capacity

WMC was significantly lower in the older sample compared to the young sample ($t$ = 6.07, $p$ < 0.001) and the variance did not differ (F = 0.69, $p$ = 0.21; see S2 Table 1 and S2 Figure 3). This is corroborated by a significant negative correlation between WMC and age in the entire sample (r = −0.48; $p$ < 0.001). The correlations between all three WMC subscores were significant in the entire sample with and without removing the effects of age. This suggests that age had very little influence on the relationship between single subscores (S2 Table SIII).



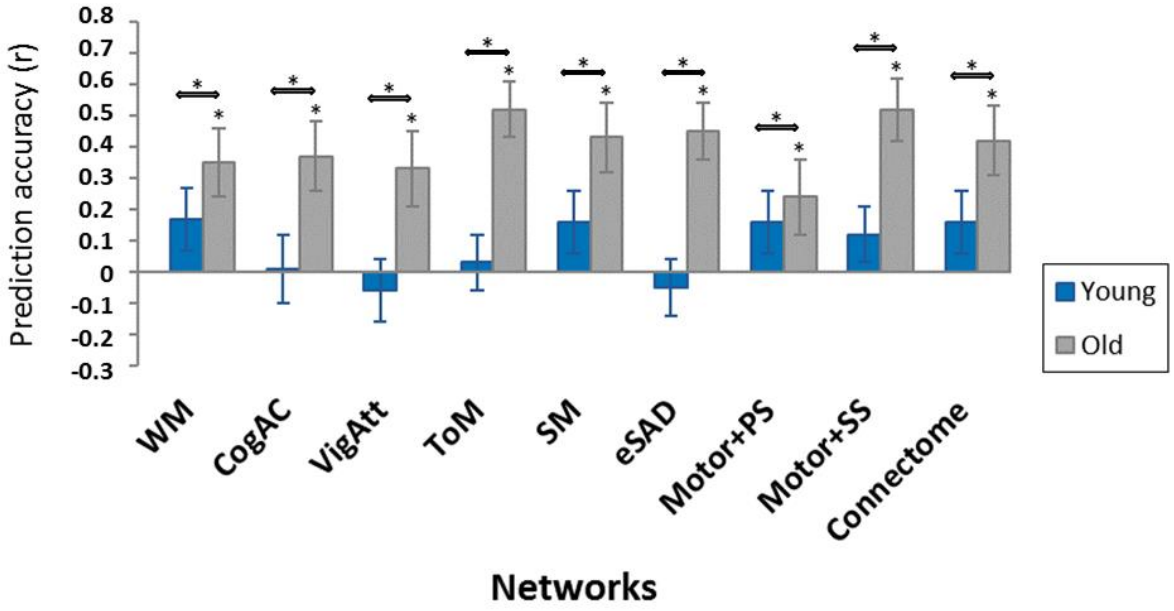

**S2 Figure 3**: Working Memory Capacity (WMC) Plotted against Age for Young (in blue) and Old (in gray) Participants

Mean WMC (horizontal line) ± standard deviation (bounded box) for the young sample was 1.93 ± 0.24 and for the old one: 1.60 ± 0.29.

## Working Memory Capacity Predictability from Network RSFC

### *Young and Old Sample*

All cognitive networks significantly predicted WMC in the older group: WM: $\bar{r}_{\text{old}}$ = 0.35; $\overline{MAE}$ = 0.30; cognitive action control (CogAC): $\bar{r}_{\text{old}}$ = 0.37; $\overline{MAE}$ = 0.28; vigilant attention (VigAtt): $\bar{r}_{\text{old}}$ = 0.33; $\overline{MAE}$ = 0.33; theory-of-mind cognition (ToM): $\bar{r}_{\text{old}}$ = 0.52; $\overline{MAE}$ = 0.24; and semantic memory (SM): $\bar{r}_{\text{old}}$ = 0.43; $\overline{MAE}$ = 0.27. All four control networks significantly predicted WMC in the older group: extended social-affective demand (eSAD): $\bar{r}_{\text{old}}$ = 0.45; $\overline{MAE}$ = 0.27; finger tapping and prosaccade eye movements (Motor+PS): $\bar{r}_{\text{old}}$ = 0.24; $\overline{MAE}$ = 0.34; finger tapping and somatosensory processing (Motor+SS): $\bar{r}_{\text{old}}$ = 0.52; $\overline{MAE}$ = 0.24; connectome-wide network (Connectome): $\bar{r}_{\text{old}}$ = 0.42; $\overline{MAE}$ = 0.27. The S2 Figure 4 and S2 Table 2 provide an overview of the averaged prediction accuracies of the RVM results. The S2 Figure 5 summarizes the scatter plots of real and predicted WMC scores based on each network.




**S2 Figure 4**: Bar Plot of Prediction Accuracies expressed as Mean (error bars: standard deviation)

Pearson correlations ($\bar{r}$) between real and mean predicted working memory capacity (WMC) scores across 250 cross-validation repeats for the young (in blue) and old (in gray) sample.

* significant ($p < 0.001$) predictions / group differences.

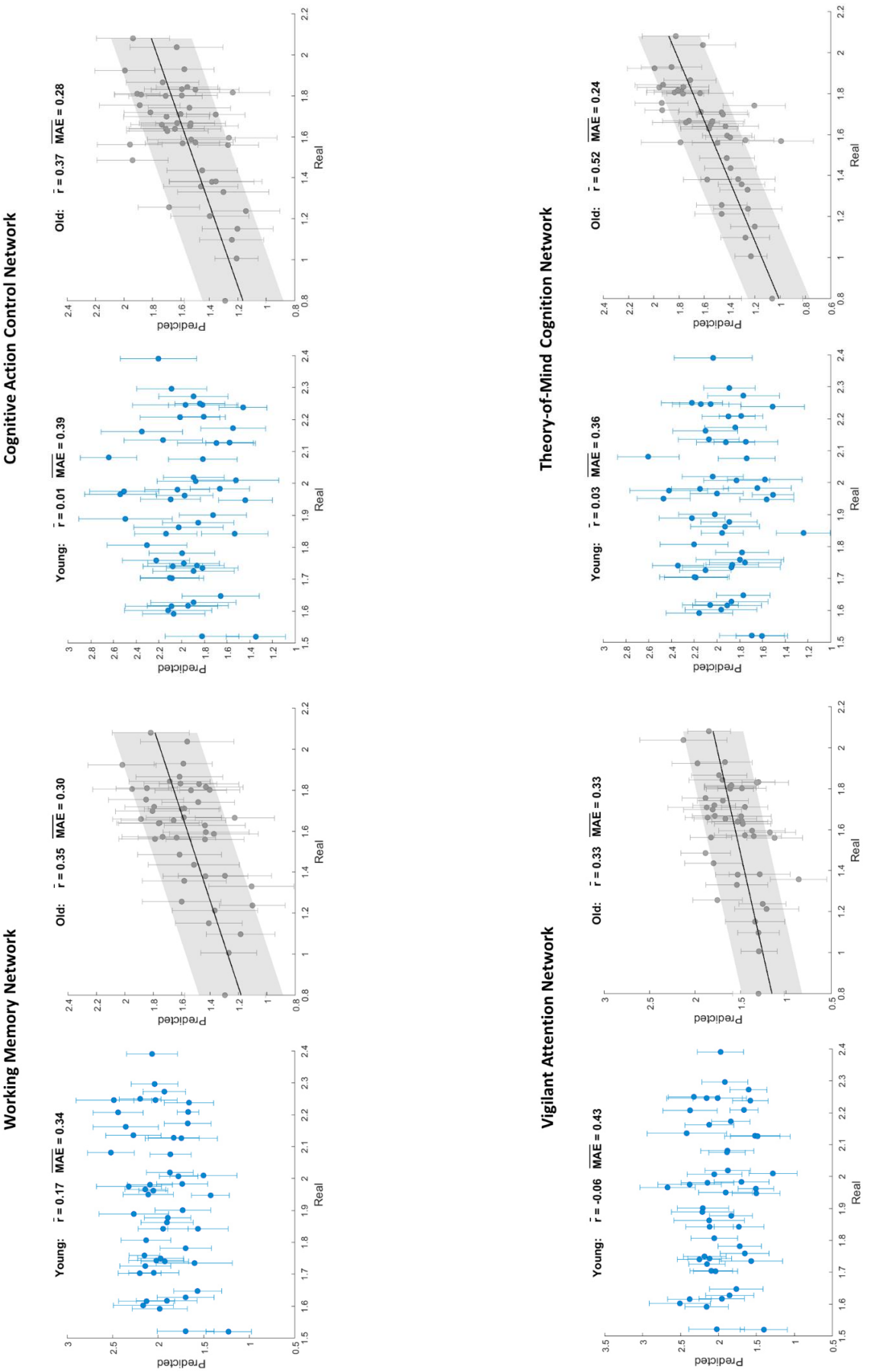
WM, working memory; CogAC, cognitive action control; VigAtt, vigilant attention; ToM, theory-of-mind cognition; SM, semantic memory; eSAD, extended social-affective default; Motor+PS, motor+prosaccades; Motor+SS, motor+somatosensory.

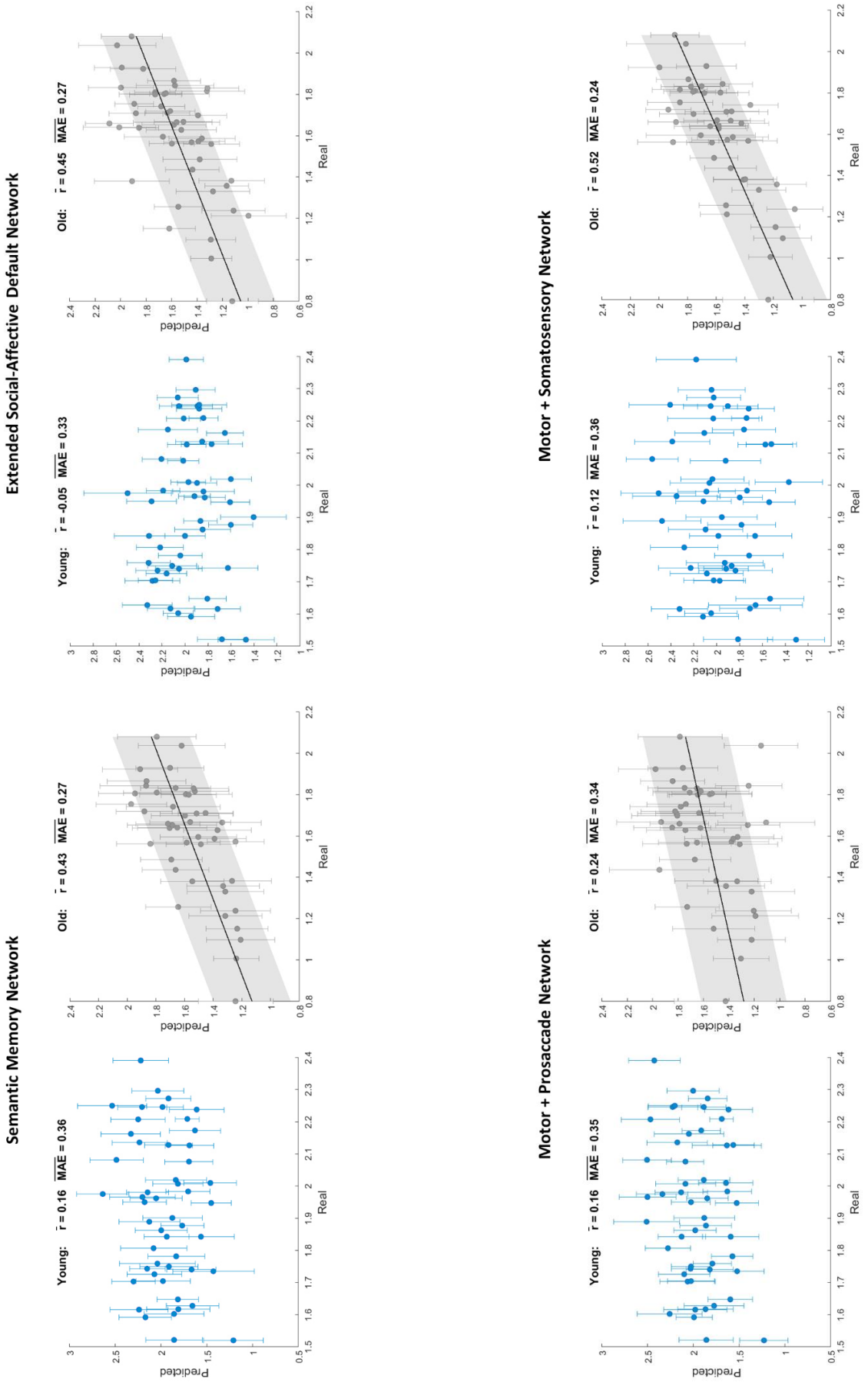
**S2 Table 2**: Predictability of Individual Working Memory Capacity based on Functional Connectivity in Nine Brain Networks

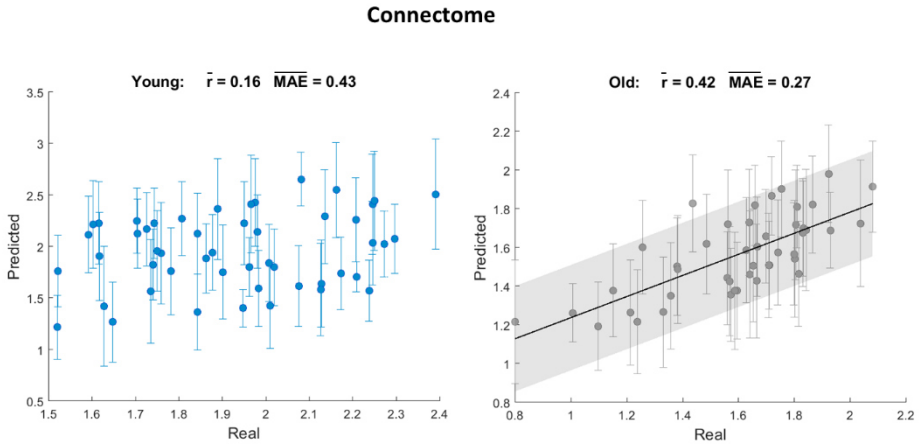
| | Networks | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **WM** | **CogAC** | **VigAtt** | **ToM** | **SM** | **eSAD** | **Motor+PS** | **Motor+SS** | **Connectome** |
| $\bar{r}_{young}$ | 0.17 | 0.01 | -0.06 | 0.03 | 0.16 | -0.05 | 0.16 | 0.12 | 0.16 |
| $\bar{r}_{old}$ | 0.35* | 0.37* | 0.33* | 0.52* | 0.43* | 0.45* | 0.24* | 0.52* | 0.42* |
| Cohen's *q* | 0.19 | 0.38 | 0.40 | 0.55 | 0.30 | 0.54 | 0.08 | 0.46 | 0.29 |

Pearson correlations between real and predicted working memory capacity (WMC) scores in the young ($\bar{r}_{young}$) and old ($\bar{r}_{old}$) sample. Cohen's *q:* effect size of age group differences in correlations (<.1: no effect; 0.1 - 0.3: small effect; 0.3 - 0.5: medium effect; >0.5: large effect).

* significant ($p < 0.001$) predictions with at least medium effect size ($\bar{r} \geq 0.24$, corresponding to Cohen's d ≥ 0.5).


Cognitive Action Control Network
Old: r̄ = 0.37 MAE = 0.28
Young: r̄ = 0.01 MAE = 0.39
Working Memory Network
Old: r̄ = 0.35 MAE = 0.30
Young: r̄ = 0.17 MAE = 0.34
Theory-of-Mind Cognition Network
Old: r̄ = 0.52 MAE = 0.24
Young: r̄ = 0.03 MAE = 0.36
Vigilant Attention Network
Old: r̄ = 0.33 MAE = 0.33
Young: r̄ = -0.06 MAE = 0.43
Predicted
Real


Extended Social-Affective Default Network
Young: r̄ = -0.05 MAE = 0.33
Old: r̄ = 0.45 MAE = 0.27
Semantic Memory Network
Young: r̄ = 0.16 MAE = 0.36
Old: r̄ = 0.43 MAE = 0.27
Motor + Somatosensory Network
Young: r̄ = 0.12 MAE = 0.36
Old: r̄ = 0.52 MAE = 0.24
Motor + Prosaccade Network
Young: r̄ = 0.16 MAE = 0.35
Old: r̄ = 0.24 MAE = 0.34
Predicted
Real




**S2 Figure 5**: Predictability of Individual Working Memory Capacity (WMC) based on Functional Connectivity Patterns in Nine Brain Networks

Scatter plots show real against mean predicted WMC scores across 250 cross-validation repeats (error bars: standard deviations) for young (denoted in blue) and old (denoted in gray) participants. For significant prediction accuracies ($\bar{r}$: Pearson correlations between real and predicted scores), a linear regression line and a gray bounded line indicating the mean absolute error ($\overline{MAE}$) were added.

Furthermore, S2 Table SIV provides the detailed statistics on the WMC predictability from each network's RSFC. When compared to all other eight predictive networks in the older group, the ToM network showed significantly better predictability (between-network comparison of prediction performance r at $p < 0.001$: WM: $t = 21.39$; CogAC: $t = 19.53$; VigAtt: $t = 24.81$; SM: $t = 13.04$; Motor+PS: $t = 34.79$; Connectome: $t = 12.86$). In contrast, only the predictability of the Motor+PS network combination was significantly lower (WM: $t = -13.68$; CogAC: $t = -15.72$; VigAtt: $t = -10.69$; ToM: $t = -34.79$; SM: $t = -22.68$; eSAD: $t = -24.03$; Motor+SS: $t = -32.67$; Connectome: $t = -22.06$), whereas the Motor+SS combination exhibited significantly better predictability (WM: $t = 21.41$; CogAC: $t = 18.79$; VigAtt: $t = 22.59$; SM: $t = 11.52$; Motor+PS: $t = 32.67$; Connectome: $t = 12.76$ [see S2 Table SV]).

In contrast, in the young group none of the networks was significantly predictive of WMC, only slight trends were observed for the WM: $\bar{r}_{young} = 0.17$ and $\bar{r}_{young} = 0.16$ for the SM, Motor+PS, and Connectome networks. Using global signal regression (compared to white-matter and cerebrospinal-fluid signal removal) resulted in an increase in the specificity of predictability across networks mainly linked to a decrease in prediction accuracy (see S2 Table 3). Although global signal regression has a particular impact on WMC predictability in the old group, for which potential motion-unrelated sources are discussed later, additional analyses controlling for movement-related artifacts in RSFC data did not corroborate that residual motion effects unduly influenced WMC predictability in the old group (see S2 Table SVI for RVM results based on data for which preprocessing included censoring as well as S2 Table SVII for results of analyses that included DVARS as a predictor). Moreover, neither the

predictiveness from intra- and inter-network connections nor from the entire connectome demonstrated substantial improvements over that of individual functional networks (see S2 Table SVIII and S2 Table 2).

**S2 Table 3**: Predictability of Individual Working Memory Capacity based on Functional Connectivity in Nine Brain Networks - Global Signal Regression

| | Networks | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **WM** | **CogAC** | **VigAtt** | **ToM** | **SM** | **eSAD** | **Motor+PS** | **Motor+SS** | **Connectome** |
| $\bar{r}_{young}$ | 0.12 | 0 | 0.06 | 0.09 | 0.18 | -0.19 | 0.11 | 0.16 | 0.20 |
| $\bar{r}_{old}$ | 0.40* | 0.27* | 0.26* | 0.42* | 0.33* | 0.32* | 0.39* | 0.36* | 0.43* |
| Cohen's *q* | 0.30 | 0.28 | 0.21 | 0.36 | 0.16 | 0.52 | 0.30 | 0.22 | 0.26 |

Pearson correlations between real and predicted working memory capacity (WMC) scores in the young ($\bar{r}_{young}$) and old ($\bar{r}_{old}$) sample. * significant ($p < 0.001$) predictions with at least medium effect size ($\bar{r} \geq 0.24$, corresponding to Cohen's d ≥ 0.5).

We observed significant age-related differences in WMC predictability for all networks with effect sizes ranging from small to large: Cohen'q: WM = 0.19; CogAC = 0.38; VigAtt = 0.40; ToM = 0.55; SM = 0.30; eSAD = 0.54; Motor+SS = 0.46 and Connectome = 0.29 ($p < 0.001$; see S2 Table 2 and S2 Table SIX).

Moreover, the analyses of high- versus low-WMC participants of the older subsample revealed that overall predictability in the elderly might have been mainly driven by low-WMC older adults for the majority of networks: WM: $\bar{r}_{old\_low}$ = 0.37, $\bar{r}_{old\_high}$ = 0.22; CogAC: $\bar{r}_{old\_low}$ = 0.41, $\bar{r}_{old\_high}$ = 0.19; VigAtt: $\bar{r}_{old\_low}$ = 0.40, $\bar{r}_{old\_high}$ = 0.18; ToM: $\bar{r}_{old\_low}$ = 0.33, $\bar{r}_{old\_high}$ = 0.30; SM: $\bar{r}_{old\_low}$ = 0.49, $\bar{r}_{old\_high}$ = 0.29; Motor+PS: $\bar{r}_{old\_low}$ = 0.28, $\bar{r}_{old\_high}$ = -0.02; Motor+SS: $\bar{r}_{old\_low}$ = 0.40, $\bar{r}_{old\_high}$ = 0.24 (see S2 Table 4, S2 Table SX for additional predictions based on intra- and inter-network connectivity, S2 Tables SXI and S2 SXII for statistics).

**S2 Table 4**:Predictability of Individual Working Memory Capacity based on Functional Connectivity in Nine Brain Networks in Low- and High-WMC Older Adults

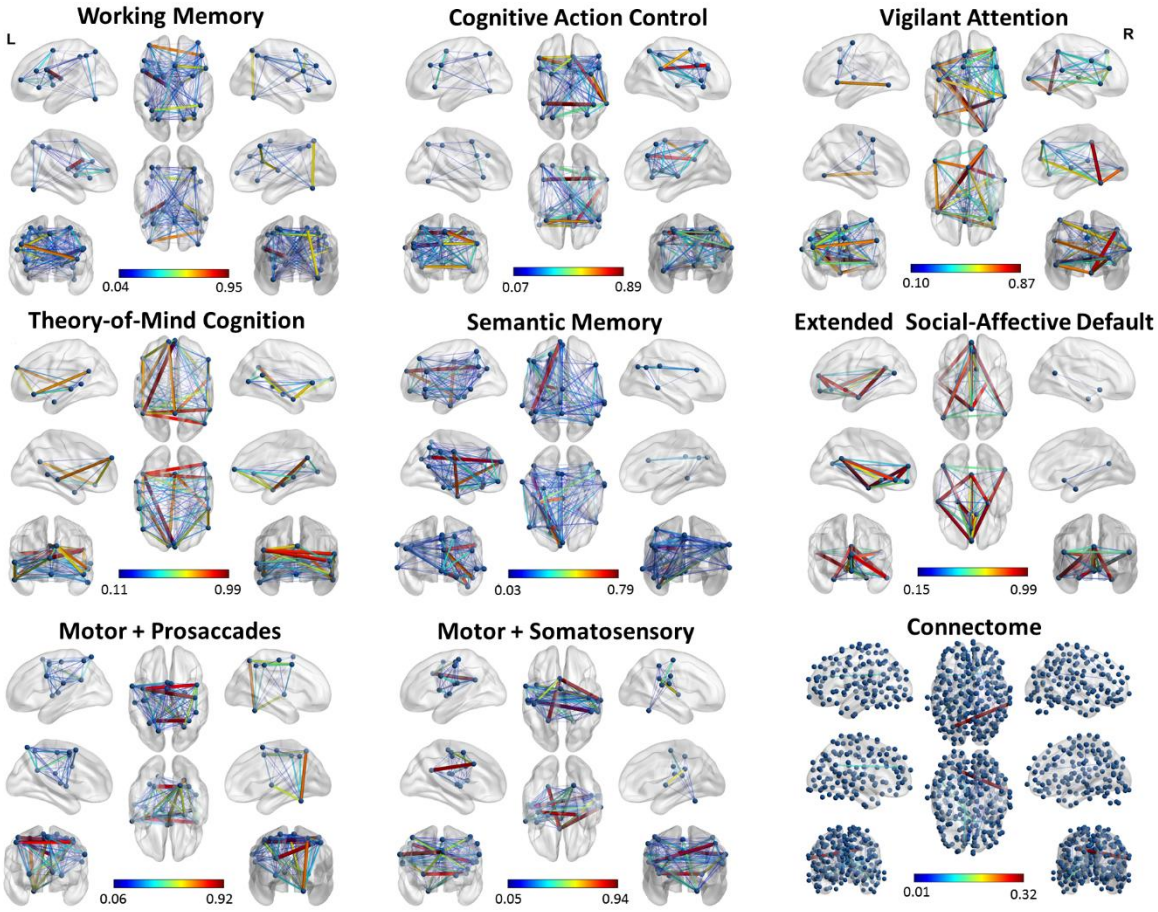
| | Networks | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **WM** | **CogAC** | **VigAtt** | **ToM** | **SM** | **eSAD** | **Motor+PS** | **Motor+SS** | **Connectome** |
| $\bar{r}_{old\_low}$ (n = 24) | 0.33* | 0.34* | 0.25* | 0.37* | 0.41* | 0.42* | 0.28* | 0.45* | 0.35* |
| $\bar{r}_{old\_high}$ (n = 21) | 0.08 | 0.12 | 0.23 | 0.33* | 0.21 | 0.18 | -0.02 | 0.31* | 0.26* |
| Cohen's *q* | 0.26 | 0.23 | 0.02 | 0.05 | 0.22 | 0.27 | 0.31 | 0.16 | 0.10 |

Pearson correlations between real and predicted working memory capacity (WMC) scores in the old sample with low ($\bar{r}_{old\_low}$) and high ($\bar{r}_{old\_high}$) WMC. Cohen's q: effect size of differences in correlations between networks in low and high WMC older adults (<.1: no effect; 0.1 - 0.3: small effect; 0.3 - 0.5: medium effect; >0.5: large effect).

* significant (p < 0.001) predictions with at least medium effect size ($\bar{r} \geq 0.24$, corresponding to Cohen's d ≥ 0.5).

*Relevance of Single Connections*

As RVMs generates sparse solutions, we could identify specific connections within each of the cognitive networks that were frequently used by the prediction models (i.e., in at least 90% of the 2500 [10 foldings × 250 repeats] models per network), hence representing consistent and potentially relevant contributions to predicting WMC. In the older group, these frequently used connections were as follows (see S2 Figure SI): for the WM network, the connection between left inferior frontal gyrus and left thalamus, and for the ToM network, the connection between right superior medial gyrus/frontal pole and left angular gyrus/temporo-parietal junction. For the CogAC, VigAtt and SM networks, none of the connections met our criteria. For all the networks the percentage of connection usage across models are displayed in S2 Figure 6.




**S2 Figure 6**: Illustration of the Frequency with which Connections were used in each of the Nine Functional Brain Networks for Predicting Working Memory Capacity (WMC) in the Old Sample

Displayed are only nodes with a ''relevant'' connectivity (edge) value attached to them. Color indicates the percentage of use across 2500 cross-validation repeats per network (ranges are indicated with the color bars).

Augmented reality app support for this figure can be downloaded under https://osf.io/wru83/ or via

For further information please see supplement.

## Discussion

We examined whether and to what degree individual RSFC patterns in any of eight meta-analytically defined functional brain networks and a connectome-wide network predicted WMC in previously unseen young and old participants using ML-based regression analysis with the aim to investigate age-related differences (young vs. old adults). Our results demonstrate that individual WMC could be predicted from all five cognitive WM-related networks ($\bar{r} \geq 0.33$) with the highest accuracy of $\bar{r} = 0.52$ (ToM network), whereas predictability from the WM-unrelated networks varied with differential degree, with the Motor+PS network showing the lowest significant predictability ($\bar{r} = 0.24$) in the older group. In the young group, none of the networks was predictive. WMC predictability across networks in the old group was primarily linked to lower WMC.

### Age Differences in Working Memory Capacity Predictability

In the old sample, individual WMC could be similarly well predicted from the RSFC pattern of the WM network and networks both closely related to WM (i.e., CogAC and VigAtt) and distantly related to WM (i.e., ToM and SM). This demonstrates that the interregional coupling in a task-unconstrained state within robustly defined brain networks recruited for executive functions and higher-order cognitive tasks contains information about individual WM performance. Moreover, WM-unrelated networks associated with task-negative, social-affective and introspective processes (eSAD), finger tapping and prosaccade eye movements (Motor+PS) and finger tapping and somatosensory processing (Motor+SS) predicted WMC in advanced age. Thus, the strength of functional coupling (at rest) between these regions (defined by consistent activation during tasks) is associated with WM abilities tested outside the MRI scanner. The similarity to which WMC is predicted across different networks, related or unrelated to WM, is potentially linked to a decreased segregation of functional brain networks in advanced age (Chan et al., 2014a, 2017), which in turn may be related to the often proposed neural-level dedifferentiation with aging (i.e., a declining specificity of neuro-functional systems; Goh, 2011; Grady, 2012; Sala-Llonch et al., 2015). The fact that networks become less segregated with age may lead to a situation where predictive information on individual WMC can be extracted from a broad range of networks. Alternatively, this “broadened” predictability of WMC may reflect widespread age-related changes that lead to similarly reduced network integrity within different networks (Varangis et al., 2019; Zonneveld et al., 2019), through which all the networks sampled here come to contain reasonably predictive information on performance.

While all of the cognitive networks may be expected to relate to some degree to WM, given some shared neural and behavioral variance between WM and other executive and cognitive processes, it should be noted that the predictive capacity of the CogAC and VigAtt networks was not primarily driven by their partial spatial overlap with regions of the WM network (Camilleri et al., 2017; Müller et al., 2015). That is, spatial similarity does not automatically lead to a similar pattern of RSFC—performance associations (see S2 Figure 6). The significant predictability of WMC in the old sample from the RSFC patterns of multiple networks (WM, CogAC, VigAtt, ToM, SM, eSAD, Motor+PS and Motor+SS) extends previous aging research that revealed age differences in univariate associations between WM performance and RSNs (Charroud et al., 2016; Jockwitz et al., 2017; Sala-Llonch, Arenaza-Urquijo, et al., 2012).

In addition, not finding any substantial improvement in predictiveness from intra- and inter-network connectivity over individual networks suggests, first, that it is not the sheer (higher) number of features that determines prediction performance here, and second, that it is not the connectivity between the different networks that provides higher information content with respect to WMC. In line with this, even the connectome-based prediction, which rests on an even higher number of connections, was not superior, suggesting that no additionally predictive information can be distilled from a functionally agnostic, though spatially comprehensive, brain-wide representation of RSFC, as compared to sparse but functionally meaningful brain networks. Alternatively, finding no substantial improvement in predictiveness for the whole-brain connectome might partly also be due to a less favorable feature-to-sample ratio.

The generally low predictability of WMC in young adults based on the networks investigated here (chosen according to theoretical considerations as detailed in the introduction) indicates that RSFC patterns within these networks do not hold information on individual WM performance in younger age. While this remains somewhat surprising, particularly for the WM network, it may be attributable to the differences in task demands between WM paradigms used in the scanner (and hence defining the meta-analytic network) and the WMC score employed here (Kane, Conway, Miura, et al., 2007). This assumption would reinforce the notion of a higher specificity in brain-behavior relations in young adults, as compared to a less segregated and/or altered integrity situation among the elderly, leading to a more global predictability of cognitive capacities from a broad range of brain networks (cf. Ward et al., 2015). Alternatively, this observation could also simply mean that young adults reconfigure their networks in task states more extensively to meet task-specific demands and, therefore, RSFC patterns at rest are less predictive, whereas task and rest configurations are more similar to, or predictive of, each other in advanced age. Ultimately, the overall low predictability, with only slight predictive trends for some networks, indicates a lack of shared variance between RSFC and WMC. Accordingly, young

adults appear to not exhibit typical network-based RSFC patterns that correspond to certain WMC levels, at least in the functional networks investigated in relation to the composite WMC score used here.

The better overall prediction in the older group might be related to factors of age-related neural decline that include brain atrophy and white-matter degeneration (Allen et al., 2005; Cabeza et al., 2016b; Cox et al., 2016), which may be related to altered network integrity and, hence, altered within-network processing efficiency. Together, these may lead to brain organizational changes that strengthen the association between WMC and the integrity of brain networks as assessed by RSFC. This suggests that the composite WMC score contains information related to advanced age. Hence, the high predictability across networks in older adults may, in part, result from age-related neural reorganization that is associated with performance and includes RSFC changes across different networks (Sala-Llonch et al., 2015). These age-related changes in older adults were then picked up by the prediction models, leading to better prediction performance. Importantly, predictability across networks differed between low- and high-WMC older adults. Differential age-related neural plasticity may be related to low versus high WM abilities represented by reorganization mechanisms linked to a decreased segregation of functional brain networks. This seems to be associated with reduced functional specificity across networks and/or reduced network integrity within different networks as well as, possibly, compensation through reorganization. Each reorganizational process may manifest itself in altered patterns of within-network RSFC, which may drive associations between network RSFC patterns and WMC. The higher predictability across cognitive networks (closely and distantly linked to WM) as well as task-negative and motor-sensory networks (WM-unrelated) in older adults with lower WMC may be related to a stronger association such as a blurring of functionally distinct network systems almost exclusively linked with declined performance. This might represent reorganization mechanisms related to a decreased segregation of functional brain networks (e.g., a tighter link between cognitive, task-negative and motor-sensory systems) manifested in altered patterns of within-network RSFC, and may drive associations with lower WMC scores. Alternatively, the high predictability across networks might be linked to widespread age-related changes leading to a weakening of within-network connectivity associated with an increase in networks' susceptibility to inference and, hence, performance deterioration (Stevens et al., 2008; Varangis et al., 2019; Zonneveld et al., 2019). These alterations may lead to similarly reduced network integrity in distinct networks, which are linked to low WMC. Either way or in combination, this suggests that especially very low performance levels in the old subsample are predictable from RSFC across networks possibly because the network changes are so pronounced that they cannot be compensated during WM-related task-demands. As a consequence, reduced WM functioning may result from this decreased network

segregation and/or reduced network integrity due to a loss of effective neural communication. Such a decrease in functional specificity of multiple brain systems has previously been shown to have a negative impact on WM functioning (Chan et al., 2014a, 2017; Goh, 2011). These assumptions are based on graph-theoretical analyses of major RSNs demonstrating that aging is concomitant with a loss in distinctiveness of functionally specific networks (Geerligs et al., 2015) and decline in episodic memory performance (Chan et al., 2014a). In response to detrimental neuro-functional changes with age such as less segregated networks, older adults may also show compensatory neural reorganization to maintain cognitive functioning, including altered RSFC patterns associated with increased neural efficiency in particular systems (Cabeza et al., 2018). Concretely, we found RSFC patterns associated with high WMC for the ToM network, rather distantly related to WM but linked to higher-order social cognition, and for control networks involved in motor and somatosensory processing (Motor+SS). The association between higher WMC and significantly better predictiveness of the higher-order social-cognition network (compared to other cognitive networks) but significantly lower predictability from motor-sensory systems (Motor+PS: $\bar{r}_{old\_high}$ = -0.02, Motor+SS: $\bar{r}_{old\_high}$ = 0.31; compared to the higher predictability of motor-sensory networks in lower performers Motor+PS: $\bar{r}_{old\_low}$ = 0.28, Motor+PS: $\bar{r}_{old\_low}$ = 0.45) may be related to network configurations more responsive to neuroplastic adaptation to improve cognitive functions (Gallen et al., 2016; Iordan et al., 2018). Hence, network configurations in older adults with higher WMC may constitute a marker for compensatory re-configuration that may be relevant for (and thus, predictive of) task performance, counteracting the neuro-functional deterioration of cognitive systems in advanced age. Alternatively, this may indicate the beginning of neural-level dedifferentiation with aging, at an as-yet less pronounced stage of decline than exhibited in old adults with low WMC. In turn, RSFC patterns associated with declined WMC may indicate a marker for less efficient network configurations during WM task performance (and possibly other cognitive functions that depend on WMC) potentially due to less segregated network systems (Chan et al., 2014a; Grady, 2012) and/or altered network integrity (Varangis et al., 2019; Zonneveld et al., 2019).

Eventually, the pattern of our results suggests that normal aging is accompanied by some rather global brain reorganization, broadly affecting brain systems linked to various functions including WMC (Pläschke et al., 2017). Accordingly, brain systems involved in executive functions and other higher-order cognitive functions, as well as perceptuo-motor systems would be affected by this age-related reorganization, which seems to share some variance with normal age-related WMC decline.

## Contribution of Network Connections to Working Memory Capacity Predictability in Advanced Age

In the older group, the most consistently informative connections (i.e., used > 90% throughout all prediction models) of the WM and ToM networks may, at least in part, account for inter-individual differences in WMC**.** In particular, the connection between the left inferior frontal gyrus (p. opercularis) and the left thalamus of the WM network may plays a potential role in gating access to WM within the basal ganglia-thalamo-cortical loops (Bäckman et al., 2006; Nyberg & Eriksson, 2016; Schroll et al., 2012). Within the ToM network, the most prominent connection is located between the right superior medial gyrus / frontal pole (FP) and the left angular gyrus / temporo-parietal junction (AG/TPJ). The AG/TPJ has been associated with the retrieval of verbal material implicated in verbal WM, whereas, the FP has been associated with the planning and organization of future actions. Both regions may hence subserve cognitive processes that overlap between ToM and WM. Therefore, this connection's strength may reflect a substrate of the crucial interplay between retrieval of verbal information and the planning of task execution associated with WM tasks.

The observed key connections seem to play a relevant role in the corresponding network at rest, suggesting that older adults with low WMC (potentially related to less segregated systems/deteriorated network integrity) might recruit these networks differently in demanding task settings than do older adults with larger WMC (possibly linked to compensatory reorganizational adaptations; see S2 Figure 3, S2 Table 4 and S2 Figure SI).

## Conceptual Considerations and Outlook

Using ML in an out-of-sample prediction framework, we investigated the association between WMC and the multivariate intrinsic coupling pattern within functional brain networks and its modulation by age, which extends results of previous univariate approaches examining the relationship between cognitive decline and RSFC in advanced age (Andrews-Hanna et al., 2007; Sala-Llonch, Peña-Gómez, et al., 2012).

We would like to highlight that our predictions are based on RSFC in meta-analytically defined functional networks, which offers the key advantage of being able to relate WMC to particular well-circumscribed functional systems, allowing for a specific interpretation of functionally distinct brain network–WMC associations revealed by ML-based predictions. Remarkably, our prediction performance of about r = 0.40 in the older group based on sparse single functional networks, as opposed to whole-connectome approaches, can compete with WM performance predictions from

combined measures of structural and functional imaging (alpha span and digit backwards: r = 0.35) in a sample of 132 older adults (Y. Wang et al., 2013).

Furthermore, our observed prediction performance is quite noteworthy given the relatively small sample size in the groups and the application of a robust and rather conservative approach to testing model generalizability (viz., 250 repetitions of a 10-fold cross-validation scheme), than using the optimistic leave-one-out approach known to be prone to overfitting (Varoquaux et al., 2016). However, for the young sample we cannot exclude that the absent to low predictability might be related to the moderate sample size. Besides, it needs to be acknowledged that the meta-analytical networks were derived from imaging studies primarily done in young and middle-aged adult samples. Therefore, it is likely that networks defined from studies in older samples would reveal age-specific differences in network topology. For instance, additional regions might turn out to be implicated in altered network configurations linked to reorganizational processes in advanced age and, hence, may result in differences in brain-behavior associations between young and older adults (Burianová et al., 2013). As such, the observed age-related prediction differences may also reflect topological differences in network architecture between age groups. Nevertheless, because the meta-analyses defining the networks comprised samples with varying mean age and age range, we would argue that they reflect the normative definition of the spatial network layout, even if this means a certain bias against the average network layout that may develop in advanced age. Despite proper state-of-the-art removal of variance related to potential cofounds (Ciric et al., 2017; Pervaiz et al., 2020; Power et al., 2012; Satterthwaite et al., 2013) as well as motion-related control analyses, we cannot entirely exclude that the alteration in WMC predictability when applying GSR may in part be related to residual motion-related effects. However, the global signal may contain neural signal of interest that is unduly removed, which in turn may have contributed to reduced predictability. In line with this, recent evidence points to the need to be especially cautious with applying GSR when comparing groups with different noise characteristics, as in young versus older adults, or with varying neural network structures (Murphy & Fox, 2017).

Given that multiple functional networks were predictive of WMC and the connectome-wide network showed similar predictability, we cannot rule out that RSFC between regions distributed across the entire brain (i.e., outside our pre-defined networks) is a marker for WMC in advanced age. Support for this notion stems from data-driven whole-brain approaches, demonstrating that RSFC between regions outside the well-known attention-related network can be crucial to predict sustained-attention performance (Rosenberg et al., 2016). This may similarly apply to WMC, particularly in younger adults. Moreover, we cannot exclude that factors of non-neural origin such as physiological changes linked to aging and their impact on the hemodynamic signals (D'Esposito et al., 2003; West et

al., 2019) may have contributed to our findings. Hence, the relationship between RSFC and cognition in aging definitively demands further investigation with the aim of precise predictions on a single-subject level. One of the highlights is the use of the RVM, which offers the advantage of a better localization and interpretability of connections that mainly drove the predictions by providing considerably sparse solutions with superior generalizability (Tipping, 2001; Y. Wang et al., 2010). Therefore, a more detailed evaluation of the neural mechanisms driving the predictions can be achieved.

Compared to previous studies addressing such age-related brain-behavior relationships in a data-driven way (Charroud et al., 2016; Y. Wang et al., 2013), our approach offers the chance to improve our understanding of how and to what degree individual differences in particular cognitive functions (here: working memory) are represented and potentially implemented by particular features (here: RSFC) of a priori defined functional networks. Using meta-analytically derived functional networks in combination with performance prediction, we can evaluate whether particular features of networks known to be involved in certain cognitive functions do in fact contribute to inter-individual behavioral variation in this function, and how this is affected by age. As we have shown, individual RSFC patterns do not always translate into individual performance levels (here: WMC), and the average level of predictability per group also seems to be related to the specificity of the predictability across networks: With both overall low predictability (in young adults) and overall rather high predictability (in older adults), specificity is low, which appears like floor and ceiling effects, respectively.

Although our data and analyses do not reveal the specific mechanisms underlying the generally better WMC predictability in advanced age, the network-specific analyses allowed us to reveal that normal aging is linked to a non-specific (i.e., network-independent) pattern of RSFC–performance relationships that spans across rather distinct networks. This would not have been possible with previous approaches based on the whole-brain connectome, which even in young samples often yielded patterns of RSFC among widely distributed and (seemingly) unrelated brain regions to be predictive of a given behavioral or cognitive feature (Finn et al., 2015; Rosenberg et al., 2016). Overall, the present study may answer as many questions as it raises new ones, but we hope that this will spur future research to unravel the neural mechanisms driving these predictions and their age-related differences. We argue that our approach of combining meta-analytically defined functional networks with multivariate pattern-regression using a robust cross-validation scheme provided new insights into aging-related brain reorganization by linking WMC to brain network integrity.

## Conclusion

We investigated whether and to what degree the RSFC pattern of eight functional brain networks and a connectome-wide network predict individual WMC in young and old adults. By using ML-based regression modeling in a robust cross-validation scheme, age differences in predictability were examined. The comparison of prediction performance in young and old participants revealed differences in brain-behavior associations.

While a general unpredictability of the networks' connectivity patterns was observed in young adults, each network predicted WMC in old adults, suggesting neurobiological adaptation related to WM task demands predictable from resting-state interregional coupling. In advanced age, a similar degree of predictive power across diverse networks suggests different possibilities or combinations of neural-level reorganization such as a decreased segregation of functional networks, brain-wide alterations in network integrity, and/or compensatory connectivity changes as common factors underlying inter-individual variation in WMC. Our results, thus, offer novel insights into age-related reorganization of functional brain networks linked to low and high WMC. Finally, our study underlines the value of RSFC as a marker for individual WMC in advanced age and potentially as a source for examining neural mechanisms linked to cognitive deterioration by using ML-based prediction.

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# Supplement

**S2 Table SI**: Overview of the Meta-analytically derived Brain Networks

| Network Abbreviation | Network | Contrast | Nodes | Reference |
|---|---|---|---|---|
| **WM** | working memory | ME: n-back, sternberg, delayed matching to sample and delayed simple matching tasks | 23 | (Rottschy et al. 2012) |
| **CogAC** | cognitive action control | ME: stroop-task, spatial interference task, stop-signal task and go/no-go task | 19 | (Cieslik et al. 2015) |
| **VigAtt** | vigilant attention | ME: detection task, discrimination task | 16 | (Langner et al. 2013) |
| **ToM** | theory-of-mind cognition | theory-of-mind > non-social baseline | 15 | (Bzdok et al. 2012) |
| **SM** | semantic memory | access to word meaning > processing word structure | 23 | (Binder et al. 2009) |
| **eSAD** | extended social-affective default | regions consistently connected to multiple of default mode network ∩ social cognition or default mode network ∩ affective processes seed regions (Schilbach et al. 2012) | 12 | (Amft et al. 2015) |
| **Motor+PS** | finger tapping and prosaccade eye movements | finger tapping > baseline; excl. regions associated with visually paced finger-tapping tasks and prosaccades > baseline | 19 | (Witt et al. 2008 & Cieslik et al. 2016) |
| **Motor+SS** | finger tapping and somatosensory processing | finger tapping > baseline; excl. regions associated with visually paced finger-tapping tasks and right hand stimulation > baseline (whole-brain studies) | 20 | (Witt et al. 2008 & Lamp et al. 2019) |
| **Connectome** | connectome-wide | functional areas defined by task-based fMRI meta-analyses and the RSFC-mapping technique | 264 | (Power et al. 2011) |

ME: main effect

**S2 Table SII**: Network Coordinates and Corresponding Brain Regions

| **Working Memory (WM)** (Rottschy et al. 2012) | | | |
|---|---|---|---|
| **x** | **y** | **z** | **Macroanatomical Region** |
| -32 | 22 | -2 | L Anterior Insula |
| -48 | 10 | 26 | L Inferior Frontal Gyrus (p. Opercularis) |
| -46 | 26 | 24 | L Inferior Frontal Gyrus (p. Triangularis) |
| -38 | 50 | 10 | L Anterior Middle Frontal Gyrus |
| 36 | 22 | -6 | R Anterior Insula |
| 50 | 14 | 24 | R Inferior Frontal Gyrus (p. Triangularis) |
| 44 | 34 | 32 | R Middle Frontal Gyrus |
| 38 | 54 | 6 | R Anterior Middle Frontal Gyrus |
| 2 | 18 | 48 | L Posterior Medial Frontal |
| -28 | 0 | 56 | L Posterior Middle Frontal Gyrus |
| 30 | 2 | 56 | R Posterior Middle Frontal Gyrus |
| -42 | -42 | 46 | L Inferior Parietal Lobule/Intraparietal Sulcus |
| -34 | -52 | 48 | L Inferior Parietal Lobule/Intraparietal Sulcus |
| -24 | -66 | 54 | L Superior Parietal Lobule |
| 42 | -44 | 44 | R Inferior Parietal Lobule/Intraparietal Sulcus |
| 32 | -58 | 48 | R Angular Gyrus/Intraparietal Sulcus |
| 16 | -66 | 56 | R Superior Parietal Lobule |
| -12 | -12 | 12 | L Thalamus |
| -16 | 2 | 14 | L Nucleus Caudate |
| -16 | 0 | 2 | L Globus Pallidum |
| 12 | -10 | 10 | R Thalamus |
| -34 | -66 | -20 | L Cerebelum/Fusiform Gyrus |
| 32 | -64 | -18 | R Cerebelum/Fusiform Gyrus |

| **Cognitive Action Control (CogAC)** (Cieslik et al. 2015) | | | |
|---|---|---|---|
| **x** | **y** | **z** | **Macroanatomical Region** |
| 36 | 22 | -4 | R Anterior Insula |
| 2 | 16 | 48 | L Posterior Medial Frontal |
| 48 | 12 | 30 | R Inferior Frontal Gyrus (p. Opercularis) |
| 36 | 2 | 54 | R Middle Frontal Gyrus |
| 48 | 30 | 24 | R Inferior Frontal Gyrus (p. Triangularis) |
| -38 | -44 | 46 | L Inferior Parietal Lobule/Intraparietal Sulcus |
| -24 | -66 | 48 | L Superior Parietal Lobule |
| 40 | -46 | 46 | R Inferior Parietal Lobule/Intraparietal Sulcus |
| 60 | -44 | 24 | R Supramarginal Gyrus |
| 30 | -62 | 52 | R Superior Parietal Lobule |
| -44 | 10 | 30 | L Precentral Gyrus |
| -34 | 20 | -4 | L Anterior Insula |
| -26 | 2 | 52 | L Middle Frontal Gyrus |
| 6 | -18 | -2 | R Thalamus |
| -40 | -66 | -10 | L Inferior Occipital Gyrus |
| 48 | 19 | 6 | R Inferior Frontal Gyrus (p. Opercularis) |

| | | | |
|---|---|---|---|
| 8 | 29 | 30 | R Midcingulate Cortex |
| -45 | 27 | 30 | L Inferior Frontal Gyrus (p. Triangularis) |
| 11 | 7 | 7 | R Nucleus Caudate |

**Vigilant Attention (VigAtt)**
(Langner et al. 2013)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| -2 | 8 | 50 | L/R Anterior Paracentral Lobule |
| 8 | 32 | 46 | R Superior Medial Gyrus |
| 0 | 26 | 34 | L Midcingulate Cortex |
| 50 | 8 | 32 | R Precentral Gyrus |
| 40 | 22 | -4 | R Anterior Insula |
| 46 | 36 | 20 | R Anterior Middle Frontal Gyrus |
| -40 | -12 | 60 | L Precentral Gyrus |
| -46 | -68 | -6 | L Inferior Occipital Gyrus |
| -48 | 8 | 30 | L Precentral Gyrus |
| 62 | -38 | 17 | R Inferior Parietal Lobule |
| 8 | -12 | 6 | R Thalamus |
| 32 | -90 | 4 | R Middle Occipital Gyrus |
| -42 | 12 | -2 | L Anterior Insula |
| -10 | -14 | 6 | L Thalamus |
| 6 | -58 | -18 | Cerebellar Vermis |
| 44 | -44 | 46 | R Inferior Parietal Lobule |

**Theory-of-Mind Cognition (ToM)**
(Bzdok et al. 2012)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| 0 | 52 | -12 | R Mid Orbital Gyrus |
| 2 | 58 | 12 | R Superior Medial Gyrus |
| -8 | 56 | 30 | L Superior Medial Gyrus |
| 2 | -56 | 30 | L Precuneus |
| 56 | -50 | 18 | R Superior Temporal Gyrus |
| -48 | -56 | 24 | L Angular Gyrus |
| 54 | -2 | -20 | R Anterior Middle Temporal Gyrus |
| -54 | -2 | -24 | L Anterior Middle Temporal Gyrus |
| 52 | -18 | -12 | R Middle Temporal Gyrus |
| -54 | -28 | -4 | L Middle Temporal Gyrus |
| 50 | -34 | 0 | R Posterior Superior Temporal Sulcus |
| -58 | -44 | 4 | L Posterior Superior Temporal Sulcus |
| 54 | 28 | 6 | R Inferior Frontal Gyrus (p. Triangularis) |
| -48 | 30 | -12 | L Inferior Frontal Gyrus (p. Orbitalis) |
| 48 | -72 | 8 | R Occipital Lobe (V5/MT) |

**Semantic Memory (SM)**
(Binder et al. 2009)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| -46 | -69 | 28 | L Angular Gyrus |
| -50 | -56 | 31 | L Angular Gyrus |
| -64 | -44 | -4 | L Posterior Middle Temporal Gyrus |
| -47 | -24 | -17 | L Middle Temporal Gyrus |
| -40 | -12 | -30 | L Inferior Temporal Gyrus |
| -8 | -57 | 17 | L Precuneus |
| -20 | 36 | 44 | L Superior Frontal Gyrus |
| -53 | 27 | -4 | L Inferior Frontal Gyrus (p. Orbitalis) |
| 54 | -59 | 30 | R Angular Gyrus |
| 43 | -72 | 31 | R Middle Occipital Gyrus |
| -1 | 51 | -7 | L Mid Orbital Gyrus |
| -5 | 56 | 24 | L Superior Medial Gyrus |
| -31 | -34 | -16 | L Fusiform Gyrus |
| -8 | 29 | -10 | L Anterior Cingulate Cortex |
| -46 | 25 | 23 | L Inferior Frontal Gyrus (p. Triangularis) |
| 64 | -41 | -2 | R Posterior Middle Temporal Gyrus |
| -43 | -53 | 55 | L Inferior Parietal Lobule |
| -1 | -18 | 40 | L Midcingulate Cortex |
| -2 | -56 | 46 | L Precuneus |
| 51 | 20 | 26 | R Inferior Frontal Gyrus (p. Triangularis) |
| 64 | -38 | 32 | R Supramarginal Gyrus |
| -23 | 26 | -16 | L Inferior Frontal Gyrus (p. Orbitalis) |
| -5 | -39 | 40 | L Midcingulate Cortex |

**Extended Social-Affective Default (eSAD)**
(Amft et al. 2015)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| 0 | 38 | 10 | Anterior Cingulate Cortex |
| -24 | -10 | -20 | L Hippocampus/Amygdala |
| 24 | -8 | -22 | R Hippocampus/Amygdala |
| -2 | -52 | 26 | L Posterior Cingulate Cortex/Precuneus |
| -2 | 32 | -8 | L Subgenual Cingulate Cortex |
| -46 | -66 | 18 | L Posterior Middle Temporal Gyrus |
| 50 | -60 | 18 | R Posterior Middle Temporal Gyrus |
| -2 | 52 | 14 | L Superior Medial Gyrus |
| -6 | 10 | -8 | L Caudate Nucleus |
| 6 | 10 | -8 | R Caudate Nucleus |
| -2 | 50 | -10 | L Mid Orbital Gyrus |
| -54 | -10 | -20 | L Anterior Middle Temporal Gyrus |

**Motor + Prosaccades (Motor+PS)**
(Witt et al. 2008; Cieslik et al. 2016)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| -39 | -21 | 54 | L Postcentral Gyrus |
| 41 | -16 | 57 | R Precentral Gyrus |
| -3 | -2 | 54 | L Posterior Medial Frontal |
| -57 | 2 | 32 | L Precentral Gyrus |
| -53 | -24 | 21 | L Supramarginal Gyrus |
| -23 | -7 | 1 | L Globus Pallidum |
| 25 | -8 | 3 | R Globus Pallidum |
| -22 | -52 | 26 | L Cerebellum |
| 18 | -54 | -22 | R Cerebellum |
| 4 | 6 | 62 | R Posterior Medial Frontal |
| -2 | 8 | 58 | L Posterior Medial Frontal |
| -40 | -2 | 50 | L Precentral Gyrus |
| -16 | -68 | 62 | L Precuneus |
| -30 | -56 | 56 | L Superior Parietal Lobule |
| 24 | -62 | 56 | R Superior Parietal Lobule |
| 44 | 4 | 50 | R Precentral Gyrus |
| -10 | -16 | 6 | L Thalamus |
| 32 | -52 | 48 | R Inferior Parietal Lobule |
| 43 | -39 | 49 | R Inferior Parietal Lobule |

**Motor + Somatosensory (Motor+SS)**
(Witt et al. 2008; Lamp et al. 2019)

| x | y | z | Macroanatomical Region |
|---|---|---|---|
| -39 | -21 | 54 | L Postcentral Gyrus |
| 41 | -16 | 57 | R Precentral Gyrus |
| -3 | -2 | 54 | L Posterior Medial Frontal |
| -57 | 2 | 32 | L Precentral Gyrus |
| -53 | -24 | 21 | L Supramarginal Gyrus |
| 45 | -38 | 48 | R Inferior Parietal Lobule |
| -23 | -7 | 1 | L Globus Pallidum |
| 25 | -8 | 3 | R Globus Pallidum |
| -22 | -52 | 26 | L Cerebellum |
| 18 | -54 | -22 | R Cerebellum |
| -48 | -20 | 20 | L Rolandic Operculum |
| -54 | -20 | 48 | L Postcentral Gyrus |
| -44 | -26 | 58 | L Postcentral Gyrus |
| -38 | -12 | 4 | L Insula Lobe |
| -40 | 4 | 10 | L Insula Lobe |
| 56 | -22 | 20 | R Rolandic Operculum |
| 56 | -34 | 18 | R Superior Temporal Gyrus |
| 56 | -38 | 28 | R Supramarginal Gyrus |
| 60 | -20 | 32 | R Postcentral Gyrus |
| -4 | 14 | 36 | L Midcingulate Cortex |

R= right; L = left; for consistency, coordinates (MNI-space) are assigned to the most probable brain areas as revealed by the SPM Anatomy Toolbox ( Version 2.1; Eickhoff, Heim, Zilles, & Amunts, 2006; Eickhoff et al., 2007, 2005).

For the Connectome-wide Network (Connectome) please see Power et al. 2011 Supplementary Material Table S02.

**Supplementary Method Section to 2.4 RVM Features and Prediction**

To further elucidate whether motion-related effects may contribute to WMC predictability, DVARS was added as a predictor to the network connectivity matrices before running RVM predictions. This allowed us to investigate whether RVM performance would increase overall and whether DVARS would receive more than 90% non-zero weights over the total of 2500 predictive models calculated, that is, whether it would be considered a frequently used, and thus, particularly relevant feature.

**S2 Table SIII**: Pearson Correlations among Working Memory Capacity Subscores

| | All | Young | Old |
|---|---|---|---|
| **CorsiF - CWMspan** | 0.39*/0.32* | 0.13 | 0.54* |
| **CorsiR - CWMspan** | 0.36*/0.29* | 0.02 | 0.43* |
| **CorsiF - CorsiR** | 0.54*/0.43* | 0.45* | 0.37* |

*Note.* For the full sample (All), zero-order (without controlling for age)/partial (controlling for age) correlations are reported.

CWMspan, complex verbal working memory span: reading span + operation span; CorsiF, visuo-spatial working memory forward span: Corsi block-tapping forward; CorsiR, visuo-spatial working memory reverse span: Corsi block-tapping reverse.

* significant at $p_{corr} < 0.05$

**S2 Table SIV**: Statistics on the Predictability of Working Memory Capacity from Network-based Resting-state Functional Connectivity

| Network / Sample | Mean Difference | *t* |
|---|---|---|
| **WM** | | |
| young | 0.17 | 25.77* |
| old | 0.35 | 52.47* |
| **CogAC** | | |
| young | 0.01 | 0.95 |
| old | 0.37 | 55.12* |
| **VigAtt** | | |
| young | -0.06 | -9.89* |
| old | 0.33 | 44.52* |
| **ToM** | | |
| young | 0.03 | 4.79* |
| old | 0.52 | 89.18* |

| | | |
|---|---|---|
| **SM** | | |
| young | 0.16 | 24.65* |
| old | 0.43 | 62.53* |
| **eSAD** | | |
| young | -0.05 | -8.32* |
| old | 0.45 | 79.72* |
| **Motor+PS** | | |
| young | 0.16 | 24.87* |
| old | 0.24 | 30.40* |
| **Motor+SS** | | |
| young | 0.12 | 19.18* |
| old | 0.52 | 79.06* |
| **Connectome** | | |
| young | 0.16 | 26.13* |
| old | 0.42 | 59.45 |

One-sample t-tests on prediction accuracies (r) different from a zero mean across all 250 cross-validation repeats of the relevance vector machine; *t** significant at threshold $p < 0.001$.

**S2 Table SV**: Statistics on Prediction Accuracy Differences between Networks in the Old Sample

| Networks | | WM | CogAC | VigAtt | ToM | SM | eSAD | Motor +PS | Motor +SS | Connectome |
|---|---|---|---|---|---|---|---|---|---|---|
| | r | 0.35 | 0.37 | 0.33 | 0.52 | 0.43 | 0.45 | 0.24 | 0.52 | 0.42 |
| | | Cohen's q effect sizes | | | | | | | | |
| **WM** | | | 0.02 | 0.02 | **0.21** | 0.09 | **0.12** | **0.12** | **0.21** | 0.08 |
| **CogAC** | | -3.18 | | 0.05 | **0.19** | 0.07 | **0.10** | **0.14** | **0.19** | 0.06 |
| **VigAtt** | | 2.63 | 5.54* | | **0.23** | **0.12** | **0.14** | **0.10** | **0.23** | **0.11** |
| **ToM** | | **-21.39*** | **-19.53*** | **-24.81*** | | **0.12** | 0.09 | **0.33** | 0 | **0.13** |
| **SM** | | -10.69* | -7.31* | **-13.14*** | **13.05*** | | 0.03 | **0.22** | **0.12** | 0.01 |
| **eSAD** | | **-12.57*** | **-9.64*** | **-14.81** | 10.33* | -2.57 | | **0.24** | 0.09 | 0.04 |
| **Motor +PS** | | **13.68*** | **15.72*** | **10.69*** | **34.79*** | **22.68** | **24.03*** | | **0.33** | **0.20** |
| **Motor +SS** | | **-21.40*** | **-18.79*** | **-22.59*** | 0.99 | **-11.52*** | -8.38* | **-32.67*** | | **0.13** |
| **Connectome** | | -9.97* | -6.28* | **-11.85** | **12.86*** | 0.88 | 3.28 | **-22.06*** | **12.76*** | |
| | | ***t*** | | | | | | | | |

r: Pearson correlations between real and predicted working memory capacity (WMC) scores. Cohen's *q:* effect size of differences in correlations between networks (<.1: no effect; 0.1 - 0.3: small effect; 0.3 - 0.5: medium effect; >0.5: large effect). In red are highlighted small and medium effect sizes. *t** significant at threshold $p < 0.001$.

**S2 Table SVI**: Predictability of Individual Working Memory Capacity based on Functional Connectivity in Nine Brain Networks – Censoring

| | Networks | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **WM** | **CogAC** | **VigAtt** | **ToM** | **SM** | **eSAD** | **Motor+PS** | **Motor+SS** | **Connectome** |
| $\bar{r}_{young}$ | 0.17 | -0.02 | -0.10 | 0.02 | 0.16 | -0.06 | 0.16 | 0.13 | 0.17 |
| $\bar{r}_{old}$ | 0.37* | 0.38* | 0.33* | 0.54* | 0.44* | 0.43* | 0.24* | 0.47* | 0.41* |

Pearson correlations between real and predicted working memory capacity (WMC) scores in the young ($\bar{r}_{young}$) and old ($\bar{r}_{old}$) sample. * significant ($p < 0.001$) predictions with at least medium effect size ($\bar{r} \geq 0.24$, corresponding to Cohen's d ≥ 0.5).

**S2 Table SVII**: Predictability of Individual Working Memory Capacity based on Functional Connectivity in Nine Brain Networks – DVARS as a Predictor

| | Networks | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **WM** | **CogAC** | **VigAtt** | **ToM** | **SM** | **eSAD** | **Motor+PS** | **Motor+SS** | **Connectome** |
| $\bar{r}_{young}$ | 0.40 | 0.08 | -0.05 | 0.10 | 0.36 | -0.04 | 0.34 | 0.25 | 0.41 |
| $\bar{r}_{old}$ | 0.32* | 0.35* | 0.29* | 0.54* | 0.42* | 0.45* | 0.17* | 0.55* | 0.43* |

Pearson correlations between real and predicted working memory capacity (WMC) scores in the young ($\bar{r}_{young}$) and old ($\bar{r}_{old}$) sample. * significant ($p < 0.001$) predictions with at least medium effect size ($\bar{r} \geq 0.24$, corresponding to Cohen's d ≥ 0.5). DVARS was not among the most frequently used connection in any of the networks.

**S2 Table SVIII**: Predictability of Individual Working Memory Capacity based on Inter-network Functional Connectivity

| | Networks | | | | |
|---|---|---|---|---|---|
| | **WM+ CogAC** | **WM+VigAtt** | **WM+ToM** | **WM+SM** | **WM+eSAD** |
| $\bar{r}_{young}$ | 0.13 | 0.08 | 0.07 | 0.10 | 0.06 |
| $\bar{r}_{old}$ | 0.39* | 0.48* | 0.46* | 0.37* | 0.36* |

Pearson correlations between real and predicted working memory capacity (WMC) scores in the young ($\bar{r}_{young}$) and old ($\bar{r}_{old}$) sample. * significant ($p < 0.001$) predictions with at least medium effect size ($\bar{r} \geq 0.24$, corresponding to Cohen's d ≥ 0.5). All networks showed significant group differences between young and old sample ($p < 0.001$).

**S2 Table SIX**: Differences between Young and Old in the Predictability of Working Memory Capacity from Network-based Resting-state Functional Connectivity

| **Network** | **Mean Difference** | ***t*** |
|---|---|---|
| **WM** | -0.18 | -19.12* |
| **CogAC** | -0.36 | -38.58* |
| **VigAtt** | -0.39 | -40.01* |
| **ToM** | -0.49 | -59.13* |
| **SM** | -0.27 | -29.49* |

| | | |
|---|---|---|
| **eSAD** | -0.50 | -61.86* |
| **Motor+PS** | -0.08 | -7.46* |
| **Motor+SS** | -0.40 | -45.29* |
| **Connectome** | -0.26 | -27.36* |

Independent sample t-tests on prediction accuracies (r) across the 250 cross-validation repeats of the relevance vector machine; *t** significant at threshold $p < 0.001$.

**S2 Table SX**: Predictability of Individual Working Memory Capacity based on Inter-network Functional Connectivity in Older Adults with Low and High Working Memory Capacity

| | **Networks** | | | | |
|---|---|---|---|---|---|
| | **WM+ CogAC** | **WM+VigAtt** | **WM+ToM** | **WM+SM** | **WM+eSAD** |
| $\bar{r}_{old\_low}$ (n = 24) | 0.33* | 0.38* | 0.33* | 0.34* | 0.30* |
| $\bar{r}_{old\_high}$ (n = 21) | 0.16 | 0.30* | 0.26* | 0.16 | 0.13 |
| Cohen's *q* | 0.14 | 0.04 | 0.12 | 0.13 | 0.09 |

Pearson correlations between real and predicted working memory capacity (WMC) scores in the old sample with low ($\bar{r}_{old\_low}$) and high ($\bar{r}_{old\_high}$) WMC. Cohen's *q:* effect size of differences in correlations between networks in low- and high-WMC older adults (<.1: no effect; 0.1 - 0.3: small effect; 0.3 - 0.5: medium effect; >0.5: large effect).

* significant ($p < 0.001$) predictions with at least medium effect size ($\bar{r} \geq 0.24$, corresponding to Cohen's d ≥ 0.5). All networks showed significant group differences between low- and high-WMC older adults ($p < 0.001$).

**S2 Table SXI**: Statistics on the Predictability of Working Memory Capacity from Network-based Resting-state Functional Connectivity in Older Adults with Low and High Working Memory Capacity

| **Network / Sample** | **Mean Difference** | ***t*** |
|---|---|---|
| **WM** | | |
| Low WMC | 0.33 | 35.56* |
| High WMC | 0.08 | 7.34* |
| **CogAC** | | |
| Low WMC | 0.34 | 35.34* |
| High WMC | 0.12 | 11.25* |
| **VigAtt** | | |
| Low WMC | 0.25 | 26.25* |
| High WMC | 0.23 | 19.03* |
| **ToM** | | |

| | | |
|---|---|---|
| Low WMC | 0.37 | 43.10* |
| High WMC | 0.33 | 29.17* |
| **SM** | | |
| Low WMC | 0.41 | 41.52* |
| High WMC | 0.21 | 20.83* |
| **eSAD** | | |
| Low WMC | 0.42 | 55.75* |
| High WMC | 0.18 | 17.60* |
| **Motor+PS** | | |
| Low WMC | 0.28 | 24.33* |
| High WMC | -0.02 | -1.56 |
| **Motor+SS** | | |
| Low WMC | 0.45 | 49.31* |
| High WMC | 0.31 | 25.79* |
| **Connectome** | | |
| Low WMC | 0.35 | 32.83* |
| High WMC | 0.26 | 24.07* |

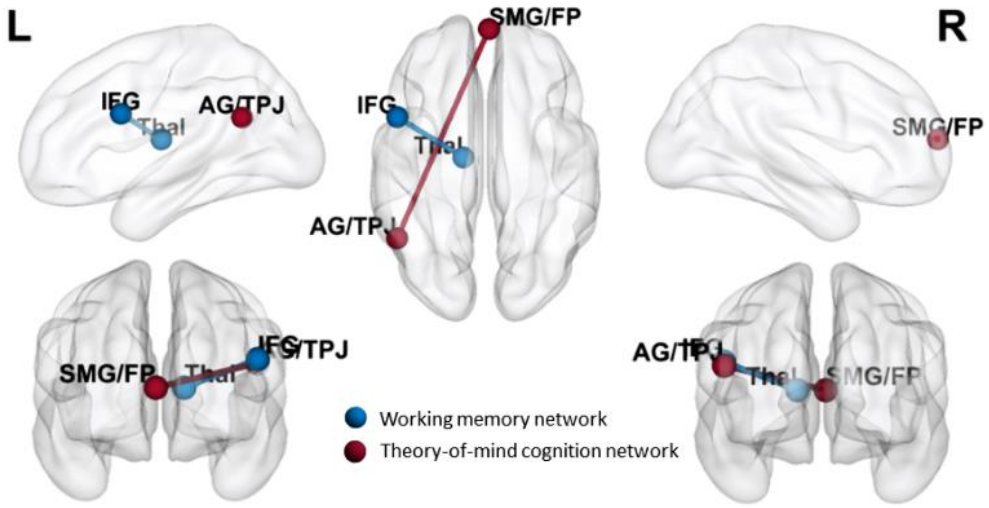
One-sample t-tests on prediction accuracies (r) different from a zero mean across all 250 cross-validation repeats of the relevance vector machine; *t** significant at threshold $p < 0.001$.

**S2 Table SXII**: Differences between Older Adults with Low and High Working Memory Capacity in the Predictability of Working Memory Capacity from Network-based Resting-state Functional Connectivity

| Network | Mean Difference | *t* |
|---|---|---|
| **WM** | -0.25 | -17.51* |
| **CogAC** | -0.22 | -14.72* |
| **VigAtt** | -0.02 | -1.65 |
| **ToM** | -0.04 | -2.65* |
| **SM** | -0.20 | -13.73* |
| **eSAD** | -0.24 | -18.87* |
| **Motor+PS** | -0.30 | -19.63* |
| **Motor+SS** | -0.14 | -9.35* |

| | | |
|---|---|---|
| **Connectome** | -0,09 | -5.40* |

Independent sample t-tests on prediction accuracies (r) across the 250 cross-validation repeats of the relevance vector machine; *t** significant at threshold $p < 0.001$.




**S2 Figures SI**: Illustration of most Frequently used Connections within the Working Memory and Theory-of-Mind Cognition Networks

Most frequently used connections in at least 90% of the total 2500 predictive models between regions within the working memory (WM) and theory-of-mind cognition (ToM) networks for the prediction of working memory capacity (WMC) in the old sample.

WM network: IFG, left Inferior Frontal Gyrus (p. Opercularis); Thal, left Thalamus.

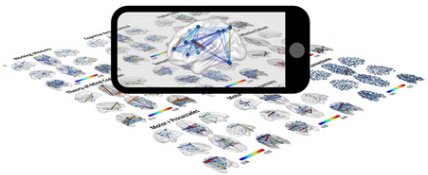
ToM network: SMG/FP, right Superior Medial Gyrus / Frontal Pole; AG/TPJ, left Angular Gyrus / Temporo-Parietal Junction

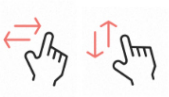
**Information on the Augmented Reality App Support**

- The app to support Figure 6 with augmented reality (AR) can be downloaded (under https://osf.io/wru83/) or via the QR-code and installed
- When opening the app, please confirm the camera access so that the AR result brains can be displayed

**Aim with the camera at Fig. 6**

**Touch the brain and drag to move it**





**Scroll with one finger horizontally/ vertically outside the brain to rotate it**
(in order to rotate the brain on different axes, use both phone screen orientations, portrait and landscape screen)

**Pinch with two fingers the brain to zoom in and out**

**With the AR app user interface at the bottom, you can switch between different results of the five main networks by tapping on the respective network abbreviations.**

The result brains as 3D models, using the BrainMesh_ICBM152_smoothed template, were exported from Matlab/BrainNet Viewer to VRML-file format. The VRML-to-OBJ-file conversion was done via the CAD Exchanger and the AR-App development with Unity3D/Vuforia.

# 4 GENERAL DISCUSSION

## 4.1 Results Summary

By applying ML algorithms, these two studies investigated the potential to associate RSFC patterns within meta-analytically defined functional brain networks with different phenotypic conditions. In study 1, pattern-classification was applied to disease and developmental conditions, and in study 2, pattern-regression was employed to cognitive performance in young and old adults. Both studies assessed the potential to make predictions from functional brain networks for individual subjects upon their clinical and developmental condition as well as cognitive capacity. With regards to the central research questions, study 1 revealed that patients with SCZ or PD were disease-specifically well classified based on different functional networks that resonate well with established impairments in these conditions. The most discriminating networks for SCZ, but not PD, were the reward processing and social-affective networks, whereas for PD, but not SCZ, the networks subserving memory, motor execution, and higher-order cognition, showed the highest accuracies. In turn, age discrimination was excellent based on all functional networks and outperformed classifications in both clinical conditions. Study 2 demonstrated that within-network functional coupling during task-free states is associated with individuals' WMC in older but not in young adults. Particularly, the WMC score of an older adult was successfully predicted from the RSFC patterns pertaining to the WM network, WM-related networks associated with executive functions and higher-order-cognition, and a task-negative network as well as WM-unrelated motor-sensory systems. Moreover, it was found that predictability differed between older adults with high versus low WMC. A similar degree of predictability across functionally different networks is associated with low WMC performance. Linking the results of both studies for NA demonstrates that the connectivity pattern of the WM network is not only informative when it comes to the distinction between young from older adults. The WM connectivity pattern also contains age-related information on individual WM performance that is not exclusively linked to the WM network but rather is extractable from a broader range of different networks. Together, the studies reinforce the notion that in SCZ and PD, networks are more disease-specifically altered, whereas NA is associated with alterations affecting a broad range of mental systems. Furthermore, these results support a connection to age-related reorganization linked to neural-level decreased segregation of functional brain networks, deterioration of network integrity within different networks, and/or compensation by reorganization as factors that may drive associations between connectivity patterns in functionally distinct networks and WMC in advanced age.

## 4.2 Contribution of Machine Learning Approaches to the Understanding of Brain-Behavior Relationships

### 4.2.1 Machine Learning Compared to Classical Statistical Approaches

The two studies underline the potential of ML algorithms as a novel approach to address classical questions of brain-behavior relationships, which have been mostly investigated with traditional univariate methods in the previous SCZ, PD, and NA literature. Traditional approaches primarily reveal isolated alteration in single connections associated with phenotypical conditions yielding a rather mechanistically understanding of the pathophysiology. Such an obtained neurobiological insight commonly relies on within-sample group-aggregates across subjects pertaining to a disorder or developmental condition to their general population inference of the established relationship. Hence, traditional approaches rarely validate out-of-sample predictions that is whether a significant relationship between isolated alterations in single connectivities and phenotypic conditions still holds in unseen single-subjects who have not been included in fitting the model (Bzdok, 2017; Dubois & Adolphs, 2016; Orrù et al., 2012). In contrast, by applying ML, both thesis studies demonstrated that the multivariate network patterns of an individual can be associated with disease and developmental conditions as well as cognitive performance and allow for out-of-sample generalization to the individual case through successful predictions based on unseen single-subjects.

The ultimate goal, at least for clinical practice, is to use neuroimaging data (brain scans) for automated decision-making on the level of individuals for diagnostic and prognostic purposes. Therefore, the majority of ML studies have been applied to achieve the best possible accuracies necessary for a transition into clinical practice and personalized medicine (Arbabshirani et al., 2017; Orrù et al., 2012). This application aim often goes along with a rather subordinate demand to gain an understanding of disease mechanisms (Bzdok & Ioannidis, 2019). Instead, and in alignment with the rationale, both studies showed that applying ML to primarily approach rather classical questions on the associations between intrinsic functional networks and disease, or developmental conditions provides valuable insights into altered network patterns. ML, therefore, provides a powerful tool to ascertain brain-behavior relationships in individual subjects and may be positioned between classical neuroimaging studies reporting group-level characteristics and those ML studies aiming at identifying the most reliable markers for diagnoses and prognoses in clinical applications (Fisher et al., 2018). Together, the study results show that the application of ML reveals an association between functional network patterns and different phenotypes, providing pathophysiological understanding on a broader system level of the entire network pattern with relevance on the single-subject level. Hence, ML applications to classical questions can provide insight into generally valid associations (without any

cause-and-effect link) in brain-behavior relationships of disease and developmental conditions. As the results are valid in an idiographic perspective, this type of ML studies, between traditional approaches and diagnosis and prognosis clinical applications, may also offer valuable knowledge for personalized medicine, targeting functional network-based therapeutic interventions, as discussed below.

### 4.2.2 Functional Specificity

The thesis examined brain-behavioral associations with a new combination of different methodological approaches that offered functional specificity in the interpretation of results. In studies 1 and 2, disease and aging as well as age-related cognitive decline was related to alterations in different well-circumscribed functional brain systems.

Meta-analytical networks, chosen in a hypothesis-driven manner based on previous literature on regional activation changes in the examined conditions, provide a functionally meaningful sparse feature space, as compared to the complexity and functional non-specificity of whole-brain imaging data. The applied approach contrasts with often-used feature selection methods, e.g., based on the importance of features for the classification task via t-tests or dimensionality reduction methods, such as principal component analyses. However, the results in the first case are often isolated connections representing the most discriminant features linked to the target phenotype and rarely form coherent functional brain systems, or in the latter case, show no obvious relation to the disease and developmental conditions (Khosla et al., 2019). Nevertheless, prediction accuracies of such studies are similarly good as in the thesis studies (Arbabshirani et al., 2017), however, resulted in a lack to connect findings with meaningful functionally defined networks.

The classification and continuous prediction results of both studies likewise showed that a meaningfully reduced feature space could be utilized in combination with state-of-the-art ML to deliver differential effects within and between groups. Moreover, results yielded increased functional specificity of brain-behavior relationship with superior interpretability compared to ML studies on whole-brain data (Y. Chen et al., 2015; Tang et al., 2012) or RSN based on data-driven approaches (Cole et al., 2010; Poldrack, 2011). Therefore, the studies allowed the interpretation of the prediction accuracies based on well-defined functional systems in relation to behavior, brain disorders, and developmental states. Especially when the ML-based research is directed towards a better understanding of deviant conditions, it is crucial to also pay attention to the feature space and the associated interpretation possibilities. In comparison, in ML-studies for clinical application, researchers are more concerned with achieving the highest possible sensitivity and specificity in detecting a disease versus, e.g., no disease or predicting behavioral measures. Thus, it is not necessarily important which mechanisms are the underlying drivers and whether they produce interpretable neurobiological

findings (Bzdok & Ioannidis, 2019; Scheinost et al., 2019). Together, the studies showed that meta-analytical networks as a priori feature selection is a powerful reduction approach for high-dimensional neuroimaging data to enable effective phenotypic classifications and predictions. Moreover, this feature selection offers increased interpretability at the level of well-defined functional brain networks.

### 4.2.3 Resting-state fMRI and the Potential of Multi-modal Approaches

Both studies used meta-analytical networks derived from task-based fMRI assessed via RSFC. To some extent, this approach linked different brain organizational principals measured via two modalities insofar that RSFC is assessed while at the same time the meta-analytical network configuration incorporates reliable knowledge about the localization of brain activity linked to specific mental processes. This combined setup allows speculating about the notion that altered RSFC pattern might also be associated with altered network recruitment during task-demands. Such a probable relationship, although not directly investigated, seems plausible given that this agrees well with previous task-based studies on diverse altered activation in functional network findings which both studies are based on.

The prediction performance in both studies range between moderate (for some network-based classifications of SCZ and PD, as well as WMC predictions) to excellent (for a range of networks in young-old classifications). This can be considered as quite remarkable given that the predictions are based on only a single modality (i.e., FC at rest). Nevertheless, it is equally evident that an individual modality is likely insufficient to elucidate the whole complexity of brain-behavior relationships (Eickhoff & Grefkes, 2011). Therefore, one should not neglect the importance of leveraging different cross-information of brain structural and functional neuroimaging measures by using multi-modal approaches (including, e.g., gray-matter density and white-matter connectivity) to assess clinical and developmental conditions as well as cognitive performance (Sui et al., 2012; Y. Wang et al., 2013). Yet, studies demonstrated successfully that the ML approach is suitable to combine features of multiple imaging modalities, resulting in predictive capacities mostly exceeding those compared to a single modality (Meng et al., 2017; Sui et al., 2013; Y. Wang et al., 2013; Wee et al., 2012). Hence, a multi-modal fusion of neuroimaging data for ML applications may provide additional valuable insights into brain-behavior relationships that are not attainable from only studying intrinsic connectivity. To apply a multi-modal approach for the two studies would have been an alternative. For instance, this could have resulted in increased sensitivity to more effectively discriminate disease-specific profiles of networks that yielded similar classification accuracy for SCZ and PD. To gain a potential enhanced distinction in disease profiles would indicate abnormalities only detectable in specific modalities other

than RSFC. Furthermore, the possibility of a more distinct classification pattern of different networks in NA as well as an association between networks and cognitive capacity, might be detectable from joint brain organizational information provided by multiple modalities. However, a multi-modal approach was not performed since the aim was to evaluate in an initial step whether ML can be applied to examine classical brain-behavior relationships. Nevertheless, future studies that address such questions from multi-modal ML-based predictions may add important knowledge.

## 4.3 Insights into Disease and Developmental Conditions from Machine Learning Approaches

With an as-yet unique methodological combination, both studies provided evidence for meaningful multivariate patterns within functional brain networks at rest related to disease-specific and developmental conditions as well as inter-individual differences in cognitive performance that enables the characterization at the level of individuals. The manifestation of disease characteristics in patterns of affected brain networks revealed a heterogeneous profile among and across clinical populations as indicated by the distinct classification performance of networks pertaining to functions known to be affected by SCZ and PD, respectively. In turn, age-related changes represented a more homogeneous profile across both studies as all networks are similarly accurate in distinguishing young from old adults. In line with this result, most networks are similarly predictive for inter-individual differences in older adults with low cognitive performance. ML approaches, in this regard, allow for obtaining knowledge on networks in their ability to characterize a mental condition and the reorganization processes of networks linked to declined cognitive performance. Hence, the novel neuro-functional insight gained is the degree of predictive power in functional networks that relate to differential neurobiological disturbances in the features of network connectivity of an individual compared to the classical discovery of affected single connectivities at the group level.

Depicted in a lifespan perspective, considering the distinct disease onsets of SCZ (‘‘early’’) and PD (‘‘late’’) and both diseases opposing the normal course of aging, the classification study illustrates how network systems are differently affected across life, depending on these diseases and developmental conditions. The commonality of altered dopamine systems between the three conditions was mirrored in the networks that best classified either condition. In particular, networks that are substantially modulated via dopaminergic transmission, such as the reward (SCZ, NA) and the motor execution (PD) networks. Altered social-affective networks in SCZ suggest a relationship to dysfunctional developmental processes as empathy, emotion processing, and emotion regulation develop rather early in childhood and during adolescence (Decety, 2010; Herba et al., 2006; albeit the evolvement and

adaptations continues throughout life). The emotion regulation and its intersection with executive functions, on the other hand, may link to cognitive deficits due to accelerated neurodegeneration and/or aberrant neurodevelopmental processes of cognitive decline in SCZ (Duggirala et al., 2020; Perlman & Pelphrey, 2010; Pino et al., 2014). In contrast, for PD dysfunctional memory and social/higher-order cognition networks as well as the fact that networks are rather selectively affected, may indicate accelerated neurodegeneration in later stages of life (compared to SCZ and NA around a similar age range). This accelerated process seems to be primarily related to the deterioration of cognitive functions (Aarsland et al., 2017). In particular, dysfunctional theory-of-mind cognition has been linked to deficits in cognitive control in PD (Foley et al., 2019). For aging, the findings of both studies show a rather diffuse picture of deteriorations affecting a broader range of networks and associated mental functions to a similar degree and which are rather linked to reduced cognitive performance. This may reflect possible continuous alterations of global neural-level reorganization (compared to more selective accelerated network changes in PD) that manifests in the integrities of networks and a decrease of more general cognitive processes such as various executive functions and information processing (Brown et al., 2012; Guest et al., 2015; Salthouse et al., 2003). Ultimately, such alterations affect a wide range of behavior at the intersection with these cognitive processes, including lower- and higher-order cognition in NA (Diamond, 2013; Mutter et al., 2006; Salthouse, 1991, 1996; Unsworth et al., 2014). Overall, the application of ML in a comparative manner between SCZ, PD, and NA, revealed insights at the level of disturbed network patterns of individual subjects that link to shared neurobiological commonalities but also phenotypical differences of these conditions. Particularly, they link to commonalities in dopamine alterations and different neural-processes across the life span, such as neurodevelopment, accelerated and NA-related neurodegeneration.

### 4.3.1 Schizophrenia and Parkinson's Disease

When comparing SCZ and PD, study 1 provided evidence for disease-specific disturbed RSFC patterns in task-unconstrained conditions within networks known for dysfunctional recruitment under task demands. The findings imply that based on easily accessible RS-fMRI scans of a single-subject, extracted FC provides a potential marker with discriminative qualities for different neurodegenerative and psychiatric disease conditions associated with disease-specific networks. Together with the advantages of RS-fMRI in clinical populations, the simplicity of acquisition (Fox & Greicius, 2010), several consensuses with insights from task-based fMRI (New et al., 2015; Schilbach et al., 2016; Smith et al., 2009) and ample information regarding individual clinical characteristics (Hou et al., 2016; W. H. Lee et al., 2018; Vaidya & Gordon, 2013), it might be argued that RS-fMRI serves as a pivotal source to elucidate clinical conditions. Thus, these findings support the notion that the acquisition of large

amounts of clinical data can be utilized to develop reliable and valid ML-based models as tools to serve a better understanding of these diseases and to aid in clinical routine.

The demonstration that disease-related network patterns exist, indicating a deviant recruitment of respective neural-circuits, could offer a source to elucidate disease-pattern-mechanisms that manifest at the level of the holistic configuration within network systems. It would be obvious that diseases have specifically disturbed network patterns (even if the classification performance of a particular network is similar across diseases) that indicate, e.g., specific dysfunctional integrity or segregation within the network. However, the thesis results leave such questions unanswered as there are currently only limited suitable methods in connection with ML to detect and interpret such changes in more detail at the system network level (Holzinger et al., 2019; Kohoutová et al., 2020). Efforts to develop such methods could, though, offer insights into diseases at a novel functional level, i.e., about the specific mechanisms within the network pattern. Gaining such a functional understanding underlying the predictability of the ML models would provide knowledge on how the altered configuration pattern of the entire network operates.

Although not further investigated within the scope of the thesis, it would be obvious to assume that well-classifying networks in SCZ and PD would also contain informative patterns that at least in part allow predicting behavioral measures linked to the disease conditions. Evidence for such brain-behavior relationships stems from studies that demonstrated the prediction of schizophrenia-related positive, negative, and disorganization symptoms (W. H. Lee et al., 2018) as well as the prediction of clinical scores in PD (Hou et al., 2016) from FC at rest. Moreover, it has also been shown that network-based RSFC exhibits changes already in the prodromal stages of SCZ and PD (Rolinski et al., 2016; H. Wang et al., 2016). Thus, RSFC may constitute a relevant marker for early detection of dysfunctions related to both disorders and may also serve as a target for early interventions.

While these studies have been dedicated towards the achievement of reliable diagnostic and prognostic tools for the transition into clinical practice, the investigation of the predictive capacity in functional networks may aid to elucidate pathophysiological dysfunctions linked to clinically relevant behavior or early disease-related changes. To detect networks underlying such alterations with increased knowledge on the disturbed mechanistic of FC pattern may serve as targets for a different branch of personalized medicine that focus on therapeutic interventions. For instance, target networks for interventions such as neuromodulation, including neuropharmacology, transcranial magnetic stimulation, and neurofeedback to alter neural circuits and symptoms. (Ruiz et al., 2013; Yahata et al., 2017; Yamada et al., 2017).

### 4.3.2 Normal Aging

The studies presented in this thesis demonstrated that NA is linked to changes in neuro-behavioral patterns that allow the differentiation between young and older adults as well as the prediction of individual cognitive performance in advanced age based on diverse functional networks. Furthermore, these findings reveal that networks with high classification performance also contain behaviorally relevant information in advanced age. The similarity in which functional brain networks are informative is quite intriguing and reinforces the notion that aging affects a wide range of different brain systems that are also linked to inter-individual differences in cognitive performance. Together, the results suggest neural-level reorganization and underline the importance of RSFC as an age-related maker for cognitive deterioration. The improved understanding of neural-level RSFC reorganization lies in the level of RSFC in functional brain networks and the result of alterations across the variety of networks. These findings provide a neurobiological understanding that has not been covered yet with univariate or ML approaches. Since in previous studies on whole-brain FC or RSN alteration, findings are based on single or only a few networks examined simultaneously (Jockwitz et al., 2017; La Corte et al., 2016; Meier et al., 2012; Vergun et al., 2013).

Although the present approach provides novel insights into age-related reorganization of functional brain networks from a multivariate and individual subject perspective, several limitations certainly need to be addressed. The underlying mechanisms of brain-behavior relationships require further investigation, given the overall predictability of functional brain networks associated with advanced age. While the current findings agree well with a neuro-functional reorganization of various networks that has been proposed in the aging literature (Chan et al., 2014b; Goh, 2011; Meier et al., 2012; Sala-Llonch et al., 2015), it cannot be excluded that other age-related processes are ultimately influencing all networks and behavior. Factors of neural origin other than FC and/or non-neural origin, as outlined in the discussion of each study, may have influenced the finding. Hence, a more precise interpretation of age-related connectivity changes and reorganizational processes might only be stated once these have been contrasted simultaneously with other structural and functional brain organizational measures (Fjell & Walhovd, 2010; Hedden, 2007). Additionally, in the same study, physiological changes linked to aging need to be measured separately and disentangled from neural signals (D'Esposito et al., 2003; West et al., 2019; Wright & Wise, 2018).

Additionally, it needs to be acknowledged that meta-analytical networks are derived from imaging studies based on young adult samples. Therefore, it cannot be excluded that networks defined via advanced age samples would potentially include additional regions implicated in dedifferentiated or compensatory neural processes (i.e., incorporating altered network configurations linked to

reorganizational processes), and hence, may result in different brain-behavior associations (Burianová et al., 2013).

Moreover, for a more detailed understanding of the particular reorganizational mechanisms (dedifferentiation or compensation) underlying better or worse performance in older adults, brain-phenotype relationships need to be further disentangled. For instance, by juxtaposing the predictability in cohorts with maintained and deteriorated cognitive performance ideally across various scores of cognitive functions and brain networks.

Furthermore, the network-phenotype associations driving the classifications and performance prediction did not provide details on the age-related alterations within the connectivity patterns of networks. Although the application of RVM allows the assessment of frequently used connections, no direct inference can be drawn about the nature of the change. Post-hoc statistics can be applied to reveal significant age-related decrease or increase in connectivity of relevant connections based on the input RSFC matrices. However, it is ultimately the overall pattern of connectivity in their interaction that allowed the performance predictions. As discussed in the SCZ and PD insights section, currently, details on the altered configuration pattern at a functional level, i.e., how the altered configuration pattern of the entire network operates, are insufficiently assessable.

Even though the thesis addressed classical questions of brain-behavior relationships with pattern-based predictive modeling, the results may provide valuable information for diagnostic utility in clinical routine. By demonstrating the importance of FC as an age-related marker for cognitive deterioration at the individual level, subtle alterations in FC in very early stages of progressive neurodegeneration might also be detectable and linked to deficient cognitive performance (Badhwar et al., 2017). ML algorithms may identify such subtle abnormalities in FC and could aid in the early detection of degenerative processes. The early identification of such conditions would be an essential step forward and would offer the possibility for prompt interventions before a potential manifestation of a neurodegenerative disorder. Indeed, some successful studies revealed that cognitive impairment related to Alzheimer's disease (AD) could be predicted from FC on an individual level in a heterogeneous sample including NA, MCI and AD participants (Q. Lin et al., 2018) as well as long-term memory impairment in patients with MCI (Meskaldji et al., 2016). While evidence also indicate a combination of modalities to establish predictive markers (Daoqiang Zhang et al., 2012), by further developing predictive models based on well-circumscribed networks connectivity may in parallel offer a target for therapeutic interventions to modulate different FC measures and cognitive performance (Cao et al., 2016; Deng et al., 2019).

Especially changes on the network level seem to be reliable markers for NA as well as aging-related diseases (Cha et al., 2013; Chan et al., 2014b; Gomez-Ramirez & Wu, 2014). The usefulness of a network approach has already been demonstrated for the classification of MCI/AD patients (Koch et al., 2012). Therefore, characterizing various connectivity profiles of brain networks, ranging from NA to various pathological aging conditions and to also link these to cognitive performance, could serve as a crucial step towards diagnostic and prognostic applications (Hojjati et al., 2017, 2019; L. Lin et al., 2018). This profile approach may lead to detect subtle neural changes already in advanced age individuals linked to a high-risk for pathological aging via a neuroimaging scan by predicting risky cognitive scores and classification labels. Such predictive tools could aid clinical practice enormously by being potentially advantageous in elderly populations over standardized assessments of cognitive functioning that can be challenging and time-consuming, which however, are the current approach to examine cognitive deficits (Q. Lin et al., 2018). Thereby, the preliminary studies that link FC with aging and cognition, as well as the thesis findings, provide promising evidence that FC derived from a RS-fMRI scan can contribute to the development of reliable markers for cognitive decline in healthy aging and a potential transition into pathological conditions such as MCI or AD.

## 4.4 Methodological Considerations and Outlook

### 4.4.1 Current Status of Neuroimaging-based Personalized Medicine

Since the thesis results have been reiteratively discussed in terms of personalized medicine, the current state of clinical utility is outlined in the following section. While automated tools for diagnostic and prognostic purposes are eagerly awaited and constitute an intensively investigated topic of current research, it must also be noted that its current utility in clinical routine is still immature. Although the accuracies reported in previous studies seem good for clinical applications at first glance, e.g., for the diagnosis of SCZ (vs. HC) and prognosis of illness course being partly over 80% (Arbabshirani et al., 2013, 2017; Janssen et al., 2018; Rashid & Calhoun, 2020), the majority of studies were based on small samples, biased CV schemes and rare validation on independent test samples. These settings have raised concerns on the validity as such methodological choices may have led to systematic overestimations (Cearns et al., 2019). For the acceptance of, e.g., the clinical application of brain imaging in psychiatry for clinical diagnoses and for aiding in treatment decisions, First et al. (2018) postulate biomarkers with a sensitivity of at least 80 % for detecting a particular psychiatric disease and a specificity of at least 80% for distinguishing this disease from healthy controls other psychiatric disorders. Further, the marker needs to be reliable, reproducible and validated in at least two independent study samples by at least two independent investigators. Although, first promising

studies emerged (Kalmady et al., 2019; Koutsouleris et al., 2018), it has also been shown that across-sample or true hold-out predictions usually achieve worse results (Woo et al., 2017). In this context, it should also be mentioned once again that, in theory, although we did not attempt clinical utility but to attain neurobiological insight, our classifications with sensitivities and specificities of around > 70 % would not have been sufficient for reliable applications. Furthermore, the classification models would have needed to be tested for their generalizability in independent larger samples. In conclusion, at the present stage, the applications in clinical practice that use neuroimaging markers for automated decision-making in psychiatry and neurology are still futuristic visions in this field (First et al., 2018). This excludes amyloid positron emission tomography scans which aid in decisions to exclude the diagnosis of AD.

### 4.4.2 Meta-analytical Networks and Individual Definition of Network Nodes

Although meta-analytically derived networks are not individual-specific, their use as the base for individual differences approaches offers the advantage that these networks represent a reliable and robust convergence of a region across a vast majority of subjects. Hence, there is a high likelihood that the macro-/micro-anatomical reference for a given network of a single subject is being located in alignment with the meta-network. Likewise, it can be assumed that individual differences in phenotypes are linked with the meta-networks as these have been aggregated on different individuals who vary in the target behavior. Therefore, networks should also carry information that allows predictions on a single-subject level to a substantial degree as mirrored in the thesis study results. Although this individual variance stems from young participants in the meta-analyses networks that were utilized here, variation due to disease and aging conditions have been found to be based on deviation within the networks associated with HC (Minzenberg et al., 2009; New et al., 2015; Roski et al., 2013; Schilbach et al., 2016; Yaple et al., 2019). Together, this demonstrates the relevance of meta-analysis networks for individual differences approaches such as ML-based predictions. Recently, it has been found based on resting-state measures that functional brain networks can vary substantially at given cortical locations across individuals as well as between an individual and the group-average (Gordon, Laumann, Adeyemo, & Petersen, 2017; Laumann et al., 2015). Even variations occur to the extent to which individual differences occur in the system membership of cortical regions (Gordon, Laumann, Adeyemo, Gilmore, et al., 2017). Furthermore, brain-behavior relationships are higher when networks are individualized than based on the group-average (Kong et al., 2019). Likewise, single brain regions vary essentially in their stereotactic location, subdivision position, as well as distribution and magnitude of FC across the cerebral cortex from individual-to-individual (Sylvester et al., 2020). Hence, future ML-based prediction studies may benefit from combining both approaches by leveraging the

advantages of meta-analyses and individualized approaches to define individualized functional networks that are still converging with the knowledge gained from meta-analyses.

### 4.4.3 The Importance of Various Connectivity Measures

Only connection strength was examined in the studies reported in this thesis. It should be noted that there is an array of other connectivity analyses possible, which provide other important connectivity measures to gain a more holistic insight into the brain architecture at rest. Examples are the fractional amplitude of low-frequency fluctuations, which reflect the ratio of low-frequency power to that of the entire frequency range within individual regions spontaneous brain activity (Zou et al., 2008); the regional homogeneity, which represents FC at a local-level between nearest surrounding voxels (Zang et al., 2004); and graph theory analysis. The latter quantifies the topology of networks into different local and global properties, often after binarizing the FCs of networks (Bullmore & Sporns, 2009). Common units include small worldness, a network organization in which nodes exhibit dense short-range connection with only a few long-range connections, or hubs, nodes that are densely connected to other nodes and play a crucial role in the degree of efficiency of a network (van den Heuvel & Hulshoff Pol, 2010). It has been found that small worldness is altered in SCZ patients (Q. Yu et al., 2011) and that specific hub nodes are differently expressed in HC, MCI and AD that may relate to compensatory effects (Khazaee et al., 2017). Moreover, the aging brain shows deterioration in local efficiency in motor-sensory RSN that can be linked to cognitive performance (Varangis et al., 2019). These studies indicate the important role of other FC properties in disease and aging conditions. Accordingly, it would be interesting if future studies use multiple connectivity measures to investigate the predictive accuracy of diseases or healthy and pathological aging or behavioral measures, e.g., in terms of multi-RS measures of functional networks as input features for ML algorithms.

### 4.4.4 The Impact of the Length of RS-fMRI Scans on Capturing Inter-individual Differences

Furthermore, the question arises to what extent a scan length of 5 - 11 minutes as used here is sufficient to reliably detect inter-individual differences related to diseases, developmental stages, or cognitive abilities. It has previously been shown that stable intra-individual FC estimates are achieved with a scan duration of only 5 minutes (Van Dijk et al., 2009) but that reliability is strongly improved if the duration is increased from 5 to up to 13 minutes (Birn et al., 2013). In addition, it was also found that a scan length of 3-4 minutes was sufficient to differentiate subjects from each other, i.e., to detect inter-individual differences (Airan et al., 2016). These results indicate that our scan length (i.e., 5 - 11 min) should provide intra-individual reliability as well as capture inter-individual differences of RSFC. However, further investigations are needed to clarify whether longer scanning time may more reliably

detect differences, which are primarily linked to clinical and age-related differences that go beyond the ''normal'' inter-individual differences that occur from subject-to-subject detectable at shorter scan duration (Shah et al., 2016). Such investigations could be of particular importance when classifying single-subjects with neurodegenerative, psychiatric, or developmental conditions or predicting behavioral measures. Longer scans may enhance the detection of systematic FC characteristics associated with clinical or age-related inter-individual differences at a single-subject level. In line with this notion, a study has shown superior predictability of individual cognitive performance levels from connectivity profiles based on approx. one hour of RS-fMRI measurement (Finn et al., 2015).

The aforementioned studies and this thesis have investigated static measures of RSFC, which represent the average RSFC over the RS scan duration. The dynamics of within-network RSFC (i.e., changes in RSFC over the scan duration; Preti et al., 2017), were not considered here. Recently, however, it has been demonstrated that dynamic FC captures more behavioral variance and specifically encodes task-based measures such as WM performance (Liégeois et al., 2019). Moreover, in SCZ, dynamic FC was shown to be associated with the inner dynamics of thought disruption, a core feature of the disease (Du et al., 2016). Hence, examining the dynamic properties of RSFC may capture pivotal information on disease- or performance-related inter-individual differences, which may not be attainable via static measures of RSFC.

Future research should address the influence of scan duration on predictions at the single-subject level in ML studies. This scan setting may need to be addressed differently than in previous studies that focus on assumptions for univariate analyses that aim to identify group differences. The examination of dynamic FC may explain important additional phenotypical variance that could be utilized to boost single-subject predictions.

# 5 SCENARIO OF INDIVIDUALIZED NETWORK-BASED THERAPEUTIC INTERVENTIONS

Previous ML-based studies aimed at extracting disease-related structural and functional neural markers to achieve the best possible classification performance or prognosis of illness course and treatment response. In contrast, the gain of neuro-functional insight into pathological and developmental profiles of disturbed networks may pave the way to a treatment-decision tool. Such a tool could provide individual-centered advice for cognitive and behavioral training/therapy or neurofeedback training in the sense of individualized network-based therapeutic interventions. This approach requires the combination of elucidating disease mechanisms based on functional networks that, in parallel, offer a personalized neural network-based therapeutic target based on the neural foundation of a psychiatric or neurodegenerative condition (Yamada et al., 2017). For example, fMRI-brain-computer interface approaches such as fMRI-neurofeedback have successfully been applied to directly modulate altered brain network connectivity with training, resulting in measurable behavioral modifications in SCZ (Ruiz et al., 2013) and PD patients (Subramanian et al., 2016). Accordingly, one aim might rather be to find theranostic markers, i.e., network makers that aid beyond the diagnosis of patients and predicting disease progression by also being relevant as therapeutic targets (Duda & Sweet, 2019; Gomez-Ramirez & Wu, 2014; Yamada et al., 2017). This may constitute a potentially different branch towards personalized medicine in everyday clinical practice.

Considering the preliminary thesis results, the ability to extract specific reliable and valid network profiles for different psychiatric, neurodegenerative, and developmental conditions on a single-subject level is possible. Additionally, presuming that such networks profiles can be replicated through investigations in larger samples and across different sites on validation samples. Some approaches from the Methodological Consideration and Outlook section might be useful to achieve extreme individualized and phenotype-specific network profiles. This could lead to potential characteristic network-disease ‘‘fingerprints’’ (see Figure 3A), i.e., a specific profile of various predictive and non-predictive functional networks for a given disease compared to various other diseases as well as for disease subtypes and developmental stages. These network-disease ‘‘fingerprints’’, in turn, may constitute functionally specific targets for treatment options based on the affected brain systems and their relation to behavior as already known from clinical and developmental conditions (theranostic markers, Figure 3B). Behavioral and/or symptom score predictions from these networks and clinical consultation may reveal superior specificity in such network-disease ‘‘fingerprints’’ and improve the individualization of treatment decisions. Such individualized network-based interventions may also

reveal profiles in clinical cases not obviously categorizable or risk cases in potential transition periods such as ultra-high-risk psychosis or MCI patients.

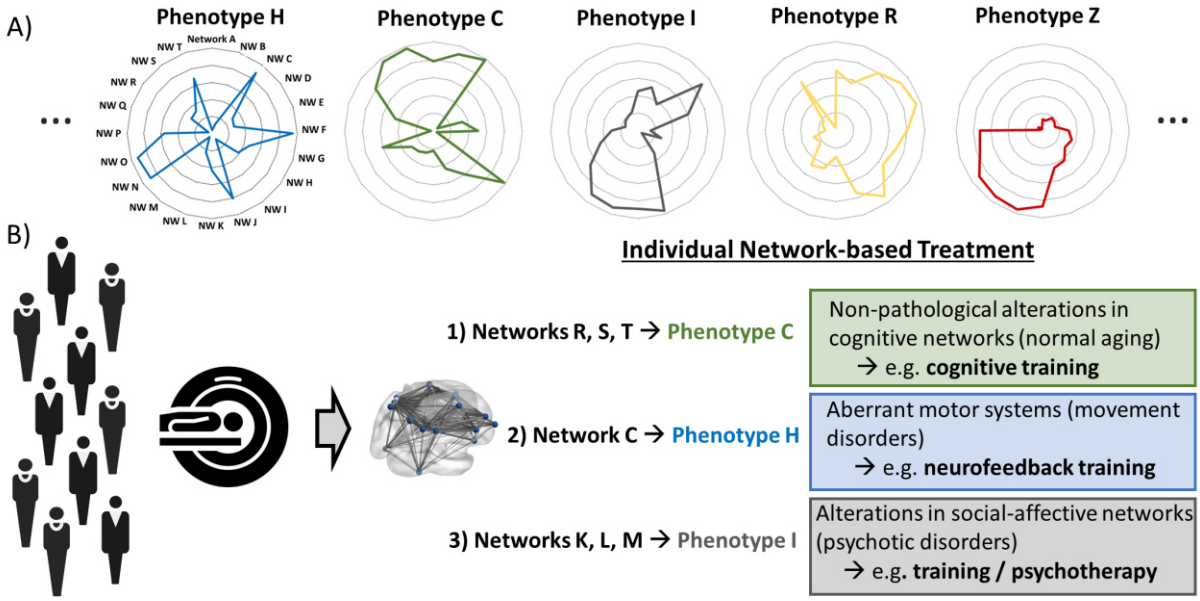



**Figure 3**:Scenario-Flow of Individualized Network-based Therapeutic Interventions

**A)** After extracting the different information from networks related to different diseases, disease subtypes, and neurodevelopmental stages using ML methods. **B)** Based on neuroimaging scans, single-subject classifications using models trained on these different conditions may yield an individual-specific profile of network-disease/developmental condition labels upon which therapeutic recommendations can be given. For example, different networks may be labeled with normal aging, Parkinson's disease, and schizophrenia and could potentially lead to following recommendations, **1)** Non-pathological alteration in cognitive networks as known from normal aging might be treatable or decreased in their progression with cognitive trainings targeting these specific functions/networks. **2**) Aberrant motor systems as known from, e.g., movement disorders such as Parkinson's disease that could potentially be modified with fMRI-based neurofeedback motor training. **3)** Alterations in social-affective networks as known from psychotic disorders, might improve with, e.g., training/psychotherapy targeting these functions/networks.

Certainly, the scenario is very optimistic and futuristic as the scientific basis is insufficiently anchored in the results of the thesis and the existing literature. Furthermore, it requires discussions on the ethical implications (Eickhoff & Langner, 2019). Nevertheless, such a scenario is not unlikely given the possibilities and developments in artificial intelligence and the efforts in the field of personalized medicine.

# 6 CONCLUSION

The thesis aimed to investigate the potential of RSFC patterns in a variety of functional networks to distinguish SCZ and PD patients from HCs as well as old from young adults. Moreover, it examined whether and to what degree the RSFC pattern of functional networks predict individual cognitive performance in young and old adults.

By using ML-based single-subject predictions, the thesis has shown that the RSFC patterns in various functional brain networks of an individual differently predicted SCZ and PD, based on networks that resonate well with known clinical and pathophysiological features. Most discriminating for SCZ were the reward processing and social-affective networks, whereas for PD, networks subserving memory, motor execution, and higher-order cognition, showed the highest accuracies. In contrast, the young-old classification was highly accurate for all networks. Additionally, diverse networks including both those that are related and unrelated to WM, predicted inter-individual differences in WMC differently in older adults. These studies suggest resting-state connectivity as a marker of functional network dysregulation in SCZ and PD as well as neural-level reorganization associated with altered network integrity in advanced age in a more global way. Together, the results improve the neurobiological understanding of SCZ, PD, and NA that is grounded in the pattern of functional networks RSFC on a single-subject level, which extends the results of previous univariate approaches. Moreover, these findings suggest that ML approaches can serve as powerful tools for the investigation of questions on brain-behavior relationships that have been so far investigated using more classical approaches.

Although the use of functional networks offers functional specificity in the interpretation of results, the underlying mechanisms of aberrant network patterns driving the predictions in SCZ, PD, and advanced age cannot be elucidated in detail in this approach. Moreover, the contributions of neural and non-neural effects to the findings in older adults need further investigation in future studies. Based on the methodological considerations, further research is also needed to determine the effects of multi-modal/ multi-RS measures, including static and dynamic FC, individual network node selection, and scan duration on prediction performance within and across disease and developmental conditions.

While single-subject based predictions for disease diagnosis and prognosis of illness course and treatment response for the application in clinical routine is on the way to mature, the present findings may point to the potential of theranostic markers for personalized medicine. The investigation of theranostic markers may lead to a different branch of personalized medicine that aims at individualized network-based therapeutic interventions.

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# APPENDIX

# List of Publications

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. Human Brain Mapping, 38(12), 5845–5858. https://doi.org/10.1002/hbm.23763

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. (2018). Corrigendum to "On the integrity of functional brain networks in schizophrenia, Parkinson's disease, and advanced age: Evidence from connectivity-based single-subject classification." Human Brain Mapping, 39(11), 4633–4635. https://doi.org/10.1002/hbm.24406

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

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## List of Abbreviations

| | |
|---|---|
| **Acc.** | Accuracy |
| **AD** | Alzheimer's disease |
| **AG** | Angular gyrus |
| **ALE** | Activation likelihood estimation |
| **AM** | Autobiographical memory |
| **AUC** | Area under the receiver operating characteristics curve |
| **bAcc.** | Balanced accuracy |
| **BDI-II** | Beck Depression Inventory-II |
| **BOLD** | Blood oxygen level-dependent |
| **Connectome** | Connectome-wide network |
| **CV** | Cross-validation |
| **DemTect** | Mild Cognitive Impairment and Early Dementia Detection assessment |
| **DSM** | Diagnostic and Statistical Manual of Mental Disorders |
| **DVARS** | Derivative of root mean squared variance over voxels |
| **EmoSF** | Emotional scene and face processing |
| **Empathy** | Empathic processing |
| **ER** | Cognitive emotion regulation |
| **FC** | Functional connectivity |
| **fmri** | Functional magnetic resonance imaging |
| **FP** | Frontal pole |
| **FWHM** | Full width at half maximum |
| **GEN** | General Psychopathology Scale |
| **HC** | Healthy control |
| **$HC_{PD}$** | Matched healthy controls of Parkinson's disease sample |
| **$HC_{SCZ}$** | Matched healthy controls of the schizophrenia sample |
| **H & Y Scale** | Hoehn and Yahr Scale |
| **ICA** | Independent component analysis |
| **ICD** | International Classification of Diseases |
| **IFG** | Inferior frontal gyrus |
| **LEDD** | Levodopa equivalent daily dose |
| **$\overline{MAE}$** | Mean absolute error |
| **MCI** | Mild cognitive impairment |
| **ML** | Machine learning |
| **MNI** | Montreal Neurological Institute |
| **MNS** | Mirror neuron system |
| **MoCA** | Montreal Cognitive Assessment |
| **Motor** | Motor execution |
| **Motor+PS** | Finger tapping and prosaccade eye movements |
| **Motor+SS** | Finger tapping and somatosensory processing |
| **NA** | Normal aging |
| **NS** | Negative Symptoms Scale |
| **OZP** | Olanzapine equivalent dose |
| **PANSS** | Positive and Negative Symptom Scale |
| **PD** | Parkinson's disease |
| **PS** | Positive Symptoms Scale |
| **$\bar{r}$** | Mean Pearson correlation coefficient |
| **Rew** | Reward-related decision making |
| **ROC** | Receiver operating characteristics |
| **RS** | Resting-state |
| **RSFC** | Resting-state functional connectivity |
| **RSN** | Resting-state network |
| **RVM** | Relevance vector machine |
| **SCID-P** | Structured Clinical Interview based on the Diagnostic and Statistical Manual of Mental Disorders / patient version |
| **SCZ** | Schizophrenia |
| **SD** | Standard deviation |
| **Sens.** | Sensitivity |
| **SM** | Semantic memory |
| **Spec.** | Specificity |
| **SPL** | Superior parietal lobule |
| **SVM** | Support vector machine |
| **ToM** | Theory-of-mind cognition |
| **TPJ** | Temporo-parietal junction |
| **UPDRS** | Unified Parkinson's disease Rating Scale |
| **VigAtt** | Vigilant attention |
| **WM** | Working memory |
| **WMC** | Working memory capacity |

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