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Left frontal hub connectivity enhances task-related brain network segregation and cognition in aging – implications for cognitive reserve

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Abbreviations

AD - Alzheimer's Disease

ACME - Average Causal Mediation Effect

ADE – Average Direct Effect

BA - Broca Area

CR - Cognitive Reserve

FDG-PET - Fluor-Desoxy-Glucose-Positron Emission Tomography

FMRI - Functional Magnetic Resonance Imaging

FPCN - Fronto Parietal Control Network

LFC - Left Frontal Cortex

MCI - Mild Cognitive Impairment

MNI - Montreal Neurological Institute

MRI - Magnetic Resonance Imaging

RANN - Reference Ability Network Study

ROIS - Regions Of Interest

RFMRI - Resting-State-fMRI

TFMRI - Task-Related-fMRI

Contents

1. Zusammenfassung

Die globale funktionale Konnektivität des linken Frontalkortex (LFC) - ein gut vernetzter Knotenpunkt (Hub) des Kontrollnetzwerkes - ist mit verbesserter fluider Intelligenz sowie relativ gut erhaltenen kognitiven Fähigkeiten, trotz alters- oder Alzheimer-bedingter Neuropathologie, assoziiert. Daher stellt dieser LFC Hub ein potenzielles Korrelat kognitiver Reserve dar. Jedoch sind die funktionellen Mechanismen, die der Assoziation zwischen globaler funktionaler Konnektivität und verbesserter fluider Intelligenz unterliegen, noch größtenteils unbekannt. Da der LFC Hub einen Teil des kognitiven Kontrollnetzwerkes darstellt und davon auszugehen ist, dass dieser die Aktivität und Inaktivität anderer funktioneller Hirnnetzwerke steuert bzw. kontrolliert, ist die Haupthypothese dieser Doktorarbeit, dass der Assoziation zwischen globaler funktioneller Konnektivität des LFC Hub und besserer kognitiver Fähigkeiten (bspw. fluide Intelligenz) eine erhöhte Netzwerk Segregation zugrunde liegt. Funktionelle Netzwerk Segregation ist definiert als das Ausmaß der Hirnorganisation in abgetrennte Netzwerke, die durch eine erhöhte intra-Netzwerk Konnektivität und eine erniedrigte inter-Netzwerk Konnektivtät ausgezeichnet sind. Die Haupthypothese wurde überprüft, indem ein Datensatz mit 255 gesunden Studienteilnehmern, die alle an zwölf verschiedenen Aufgaben in einem MRT teilnahmen, analysiert wurde. Für jeden Studienteilnehmer wurde die globale, funktionelle LFC Konnektivität pro Aufgabe bestimmt und die Assoziationen mit der jeweiligen Aufgabenleistung sowie der Netzwerk Segregation getestet. Es zeigte sich ein positiver Zusammenhang zwischen höherer globaler LFC Konnektivität mit Aufgaben aus dem Teilbereich der fluiden Intelligenz, welche durch eine erhöhte funktionelle Netzwerk Segregation teilweise

mediiert wurde. Diese Ergebnisse deuten darauf hin, dass Netzwerk Segregation einen potenziell funktionellen, protektiven Hirnmechanismus darstellt, durch den der LFC Hub einen positiven Einfluss auf die Kognition im normalen Altern ausübt. Dieser Zusammenhang stellt eine Möglichkeit dar, wie der LFC Hub nicht nur im normalen Altern, sondern auch bei neurodegenerativen Erkrankungen wie der Alzheimer-Krankheit die kognitive Reserve erhöht und somit den asymptomatischen Krankheitsverlauf verlängert.

2. Abstract

Global functional connectivity of the left frontal cortex (LFC), a hub of the cognitive control network, is associated with higher fluid intelligence and relatively preserved cognition despite age- and Alzheimer's disease (AD)-related brain changes, rendering LFC connectivity a candidate substrate of cognitive reserve. Yet, the mechanisms by which LFC connectivity supports cognition are unclear. Given that the control network, and in particular the LFC, is thought to orchestrate activity of other functional networks, the main hypothesis underlying this doctoral thesis was that the association between LFC connectivity and higher cognitive abilities such as executive function is mediated via an enhanced network segregation. Functional network segregation is defined as the degree of how much the brain is organized in distinct networks that are characterized by a higher intra-network connectivity and a lower inter-network connectivity. The main hypothesis was tested by examining a data set containing information about 255 participants aged between 20 and 80 years who participated in twelve fMRI tasks covering a range of four cognitive domains. For each participant, global LFC connectivity was assessed and associations with performance scores and network segregation were tested. Higher global LFC connectivity was associated with higher performance scores in fluid reasoning tasks which was partially mediated by an enhanced network segregation. These findings show that LFC connectivity increases fluid reasoning task performance in normal aging via an enhanced brain network segregation, suggesting a potential mechanism by which LFC connectivity supports cognitive function, and potentially cognitive reserve.

3. Introduction

3.1. Our aging society

Our world population is facing a demographic transition of large extent: we will soon have more elderly than children and more people at extreme old age than ever before (WHO, 2011). In 2012, when the global population reached seven billion people worldwide, 8 percent were aged 65 years and older (WHO, 2015). It was only three years later in 2015 that the older population rose by 55 million people and the proportion of the elderly shifted to 8.5 percent (WHO, 2015). This rapid demographic transition is partly driven by the effects of falling fertility rates, increases in life expectancy due to better disease prevention, healthier lifestyle and better available therapeutics (Bloom et al., 2011; Piggott & Woodland, 2016). Hence, more developed countries such as Japan, Germany or countries in Western Europe, which all have a growing elderly population while decreases in the fraction of the youth, will be most affected by this demographic trend in near future (United Nations, 2011). While this trend appears to have the greatest effect on more developed countries, it is also observed in all developing countries (e.g., countries in Africa or South America) with the exception of 18 countries designated as "demographic outliers" (United Nations, 2005).

With a shift of that dimension in the average lifespan of the world population, age-related neurodegenerative diseases such as Alzheimer's disease (AD) are on the verge (Reitz et al., 2011). As the world population continues to age, the amount of individuals at risk of AD increases as well, particularly among the elderly (i.e., > 85 years) (Alzheimer's Association, 2020). While in 2010 there were only 35.6 million cases of AD worldwide,

this number is projected to be duplicated every 20 years, projecting the numbers for 2030 to 65.7 million cases and 115.4 million cases in 2050 (Mayeux & Stern, 2012).

3.2. Alzheimer's disease & dementia

AD, the most common cause of dementia in western nations, is an irreversible, neurodegenerative disease that affects primarily people older than 65 years (Fiest et al., 2016; Ott et al., 1998). Individuals that are older than 85 years face an even higher risk of up to 50% to develop AD and subsequently a more rapid rate of cognitive decline (Duthey, 2013). In addition, unmodifiable risk factors for AD include a positive family history and genetics (Duthey, 2013). The most important heritable risk factor for developing AD is a change in the e4 allele of the apolipoprotein E also termed as ApoE (Elias-Sonnenschein et al., 2011). Heterozygoty of this allele increases the risk for AD 3-4 times, while homozygoty increases the risk 8-12 times (Alzheimer's Association, 2020). Although most cases are not genetically inherited, about 1% of AD cases have been identified as genetically driven by autosomal dominant mutations (Alzheimer's Association, 2020).

The neuropathologic cascade of AD starts years before the onset of symptoms with two proteins accumulating in the brain: the senile plaques ß-amyloid and neurofibrillary tangles called tau (Serrano-Pozo et al., 2011). While extracellular ß-amyloid accumulates decades before first symptoms arise, tau accumulates within neurons and emerges in later disease stages than ß-amyloid-pathology (Jack et al., 2010; Selkoe & Hardy, 2016). The initial causal mechanism that starts the development of senile plaques

and neurofibrillary tangles is still unknown to date. The deposition of both proteins is hypothesized to cause neuronal loss and dysfunction which ultimately leads to cognitive decline (Perl, 2010). Specifically, this cognitive dysfunction is defined as dementia which is a general term describing a broad variety of different symptoms including loss of memory, reduction in verbal skills, problem-solving and other cognitive abilities that affect people in their daily lives and routines (WHO, 2020). These symptoms are later in stage often accompanied by deterioration in emotional control, social behavior and motivation (WHO, 2020). Hence, dementia is not a disease on its own, but rather a complex of symptoms (i.e., syndrome) that can be caused by a range of different diseases, with AD being the number one candidate contributing to 60-70% of all cases worldwide (Burns et al., 2002). Other diseases that can lead to dementia include Parkinson's disease, stroke, traumatic brain injury, vascular disease, HIV, Huntington's disease or Lewy-body-disease but also a variety of other diseases (Hanagasi et al., 2017; Kaul, 2009; Paulsen, 2011; Pendlebury et al., 2019; Peterson et al., 2019).

Even though the main risk factor for developing AD and dementia is age, dementia is not a part of normal aging. It is the result of a pathologic chronic dysfunction in the brain and differentiates from healthy aging by the severity of cognitive decline and a loss of independence in daily function (McKhann et al., 2011). Age-related cognitive decline is subtle and mostly affect perceptual speed, attentional control and executive function contrary to cumulative knowledge and experiential skills which are well-preserved in higher age (Murman, 2015). While cumulative knowledge and experiential skills are referred to as crystallized knowledge, skills such as problem-solving, logical thinking or the general ability to reason are referred to as fluid intelligence which depends only minimally on prior learning experiences (Brown, 2016). Moreover, fluid intelligence

peaks in early adolescence and starts to decline progressively around the age of 30 to 40 while crystallized intelligence is longer preserved (Hartshorne & Germine, 2015). Some studies have shown that a frontal dysfunction can be linked to the age-related changes in fluid intelligence suggesting that disturbances in the frontal lobe may specifically contribute to the cognitive decline in normal aging (Bugg et al., 2006).

There is, however, an increasing amount of research demonstrating that the prevalence of age-related cognitive decline and dementia can be reduced and the onset of dementia may be delayed by numerous lifestyle factors including education, leisure activities, physical activity or eating a healthy diet (Clare et al., 2017; Stern et al., 1994). Thus, the trajectories of normal and pathological aging are both susceptible by protective factors which contribute to the concept of cognitive reserve (Stern, 2003).

3.3. The concept of cognitive reserve

Remarkably, patients diagnosed with AD are affected differently by the burden of neuropathology (e.g., deposition of tau tangles or ß-amyloid plaques) showing that although two individuals may have the same relative level of neuropathology, the onset of dementia and severity of cognitive decline can vary significantly (Stern, 2009). One of the first studies to observe that neuropathology caused by AD does not inevitably lead to full developed dementia was Katzman et al. in 1988. Katzman and colleagues reported ten cases of cognitively normal, elderly individuals (i.e., no cognitive impairment) which showed progressed AD-related neuropathology in their brain tissue postmortem (Katzman et al., 1988). However, these patients did not suffer from dementia or cognitive decline despite the presence of AD-related neuropathology (Katzman et al., 1988). This research demonstrated that a lack of symptoms in AD cannot be fully explained by a lower extent of AD-neuropathology but is probable to be attributed to other factors such as protective brain mechanisms or functional properties. In addition, multiple studies demonstrated that a lower level of education is a potential risk factor for developing dementia, indicating that intellectual enrichment and a higher general cognitive ability might impact the risk of symptom onset in AD (Katzman, 1993; Stern et al., 1992). This was also shown by the famous nun study that confirmed that life experiences over an extended period of time (i.e., higher occupational activity, education) in early, mid and late life have strong associations with the risk of AD, which further supported the findings of Katzman (Mortimer et al., 2003).

In summary, multiple studies demonstrated that the risk of dementia can be reduced by a variety of lifestyle choices and that AD-related neuropathology can exist at a relative

level without necessarily leading to dementia or cognitive decline. These findings suggest that there might be an underlying functional mechanism protecting these cognitively normal (i.e., asymptomatic) elders from the effects of AD's neuropathology. This protective mechanism is defined as cognitive reserve or resilience (Cabeza et al., 2018; Stern et al., 2020).

Cognitive reserve (CR) describes the phenomenon of lower cognitive decline than anticipated based on the level of age-related or pathological brain changes (Stern, 2009). The theory of CR propounds that life-long experiences shape the ability to ameliorate the effect of neuropathology such occurring in AD on cognitive abilities. Thus, CR does not slow down the development of brain pathologies or age-related brain changes, rather CR delays the onset of symptoms. Hence, individuals with a higher level of CR experience a longer pre-dementia disease trajectory compared to those with lower CR. Katzman estimated that secondary education delays the onset of AD-dementia by five years into the future showing that CR could be used as a nonpharmacological approach for disease prevention (Katzman, 1993). Essentially, CR is not only observed in AD but also in other diseases including Parkinson's disease, Lewy-body disease, stroke, multiple sclerosis or traumatic brain injury (Gonzalez-Fernandez et al., 2011; Hindle et al., 2014; Kesler et al., 2003; Perneczky et al., 2008; Sumowski & Leavitt, 2013). Moreover, the concept of CR has also been shown to be relevant for age-related cognitive decline (Tucker & Stern, 2011; Whalley et al., 2004) which demonstrates that CR resembles a general protective feature that takes effect not only in a wide range of different diseases but also affects normal age-related cognitive decline. Hence, protective brain mechanisms that underly CR in normal aging, may also be attributed to CR in AD or other neurodegenerative diseases.

As illustrated in Figure 1, age- or AD-related brain changes ultimately lead to a decline in cognitive function, or even to a more drastic decline: dementia. However, individuals with a comparably high CR, experience the consequences caused by age-related brain changes or AD-neuropathology later and are thus later affected by dementia. This shows that CR prolongs the asymptomatic disease trajectory and individuals maintain their relative cognitive function longer. Nevertheless, the functional protective mechanisms supporting CR are still unclear and more information must be gathered to understand how these protective brain mechanisms support CR and delay the onset of age- or AD-related cognitive decline.

Figure 1: Illustrated concept of cognitive reserve

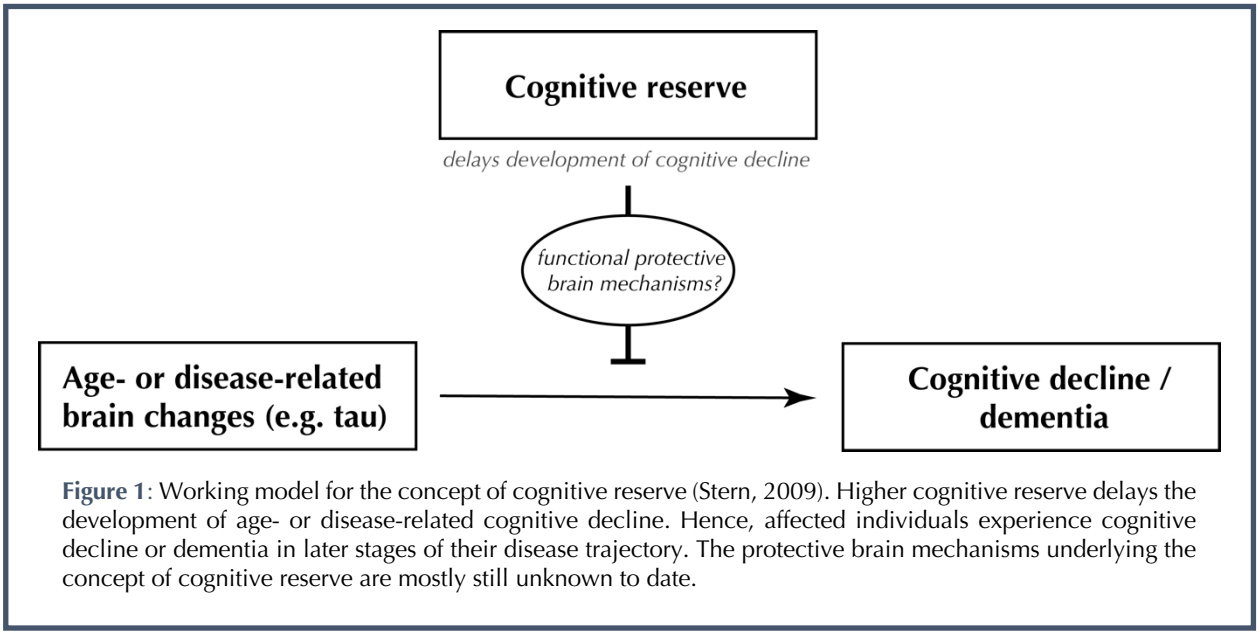

Figure 1: Working model for the concept of cognitive reserve (Stern, 2009). Higher cognitive reserve delays the development of age- or disease-related cognitive decline. Hence, affected individuals experience cognitive decline or dementia in later stages of their disease trajectory. The protective brain mechanisms underlying the concept of cognitive reserve are mostly still unknown to date.

Considering CR is associated with a delayed onset of dementia and an extended individual life trajectory without increased social health costs, CR offers a great opportunity for a possible secondary prevention of AD. Previous studies have shown that a one-year delay of the onset of dementia would lead to an age-dependent decrease in

dementia-prevalence of over 10% (Zissimopoulos et al., 2014). Understanding how CR works by examining contributing factors and analyzing the underlying mechanisms is key to further exploit the opportunity to prevent, delay or halt the consequences of AD and lower the potential costs for our aging society. To date, there are numerous protective factors known that may enhance or contribute to CR. For instance, studies have demonstrated that higher educational and occupational attainment is associated with higher CR (Stern et al., 1994) showcasing that CR is actually susceptible to lifestyle choices and not a static property people are born with. Other studies indicate that higher brain volume is associated with better cognitive performance after brain injury and thus contributing to CR (Kesler et al., 2003). Although some of the factors that enhance CR are well known, the neural implementation of CR is still mostly unrevealed. There are, however, studies indicating that CR is supported by possible functional brain differences including advanced neural flexibility and increased neural network function obtained due to diverse life experiences (Baroncelli et al., 2010; Hu et al., 2013; Xu et al., 2015). Other studies postulate that an increase in brain network efficiency leads to a higher capability for information processing (Barulli & Stern, 2013; Stern, 2006). Functional brain features such as network efficiency or network segregation can be explored by using functional magnetic resonance imaging (fMRI).

3.4. Functional MRI & functional connectivity

Functional Magnetic Resonance Imaging (fMRI) is a non-invasive, neuroimaging approach introduced in the early nineties (Bandettini et al., 1992; Kwong et al., 1992) to measure in vivo brain activity and connectivity. The most common method used to detect brain activity operates by utilizing the principle that an increase in local neuronal activity leads to a higher demand of energy and subsequently to an enhanced cerebral blood flow with higher levels of oxygenated and lower levels of deoxygenated hemoglobin. This underlying principle is termed blood oxygenated level dependent (BOLD) contrast technique (Ogawa et al., 1990) which originates from a characteristic feature of hemoglobin in MRI: oxygenated hemoglobin is less magnetic compared to deoxygenated hemoglobin and this difference is detectable in fMRI. Thus, the fMRI-assessed BOLD magnitude is an indirect measure of neural activation and represents a score consisting of local cerebral blood flow, blood volume and oxygenation level (Soares et al., 2016). In summary, the BOLD contrast is used to visualize areas in the brain with increased local neural activity compared to other regions. One of the advantages of fMRI is the relatively high spatial resolution; a standard 3 Tesla MRI can feature an isotropic resolution of ~3mm. After preprocessing the fMRI-images, the resultant interdependencies of local neuronal activity are most commonly represented as a statistical map reflecting connectivity across different brain regions (see Fig. 2). The size for the x- and y-axis is dependent on the applied brain atlas which sets the coordinates of predefined regions. This statistical map reveals temporal dependent co-activation patterns between different brain regions using a traditional notion of similarity such as Pearson's correlation. Methodically, these co-activation patterns or degrees of

correlation are defined as functional connectivity (FC) which describes a statistical dependence among neurophysiological events (BOLD-signal) of anatomically separate brain regions (Aertsen et al., 1989; Friston et al., 1993).

Conceptually, two brain regions exhibit FC if there is a statistical relationship between the recorded events of activity. For example, if region A is coupled to region B by constantly being correlated in rise and fall of activity, it exhibits a high FC to region B. This concept defined as functional connectivity follows the neuroscientific Hebbian theory: "cells that fire together, wire together", or more precisely "what fires together is wired together".

FC can be detected in different brain states: resting-state or task-related fMRI. Resting-state fMRI (rfMRI) is a stimulus-independent method to examine spontaneous FC at a consistent brain state (Biswal, 2012). During a resting-state experiment the participants are asked to remain calm, have their eyes closed and restrict their thoughts as much as possible. Application of this technique has allowed the discovery of multiple networks ("resting-state networks") that are synchronized in their BOLD fluctuations at rest (Biswal et al., 1995; Raichle et al., 2001). In contrast, task-related fMRI (tfMRI) represents a stimulus-dependent method to examine BOLD-fluctuations while the study subject is engaged in a particular task (e.g., memory recall, motor execution or visuo-spatial tasks). Further studies revealed that synchronized BOLD-fluctuations found in rfMRI (i.e., brain networks) correspond well to similar coactivation patterns in tfMRI (Toro et al., 2008). In comparison, tfMRI coactivation patterns showed a higher global efficiency than rfMRI which suggests a more efficient information transformation during task performance (Di et al., 2013).

Since the emergence of functional connectivity, a new neuroscientific discipline of examining the brain has evolved: connectomics, i.e. understanding cognitive processes as the resultant of communication between different brain regions that are forming large-scale and complex networks (Rubinov & Sporns, 2010).

Figure 2: Functional connectivity matrix (statistical heatmap)

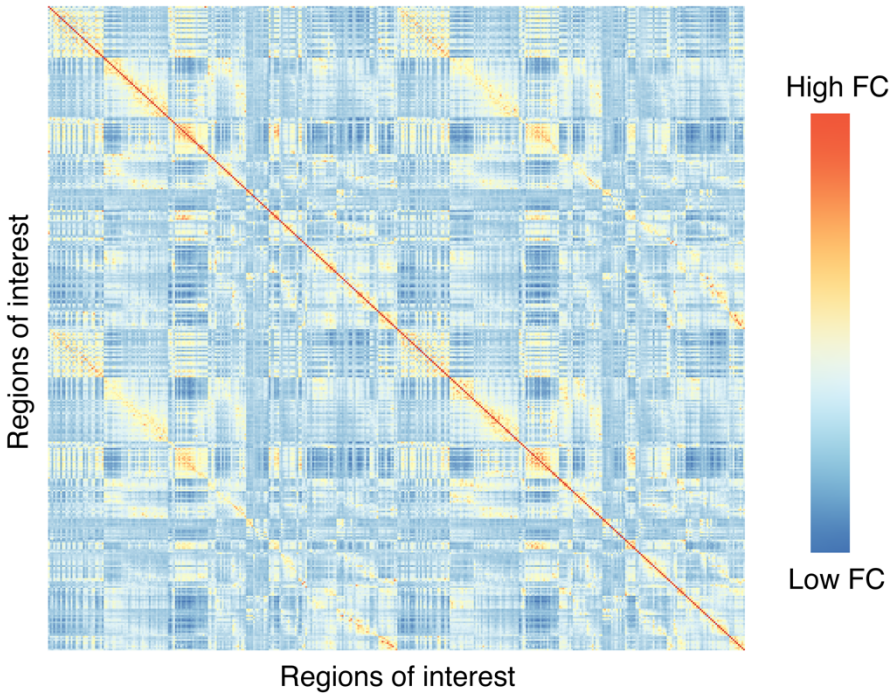

Figure 2: Heatmap illustrating a statistical map containing FC values between different regions of interest (ROIs). Values for this statistical map originated from data of the RANN study (see Chapter 4.1.) illustrating the meaned FC of 255 subjects. The number of ROIs is dependent on the applied brain atlas. Here, the Schaefer 400 atlas was applied (Schaefer et al., 2018). Blue values represent negative FC while yellow/red values represent positive FC. The dark red line ranging from top left corner to bottom right corner resembles FC values between the same brain region (i.e., therefore constant red line and thus high FC).

3.5. The brain is a network

The human brain is a complex network consisting of a substantial amount of different brain regions (i.e., network nodes) that are functionally and structurally connected with each other. Throughout these connections, brain regions and neurons form an integrative organization in which information is processed and transferred between different structures and functionally linked brain regions. Functional transmission between distinct brain regions is presumed to play a fundamental part in overall cognitive function, relying on the permanent incorporation of information across different regions of the brain (Zeki & Shipp, 1988).

Conceptualizing the brain as a network provides the possibility to examine how FC and information processing are altered in neurodegenerative diseases including AD (Bullmore & Sporns, 2009). The brain shares the same defining properties as other networks seen in technology, nature or human society: they all consist of nodes (e.g., regions, neurons) that are linked via connecting edges (e.g., white matter tracts, FC). This theoretical framework defined as graph theory is used to mathematically analyze neural systems in terms of graphs or networks comprising nodes (Bullmore & Sporns, 2009).

Instead of understanding the brain as just one single network, the brain functions as a network throughout multiple spatial and temporal scales. At the microscopic scale, neuronal cells represent nodes and the connecting synapses between them are represented as links. At the systemic scale, to which fMRI is sensitive, the cerebral cortex is organized into distinct regions (nodes) which are structurally connected by white matter tracts (links) and functionally via synchronized infraslow-frequencies (Marek & Dosenbach, 2019). The complete network map of an organism's brain, its connectome,

is comprised of functional and structural connections throughout the human brain and plays a key role in cognitive processes (Sporns et al., 2005). The goal of connectome studies is used to further investigate the architecture of brain networks and how this organization shapes brain function. This network map is approximately organized into 15-20 distinct functional sub-networks (Gordon et al., 2016) which differ in function and scale. The structure and organization of functional subnetworks is critical for cognitive processes and thus a possible target for neurodegenerative diseases leading to cognitive decline and dementia. Neurodegenerative diseases such as AD lead to a disruption of connectivity and ultimately to a reduced functionality of networks that underly cognition (Zhang et al., 2010).

Recent studies demonstrated, that well inter-connected regions in the brain might protect the functional organization of brain networks from neuropathology and could therefore be considered as potential substrates of CR (Franzmeier et al., 2017B; Franzmeier et al., 2018).

3.6. LFC hub connectivity as a substrate of cognitive reserve

Just like networks in nature, technology and society, the brain has regions that exhibit higher connectivity (i.e., higher wiring) and regions that exhibit lower connectivity (van den Heuvel & Sporns, 2013b). Regions with higher connectivity either feature many functional or anatomical links or are more diversely connected throughout the brain (Grayson et al., 2014; Liska et al., 2015). In graph theoretical terms these brain regions with exceptionally high numbers of connections to other brain regions are defined as network hubs and are considered to play an essential role in integrative and coordinative mechanisms (Power et al., 2013; van den Heuvel & Sporns, 2013a). In the illustrated example (see Fig. 3), the blue point exemplifies a typical hub, i.e. a node having more connections throughout the network compared to other nodes. Removing the blue point from the illustration would fundamentally deconstruct the portrayed network of nodes while removing a gray node in the periphery would only slightly damage the organizational structure. The blue hub enables the communication between different nodes and regions that are only connected via this specific key point. Accordingly, hubs can be also found in the brain and are usually referred to as “rich club” or “diverse club” (Bertolero et al., 2017; van den Heuvel & Sporns, 2011). These findings demonstrate that hubs are critical for the efficiency of network organization by playing a key role in brain communication and neural integration.

Figure 3: Illustration of a brain hub

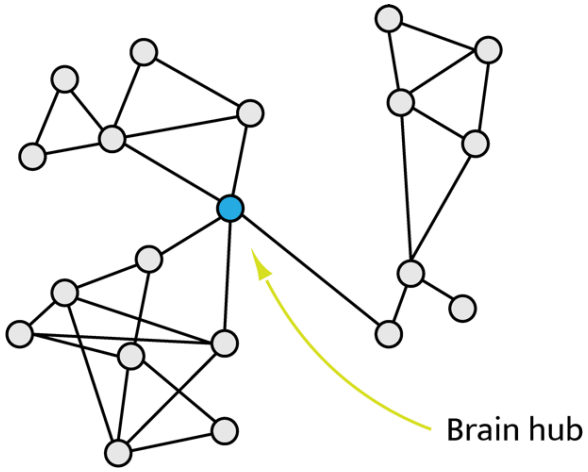

Figure 3: Illustration demonstrating the concept of network hubs. The blue node represents the typical network organization for a hub as gateway for connecting different gray nodes throughout the network. Removing one gray node would not necessarily lead to major network disruption while removing the blue node would destroy the organizational structure and lead to major communication issues.

Moreover, individuals with highly inter-connected hubs and a consistently modular network structure showed increased cognitive performance regardless of the task they were engaged in (Bertolero et al., 2018). Specifically, further studies revealed that well interconnected hubs prominently existing in the frontoparietal control network (FPCN) and cingulo opercular network, are associated with greater cognition and fluid reasoning abilities (Gratton et al., 2018). In particular, a specific hub in the frontoparietal control system, the left frontal cortex hub (LFC, covering BA 6/44) close to the Broca area, has been linked to neuro-protective factors such as fluid intelligence and education (Cole et al., 2012) and might therefore serve as a potential candidate substrate of CR (Franzmeier et al., 2018). Additionally, higher brain-wide connectivity of the LFC hub at a certain extent of neuropathology (here: posterior-parietal FDG-PET hypometabolism) has been associated with better memory performance (Franzmeier et al., 2017A) and higher functional network efficiency in AD (Franzmeier et al., 2018). Further, Cole and

colleagues showed that the LFC hub and other hubs of the FPCN are orchestrating the activity of other networks by rapidly updating their FC dependent on the specific task context (Cole et al., 2013). In general, higher global FC is used as a measure of interconnectedness and presumed to showcase the extent of control a brain region might exhibit over another. Specifically, the LFC is postulated to act as a flexible hub, increasing its connectivity to regions relevant for the current task demand (Miller & Cohen, 2001). Following this theory, increased LFC hub connectivity to specific memory-related functional networks (e.g., default-mode network, dorsal attention network) has been associated with higher memory performance at a given level of neuropathology as well (Franzmeier et al., 2017B). This demonstrates that hubs of the FPCN (particularly the LFC hub) contribute to an overall controlling function in the brain while also being associated with protective factors against cognitive decline and dementia. Investigating the potential underlying mechanisms that could explain the protective and functional role that hubs of the FPCN and specifically the LFC hub play, might be key in the further understanding of CR and thus an important step to defeat AD. Hence, in this doctoral thesis a potential protective brain mechanism was investigated by which the LFC hub might distribute control over other regions of the brain and enhances functional network organization to optimize cognitive function in defiance of age-related or neuropathological brain changes. This protective brain property or mechanism is commonly referred to as system or network segregation (Chan et al., 2014).

3.7. Network segregation

Research on networks revealed that the brain exhibits organizational properties that support brain efficiency and resistance to perturbation (Strogatz, 2001). One of these properties is the organization in subnetworks consisting of nodes that exhibit a high intra-network FC and a comparably lower inter-network FC: network segregation. This functional property is defined as the difference of mean intra-network FC (Z_{intra}) and mean inter-network FC (Z_{inter}) as a proportion of mean intra-network FC (Z_{intra}) (Chan et al., 2014).

$$formula:$$

$$\text{network segregation} = \frac{Z_{intra} - Z_{inter}}{Z_{intra}}$$

As illustrated in Figure 4, this specific FC pattern leads to a higher extent of segregation for subnetworks which in turn is beneficial for effective network function (Tononi et al., 1994). However, while an excess in segregation of subnetworks can result in a decrease of interaction between brain regions, a too high extent of inter-network connectivity can lead to a more rapid disease progression (Salathe & Jones, 2010). Furthermore, this specific functional organization is proposed to be beneficial for energetically demanding cognitive processes and thus linked to a higher extent of brain efficiency (Manza et al., 2020), i.e. lower cost. Previous studies showed that higher rfMRI assessed network segregation is associated with higher cognitive performance across the adult lifespan (Chan et al., 2014). Thus, network segregation is not only associated with enhanced cognitive performance in some cognitive domains but also represents an age-related brain property that decreases across the healthy lifespan.

Consequently, network segregation can be conceptualized as an indirect age-invariant brain efficiency marker as it is associated with higher cognitive performance independent of age. This leads to the question whether network segregation could serve as one functional brain mechanism by which LFC enhances cognitive function in normal aging, thus supporting the concept of CR.

Figure 4: Conceptual illustration of network segregation

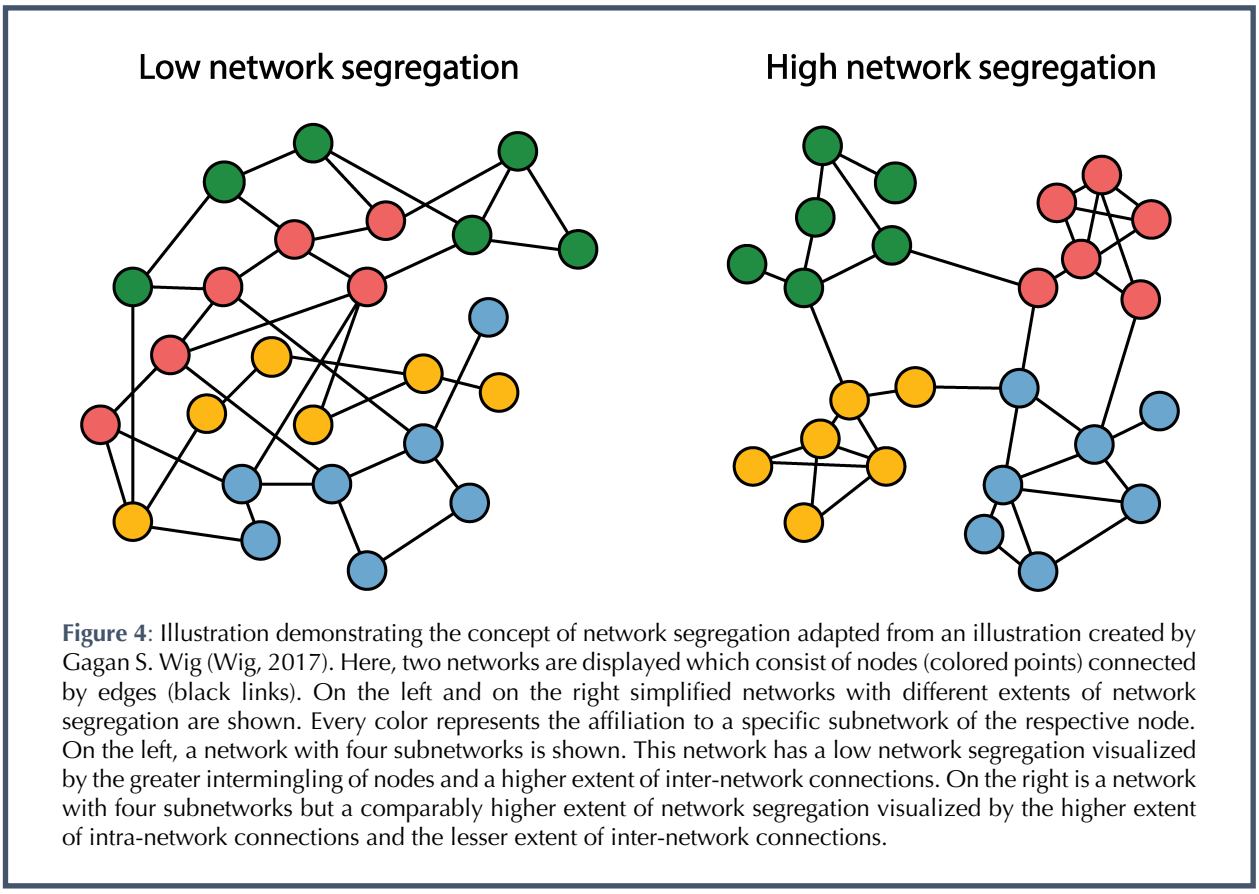

Figure 4: Illustration demonstrating the concept of network segregation adapted from an illustration created by Gagan S. Wig (Wig, 2017). Here, two networks are displayed which consist of nodes (colored points) connected by edges (black links). On the left and on the right simplified networks with different extents of network segregation are shown. Every color represents the affiliation to a specific subnetwork of the respective node. On the left, a network with four subnetworks is shown. This network has a low network segregation visualized by the greater intermingling of nodes and a higher extent of inter-network connections. On the right is a network with four subnetworks but a comparably higher extent of network segregation visualized by the higher extent of intra-network connections and the lesser extent of inter-network connections.

3.8. Aims of this thesis

The goal of this doctoral thesis was to investigate a potential mechanism underlying the association between global task-related LFC hub connectivity and higher cognitive performance in normal aging. The main hypothesis postulates that task-related LFC hub connectivity contributes to cognitive function in normal aging by enhancing network segregation.

4. Methods

4.1. Study sample

The data represented in this doctoral thesis originates from the "Reference-Ability-Neural-Network-Study" also referred to as RANN (Stern et al., 2014) which was provided by Yaakov Stern and Christian Habeck from Columbia University. 255 healthy participants were included which were all in the age range from 20 to 80 years and all participated in a set of twelve different cognitive tasks. Three tasks each represent one of the four reference abilities (i.e., cognitive domains): **fluid reasoning**, **vocabulary**, **episodic memory** and **perceptual speed**. These reference abilities are hypothesized to cover the vast majority of age-related cognitive changes across four cognitive domains (Salthouse & Davis, 2006). All participants underwent screening for dementia or MCI before attending the study which was assessed with the Mattis Dementia Rating Scale (MDRS). Further premises for the study participants were to speak English as their native language, to be dominantly right-handed and have at minimum a basic skill level at reading. Demographic features of these participants are represented in Table 1.

Table 1: Participant Demographics

Decade	N	%F	Education	AMNART IQ	DRS
20-29	30	66.3%	15.1 (±2.2)	113(±8.4)	140.4 (±2.7)
30-39	37	62.2%	16.4 (±2.5)	112(±7.6)	139.7(±2.6)
40-49	33	51.6%	15.9 (±2.6)	114 (±8.4)	138.6 (±1.7)
50-59	48	52.1%	16.1 (±2.0)	117 (±8.2)	140.7 (±2.9)
60-69	68	52.9%	17.1 (±2.4)	118 (±8.6)	139.7 (±3.3)
70-80	39	74.4%	12.0 (±2.5)	121 (±6.2)	140.1 (±2.8)

Table 1: Overview of the study participants from the RANN study. Participants were divided into six different age groups to demonstrate age-group-specific participants demographics. %F represents the percentage of females in that particular cohort. Education was assessed as years of education. AMNART IQ was estimated based on American National Adult Reading Test. DRS stands for Mattis Dementia Rating Scale. Mean standard deviation are displayed in brackets.

4.2. Task description

In brief, all study subjects participated in twelve computerized tasks which were performed in two separate fMRI-based sessions (see Fig. 5). The cognitive domain **vocabulary** was tested by the following tasks: *synonyms*, *antonyms* and *picture naming*. Here, subjects were required to match a particular word to its correspondent synonym and antonym or to terms that were comparable or different. In the third task - *picture naming* - participants were asked to label images that were displayed for 4.5 seconds on a screen. The performance was measured in correct trials completed. The cognitive domain **perceptual speed** was covered by the tasks: *digit symbol*, *letter* and *pattern comparison*. These tasks tested the ability to react as quickly and precisely as possible which was measured in reaction time. The third cognitive domain **fluid reasoning** was tested by the following tasks: *paper folding*, *matrix reasoning* and *letter sets*. This domain refers to the ability of basic mental processes of reasoning that depend minimally on prior learning. Again, the performance was measured in correct trials completed. The fourth cognitive domain **episodic memory** was again covered by three tasks: *logical memory*, *word order recognition* and *paired associates*. Here, participants were required to memorize specific details from presented stories, to remember paired words or words in a specific order. Again, performance was measured in correct trials completed. For a more detailed task description please see: Stern et al., 2014, "The Reference Ability Neural Network Study: motivation, design, and initial feasibility analyses".

4.3. Overview of analysis regime

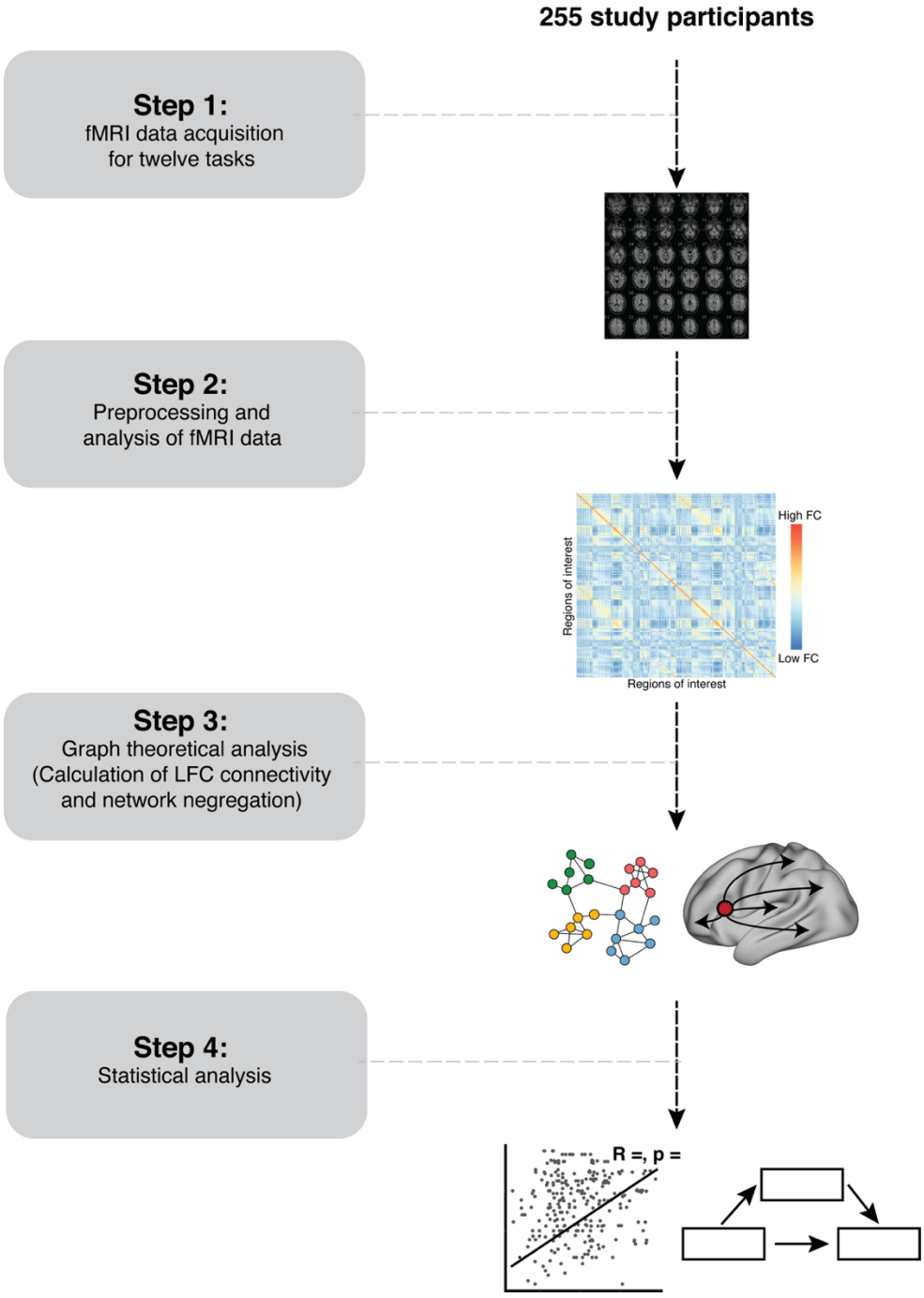

Figure 5: Overview of analysis regime: **1**) 255 study participants underwent twelve fMRI tasks covering a range of four reference abilities (i.e., cognitive domains). **2)** EPI sequences for each participant and each fMRI task were acquired and preprocessed using SPM 12 (Statistical Parametric Mapping). The fMRI data was analyzed using a fixed general linear model (GLM) to create design matrices for the following step. Next, a cPPI (correlational psychophysiological interaction analysis) was conducted to retrieve task-related LFC hub connectivity and correlation matrices showing condition-specific functional connectivity for 400+1 different ROIs. **3)** Global LFC hub connectivity and network segregation scores were computed for each task and study participant. **4)** Statistical analysis was applied to further investigate the data set and analyze the associations of LFC hub connectivity with fMRI task performance and network segregation. The EPI image displayed was published by "PGP-Scientists, Personal Genome Project" and is licensed under CC0.

4.4. fMRI data acquisition

All fMRI sequences were obtained using a 3.0T Philips Achieva Magnet (MRT). Each study participant underwent a 2.5-hour fMRI imaging session twice in which they engaged in twelve distinct tasks (see Chapter 4.2.). In addition, a T1-weighted image was created to determine the exact position of each participant. Every fMRI scan used a 240 mm field of view. The fMRI images were generated using an echo-planar imaging (EPI) sequence sensitive to BOLD (TE/TR = 20/2000 ms, flip = 72°). EPI sequences were utilized since this technique allows fast image acquisition and is thus less sensitive to motion (Poustchi-Amin et al., 2001). Each scan produced 41 slices of brain volumes (3mm thick axial images, 112x112 (voxels) in-plane resolution). A neuroradiologist reviewed each subject's scans. Any significant findings were transferred to the participant's primary care physician.

4.5. Preprocessing of fMRI data

To minimize artifacts created at data acquisition, each individual's twelve fMRI scans were preprocessed using Statistical Parametric Mapping (SPM) 12 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK). First, to accomplish a higher comparability between subjects all functional and structural images were warped into a standardized MNI template which was achieved utilizing a non-linear algorithm employed in SPM 12 (Ashburner, 2007). Second, the fMRI images were corrected for possible motion artifacts as too much movement changes the origin of the measured signal. As last preprocessing step, slice-time- and field-map correction was applied and the fMRI images were

subsequently smoothed to decrease noise signal which was achieved by using an 8 mm FWHM (full with at half maximum) kernel.

4.6. Definition of LFC and regions of interest (ROIs)

First, the coordinates of the LFC hub were created by following a protocol from a previous task-related fMRI study using a 3D-sphere shaped ROI (MNI coordinates: x= -42, y=6, z= 28) with a radius of 8 mm. The LFC seed ROI was overlaid onto the gray matter-masked fMRI data series to obtain the task-related functional connectivity within the defined LFC ROI (Franzmeier et al., 2017C). Using the pre-established Schaefer atlas (Schaefer et al., 2018), the rest of the brain was parcelled into 400 distinct ROIs (see Fig. 6) which were subdivided into a seven subnetwork system (Yeo et al., 2011). Global positive functional connectivity of the LFC hub was computed by meaning the positive connectivity of the hub to every other ROI in the 400 ROI Schaefer atlas. Note that negative functional connectivity of the LFC hub and the 400 Schaefer ROIs were excluded due to an unclear interpretation of the result.

Figure 6: 400 ROI brain parcellation

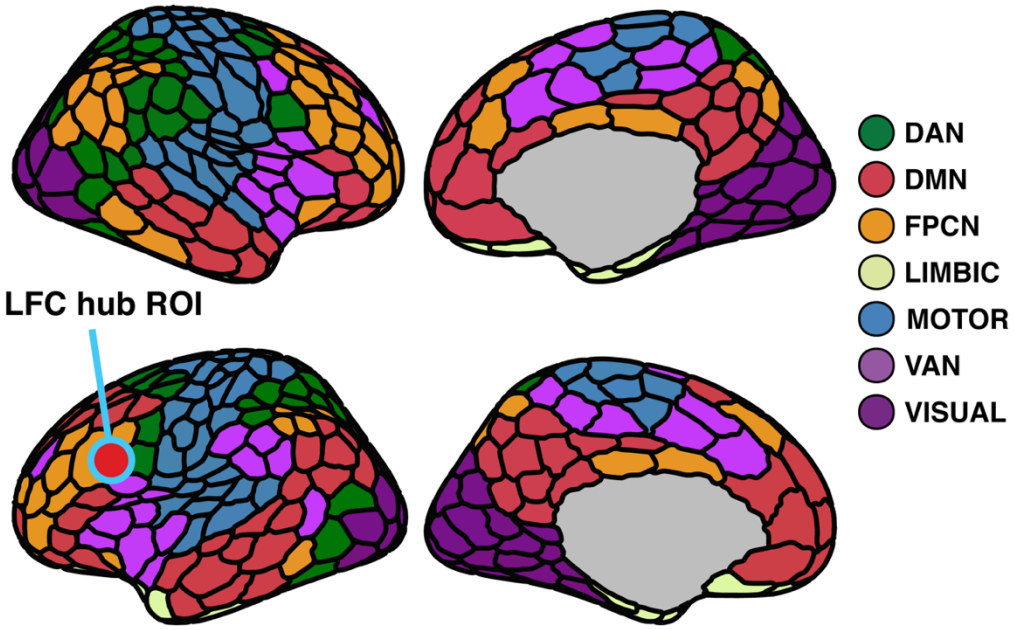

Figure 6: Illustrated 400 ROI brain parcellation (Schaefer et al., 2018) that was constructed by using the R library *ggseg* (Mowinckel & Vidal-Piñeiro, 2020). Task-related FC was calculated for each ROI in the Schaefer 400 atlas and for the Left Frontal Cortex hub (LFC) ROI (MNI coordinates x = 42, y = 6, z = 28) which is superimposed in red with a blue circle. Abbreviations: DAN = Dorsal Attention Network, DMN = Default Mode Network, FPCN = Fronto Parietal Control Network, Limbic = Limbic Network, Motor = Motor Networks, VAN = Ventral Attention Network, Visual = Visual Motory Network.

4.7. Analysis of task-related fMRI data

After preprocessing, the subject level tfMRI data was analyzed utilizing a fixed-effects general linear model (GLM) which was achieved with SPM 12. This statistical method is employed to distinguish between noise and the stimulus-dependent signal (Monti, 2011) and is a prerequisite for the subsequent analysis. For each participant, the experimental design matrix was created by entering six motion regressors, time and dispersion derivatives and two condition regressors: (1) task mode on (2) task mode off. Each regressor variable was convoluted with the canonical hemodynamic response function (HRF) which represents the characteristic BOLD impulse response that can be attributed to neuronal activity (i.e., neurovascular coupling).

4.8. Correlational psychophysiological interaction (cPPI) analysis

The psychophysiological interaction (PPI) analysis is a statistical method for examining condition-specific changes in the activity and relationship between different brain regions (e.g., ROIs) (O'Reilly et al., 2012). This statistical approach is suitable to measure how higher condition-specific activity of one brain region is associated with condition-specific activity in another brain region (Friston et al., 1997). In comparison, the GLM contrast may show neural activity in different brain regions of interest but based on this method one cannot distinguish between independent or interactive neural activity. Hence, a PPI analysis is used to analyze condition-specific inter-regional covariations of neural activity. Specifically, in this doctoral thesis, a correlational psychophysiological interaction (cPPI) analysis was conducted to obtain task-related functional connectivity of the LFC hub and every ROI in the Schaefer 400 atlas. The cPPI analysis was performed

by using the pre-established cPPI-Toolbox (Fornito et al., 2012) which required the first-level design matrices created with the GLM model (see Chapter 4.7.). First, the extracted time courses belonging to the LFC ROI and the 400 Schaefer ROIs were deconvolved using the empirical Bayesian method (Gitelman et al., 2003), then multiplied with the condition regressors: (1) task mode on and (2) task mode off and subsequently reconvolved with a canonical HRF creating the region-specific cPPI interaction regressors which represent the conditional changes of neural activity in the respective ROI. For subject-level cPPI analysis, a design matrix was produced that included the (1) PPI interaction regressors, (2) deconvolved LFC and ROI BOLD time courses, (3) condition regressors and (4) covariates of no interest (motion parameters and time derivatives). Subsequently, the cPPI-Toolbox computed FC matrices representing the task-related (i.e., condition-specific) FC of 400 Schaefer ROIs and the LFC hub while engaged in the respective fMRI task. In total, twelve FC maps per study participant were constructed representing condition-specific covariations of neural activity.

4.9. Calculation of network segregation

Network segregation was computed for each subject and every task to retrieve task-related network segregation scores (255 participants x 12 tasks). Following a pre-established approach (Chan et al., 2014), the network segregation scores were calculated by the difference in mean intra-network FC and mean inter-network FC as a proportion of mean intra-network FC, as noted in the following formula:

$$formula:$$

$$\text{network segregation} = \frac{Z_{intra} - Z_{inter}}{Z_{intra}}$$

Z_{intra} resembles the extent of intra-network FC and Z_{inter} resembles the extent of inter-network FC. Z_{intra} was calculated as the mean Fisher z-transformed r between nodes within the same subnetwork and Z_{inter} was calculated as the mean Fisher z-transformed r between nodes of one subnetwork to nodes of all other subnetworks. For this formula, all negative FC values were disregarded and only positive FC values were retained. No threshold for positive FC was applied.

4.10. Statistical analysis

To investigate whether network segregation as a functional brain property (mediator variable) can serve as an underlying mechanism by which LFC hub connectivity (independent variable) enhances cognitive performance (outcome variable) a causal mediation model was conducted. Causal mediation models serve to clarify mechanisms that underly the relationship between two variables.

First, for conducting a causal mediation model three obligatory criterions must be met: (1) the independent variable (LFC hub connectivity) significantly predicts the outcome variable (task performance), (2) the independent variable significantly predicts the potential mediator (network segregation) and (3) the mediator variable remains a significant predictor of the outcome variable when the independent variable is included in the regression analysis (Baron & Kenny, 1986). To meet these three criterions, linear regression models were conducted for all twelve fMRI data sets to test all three associations between (1) LFC hub connectivity and fMRI task performance, (2) LFC hub connectivity and network segregation, (3) network segregation and fMRI task performance. In each linear regression model, control variables (i.e., age, gender and education) were utilized to account for confounding effects. All reported regression models were calculated using the *lm* command as implemented in the R base library (R Development Core Team, 2018).

After significant effects were found for all three multiple linear regression models, a causal mediation model was applied to assess whether network segregation (i.e., mediator variable) can mediate the association between global task-related LFC hub

connectivity (i.e., independent variable) and task performance (i.e., outcome variable). The calculation of the causal mediation analysis was achieved by utilizing the *mediate* command as implemented in the R package "mediation" (Tingley et al., 2014). For each conducted causal mediation analysis, the significance of the indirect effect (average causal mediation effect = ACME) and direct effect (average direct effect = ADE) was computed via non-parametric bootstrapping (n = 1000 iterations) and the mediations were considered as a full (i.e, complete) mediation when ACME was significant and the ADE was insignificant. However, when ACME and ADE were both significant, the result was interpreted as partial mediation. All associations and variance explained were considered significant at a threshold of $p < 0.05$.

5. Results

5.1. LFC hub connectivity predicts fluid reasoning performance

As a first analysis step, the aim was to explore whether global LFC hub connectivity is predictive of task performance in any of the four cognitive domains (memory, fluid reasoning, perceptual speed, vocabulary). The associations between global task-related LFC hub connectivity and task performance were assessed for each of the twelve tasks with the following linear regression model:

$$model:$$

$$task\ performance\ x\ LFC\ connectivity + gender + age + education + \epsilon$$

Higher task-related LFC hub connectivity during fluid reasoning tasks was significantly associated with better task performance in two tasks belonging to the cognitive domain fluid reasoning (*letter sets*: $ß = 0.192$, $p < 0.01$ and *paper folding*: $ß = 0.170$, $p < 0.01$). However, there were no significant associations with task performances in the other three cognitive domains (i.e., memory, perceptual speed and vocabulary) and also no significant association with one task performance (*matrix reasoning*) in fluid reasoning. All regression models were controlled for age, gender and education. Scatter plots for associations between global LFC hub connectivity and fMRI task performance are illustrated in Figure 7.

Figure 7: Scatter plots illustrating the associations between global LFC connectivity and task performance

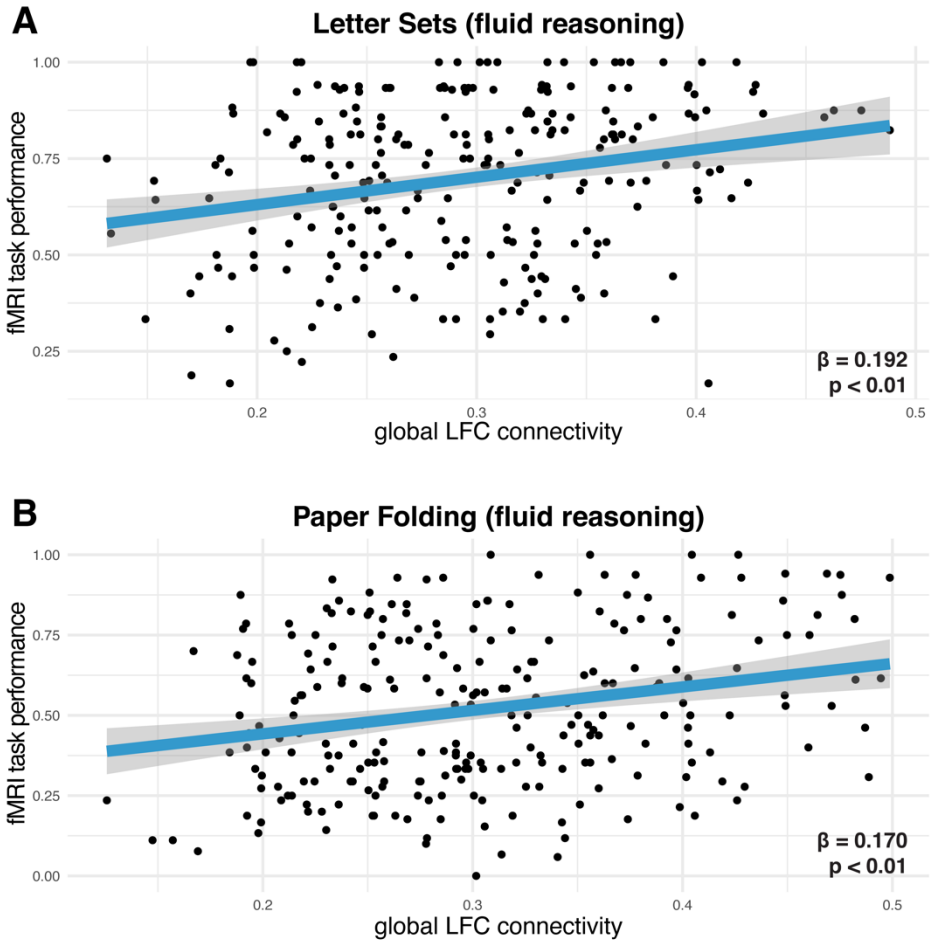

Figure 7: Scatter plots illustrating the observed significant associations between **A**) task-related LFC hub connectivity and fMRI task performance in *letter sets* (cognitive domain: fluid reasoning) and **B**) task-related LFC hub connectivity and fMRI task performance in *paper folding* (cognitive domain: fluid reasoning). Standardized ß-weights and p-values derived from linear regression analysis are shown in the lower right corner of the plots. All models were controlled for age, gender and education.

5.2. Network segregation predicts cognitive performance in tfMRI

Next, the aim was to test whether task-related network segregation (Chan et al., 2014) was predictive of fMRI task performance in any cognitive domain. Hence, the following linear regression model was applied:

$$model:$$

$$task\ performance \times network\ segregation + gender + age + education + \epsilon$$

Higher task-related network segregation was found to be positively associated with fMRI task performances in all tasks belonging to the cognitive domain fluid reasoning. The positive associations in fluid reasoning tasks were strongest in descending order: *matrix reasoning*: ß = 0.263, $p < 0.01$, *letter sets*: ß = 0.256, $p < 0.01$, *paper folding*: ß = 0.248, $p < 0.01$. However, besides positive associations with fluid reasoning task performances, there were also positive associations for one task belonging to the cognitive domain memory (*logical memory*: ß = 0.164, $p = 0.02$) and for two tasks belonging to the cognitive domain vocabulary (*synonyms*: ß = 0.194, $p < 0.01$, *antonyms*: ß = 0.227, $p < 0.01$). In conclusion, positive associations were found between task-related network segregation and fMRI task performances in every cognitive domain except for the cognitive domain perceptual speed. Again, the linear regression models were controlled for age, education and gender. Scatter plots for associations between network segregation and fMRI task performance are illustrated in Figure 8 and 9.

Figure 8: Scatter plots illustrating the associations between network segregation and task performance

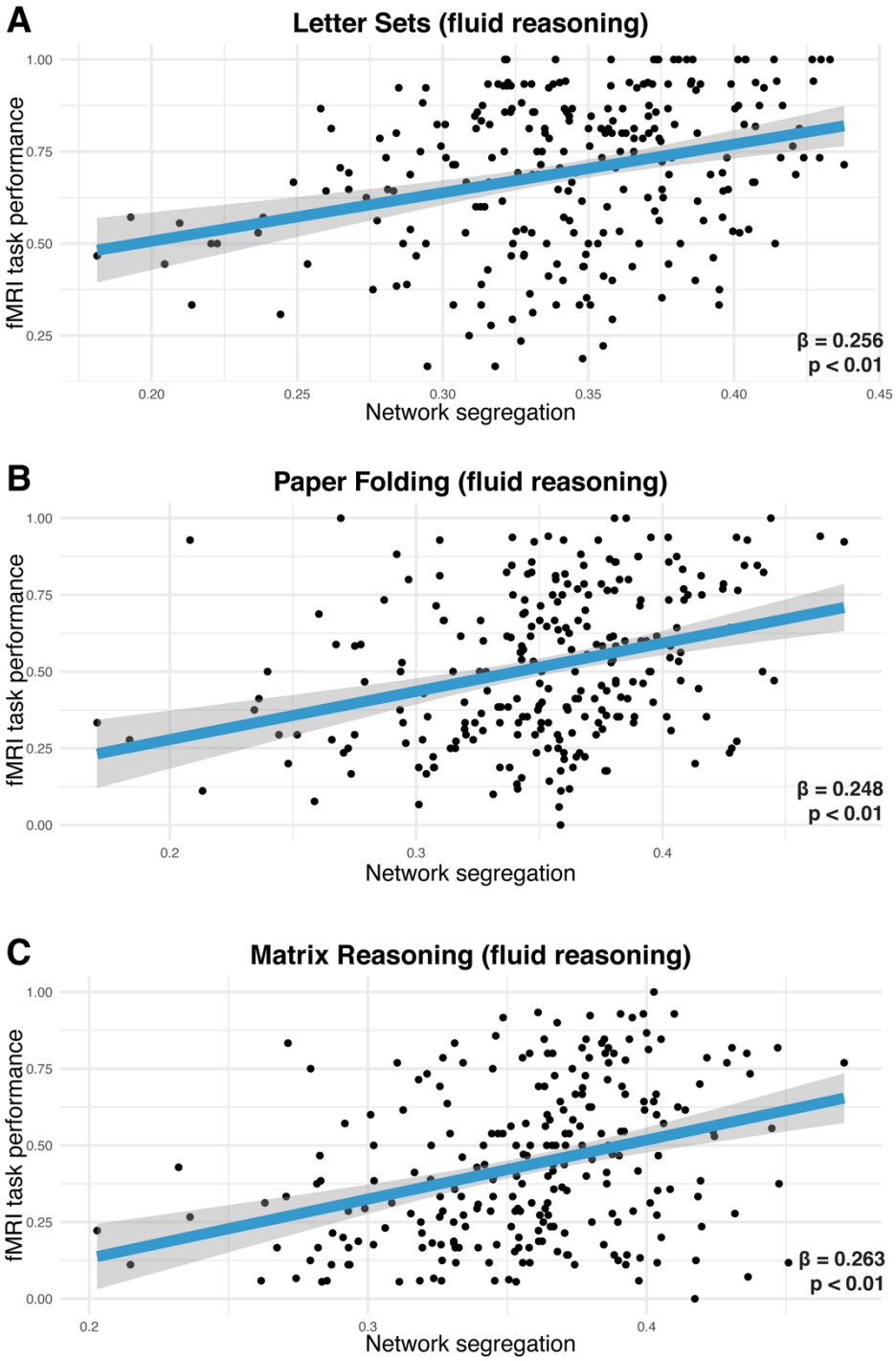

Figure 8: Scatter plots illustrating the associations between **A**) task-related network segregation and fMRI task performance in *letter sets* (cognitive domain: fluid reasoning), **B**) task-related network segregation and fMRI task performance in *paper folding* (cognitive domain: fluid reasoning) and **C**) task-related network segregation and fMRI task performance in *matrix reasoning* (cognitive domain: fluid reasoning). Standardized ß-weights and p-values derived from linear regression analysis are shown in the lower right corner of the plots. All regression models were controlled for age, gender and education.

Figure 9: Scatter plots illustrating the associations between network segregation and task performance

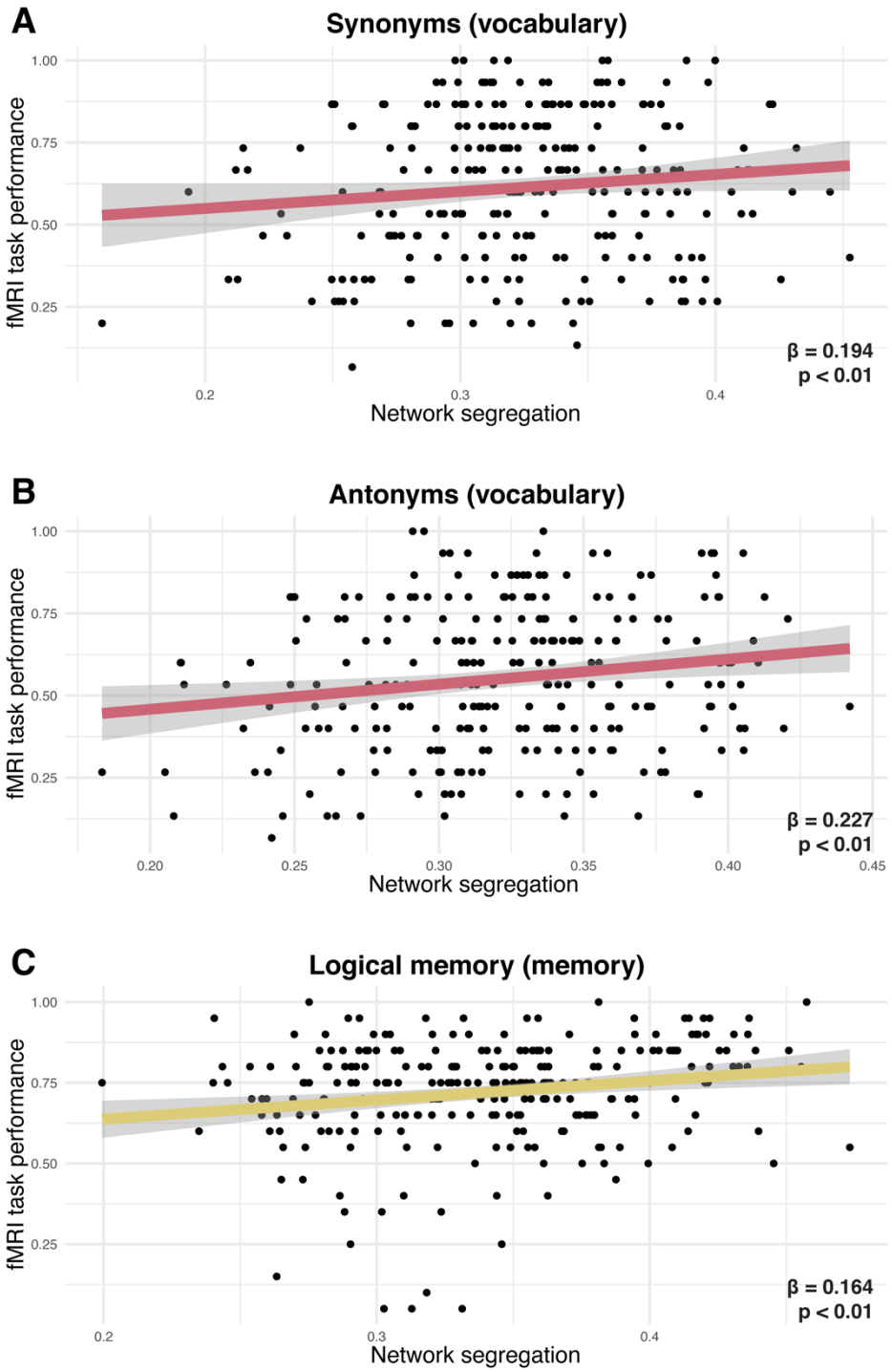

Figure 9: Scatter plots illustrating the associations between **A**) task-related network segregation and fMRI task performance in *synonyms* (cognitive domain: vocabulary), **B**) task-related network segregation and fMRI task performance in *antonyms* (cognitive domain: vocabulary) and **C**) task-related network segregation and fMRI task performance in *logical memory* (cognitive domain: memory). Standardized ß-weights and p-values derived from linear regression analysis are shown in the lower right corner of the plots. All regression models were controlled for age, gender and education.

5.3. LFC hub connectivity is associated with network segregation in fluid reasoning

The main hypothesis postulates that global, task-related LFC hub connectivity is associated with better cognitive performance in normal aging by enhancing the functional organization of brain networks (i.e., network segregation). As a prerequisite for the subsequent causal mediation analysis, the association between task-related LFC hub connectivity and network segregation was tested by conducting the following linear regression model:

$$model:$$

$$network\ segregation \times LFC\ connectivity + gender + age + education + \epsilon$$

First, positive associations between higher task-related LFC hub connectivity and task-related network segregation were observed for all tasks belonging to the cognitive domain fluid reasoning (see Fig. 10). Specifically, LFC hub connectivity was predictive of enhanced network segregation in subsequent tasks: *letter sets* ($ß = 0.25$, $p < 0.01$), *paper folding* ($ß = 0.139$, $p < 0.01$) and *matrix reasoning* ($ß = 0.2$, $p < 0.01$). Further associations between global LFC hub connectivity and network segregation were found for tasks belonging to the other cognitive domains as well. In the cognitive domain memory, the associations were not significant for the tasks *logical memory* and *word order* while there was a negative, significant association between LFC hub connectivity and *paired associates* ($ß = -0.133$, $p < 0.01$). In the cognitive domain perceptual speed, the associations were not significant for *digital symmetry* and *letter comparison* while there was a negative, significant association between LFC hub connectivity and network segregation in *pattern comparison* ($ß = -0.171$, $p < 0.01$). In the cognitive domain

vocabulary, no significant associations for any tasks were observed but negative insignificant tendencies were noticed. Again, all regression models were controlled for age, gender and education.

Figure 10: Scatter plots illustrating the associations between LFC connectivity and network segregation

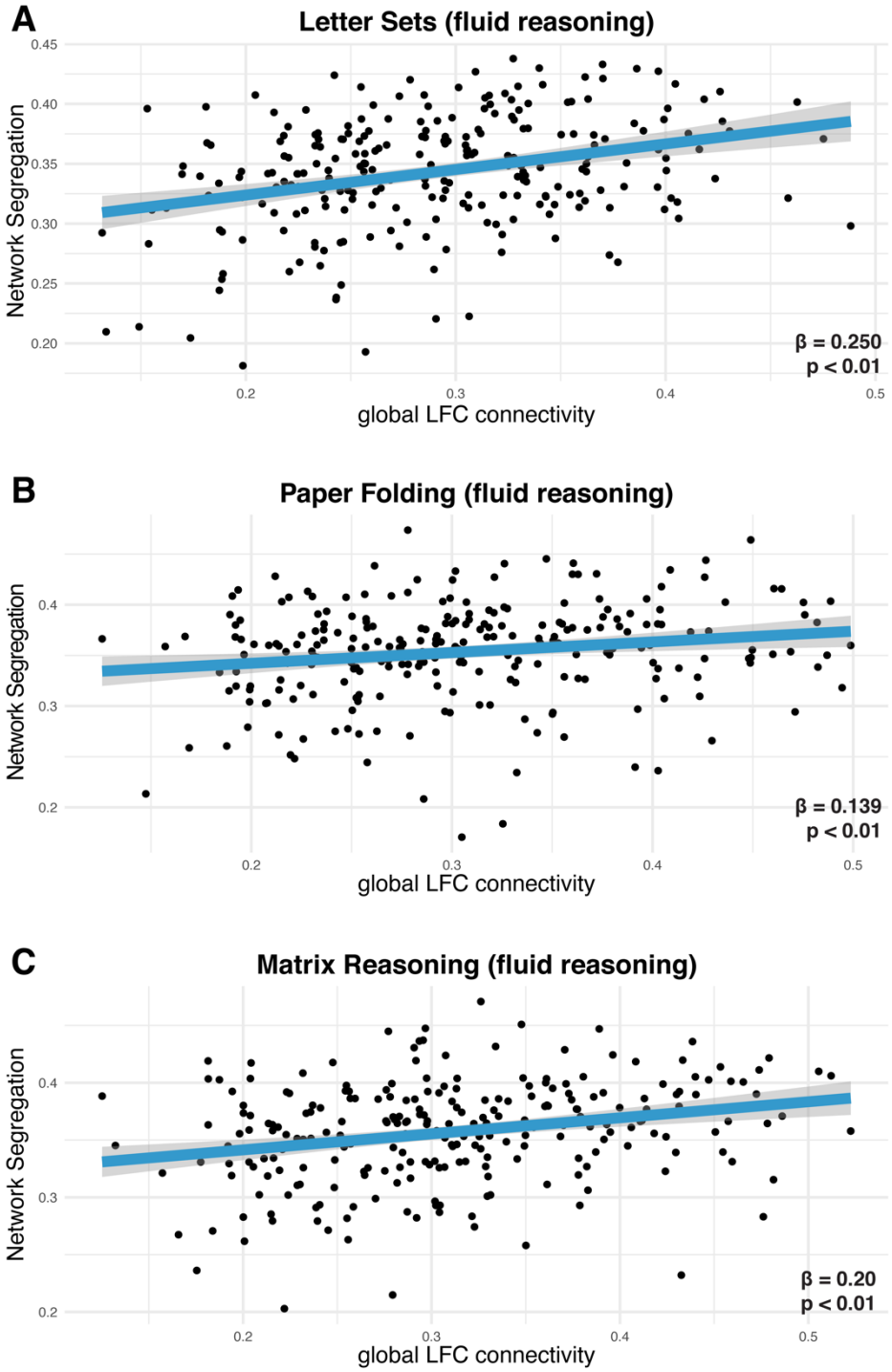

Figure 10: Scatter plots illustrating the associations between **A**) global LFC hub connectivity and network segregation in *letter sets* (cognitive domain: fluid reasoning), **B**) global LFC hub connectivity and network segregation in *paper folding* (cognitive domain: fluid reasoning) and **C**) global LFC hub connectivity and network segregation in *matrix reasoning* (cognitive domain: fluid reasoning). Standardized ß-weights and p-values derived from linear regression analysis are shown in the lower right corner of the plots. All regression models were controlled for age, gender and education.

5.4. Network segregation mediates the association between LFC hub connectivity and fluid reasoning performance

As the final step of analysis, a causal mediation model was conducted to investigate whether network segregation can mediate the association between global LFC hub connectivity and task performance in the cognitive domain fluid reasoning. Since global LFC hub connectivity was found to be positively associated with a) network segregation and b) two fMRI task performances in fluid reasoning, a causal mediation model was conducted for the respective two tasks (*letter sets and paper folding*) matching the obligatory criterions.

For the task *letter sets* (see Figure 11.A), the effect of global LFC hub connectivity on task performance was found to be partially mediated via an increased network segregation. Using non-parametric bootstrapping, the significance of the indirect effect (i.e., average causal mediation effect = ACME) and direct effect (i.e., average direct effect = ADE) was computed and unstandardized ACME's and ADE's were calculated for 1000 bootstrapping iterations. The 95% confidence interval was determined by defining the ACME and ADE at the 2.5^{th} and 97.5^{th} percentiles. The bootstrapped unstandardized ACME of network segregation was significant (ACME = 0.165, $p < 0.01$) and the 95^{th} confidence interval ranged from 0.06 to 0.29. Since the bootstrapped ADE was also found to be significant (ADE = 0.405, $p < 0.05$), the computed mediation was interpreted as a partial mediation.

A similar partial mediation was found for the second fluid reasoning task *paper folding* (see Figure 11.B) where the effect of global LFC hub connectivity on task performance was partially mediated via an increased network segregation. After applying non-

parametric bootstrapping procedures again, the ACME and ADE were both found to be significant (ACME = 0.1, $p < 0.05$ and ADE = 0.417, $p < 0.01$). Here, the 95th confidence interval of ACME ranged from 0.01 to 0.22. Thus, again, the computed mediation was interpreted as partial mediation.

Figure 11: Illustration of the causal mediation analysis

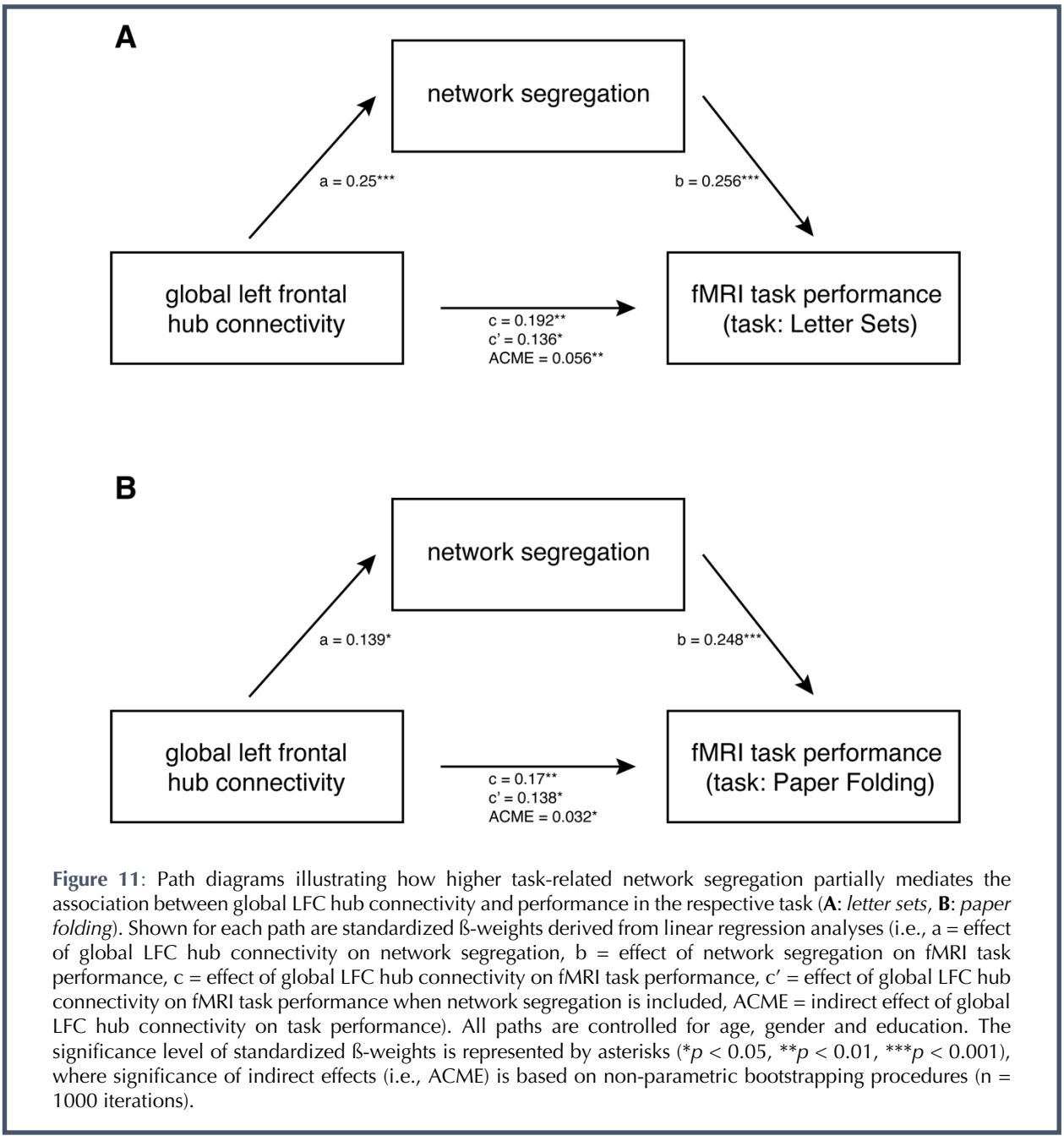

Figure 11: Path diagrams illustrating how higher task-related network segregation partially mediates the association between global LFC hub connectivity and performance in the respective task (**A**: *letter sets*, **B**: *paper folding*). Shown for each path are standardized ß-weights derived from linear regression analyses (i.e., a = effect of global LFC hub connectivity on network segregation, b = effect of network segregation on fMRI task performance, c = effect of global LFC hub connectivity on fMRI task performance, c' = effect of global LFC hub connectivity on fMRI task performance when network segregation is included, ACME = indirect effect of global LFC hub connectivity on task performance). All paths are controlled for age, gender and education. The significance level of standardized ß-weights is represented by asterisks (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$), where significance of indirect effects (i.e., ACME) is based on non-parametric bootstrapping procedures (n = 1000 iterations).

6. Discussion and Conclusion

The main goal of this doctoral thesis was to investigate a potential protective brain mechanism facilitating the association between global LFC hub connectivity and better cognitive function in normal aging. It was hypothesized that global LFC hub connectivity supports cognitive function by increasing the functional organization of brain networks, i.e. task-related network segregation.

The major findings of this doctoral thesis show that (1) task-related LFC hub connectivity is associated with an enhanced fMRI task performance in the cognitive domain fluid reasoning (2) higher task-related network segregation is associated with better task performance throughout the cognitive domains of fluid reasoning, vocabulary and memory (3) task-related LFC hub connectivity predicts increased network segregation in tasks belonging to the cognitive domain fluid reasoning, and (4) increased network segregation partially mediates the association between global LFC hub connectivity and task performance in fluid reasoning.

First, the association between brain-wide LFC hub connectivity and fMRI task performance in four different cognitive domains was tested. Here, positive associations were found for all three fMRI task performances belonging to the cognitive domain fluid reasoning (i.e., fluid intelligence). In every other cognitive domain, no significant associations were found. These findings are in line with results of prior studies which revealed an association between the frontoparietal control system (i.e., including the LFC hub) and fluid intelligence (Cole et al., 2015; Cole et al., 2012). As fluid intelligence in particular decreases with advanced age (Horn & Cattell, 1967), higher LFC hub

connectivity may thus represent a key feature to comprehend how some individuals maintain cognitive function at a relative high level despite age-related brain changes. Nevertheless, there is still a lack of information about brain mechanisms supporting the association between higher, global LFC hub connectivity and relatively preserved fluid intelligence in older individuals.

Next, to investigate whether network segregation could serve as such a protective brain mechanism, the association between network segregation and cognitive performance was tested. Throughout three cognitive domains (i.e., fluid reasoning, vocabulary and memory) higher network segregation predicted increased fMRI task performance. Overall, these results demonstrate that the segregation of subnetworks is beneficial for cognitive performance in normal aging and may thus represent a functional brain mechanism. Moreover, functional brain mechanisms portray a possible gateway to comprehend inter-individual differences in age- and AD-related cognitive decline. Since positive associations were found across multiple tasks (six out of twelve fMRI tasks), network segregation appears to enhance cognition throughout several cognitive domains and may thus be identified as a global functional property. However, as network segregation predicted cognitive performance strongest in fluid reasoning tasks, it's arguable that this mechanism is especially required under circumstances where attention and cognitive control are being utilized. In addition, recent evidence suggests that attention- and control-networks in particular have a more drastic age-related decrease in functional network segregation compared to sensory-motory systems indicating that an age-related cognitive decline (i.e., decrease in fluid intelligence) can be partially attributed to a reduced segregation of networks (Chan et al., 2014). Together, these results line up with previous studies showing that the segregation of networks is pivotal

for high-demand cognitive tasks whereas network integration (i.e., the higher cross-wiring of different networks) is necessary for tasks where multiple networks are involved (e.g., working memory processes) (Cohen & D'Esposito, 2016). Increased functional network segregation could therefore reflect a higher autonomy of the respective task-relevant network and lead to a less resource-dependent cognitive process (Bassett et al., 2015). Hence, higher functional network segregation might be associated with higher task performance throughout several cognitive domains as it preserves resources by enhancing the functional organization of networks.

To address the question whether network segregation could serve as a protective brain feature by which the LFC hub increases cognitive function in normal aging, associations between LFC hub connectivity and network segregation were tested. Higher LFC hub connectivity was found to predict network segregation in all tasks belonging to the cognitive domain fluid reasoning (i.e., *paper folding*, *matrix reasoning* and *letter sets*). Here again, no significant associations were found between LFC hub connectivity and task performance in the other three cognitive domains. Recent studies support these results by showing that control network hubs (i.e., the LFC hub) enable the functional organization of brain networks into difficult-to-reach states which plays an important role in executing challenging activities such as fluid reasoning (Gu et al., 2015). Thus, network segregation could offer one possible explanation on how higher global LFC hub connectivity increases brain efficiency and thereby improves cognitive performance despite age-related or pathological brain changes. In contrast, participants with lower LFC hub connectivity showed a reduced functional connectivity pattern by exhibiting less intra-connected subnetworks and more diffusely connected brain regions (see Fig. 12). These findings extend and confirm previous findings on fMRI-assessed LFC hub

connectivity and its relation to protective brain features (Franzmeier et al., 2017B; Franzmeier et al., 2018).

After all three obligatory criteria for conducting a causal mediation analysis were met (see Chapter 4.10.), network segregation was found to partially mediate the association of higher LFC hub connectivity with increased cognitive performance in fluid reasoning. Since the LFC hub has been previously associated with higher cognitive reserve in AD (Franzmeier et al., 2017B), it is assumable that network segregation could thus be identified as a potential protective brain feature underpinning functional mechanisms by which LFC increases or attributes to cognitive reserve. Specifically, as part of the FPCN, the LFC shifts its connectivity to networks across cognitive tasks and thereby orchestrates the activity of neural networks (Cole et al., 2014). Hence, the association between global LFC hub connectivity and higher network segregation could indicate that the LFC hub regulates brain activity at the network level during task performance, thus enhancing the activity of task-relevant networks while reducing the activity of task-irrelevant networks, resulting in less diffuse global brain activity but higher network segregation. However, the current study is correlational in nature and a causative interpretation is not possible but needs to await experimental manipulation of LFC hub connectivity. Together, these results imply that higher global LFC hub connectivity contributes to cognitive function in normal aging via enhancing the functional segregation of subnetworks and thereby increasing cognitive performance in certain task states (i.e., fluid intelligence).

For the interpretation of these findings, multiple limitations should be considered. In this thesis, a potential mechanism (i.e., network segregation) was investigated by which global LFC hub connectivity contributes to cognitive reserve in normal aging. While LFC

hub connectivity has been found to influence cognitive reserve in the face of major neuropathology in AD, in this study only healthy individuals were assessed who did not experience cognitive decline or were diagnosed with AD. Therefore, the transferability of these findings to patients who are diagnosed with AD may be unclear. Furthermore, recent findings suggesting that higher LFC hub connectivity is associated with better memory performance could not be replicated in this thesis (Franzmeier et al., 2017C). This might be due to the fact that this association is stronger shown in individuals who already experience significant pathological brain changes or symptoms. In addition, for the calculation of network segregation the brain was parcellated into 400 regions forming a large-scale network consisting of seven subnetworks (Schaefer et al., 2018; Yeo et al., 2011). Since the brain undergoes age-related changes throughout the life (Varangis et al., 2019), the a priori definition of seven subnetworks could be problematic for the measure of network segregation. However, studies indicate a high reproducibility for the formation of large-scale networks in aging and AD (Meunier et al., 2009). Furthermore, please note that a "causal mediation analysis" might suggest that the calculated partial mediation effect is causal and therefore directly explains the observed relationship between LFC hub connectivity and task performance in fluid reasoning. Nevertheless, this is a wrong assumption as a "causal mediation analysis" only serves to clarify the association between independent (i.e., LFC connectivity) and dependent (i.e., task performance) variables but cannot clarify the direct, causal effect. Although a significant partially mediated effect was calculated, partial mediations only account to some extent for the relationship between independent (i.e., LFC hub connectivity) and dependent variable (i.e., task performance). Hence, network segregation might be just one of many possible protective brain properties by which LFC distributes to the

phenomenon of cognitive reserve. This shows that additional protective brain properties or other possible underlying functional mechanisms might confound for the effect of network segregation.

In conclusion, these findings indicate that network segregation serves as a potential functional mechanism by which the LFC hub increases cognitive performance in normal aging. Since the LFC hub has been previously associated with cognitive reserve in AD and is thus considered to be associated with protective brain features, network segregation could be identified as one potential key mechanism to cope with AD-pathology. As network segregation only partially mediated the association with cognitive performance, there are still unanswered questions regarding additional functional mechanisms underlying global LFC hub connectivity and its relation to cognitive reserve. Although this thesis gives some insight into one protective mechanism by which the LFC hub increases cognitive performance and thus attributes to cognitive reserve in normal aging, these results must be further validated in study samples containing patients diagnosed with AD or other neurodegenerative diseases. To date, 110 years after the discovery of AD, there is no effective treatment available and pharmaceutical therapy remains a big challenge. However, studies have demonstrated that non-invasive stimulation of the LFC hub is possible and that an application of this therapeutic procedure results in higher connectivity and enhanced cognitive performance (Drumond Marra et al., 2015; Gratton et al., 2013). Hence, increasing the understanding of functional mechanisms and protective brain properties underlying cognitive reserve in normal aging and AD could further support the application of concepts such as transcranial brain stimulation or cognitive training as a secondary prevention approach.

Figure 12: Force-directed plots illustrating the association between LFC hub connectivity and network segregation

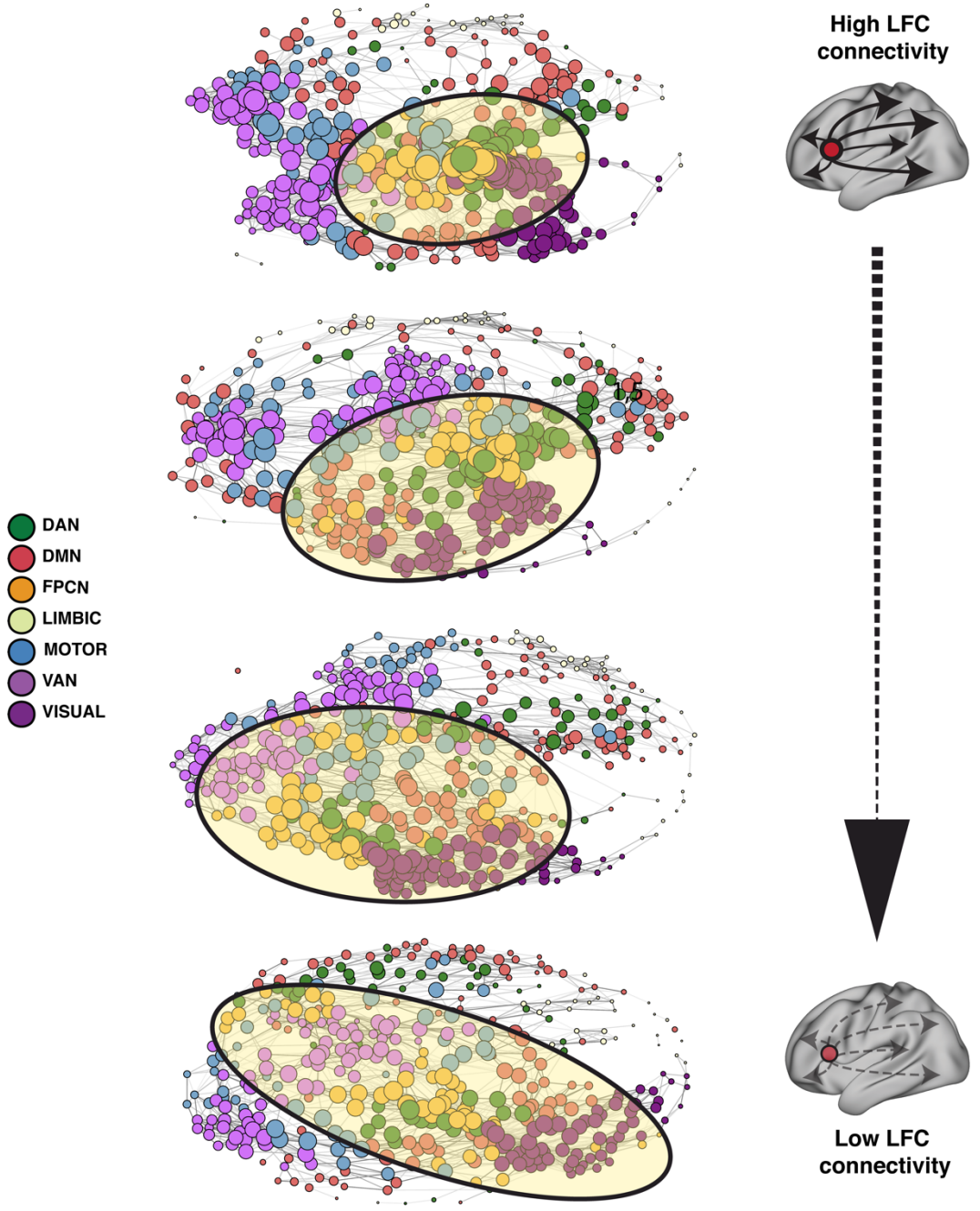

Figure 12: Force-directed plots with a spring-embedded layout created with group-meaned, task-related FC derived from the task *letter sets* (cognitive domain: fluid reasoning). Participants were divided into four cohorts based on their quartiled LFC connectivity. For every cohort, the FC matrices of each participant were meaned into one FC matrix and a force-directed plot was constructed. The node sizes are dependent on their meaned FC (i.e., bigger nodes exhibit higher FC during the task *letter sets*). Networks with greater relation to fluid reasoning (e.g., DAN and Control) exhibit higher network segregation. The DAN-network is highlighted for each quartile with a yellow, transparent circle. As LFC hub connectivity decreases, the DAN network segregates itself less from other networks and the nodes shrink in size representing a lesser extent of FC. This trend can be observed for other subnetworks as well. Abbreviations: DMN = Default Mode Network, DAN = Dorsal Attention Network, FPCN = Fronto Parietal Control Network, Limbic = Limbic Network, Motor = Motor Networks, VAN = Ventral Attention Network, Visual = Visual Motory Network.

7. References

Aertsen, A. M., Gerstein, G. L., Habib, M. K., & Palm, G. (1989). Dynamics of neuronal firing correlation: modulation of "effective connectivity". *J Neurophysiol, 61*(5), 900-917. doi:10.1152/jn.1989.61.5.900

Alzheimer's Association. (2020). 2020 Alzheimer's disease facts and figures. *Alzheimers Dement*. doi:10.1002/alz.12068

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *Neuroimage, 38*(1), 95-113. doi:10.1016/j.neuroimage.2007.07.007

Bandettini, P. A., Wong, E. C., Hinks, R. S., Tikofsky, R. S., & Hyde, J. S. (1992). Time course EPI of human brain function during task activation. *Magn Reson Med, 25*(2), 390-397. doi:10.1002/mrm.1910250220

Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol, 51*(6), 1173-1182. doi:10.1037//0022-3514.51.6.1173

Baroncelli, L., Braschi, C., Spolidoro, M., Begenisic, T., Sale, A., & Maffei, L. (2010). Nurturing brain plasticity: impact of environmental enrichment. *Cell Death Differ, 17*(7), 1092-1103. doi:10.1038/cdd.2009.193

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends Cogn Sci, 17*(10), 502-509. doi:10.1016/j.tics.2013.08.012

Bassett, D. S., Yang, M., Wymbs, N. F., & Grafton, S. T. (2015). Learning-induced autonomy of sensorimotor systems. *Nat Neurosci, 18*(5), 744-751. doi:10.1038/nn.3993

Bertolero, M. A., Yeo, B. T. T., Bassett, D. S., & D'Esposito, M. (2018). A mechanistic model of connector hubs, modularity and cognition. *Nat Hum Behav, 2*(10), 765-777. doi:10.1038/s41562-018-0420-6

Bertolero, M. A., Yeo, B. T. T., & D'Esposito, M. (2017). The diverse club. *Nat Commun, 8*(1), 1277. doi:10.1038/s41467-017-01189-w

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med, 34*(4), 537-541. doi:10.1002/mrm.1910340409

Biswal, B. B. (2012). Resting state fMRI: a personal history. *Neuroimage, 62*(2), 938-944. doi:10.1016/j.neuroimage.2012.01.090

Bloom, D. E., Boersch-Supan, A., McGee, P., & Seike, A. (2011). Population aging: facts, challenges, and responses. *Benefits and compensation International, 41*(1), 22.

Brown, R. E. (2016). Hebb and Cattell: The Genesis of the Theory of Fluid and Crystallized Intelligence. *Front Hum Neurosci, 10*, 606. doi:10.3389/fnhum.2016.00606

Bugg, J. M., Zook, N. A., DeLosh, E. L., Davalos, D. B., & Davis, H. P. (2006). Age differences in fluid intelligence: contributions of general slowing and frontal decline. *Brain Cogn, 62*(1), 9-16. doi:10.1016/j.bandc.2006.02.006

Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci, 10*(3), 186-198. doi:10.1038/nrn2575

Burns, A., Byrne, E. J., & Maurer, K. (2002). Alzheimer's disease. *Lancet, 360*(9327), 163-165. doi:10.1016/S0140-6736(02)09420-5

Cabeza, R., Albert, M., Belleville, S., Craik, F. I. M., Duarte, A., Grady, C. L., . . . Rajah, M. N. (2018). Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nat Rev Neurosci, 19*(11), 701-710. doi:10.1038/s41583-018-0068-2

Chan, M. Y., Park, D. C., Savalia, N. K., Petersen, S. E., & Wig, G. S. (2014). Decreased segregation of brain systems across the healthy adult lifespan. *Proc Natl Acad Sci U S A, 111*(46), E4997-5006. doi:10.1073/pnas.1415122111

Clare, L., Wu, Y. T., Teale, J. C., MacLeod, C., Matthews, F., Brayne, C., . . . team, C. F.-W. s. (2017). Potentially modifiable lifestyle factors, cognitive reserve, and cognitive function in later life: A cross-sectional study. *PLoS Med, 14*(3), e1002259. doi:10.1371/journal.pmed.1002259

Cohen, J. R., & D'Esposito, M. (2016). The Segregation and Integration of Distinct Brain Networks and Their Relationship to Cognition. *J Neurosci, 36*(48), 12083-12094. doi:10.1523/JNEUROSCI.2965-15.2016

Cole, M. W., Bassett, D. S., Power, J. D., Braver, T. S., & Petersen, S. E. (2014). Intrinsic and task-evoked network architectures of the human brain. *Neuron, 83*(1), 238-251. doi:10.1016/j.neuron.2014.05.014

Cole, M. W., Ito, T., & Braver, T. S. (2015). Lateral Prefrontal Cortex Contributes to Fluid Intelligence Through Multinetwork Connectivity. *Brain Connect, 5*(8), 497-504. doi:10.1089/brain.2015.0357

Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., & Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. *Nat Neurosci, 16*(9), 1348-1355. doi:10.1038/nn.3470

Cole, M. W., Yarkoni, T., Repovs, G., Anticevic, A., & Braver, T. S. (2012). Global connectivity of prefrontal cortex predicts cognitive control and intelligence. *J Neurosci, 32*(26), 8988-8999. doi:10.1523/JNEUROSCI.0536-12.2012

Di, X., Gohel, S., Kim, E. H., & Biswal, B. B. (2013). Task vs. rest-different network configurations between the coactivation and the resting-state brain networks. *Front Hum Neurosci, 7*, 493. doi:10.3389/fnhum.2013.00493

Drumond Marra, H. L., Myczkowski, M. L., Maia Memoria, C., Arnaut, D., Leite Ribeiro, P., Sardinha Mansur, C. G., . . . Marcolin, M. A. (2015). Transcranial Magnetic Stimulation to Address Mild Cognitive Impairment in the Elderly: A Randomized Controlled Study. *Behav Neurol, 2015*, 287843. doi:10.1155/2015/287843

Duthey, B. (2013). Background paper 6.11: Alzheimer disease and other dementias. *A public health approach to innovation, 6*, 1-74.

Elias-Sonnenschein, L. S., Viechtbauer, W., Ramakers, I. H., Verhey, F. R., & Visser, P. J. (2011). Predictive value of APOE-epsilon4 allele for progression from MCI to AD-type dementia: a meta-analysis. *J Neurol Neurosurg Psychiatry, 82*(10), 1149-1156. doi:10.1136/jnnp.2010.231555

Fiest, K. M., Roberts, J. I., Maxwell, C. J., Hogan, D. B., Smith, E. E., Frolkis, A., . . . Jette, N. (2016). The Prevalence and Incidence of Dementia Due to Alzheimer's Disease: a Systematic Review and Meta-Analysis. *Can J Neurol Sci, 43 Suppl 1*, S51-82. doi:10.1017/cjn.2016.36

Fornito, A., Harrison, B. J., Zalesky, A., & Simons, J. S. (2012). Competitive and cooperative dynamics of large-scale brain functional networks supporting recollection. *Proc Natl Acad Sci U S A, 109*(31), 12788-12793. doi:10.1073/pnas.1204185109

Franzmeier, N., Duering, M., Weiner, M., Dichgans, M., Ewers, M., & Alzheimer's Disease Neuroimaging, I. (2017A). Left frontal cortex connectivity underlies cognitive reserve in prodromal Alzheimer disease. *Neurology, 88*(11), 1054-1061. doi:10.1212/WNL.0000000000003711

Franzmeier, N., Duzel, E., Jessen, F., Buerger, K., Levin, J., Duering, M., . . . Ewers, M. (2018). Left frontal hub connectivity delays cognitive impairment in autosomal-dominant and sporadic Alzheimer's disease. *Brain, 141*(4), 1186-1200. doi:10.1093/brain/awy008

Franzmeier, N., Gottler, J., Grimmer, T., Drzezga, A., Araque-Caballero, M. A., Simon-Vermot, L., . . . Ewers, M. (2017B). Resting-State Connectivity of the Left Frontal Cortex to the Default Mode and Dorsal Attention Network Supports Reserve in Mild Cognitive Impairment. *Front Aging Neurosci, 9*, 264. doi:10.3389/fnagi.2017.00264

Franzmeier, N., Hartmann, J., Taylor, A. N. W., Araque-Caballero, M. A., Simon-Vermot, L., Kambeitz-Ilankovic, L., . . . Ewers, M. (2018). The left frontal cortex supports reserve in aging by enhancing functional network efficiency. *Alzheimers Res Ther, 10*(1), 28. doi:10.1186/s13195-018-0358-y

Franzmeier, N., Hartmann, J. C., Taylor, A. N. W., Araque Caballero, M. A., Simon-Vermot, L., Buerger, K., . . . Ewers, M. (2017C). Left Frontal Hub Connectivity during Memory Performance Supports Reserve in Aging and Mild Cognitive Impairment. *J Alzheimers Dis, 59*(4), 1381-1392. doi:10.3233/JAD-170360

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage, 6*(3), 218-229. doi:10.1006/nimg.1997.0291

Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. (1993). Functional connectivity: the principal-component analysis of large (PET) data sets. *J Cereb Blood Flow Metab, 13*(1), 5-14. doi:10.1038/jcbfm.1993.4

Gitelman, D. R., Penny, W. D., Ashburner, J., & Friston, K. J. (2003). Modeling regional and psychophysiologic interactions in fMRI: the importance of hemodynamic deconvolution. *Neuroimage, 19*(1), 200-207. doi:10.1016/s1053-8119(03)00058-2

Gonzalez-Fernandez, M., Davis, C., Molitoris, J. J., Newhart, M., Leigh, R., & Hillis, A. E. (2011). Formal education, socioeconomic status, and the severity of aphasia after stroke. *Arch Phys Med Rehabil, 92*(11), 1809-1813. doi:10.1016/j.apmr.2011.05.026

Gordon, E. M., Laumann, T. O., Adeyemo, B., Huckins, J. F., Kelley, W. M., & Petersen, S. E. (2016). Generation and Evaluation of a Cortical Area Parcellation from Resting-State Correlations. *Cereb Cortex, 26*(1), 288-303. doi:10.1093/cercor/bhu239

Gratton, C., Lee, T. G., Nomura, E. M., & D'Esposito, M. (2013). The effect of theta-burst TMS on cognitive control networks measured with resting state fMRI. *Front Syst Neurosci, 7*, 124. doi:10.3389/fnsys.2013.00124

Gratton, C., Sun, H., & Petersen, S. E. (2018). Control networks and hubs. *Psychophysiology, 55*(3). doi:10.1111/psyp.13032

Grayson, D. S., Ray, S., Carpenter, S., Iyer, S., Dias, T. G., Stevens, C., . . . Fair, D. A. (2014). Structural and functional rich club organization of the brain in children and adults. *PLoS One, 9*(2), e88297. doi:10.1371/journal.pone.0088297

Gu, S., Pasqualetti, F., Cieslak, M., Telesford, Q. K., Yu, A. B., Kahn, A. E., . . . Bassett, D. S. (2015). Controllability of structural brain networks. *Nat Commun, 6*, 8414. doi:10.1038/ncomms9414

Hanagasi, H. A., Tufekcioglu, Z., & Emre, M. (2017). Dementia in Parkinson's disease. *J Neurol Sci, 374*, 26-31. doi:10.1016/j.jns.2017.01.012

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

Hindle, J. V., Martyr, A., & Clare, L. (2014). Cognitive reserve in Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism Relat Disord, 20*(1), 1-7. doi:10.1016/j.parkreldis.2013.08.010

Horn, J. L., & Cattell, R. B. (1967). Age differences in fluid and crystallized intelligence. *Acta Psychol (Amst), 26*(2), 107-129. doi:10.1016/0001-6918(67)90011-x

Hu, Y. S., Long, N., Pigino, G., Brady, S. T., & Lazarov, O. (2013). Molecular mechanisms of environmental enrichment: impairments in Akt/GSK3beta, neurotrophin-3 and CREB signaling. *PLoS One, 8*(5), e64460. doi:10.1371/journal.pone.0064460

Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., Weiner, M. W., . . . Trojanowski, J. Q. (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol, 9*(1), 119-128. doi:10.1016/S1474-4422(09)70299-6

Katzman, R. (1993). Education and the prevalence of dementia and Alzheimer's disease. *Neurology, 43*(1), 13-20. doi:10.1212/wnl.43.1_part_1.13

Katzman, R., Terry, R., DeTeresa, R., Brown, T., Davies, P., Fuld, P., . . . Peck, A. (1988). Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Ann Neurol, 23*(2), 138-144. doi:10.1002/ana.410230206

Kaul, M. (2009). HIV-1 associated dementia: update on pathological mechanisms and therapeutic approaches. *Curr Opin Neurol, 22*(3), 315-320. doi:10.1097/WCO.0b013e328329cf3c

Kesler, S. R., Adams, H. F., Blasey, C. M., & Bigler, E. D. (2003). Premorbid intellectual functioning, education, and brain size in traumatic brain injury: an investigation of the cognitive reserve hypothesis. *Appl Neuropsychol, 10*(3), 153-162. doi:10.1207/S15324826AN1003_04

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., . . . et al. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci U S A, 89*(12), 5675-5679. doi:10.1073/pnas.89.12.5675

Liska, A., Galbusera, A., Schwarz, A. J., & Gozzi, A. (2015). Functional connectivity hubs of the mouse brain. *Neuroimage, 115*, 281-291. doi:10.1016/j.neuroimage.2015.04.033

Manza, P., Wiers, C. E., Shokri-Kojori, E., Kroll, D., Feldman, D., Schwandt, M., . . . Volkow, N. D. (2020). Brain Network Segregation and Glucose Energy Utilization: Relevance for Age-Related Differences in Cognitive Function. *Cereb Cortex, 30*(11), 5930-5942. doi:10.1093/cercor/bhaa167

Marek, S., & Dosenbach, N. U. F. (2019). Control networks of the frontal lobes. *Handb Clin Neurol, 163*, 333-347. doi:10.1016/B978-0-12-804281-6.00018-5

Mayeux, R., & Stern, Y. (2012). Epidemiology of Alzheimer disease. *Cold Spring Harb Perspect Med, 2*(8). doi:10.1101/cshperspect.a006239

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., . . . Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 263-269. doi:10.1016/j.jalz.2011.03.005

Meunier, D., Achard, S., Morcom, A., & Bullmore, E. (2009). Age-related changes in modular organization of human brain functional networks. *Neuroimage, 44*(3), 715-723. doi:10.1016/j.neuroimage.2008.09.062

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annu Rev Neurosci, 24*, 167-202. doi:10.1146/annurev.neuro.24.1.167

Monti, M. M. (2011). Statistical Analysis of fMRI Time-Series: A Critical Review of the GLM Approach. *Front Hum Neurosci, 5*, 28. doi:10.3389/fnhum.2011.00028

Mortimer, J. A., Snowdon, D. A., & Markesbery, W. R. (2003). Head circumference, education and risk of dementia: findings from the Nun Study. *J Clin Exp Neuropsychol, 25*(5), 671-679. doi:10.1076/jcen.25.5.671.14584

Mowinckel, A. M., & Vidal-Piñeiro, D. (2020). Visualization of brain statistics with R Packages ggseg and ggseg3d. *Advances in Methods and Practices in Psychological Science, 3*(4), 466-483.

Murman, D. L. (2015). The Impact of Age on Cognition. *Semin Hear, 36*(3), 111-121. doi:10.1055/s-0035-1555115

O'Reilly, J. X., Woolrich, M. W., Behrens, T. E., Smith, S. M., & Johansen-Berg, H. (2012). Tools of the trade: psychophysiological interactions and functional connectivity. *Soc Cogn Affect Neurosci, 7*(5), 604-609. doi:10.1093/scan/nss055

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A, 87*(24), 9868-9872. doi:10.1073/pnas.87.24.9868

Ott, A., Breteler, M. M., van Harskamp, F., Stijnen, T., & Hofman, A. (1998). Incidence and risk of dementia. The Rotterdam Study. *Am J Epidemiol, 147*(6), 574-580. doi:10.1093/oxfordjournals.aje.a009489

Paulsen, J. S. (2011). Cognitive impairment in Huntington disease: diagnosis and treatment. *Curr Neurol Neurosci Rep, 11*(5), 474-483. doi:10.1007/s11910-011-0215-x

Pendlebury, S. T., Rothwell, P. M., & Oxford Vascular, S. (2019). Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study. *Lancet Neurol, 18*(3), 248-258. doi:10.1016/S1474-4422(18)30442-3

Perl, D. P. (2010). Neuropathology of Alzheimer's disease. *Mt Sinai J Med, 77*(1), 32-42. doi:10.1002/msj.20157

Perneczky, R., Drzezga, A., Boecker, H., Ceballos-Baumann, A. O., Granert, O., Forstl, H., . . . Haussermann, P. (2008). Activities of daily living, cerebral glucose metabolism, and cognitive reserve in Lewy body and Parkinson's disease. *Dement Geriatr Cogn Disord, 26*(5), 475-481. doi:10.1159/000167791

Peterson, K., Veazie, S., Bourne, D., & Anderson, J. (2019). In *Evidence Brief: Traumatic Brain Injury and Dementia*. Washington (DC).

Piggott, J., & Woodland, A. D. (2016). *Handbook of the economics of population aging*. Amsterdam: Elsevier.

Poustchi-Amin, M., Mirowitz, S. A., Brown, J. J., McKinstry, R. C., & Li, T. (2001). Principles and applications of echo-planar imaging: a review for the general radiologist. *Radiographics, 21*(3), 767-779. doi:10.1148/radiographics.21.3.g01ma23767

Power, J. D., Schlaggar, B. L., Lessov-Schlaggar, C. N., & Petersen, S. E. (2013). Evidence for hubs in human functional brain networks. *Neuron, 79*(4), 798-813. doi:10.1016/j.neuron.2013.07.035

R Development Core Team. (2018). R: A language and environment for statistical computing. *R Foundation for Statistical Computing*.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proc Natl Acad Sci U S A, 98*(2), 676-682. doi:10.1073/pnas.98.2.676

Reitz, C., Brayne, C., & Mayeux, R. (2011). Epidemiology of Alzheimer disease. *Nat Rev Neurol, 7*(3), 137-152. doi:10.1038/nrneurol.2011.2

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage, 52*(3), 1059-1069. doi:10.1016/j.neuroimage.2009.10.003

Salathe, M., & Jones, J. H. (2010). Dynamics and control of diseases in networks with community structure. *PLoS Comput Biol, 6*(4), e1000736. doi:10.1371/journal.pcbi.1000736

Salthouse, T. A., & Davis, H. P. (2006). Organization of cognitive abilities and neuropsychological variables across the lifespan. *Developmental Review, 26*(1), 31-54.

Schaefer, A., Kong, R., Gordon, E. M., Laumann, T. O., Zuo, X. N., Holmes, A. J., . . . Yeo, B. T. T. (2018). Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cereb Cortex, 28*(9), 3095-3114. doi:10.1093/cercor/bhx179

Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med, 8*(6), 595-608. doi:10.15252/emmm.201606210

Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med, 1*(1), a006189. doi:10.1101/cshperspect.a006189

Soares, J. M., Magalhaes, R., Moreira, P. S., Sousa, A., Ganz, E., Sampaio, A., . . . Sousa, N. (2016). A Hitchhiker's Guide to Functional Magnetic Resonance Imaging. *Front Neurosci, 10*, 515. doi:10.3389/fnins.2016.00515

Sporns, O., Tononi, G., & Kotter, R. (2005). The human connectome: A structural description of the human brain. *PLoS Comput Biol, 1*(4), e42. doi:10.1371/journal.pcbi.0010042

Stern, Y. (2003). The concept of cognitive reserve: a catalyst for research. *J Clin Exp Neuropsychol, 25*(5), 589-593. doi:10.1076/jcen.25.5.589.14571
Stern, Y. (2006). Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Disord, 20*(3 Suppl 2), S69-74. doi:10.1097/00002093-200607001-00010
Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015-2028. doi:10.1016/j.neuropsychologia.2009.03.004
Stern, Y., Alexander, G. E., Prohovnik, I., & Mayeux, R. (1992). Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. *Ann Neurol, 32*(3), 371-375. doi:10.1002/ana.410320311
Stern, Y., Arenaza-Urquijo, E. M., Bartres-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., . . . Conceptual Frameworks, W. (2020). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimers Dement, 16*(9), 1305-1311. doi:10.1016/j.jalz.2018.07.219
Stern, Y., Gurland, B., Tatemichi, T. K., Tang, M. X., Wilder, D., & Mayeux, R. (1994). Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA, 271*(13), 1004-1010.
Stern, Y., Habeck, C., Steffener, J., Barulli, D., Gazes, Y., Razlighi, Q., . . . Salthouse, T. (2014). The Reference Ability Neural Network Study: motivation, design, and initial feasibility analyses. *Neuroimage, 103*, 139-151. doi:10.1016/j.neuroimage.2014.09.029
Strogatz, S. H. (2001). Exploring complex networks. *Nature, 410*(6825), 268-276. doi:10.1038/35065725
Sumowski, J. F., & Leavitt, V. M. (2013). Cognitive reserve in multiple sclerosis. *Mult Scler, 19*(9), 1122-1127. doi:10.1177/1352458513498834
Tingley, D., Yamamoto, T., Hirose, K., Keele, L., & Kosuke, I. (2014). mediation: R Package for Causal Mediation Analysis. *Journal of Statistical Software, 59*. doi:10.18637/jss.v059.i05
Tononi, G., Sporns, O., & Edelman, G. M. (1994). A measure for brain complexity: relating functional segregation and integration in the nervous system. *Proc Natl Acad Sci U S A, 91*(11), 5033-5037. doi:10.1073/pnas.91.11.5033
Toro, R., Fox, P. T., & Paus, T. (2008). Functional coactivation map of the human brain. *Cereb Cortex, 18*(11), 2553-2559. doi:10.1093/cercor/bhn014
Tucker, A. M., & Stern, Y. (2011). Cognitive reserve in aging. *Curr Alzheimer Res, 8*(4), 354-360. doi:10.2174/156720511795745320
United Nations. (2005). UN human development report. *United Nations Development Programme*.
United Nations. (2011). World Population Prospects: The 2010 Revision. *New York: UN Population Division*.
van den Heuvel, M. P., & Sporns, O. (2011). Rich-club organization of the human connectome. *J Neurosci, 31*(44), 15775-15786. doi:10.1523/JNEUROSCI.3539-11.2011
van den Heuvel, M. P., & Sporns, O. (2013a). An anatomical substrate for integration among functional networks in human cortex. *J Neurosci, 33*(36), 14489-14500. doi:10.1523/JNEUROSCI.2128-13.2013
van den Heuvel, M. P., & Sporns, O. (2013b). Network hubs in the human brain. *Trends Cogn Sci, 17*(12), 683-696. doi:10.1016/j.tics.2013.09.012

Varangis, E., Habeck, C. G., Razlighi, Q. R., & Stern, Y. (2019). The Effect of Aging on Resting State Connectivity of Predefined Networks in the Brain. *Front Aging Neurosci, 11*, 234. doi:10.3389/fnagi.2019.00234

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

Wig, G. S. (2017). Segregated Systems of Human Brain Networks. *Trends Cogn Sci, 21*(12), 981-996. doi:10.1016/j.tics.2017.09.006

World Health Organization (WHO). (2011). Global health and ageing. Retrieved from https://www.who.int/ageing/publications/global_health.pdf

World Health Organization (WHO). (2015). World report on ageing and health. Retrieved from https://apps.who.int/iris/handle/10665/18646

World Health Organization (WHO). (2020). Dementia. Retrieved from https://www.who.int/news-room/fact-sheets/detail/dementia

Xu, W., Yu, J. T., Tan, M. S., & Tan, L. (2015). Cognitive reserve and Alzheimer's disease. *Mol Neurobiol, 51*(1), 187-208. doi:10.1007/s12035-014-8720-y

Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., . . . Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol, 106*(3), 1125-1165. doi:10.1152/jn.00338.2011

Zeki, S., & Shipp, S. (1988). The functional logic of cortical connections. *Nature, 335*(6188), 311-317. doi:10.1038/335311a0

Zhang, H. Y., Wang, S. J., Liu, B., Ma, Z. L., Yang, M., Zhang, Z. J., & Teng, G. J. (2010). Resting brain connectivity: changes during the progress of Alzheimer disease. *Radiology, 256*(2), 598-606. doi:10.1148/radiol.10091701

Zissimopoulos, J., Crimmins, E., & St Clair, P. (2014). The Value of Delaying Alzheimer's Disease Onset. *Forum Health Econ Policy, 18*(1), 25-39. doi:10.1515/fhep-2014-0013

8. Appendix

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8.2. Affidavit

Frontzkowski, Lukas Karl

I hereby declare, that the submitted thesis entitled

"Left frontal hub connectivity enhances task-related brain network segregation and cognition in aging – implications for cognitive reserve"

is my own work. I have only used the sources indicated and have not made unauthorized use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given. I further declare that the submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

Hamburg, 10.01.2023 Lukas Karl Frontzkowski

8.3. Publications

Journals

Rubinski, A., Tosun, D., Franzmeier, N., Neitzel, J., **Frontzkowski**, L., Weiner, M., & Ewers, M. (2021). Lower cerebral perfusion is associated with tau-PET in the entorhinal cortex across the Alzheimer's continuum. *Neurobiology of aging*, *102*, 111–118. https://doi.org/10.1016/j.neurobiolaging.2021.02.003

Franzmeier, N., Dewenter, A., **Frontzkowski**, L., Dichgans, M., Rubinski, A., Neitzel, J., Smith, R., Strandberg, O., Ossenkoppele, R., Buerger, K., Duering, M., Hansson, O., & Ewers, M. (2020). Patient-centered connectivity-based prediction of tau pathology spread in Alzheimer's disease. *Science advances*, *6*(48), eabd1327. https://doi.org/10.1126/sciadv.abd1327

Franzmeier, N., Suárez-Calvet, M., **Frontzkowski**, L., Moore, A., Hohman, T. J., Morenas-Rodriguez, E., Nuscher, B., Shaw, L., Trojanowski, J. Q., Dichgans, M., Kleinberger, G., Haass, C., Ewers, M., & Alzheimer's Disease Neuroimaging Initiative (ADNI) (2020). Higher CSF sTREM2 attenuates ApoE4-related risk for cognitive decline and neurodegeneration. *Molecular neurodegeneration*, *15*(1), 57. https://doi.org/10.1186/s13024-020-00407-2

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

Poster Presentation

Alzheimer's Association International Conference 2020, Amsterdam, Netherlands: Left frontal hub connectivity enhances task-related brain network segregation and cognition in aging: Implications for reserve