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Neural Mechanisms of Cognitive Reserve in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common cause of age-related dementia, where neuropathological changes develop gradually over years before the onset of dementia symptoms. Yet, despite the progression of AD pathology, the decline in cognitive abilities such as episodic memory can be relatively slow. A slower decline of cognition and delayed onset of dementia relative to the progression of neuropathology has been associated with particular intellectual and lifestyle factors such as more years of education and IQ. Thus education and IQ are seen as protective factors that are associated with an increased ability to cope with brain pathology, i.e. cognitive reserve.

While numerous studies showed that education, IQ and other lifestyle factors are associated with relatively high cognitive abilities in AD, little is known about the underlying brain mechanisms of reserve. Most previous studies tested the association between protective factors such as education or IQ and differences in brain structure and function in order to identify brain mechanisms underlying reserve. Since such protective factors are global in nature and unspecific with regard to reserve, the results were highly variable. So far, there is a lack of knowledge of brain features that are associated with a higher ability to maintain cognition in the face of AD pathology. The overall aim of this dissertation was to test a priori selected functional network features that may underlie cognitive reserve.

We focused on resting-state functional networks, and in particular the fronto-parietal control network as correlate of cognitive reserve. Such functional networks are thought to be composed of brain regions that are co-activated during a particular task, where the interaction between brain regions may be critical to support cognitive function. During task-free resting-state periods, the different and often distant brain regions of such network

show correlated activity, i.e. functional connectivity. For the fronto-parietal control network, and in particular its globally connected hub in the left frontal cortex (LFC), higher resting-state connectivity has been previously shown to be associated with higher cognitive abilities as well as higher education and IQ, i.e. protective factors associated with reserve. Since that network and its LFC hub are relatively spared in AD, in contrast to more posterior parietal networks, we investigated whether higher connectivity of the fronto-parietal control network is associated with higher reserve in AD. We argued that the fronto-parietal control network is relatively stable during the initial stages of AD and may thus be well posited to subserve reserve in AD. In contrast, networks like the default mode network (DMN) that cover midline brain structures including the medial frontal lobe and the posterior cingulate may be highly vulnerable to AD pathology, given the previous observations of altered DMN connectivity and posterior parietal FDG-PET hypometabolism in AD.

In particular, the resting-state connectivity between the DMN and the dorsal attention network (DAN) may be predictive of lower episodic memory in AD. Both networks interact in a competitive (i.e. anti-correlated) way during task and resting-state, which is critical for cognitive processes such as episodic memory.

In a first step, we tested whether the resting-state connectivity between the DMN and the DAN (i.e. anti-correlated activity) is associated with lower episodic memory in subjects with amnestic mild cognitive impairment (MCI), i.e. subjects at increased risk to convert to AD dementia. Furthermore, we tested whether protective factors such as higher education moderate the association between the DMN-DAN anti-correlation and cognition. Here, the DMN-DAN anti-correlation was a measure of AD related pathological change rather than a substrate of reserve.

We could show in two independent samples of patients at risk of AD dementia that a weaker DMN-DAN anti-correlation was associated with lower episodic memory, where the decrements in episodic memory were however weaker in subjects with higher education or IQ (interaction DMN-DAN x education/IQ). These results suggest that MCI subjects with higher protective factors (education, IQ) maintain episodic memory relatively well at a given level of AD-related brain changes.

In the second step, we sought to identify those network differences that support cognitive reserve, i.e. that may explain the association between higher education and milder cognitive impairment in AD. Here, we could show that greater resting-state fMRI assessed global connectivity of the LFC, i.e. a key hub of the fronto-parietal control network, was associated with greater education and attenuated effects of neurodegeneration (measured by parietal FDG-PET hypometabolism) on memory in prodromal AD. Together, these results support the idea that global connectivity of a fronto-parietal control network hub supports cognitive reserve in AD. Based on this finding, we developed a novel resting-state fMRI index of fronto-parietal control network connectivity as a functional imaging marker of cognitive reserve. This marker is highly correlated with education and may thus be used as an imaging-based index of cognitive reserve. Together, our results provide for the first time evidence that cognitive reserve in AD is supported by higher functional connectivity of the fronto-parietal control network, in particular its LFC hub.

Overview

The thesis is structured in five main chapters. The introduction briefly summarizes the clinical course of Alzheimer's disease and highlights its' relevance for our aging society. In this context, we will review the concept of cognitive reserve that is associated with attenuated effects of Alzheimer's disease pathology on cognition and may thus help prevent dementia. We will summarize previous research on functional brain differences as a correlate of cognitive reserve and point out the major research gaps that motivated our studies to investigate the functional network changes that underlie cognitive reserve.

The main body of the thesis is presented in form of three research articles that have all been published in peer-reviewed journals from 2016 to 2017. The articles are embedded in three separate chapters in their published format, each introduced with a short summary of the article's content.

The first paper aims to assess whether protective factors including years of education & IQ moderate the impact of posterior parietal neural network failure on cognition in patients with mild cognitive impairment who are at risk of developing early stage Alzheimer's disease dementia.

The second paper aims to determine which functional network differences underlie cognitive reserve in patients with prodromal Alzheimer's disease. Specifically, the paper demonstrates that a functional hub region in the left frontal cortex belonging to the fronto-parietal control network may constitute the long sought-after neural substrate of cognitive reserve.

The third paper translates these previous findings on the neural mechanisms of cognitive reserve into a novel imaging-based measure that captures cognitive reserve-related functional properties of the fronto-parietal control network and summarizes them in a single index.

The discussion addresses how our findings may provide a general framework for future cognitive reserve research which may foster a deeper neural understanding of its' compensatory nature.

Contents

Abbreviations

AD – Alzheimer's Disease

CSF – Cerebrospinal Fluid

DAN – Dorsal Attention Network

DMN – Default Mode Network

FDG-PET – Fluordesoxyglucose Positron Emission Tomography

LFC – Left Frontal Cortex

MCI – Mild Cognitive Impairment

MRI – Magnetic Resonance Imaging

1 | Introduction

1.1. Alzheimer's disease – A Challenge for Our Aging Society

The average life expectancy in Germany has increased from approximately 55 years at the beginning of the 20th century to more than 80 years today and is expected to increase further. One of the major challenges entailed by a higher life expectancy is the growing prevalence of age-related neurodegenerative diseases, with Alzheimer's disease (AD) being the most frequent cause of dementia in elderly subjects (Fiest et al., 2016; Reitz, Brayne, & Mayeux, 2011). The fact that dementia hampers an independent lifestyle and is among the leading causes of disability in elderly individuals, makes them more costly to the society than cardiac diseases or cancer, emphasizing the urgency to contain the growing dementia prevalence (Hurd, Martorell, Delavande, Mullen, & Langa, 2013). The shift towards a higher proportion of elderly subjects in the society - about 22% of German citizens will be older than 65 years by 2017 – will impose a significant challenge both in terms of costs of health care and care giver burden (Bundesamt, 2015; Dahm, 2006).

In AD, the onset of dementia symptoms is preceded by a preclinical (i.e. symptom free) interval that can last 2-3 decades during which amyloid-beta plaques and neurofibrillary tau tangles accumulate in the brain, ensuing synaptic dysfunction and neuronal loss. The most common early cognitive symptom is episodic memory dysfunction, which characterizes the clinical syndrome of amnestic mild cognitive impairment (MCI). This MCI stage can last up to several years during which AD pathology continues to accumulate, after which it is in the majority of cases redeemed by full-blown AD dementia (Dubois et al., 2016; Jack et al., 2010; Petersen, 2004).

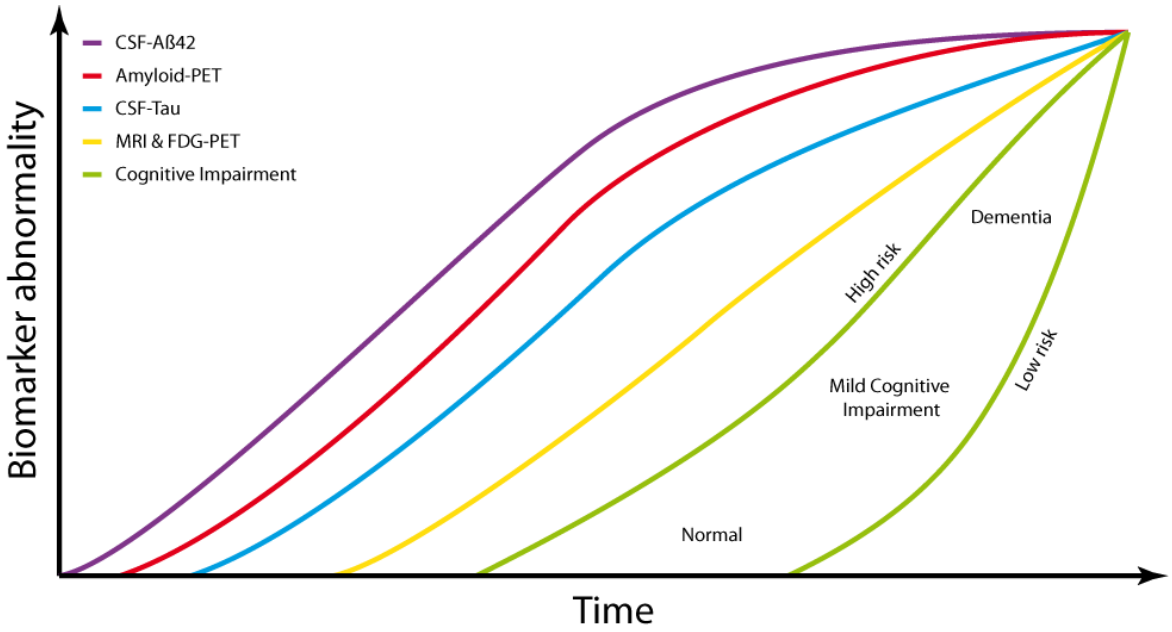

Figure 1: *Hypothetical biomarker model of the AD pathological cascade. Amyloid is identified via Cerebrospinal fluid (CSF; Purple) Aβ42 or positron emission tomography (PET) imaging (red), Tau is identified via CSF (blue). Neurodegeneration is assessed via structural MRI and FDG-PET (yellow). By convention, all curves converge at the maximum biomarker abnormality. The occurrence of cognitive symptoms is illustrated as two green curves with high and low risk extrema. Subjects who are at high risk of cognitive impairment due to AD pathology show a cognitive trajectory that is shifted to the left, whereas, the cognitive trajectory shows a right shift for subjects who are at low risk of cognitive impairment due to AD pathology. This shift of the cognitive trajectory illustrates that individuals with the same biomarker profile can have different cognitive outcomes possibly due to different levels of reserve (adopted from (Jack et al., 2013)).*

Biomarker studies based on neuroimaging (MRI, FDG-PET) and biochemical assays (cerebrospinal fluid, CSF) of primary pathologies and neurodegeneration have largely confirmed the pathological cascade in AD (see Figure 1) (Jack et al., 2013). Importantly, however, the rate of cognitive decline relative to a given level of neuropathology has been found to be highly variable. That is, subjects may experience relatively high resilience of cognitive abilities to the impact of neuropathology. Specifically, studies have shown that at a given level of AD pathology, patients with greater formal education, higher IQ or larger brains are at lower risk of experiencing cognitive impairment than those patients with lower education, lower IQ or smaller brains (see green curves in Figure 1) (Katzman

et al., 1989; Stern, 2006). This observation has led to the notion that some individuals are more resilient against the detrimental effects of AD pathology on cognitive abilities, a phenomenon commonly referred to as reserve. Since greater reserve is associated with a delayed dementia onset and a prolonged independent lifestyle in the face of AD pathology it could hold potential for secondary prevention of AD dementia.

1.2. What is Reserve?

Reserve describes the ability to maintain cognitive performance relatively well in the face of brain pathology, i.e. when developing AD. The concept of reserve has originally been formulated to explain the observation that some individuals show an attenuated effect of AD pathology on the expression of cognitive symptoms as illustrated by the green curves in Figure 1. For instance, an early histopathological study (Katzman et al., 1988) has described 10 cases with autopsy-confirmed progressed AD neocortical plaque pathology equivalent to patients with AD dementia but normal cognitive performance at time of death. Those cases with higher resilience of cognition showed a higher number of neurons letting the authors conclude that they must have had a higher reserve - potentially in the form of larger premorbid brain volume - that allowed them to maintain cognition even at a high burden of plaque pathology. These initial observations of attenuated effects of AD pathology on cognition were confirmed by independent studies reporting larger brain volume and greater neuronal density to be associated with milder memory impairment at similar levels of primary AD pathology (for a review see (Satz, Cole, Hardy, & Rassovsky, 2011)). These findings have lead to the brain reserve hypothesis, which claims that the ability to maintain cognitive function declines as a function of 1) the extent of brain damage and 2) a measure of brain reserve capacity such as the overall brain size, number of neurons or synaptic density. In this context, cognitive decline is hypothesized

to occur when pathology reduces brain reserve capacity beyond a given threshold. In other words, an individual with a larger brain reserve capacity reaches this threshold for the onset of cognitive decline later in the disease course, i.e. when more pathology has accumulated, than an individual with a lower brain reserve capacity (Barulli & Stern, 2013).

Apart from the effects of brain reserve, epidemiological studies found that socio-demographic and lifestyle factors like education (Meng & D'Arcy, 2012), intelligence (Rentz et al., 2010) and occupational or leisure time attainment (Arenaza-Urquijo, Wirth, & Chetelat, 2015) were associated with lower dementia risk. These studies have suggested that reserve is promoted by intellectual and socio-demographic factors, i.e. a type of reserve that has been coined cognitive reserve. The concept of cognitive reserve claims that the threshold for functional decline is not entirely fixed by quantitative measures of brain volume or neuronal/synaptic density but rather depends on individual experience and cognitive ability throughout the lifespan which shape aspects of brain function and cognitive processing capabilities (Stern, 2002, 2006). Accordingly, two individuals with the same level of brain damage can have different levels of cognitive reserve and thus a differential ability to maintain cognition relatively well in the face of brain pathology (Barulli & Stern, 2013). This main principle underlying the cognitive reserve concept is illustrated in Figure 2. The most consistent protective factors that have been shown to be associated with higher cognitive reserve are greater formal education and IQ along with others such as cognitively stimulating leisure time activities, occupational attainment or greater social networks (see Figure 3) (Amieva et al., 2005; Hall et al., 2007; Meng & D'Arcy, 2012; Stern, 2012; Xu, Yu, Tan, & Tan, 2015).

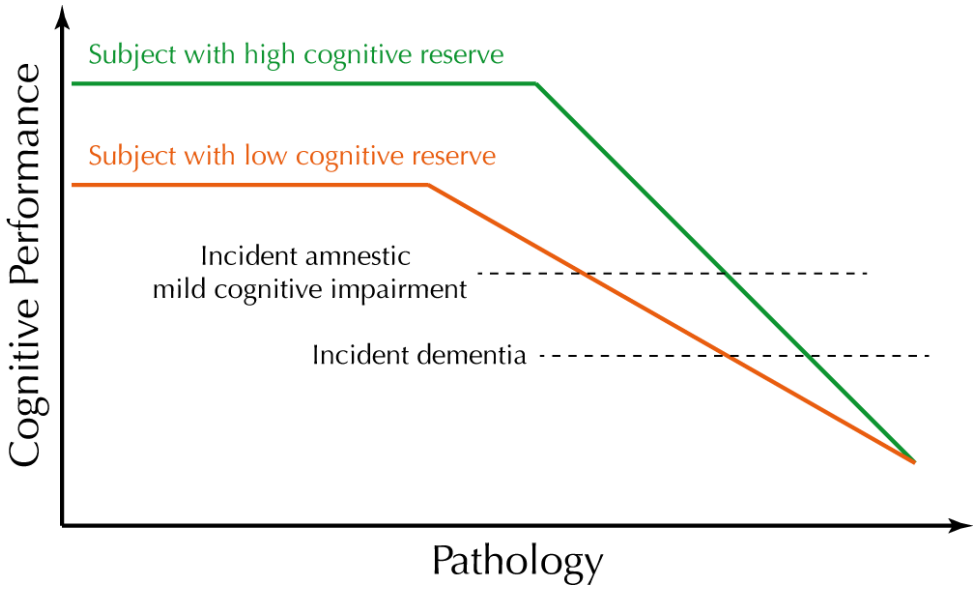

Figure 2: *Illustration of how cognitive reserve may moderate the association between AD brain pathology and the clinical expression of cognitive symptoms. The x-axis represents the level of brain pathology, which continuously increases with disease progression independent of an individuals level of cognitive reserve. The y-axis represents cognitive performance (i.e. episodic memory). Subjects with higher cognitive reserve (green line) need greater pathology levels before cognition is affected (Barulli & Stern, 2013). As a result, individuals with greater cognitive reserve require more pronounced pathology levels to meet clinical diagnosis of MCI or AD dementia. Also, at any given level of cognitive performance, pathology will be more progressed in subjects with higher cognitive reserve (Ewers, Insel, Stern, Weiner, & Alzheimer's Disease Neuroimaging, 2013; Stern, Alexander, Prohovnik, & Mayeux, 1992). The figure was adapted from (Barulli & Stern, 2013)*

Studies have provided striking empirical evidence for the cognitive reserve concept in AD, showing that protective factors are associated with relatively high cognitive performance in the face of various AD-related brain changes including amyloid-beta deposition (Rentz et al., 2010; Roe, Xiong, Miller, & Morris, 2007), cortical and hippocampal atrophy (Perneczky et al., 2009; Pettigrew et al., 2016; Soldan et al., 2013) or FDG-PET hypometabolism (Carapelle et al., 2017; Ewers et al., 2013; Morbelli & Nobili, 2014).

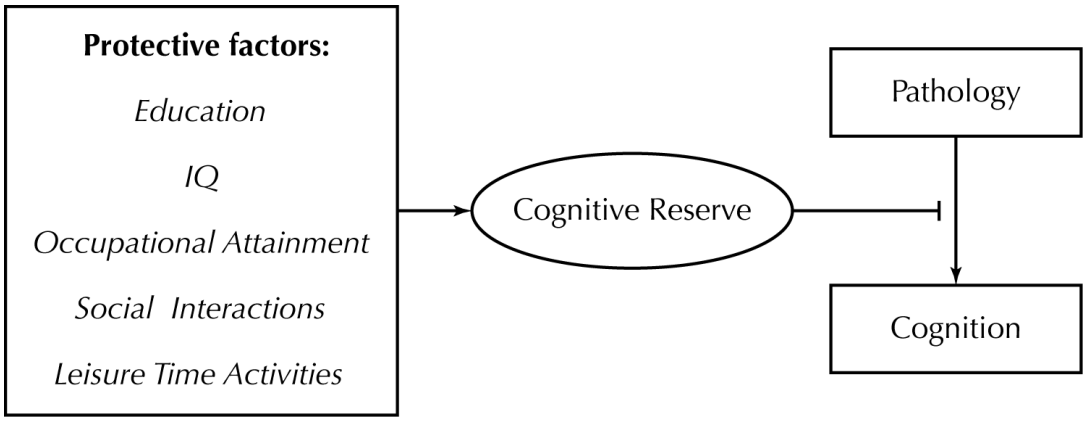

Figure 3: *A working model on moderating effects of cognitive reserve on the association between brain pathology and cognitive performance. Cognitive reserve is a latent construct that is promoted by different protective factors. Greater cognitive reserve as indicated by higher education, IQ etc., is associated with an attenuated effect of neural pathology on the clinical expression of cognitive symptoms (i.e. memory impairment).*

Importantly, the beneficial effects of education, IQ and other cognitive reserve promoting factors are most pronounced in preclinical and prodromal stages of AD (i.e. MCI), indicating that the ability to better cope with brain pathology might be highest earlier in the disease course (Scarmeas, Albert, Manly, & Stern, 2006; Stern, 2012). While these above cited studies generally support the cognitive reserve concept suggesting higher resilience of cognition in subjects with higher protective factors (education, IQ etc.), there remains the major question which neural mechanisms underlie such protective effects? Possible functional brain differences supporting cognitive reserve include higher neural plasticity and neural network function throughout the lifespan (Baroncelli et al., 2010; Hu, Long, Pigino, Brady, & Lazarov, 2013; Xu et al., 2015), or more efficient or more flexible brain networks with a higher capacity to process information in the face of pathology (Barulli & Stern, 2013; Stern, 2006). Such functional brain properties can be assessed by functional MRI.

1.3. Functional MRI

Functional MRI (fMRI) allows non-invasively measuring brain activity with a relatively high spatial resolution (i.e. about 3 mm isotropic voxel size on 3 Tesla fMRI). The basic principle of fMRI relies on a phenomenon termed neurovascular coupling, which describes a close link between neural activity and local cerebral blood-flow: Regionally increased neural activity triggers increased inflow of arterial oxygenated blood to the site of neural activation. Since oxygenated blood is less magnetic (diamagnetic), but deoxygenated blood is more magnetic (paramagnetic), the higher concentration of oxygenated blood flow disturbs less the static magnetic field of the MRI scanner. Such transient blood-oxygen-level-dependent (BOLD) differences in magnetic field disturbance can be picked up by fMRI. Higher fMRI BOLD signal thus means larger inflow of oxygenated blood believed to reflect higher neural activity (Hillman, 2014). Classically, fMRI is applied to study brain activation during cognitive tasks and has been employed in thousands of cognitive and clinical neuroscience studies. A consensus view that has emerged from the task fMRI literature is that the brain is composed of different functional networks that are activated or deactivated depending on current task demands (Smith et al., 2009; Soares et al., 2016). Another line of fMRI research has emphasized that the networks that are commonly found activated or deactivated during cognitive tasks show intrinsic functional connectivity during the cognitively undefined resting-state, i.e. when no cognitive task is presented during scanning. Here, connectivity is defined as the level of activity synchronicity or statistical interdependence of the BOLD signal (i.e. a proxy of neural activity) of spatially distinct brain regions when the scanned subject is at wakeful rest (Friston, 2011; Soares et al., 2016). This phenomenon commonly known as functional connectivity thus follows the Hebbian law “what fires together, wires together”, or in this case “what fires together is wired together”, where regions that show high levels of

functional connectivity closely resemble those networks activated during task (Smith et al., 2009) and are thus thought to form functional networks (Biswal, Yetkin, Haughton, & Hyde, 1995; Li, Liu, & Tsien, 2016).

1.4. Functional Network Changes in Alzheimer's disease

Functional neuroimaging studies have suggested that the clinical course of AD is closely tracked by disruptions of circumscribed functional brain networks (Damoiseaux, Prater, Miller, & Greicius, 2012; Wang et al., 2015). Here, especially the default-mode network (DMN), which encompasses medial portions of the frontal, parietal and temporal lobe as well as lateral parietal regions, has gained major interest. The DMN includes key-memory structures like the hippocampus and has been interpreted as a neural basis of episodic memory due to its consistent involvement in different aspects of memory (Buckner, Andrews-Hanna, & Schacter, 2008). Resting-state fMRI studies in AD have revealed that the DMN shows functional disruptions already early in the disease course, where impaired connectivity is found predominantly among posterior DMN hubs such as the posterior cingulate and precuneus ((Sorg et al., 2007), see also (Brier, Thomas, & Ances, 2014) for a review). Such AD-related disruptions in posterior DMN connectivity have been shown to be significantly correlated with deficits in verbal learning and memory (for a recent meta-analysis see (Badhwar et al., in press)). In contrast, anterior parts of the DMN show increased functional connectivity in early, but disruptions in later disease stages. This inversely u-shaped association between AD progression and anterior DMN connectivity has been argued to reflect compensatory processes early in the disease course, however, this remains speculative since an association between anterior DMN hyperconnectivity and better memory has not been shown yet (Damoiseaux et al., 2012; Jones et al., 2011). Other studies have emphasized that not only connectivity within the DMN is impaired in

AD, but that also interactions between the DMN and other networks undergo disease-related changes (Wang et al., 2015). Specifically, resting-state fMRI studies have shown that the negative connectivity or anti-correlation between the DMN and the dorsal attention network (DAN) decreases in the course of AD, what is predictive of cognitive dysfunction (Brier et al., 2012; Meskaldji et al., 2016; Zhu et al., 2016). The DAN is a functional antagonist of the DMN and encompasses bilaterally the frontal eye fields and a large portion of the intraparietal sulci. It is involved in focusing top-down attention to external demands, which is crucial for encoding of novel stimuli (Fox et al., 2005; Kim, 2015). The DMN-DAN anti-correlation thus has been proposed to subserve an adaptive mechanism to increase attention to external or internal stimuli and to reduce interference from irrelevant processes (Fox et al., 2005; Spreng, Stevens, Viviano, & Schacter, 2016). A strong DMN-DAN anti-correlation is similarly found during task-fMRI where both networks show antagonistic activation patterns during memory encoding (i.e. DAN activation and DMN deactivation) and memory recall (i.e. DMN activation and DAN deactivation) (Kim, 2015; Kim, Daselaar, & Cabeza, 2010). When challenged with a memory encoding task, AD patients show less DMN deactivations compared to healthy controls, which is assumed to mirror resting-state fMRI findings on impaired DMN function and reduced DMN-DAN anti-correlation in AD (Pihlajamaki & Sperling, 2009; Sperling et al., 2009). Overall, these studies highlight that AD is linked to 1) altered DMN integrity and 2) to altered interactions of the DMN with other networks like the DAN, both leading to memory decline. These specific functional disruptions of mainly posterior portions of the DMN in AD are likely to be explained by its anatomical overlap with the accumulation of Amyloid-beta deposition, grey matter atrophy (Buckner et al., 2009; Buckner et al., 2005; Koch et al., 2015; Pasquini et al., 2017) and FDG-PET hypometabolism (Riverol & Lopez, 2011). In contrast to these functional disruptions of

mainly posterior brain networks, frontal hub regions are less prone to functional disruptions in AD and are assumed to become functionally more crucial for cognition as the disease progresses (Engels et al., 2015; McCarthy, Benuskova, & Franz, 2014; Sui et al., 2015).

1.5. Functional Neuroimaging Evidence for Cognitive Reserve Mechanisms in Aging and Alzheimer's disease

Several studies have applied functional neuroimaging methods such as task and resting-state fMRI to disentangle the functional brain mechanisms that underlie cognitive reserve. In general, studies on neural mechanisms of cognitive reserve have taken two forms: The first class of studies has assessed how protective factors such as education or IQ relate either to task-related brain activation or resting-state functional connectivity. The second class of studies has focused on identifying functional brain mechanisms that are associated with better cognitive performance during aging or when developing AD. For the first class of studies, Boller et al. have recently applied a working-memory task in a sample of cognitively normal elderly. They have found that with increasing age, working-memory related brain activation in the left frontal and right cingulate cortex was decreased in low educated elderly but increased in highly educated elderly (Boller, Mellah, Ducharme-Laliberte, & Belleville, 2016). Another study that applied a memory recognition task in both AD dementia patients and healthy controls has shown associations between a composite score of education and IQ and greater left frontal and left hippocampal activation as well as greater left occipital and left temporal deactivation in patients, where healthy controls did not show such an association (Scarmeas et al., 2004). Again others who applied a memory-encoding paradigm have shown that a composite index of

education and IQ was associated with greater activation of right temporal and superior parietal areas in MCI and AD dementia patients where healthy controls showed inverse associations (Sole-Padulles et al., 2009). The same group has further applied a language comprehension task where education and IQ were associated with greater activation in language related left frontal areas and greater deactivations of DMN regions in MCI and AD dementia patients. In the same brain regions healthy controls again showed inverse associations (Bosch et al., 2010). In summary, results from these studies suggest that protective factors are associated with differences in task-related brain activation and that these associations are highly variable across tasks and disease stage (i.e. healthy controls vs. AD).

In a similar vein, resting-state fMRI studies have tested the association between protective factors (e.g. education, IQ, occupational attainment) and the intrinsic architecture of functional networks. In healthy elderly individuals, greater education was related to higher connectivity between several brain regions including the left frontal cortex, left angular gyrus, right hippocampus and right posterior cingulate (Arenaza-Urquijo et al., 2013). Similarly, in MCI and AD dementia patients, greater education has been associated with increased functional connectivity of the posterior cingulate cortex to the rest of the DMN (Bozzali et al., 2015). In MCI patients, greater education was related to higher connectivity mainly among bilateral regions of the fronto-parietal control network (Serra et al., 2016). Together, these results from task and resting-state studies suggest that protective factors are related to 1) a differential ability to recruit brain networks during cognitive demands and 2) to the intrinsic architecture of brain networks in aging and AD, which may mediate a better tolerance of either age- or AD-related brain changes. While these previous findings suggest that task activation or resting-state functional connectivity differences are associated with protective factors including life-style and IQ, there is a

large heterogeneity in the directionality and anatomical location of findings across studies. This heterogeneity may be due to differences in task paradigms, methods to derive resting-state fMRI connectivity (ICA, seed-based connectivity, ROI-to-ROI based connectivity) and the often exploratory nature of the studies. Importantly, those studies with a focus on the association between protective factors and functional brain differences in AD mostly lacked the investigation of a cognitive benefit, i.e. whether the functional brain differences that were associated with higher education or other factors could explain higher cognitive abilities at a given level of brain pathology.

Although not focusing on reserve, some studies aimed to identify functional brain mechanism that are associated with higher cognitive performance during aging or in the face of AD pathology. Studies in healthy elderly have shown that greater bilateral frontal lobe activation during memory tasks is related to better memory performance (Cabeza, Anderson, Locantore, & McIntosh, 2002; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; McCarthy et al., 2014). Similarly, another study in patients with preclinical AD has shown that greater memory task-related activation of fronto-parietal control network regions is associated with better memory (Elman et al., 2014). Others have reported that in MCI and AD dementia greater memory task-related activation of fronto-parietal control network regions is associated with better memory performance (Dhanjal & Wise, 2014). Together, these studies reveal a relatively consistent result pattern that greater activation of fronto-parietal control network regions is associated with better memory performance in normal aging as well as in the face of AD pathology. This is consistent with previous reports that frontal hubs become more central to cognition in aging and AD (Engels et al., 2015; McCarthy et al., 2014). Still, it is unclear whether those functional brain differences ameliorated the effect of pathology on cognition and whether such functional brain

differences were associated with protective factors (i.e. education, IQ), and thus may reflect higher cognitive reserve.

1.6. Defining Novel Criteria to Test Neural Mechanisms of Cognitive Reserve

As summarized in the previous paragraph, functional neuroimaging studies that have so far tried to identify neural mechanisms of cognitive reserve have mainly taken two forms: They have either focused on 1) identifying associations between protective factors and functional brain mechanisms or 2) on identifying functional brain mechanisms that are associated with better cognitive performance in the face of AD pathology or age-related brain changes. We argue that identifying a neural substrate of cognitive reserve essentially requires a combination of these two approaches, since a neural substrate of cognitive reserve should be associated both with protective factors as well as relatively high cognitive performance despite brain pathology. A neural mechanism that meets both these prerequisites could explain the missing link between protective factors and better tolerance of brain pathology. We thus propose novel research criteria, which may help identifying a neural substrate of cognitive reserve:

Criterion of face validity:

As stated in paragraph 1.2., epidemiological evidence has robustly shown that protective factors (i.e. education, IQ, occupational attainment etc.) are associated with attenuated effects of AD pathology on cognition, i.e. cognitive reserve. Thus, a neural mechanism of cognitive reserve should be positively correlated with these protective factors.

Criterion of cognitive benefit:

The core of the cognitive reserve concept describes the ability to maintain cognition relatively well despite brain pathology. Thus a neural mechanism that fulfills the above described criterion of face validity should in essence be also associated with a cognitive benefit in the face of brain pathology to be considered a neural substrate of cognitive reserve. Such a "cognitive benefit" can be tested in two ways: First, at a given level of cognitive performance greater expression of a neural mechanism of cognitive reserve should be associated with more severe brain pathology. Second, at a given level of brain pathology, greater expression of a neural mechanism of cognitive reserve should be associated with better cognitive performance.

1.7. A Fronto-Parietal Control Network Model of Cognitive Reserve

Here, we propose that the fronto-parietal control network (Figure 4A) may constitute a candidate system to underlie cognitive reserve in AD. First, supporting the criterion of face validity of reserve, functional properties of the fronto-parietal control network – especially its' hubness as assessed via resting-state fMRI – have been previously associated with protective factors including intelligence in young individuals (Cole, Ito, & Braver, 2015; Cole, Yarkoni, Repovs, Anticevic, & Braver, 2012; Finn et al., 2015; Hearne, Mattingley, & Cocchi, 2016) and more years of education in healthy elderly (Marques et al., 2016; Marques, Soares, Magalhaes, Santos, & Sousa, 2015) as well as patients with amnestic MCI (Serra et al., 2016). This suggests that hubness of fronto-parietal control network regions is associated with protective factors across health and disease and may constitute a long-lasting trait susceptible to environmental influences

such as education. This is consistent with the idea of cognitive reserve as a capacity that is modifiable throughout the lifespan (Stern, 2012).

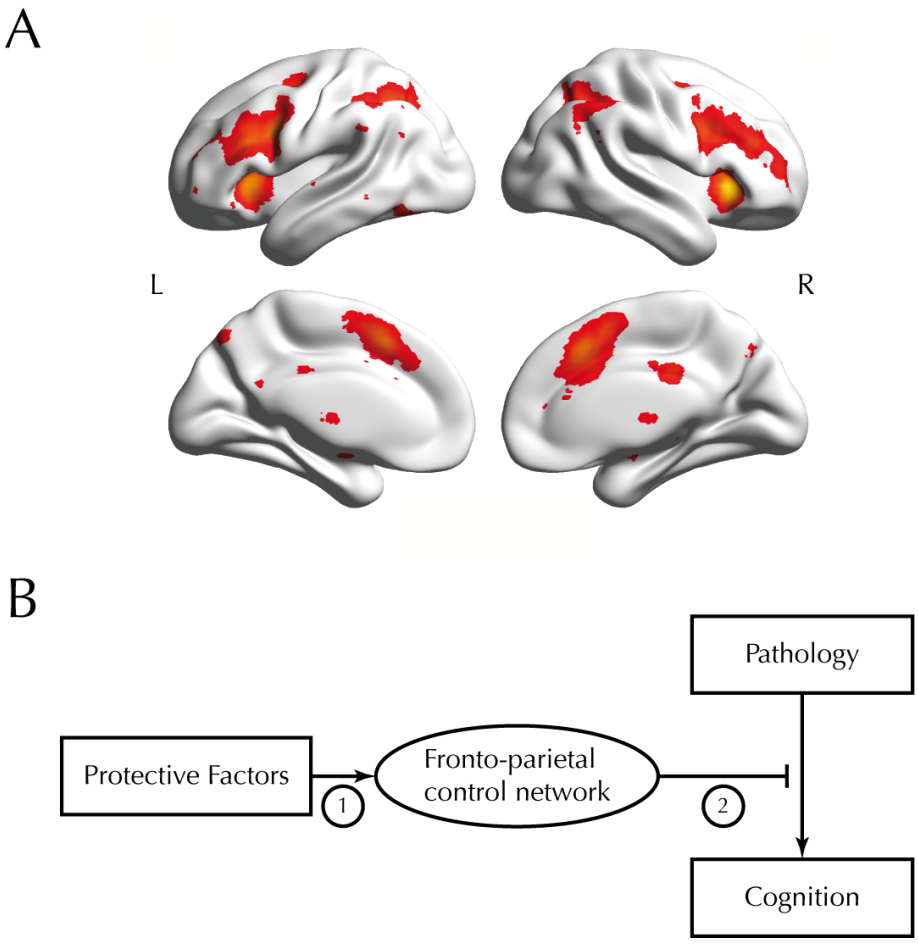

Figure 4: *(A) Spatial map of the fronto-parietal control network projected on an inflated brain template in standard space. The spatial map was meta-analytically defined following the methodology of the studies included in this thesis (Franzmeier et al., 2016; Franzmeier, Duering, et al., 2017) (B) Illustration of our fronto-parietal control network model of cognitive reserve based on our novel research criteria: Specifically, we hypothesize that (1) protective factors (i.e. education) are associated with greater hubness of the fronto-parietal control network (criterion of face validity) and that (2) greater hubness is associated with an attenuated effect of AD-related brain changes on cognition (criterion of cognitive benefit).*

Second, supporting the criterion of cognitive benefit, resting-state functional connectivity of the fronto-parietal control network has been linked to greater resilience against damage (Santarnecchi, Rossi, & Rossi, 2015) and general mental health (Cole, Repovs, & Anticevic, 2014). Further, memory task-related fronto-parietal control network hyperactivation has been linked to relatively preserved memory performance in

cognitively normal elderly (Cabeza et al., 2002; Davis et al., 2008; McCarthy et al., 2014), as well as preclinical and clinical stages of AD (Dhanjal & Wise, 2014; Elman et al., 2014), suggesting that the fronto-parietal control network may help better tolerate brain pathology.

A potential role of the fronto-parietal control network as a substrate of reserve may be explained by its central role for cognition: The fronto-parietal control network constitutes the primary control system in the brain that is critical for the regulation of activity in other functional networks that support cognitive function (Cole et al., 2013; Helfrich & Knight, 2016). This central ability of the fronto-parietal control network to modulate other networks is assumed to be mediated by its hubs that are characterized by a high level of interconnectedness to the rest of the brain, as evidenced by resting-state fMRI global connectivity (Cole, Pathak, & Schneider, 2010; Cole et al., 2012). During task demands, these fronto-parietal control network hubs can flexibly modulate connectivity with other networks in a task-specific way, which is thought to facilitate task performance, cognitive flexibility and intelligence (Cole et al., 2013; Helfrich & Knight, 2016). In view of the above described link between fronto-parietal control network hubs and protective factors, (i.e. criterion of face validity) a task-specific coupling with other networks may mediate the association between protective factors and a differential recruitment of brain networks during task demands that we have summarized in paragraph 1.5 (Bosch et al., 2010; Scarmeas et al., 2004; Sole-Padulles et al., 2009). In turn, fronto-parietal control network hyperactivation which has been shown beneficial in the face of age-related brain changes or AD pathology (i.e. criterion of cognitive benefit) (Cabeza et al., 2002; Davis et al., 2008; Dhanjal & Wise, 2014; Elman et al., 2014), may reflect greater control exerted by the fronto-parietal control network on other networks.

Together, the fronto-parietal control network may constitute a neural substrate of cognitive reserve in AD, however, no previous study has systematically addressed this question yet. The current thesis applied the novel research criteria that have been introduced in section 1.6. (see also Figure 4B) to systematically assess whether the fronto-parietal control network is a neural substrate of cognitive reserve in AD.

1.8. Aims of the Thesis

The major goal of the current thesis was to test whether 1) protective factors moderate the impact of AD-related functional network failure on memory, and 2) to test whether functional connectivity of the fronto-parietal control network, particularly its hub in the left frontal cortex, support cognitive reserve in AD These major questions were addressed in different samples of MCI subjects - who are at risk of developing AD dementia - using resting-state fMRI. We specifically used resting-state instead of task-fMRI, since task-fMRI can be difficult to perform in cognitively impaired individuals, whereas resting-state fMRI does not require active participation of the scanned subject and can thus be readily applied in clinical populations such as MCI.

To address the first aim we tested whether protective factors including education and IQ moderate the impact of AD-related network failure on memory. Specifically, we focused on functional connectivity between resting-state networks that are prone to decline in AD (DMN vs. DAN) what has been linked to memory impairments (Meskaldji et al., 2016; Zhu et al., 2016). We tested whether protective factors that are related to higher reserve (i.e. education or IQ) moderate the impact of impaired resting-state fMRI connectivity on memory. To this end, we tested in two independent samples of MCI patients, whether at a given level of DMN-DAN anti-correlation, individuals with higher education or IQ show better memory performance, i.e. indirect evidence for greater cognitive reserve.

In the second study, we applied the newly developed research criteria in another sample of MCI patients, testing whether fronto-parietal control network hubs constitute a neural substrate of cognitive reserve. Specifically, we focused on resting-state fMRI assessed hubness (i.e. global connectivity) of the left frontal cortex (LFC) – a key region of the fronto-parietal control network – that is in comparison to networks like the DMN relatively spared in AD (Buckner et al., 2009; Buckner et al., 2005) and has been previously linked to higher intelligence and education in healthy individuals and patients with amnestic MCI (Cole et al., 2012; Serra et al., 2016). By applying the new research criteria (see also Figure 4B), we tested whether global connectivity of the LFC is associated with protective factors (i.e. criterion of face validity) and better cognitive performance at a given level of AD pathology (i.e. criterion of cognitive benefit).

The third study aimed to create a novel resting-state fMRI-based measure of cognitive reserve that captures the global connectivity of fronto-parietal control network hubs that relates to protective factors and summarizes them in a single index. In comparison to static measures such as education and IQ, an imaging-based reserve index may help dynamically assess changes in neural mechanisms of cognitive reserve across different stages of AD and may thus be used for individual risk prediction or as a read out in intervention trials that aim on fostering cognitive reserve.

Together, this thesis aims to provide evidence for the cognitive reserve concept and to study its neural foundations in AD. The outcome of this thesis may offer a theoretical framework for future cognitive reserve research.

2 | Cognitive Reserve And Functional Network Changes in Mild Cognitive Impairment

2.1 Summary

In this first study we assessed whether cognitive reserve promoting protective factors (i.e. education & IQ) are associated with relatively preserved memory performance at a given level of AD-related functional brain changes. Specifically, we focused on the functional antagonism between the DMN and the DAN, i.e. an inherent feature of functional brain organization that is crucial for cognitive performance including memory as described in paragraph 1.4. Task and resting-state fMRI studies in AD have shown that this DMN-DAN antagonism decreases with disease progression which is associated with worsened memory, however, it is unclear whether individuals with higher education or IQ can better cope with this AD-related failure of functional network interactions. For the current study, we used two fully independent samples of MCI patients, where we focused on the resting-state fMRI assessed DMN-DAN anti-correlation as a marker of functional network change that is crucial for memory. We hypothesized that at a given level of pathology (i.e. reduced DMN-DAN anti-correlation), patients with higher education and IQ show better memory performance. Confirming our hypothesis, the results of the study show that a reduced DMN-DAN anti-correlation is associated with stronger memory impairments, where this association was attenuated in individuals with higher education or IQ. These findings support the idea that greater education and IQ are associated with greater cognitive reserve and thus less severe memory deficits in the face of functional network

disruptions.

2.2 Reference

This work was carried out under the supervision of Michael Ewers; N.F. and M.E. designed research and wrote the manuscript; N.F. analyzed the data; K.B. and N.F. collected the data, Y.S., S.T., K.B. and M.D. critically revised the manuscript.

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Cognitive reserve moderates the association between functional network anti-correlations and memory in MCI

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ABSTRACT

Cognitive reserve (CR) shows protective effects on cognitive function in older adults. Here, we focused on the effects of CR at the functional network level. We assessed in patients with amnestic mild cognitive impairment (aMCI) whether higher CR moderates the association between low internetwork cross-talk on memory performance. In 2 independent aMCI samples (n = 76 and 93) and healthy controls (HC, n = 36), CR was assessed via years of education and intelligence (IQ). We focused on the anti-correlation between the dorsal attention network (DAN) and an anterior and posterior default mode network (DMN), assessed via sliding time window analysis of resting-state functional magnetic resonance imaging (fMRI). The DMN-DAN anti-correlation was numerically but not significantly lower in aMCI compared to HC. However, in aMCI, lower anterior DMN-DAN anti-correlation was associated with lower memory performance. This association was moderated by CR proxies, where the association between the internetwork anti-correlation and memory performance was alleviated at higher levels of education or IQ. In conclusion, lower DAN-DMN cross-talk is associated with lower memory in aMCI, where such effects are buffered by higher CR.

1. Introduction

Cognitive reserve (CR) designates the ability to cognitively perform relatively well in the presence of neuropathology and is thought to be conferred by higher mental abilities like IQ or prolonged life-time experiences such as education. The CR hypothesis is supported by findings from epidemiologic studies showing that proxy measures of CR including IQ and years of formal education are associated with lower risk of dementia (Esiri and Chance, 2012; Meng and D'Arcy, 2012; Valenzuela and Sachdev, 2006; Wilson et al., 2002). Further support for the CR hypothesis comes from neuroimaging studies on mild cognitive impairment (MCI) and Alzheimer's disease (AD), which showed that patients with higher levels of CR proxy measures exhibited stronger neuropathology (such as amyloid pathology, gray matter atrophy, glucose hypometabolism) at relatively stable levels of cognitive performance (Ewers et al., 2013; Morbelli et al., 2013; Stern, 2006; Vemuri et al., 2011). CR-related effects at the level of functional brain networks, however, are not well understood (Barulli and Stern, 2013). Since previous fMRI studies showed circumscribed changes in functional networks that are linked to cognitive impairment in patients with MCI (for review see (Teipel et al., 2016)), the question arises whether higher levels of CR buffer the effects of lower neural network function on memory in MCI. Motivated by a previous finding in nondemented older adults, which showed that at higher levels of IQ, the association between amyloid pathology and episodic memory impairment was weaker (Rentz et al., 2010), we aimed to test whether at higher levels of CR (as measured by IQ or education), lower levels of functional connectivity between functional brain networks is associated with relatively milder memory impairment in MCI.

To assess functional network changes that underlie memory impairment, we measured resting-state functional connectivity between 2 major functional networks including the dorsal attention network (DAN) and the default mode network (DMN). Previous resting-state fMRI studies have revealed an anti-correlation between

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the resting-state signal of the DMN and the DAN (Carbonell et al., 2014; Chai et al., 2014; Fox et al., 2005), where greater DMN–DAN anti-correlation was associated with higher cognitive control and better working memory performance (Anticevic et al., 2012; Chai et al., 2014; Hampson et al., 2010; Kelly et al., 2008). The resting-state DMN-DAN anti-correlation is reminiscent of observations from task-related fMRI studies showing a task activation of the DAN concomitant with a deactivation of the DMN to be associated with higher episodic memory performance in cognitively normal individuals (Kim et al., 2010; Kragel and Polyn, 2015; Landsiedel and Gilbert, 2015). Here, we hypothesized that in amnestic MCI—a clinical syndrome characterized by memory impairment—lower levels of the DMN-DAN anti-correlation are associated with low memory performance and that such an association can be buffered by CR. Although the anti-correlation of the DAN and DMN itself was not pathologically altered before the stage of AD dementia in previous studies (Wang et al., 2007; Zhu et al., 2016), we hypothesized that the level of the anti-correlation of the DMN-DAN is predictive of memory impairment in the diseased brain (MCI) at low levels of CR. The rationale is that the reciprocal activation of the DAN and DMN has a central regulating role within the ensemble of functional networks underlying cognition (Cole et al., 2014), which becomes especially crucial to maintain successful cognitive processes including memory at the stage of MCI and low CR.

To assess the DAN-DMN anti-correlation, we applied functional connectivity analysis of the DMN-DAN anti-correlation in 2 independent samples of amnestic MCI patients for cross-validation of the results. Via sliding time window functional connectivity analysis, we identified episodes of peak anti-correlations between the networks during resting-state fMRI (Allen et al., 2014; Chang and Glover, 2010; Hutchison et al., 2013a; Sadaghiani et al., 2015; Zalesky et al., 2014). Subsequently, we tested the hypothesis that higher levels of CR proxies (IQ or years of education) moderate the relationship lower levels of peak DMN-DAN anti-correlation and memory impairment in MCI. We included patients with the clinical syndrome of amnestic MCI patients, both single- and multiple-domain amnestic types, regardless of underlying etiology. To assess whether presence of AD pathology (increased levels of amyloid PET) or genetic risk of AD (ApoE ε4 genotype) influence the effect of CR proxies on the relationship between DMN-DAN anti-correlation and memory impairment, we controlled for both amyloid PET levels and *APOE* genotype.

2. Methods

2.1. Study sample

A total of 76 patients with amnestic MCI (MCI) and 36 healthy older adults (HC) were included from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Petersen et al., 2010). For cross-validation purposes, we included a sample of 93 patients with MCI, who were recruited at the memory clinic of the Institute for Stroke and Dementia Research (ISD), Klinikum der Universitaet Muenchen, Munich (henceforth referred to as the ISD sample).

In the ADNI study, MCI was diagnosed according to the Petersen (Petersen, 2004) criteria. MCI patients showed Mini Mental State Examination (MMSE) scores between 24 and 30 (inclusive), subjective and objective memory loss as defined by scores 1.5 SD below age and education adjusted scores on the Wechsler Memory Scale Logical Memory II, a CDR of 0.5, and absence of significant levels of impairment on other cognitive domains. An individual was defined as HC when showing an MMSE score between 24 and 30 (inclusive), a CDR of 0, no signs of depression, and no objective memory loss (for further details on diagnostic guidelines and neuropsychological examinations please see the ADNI study website (https://adni.loni.usc.edu/wp-content/uploads/2010/09/ADNI_GeneralProceduresManual.pdf)).

Beyond the inclusion criteria defined by ADNI, additional requirements for the inclusion in the present study had to be met, consisting of the availability of resting-state fMRI, T1-weighted MRI images, [18-F] AV-45 amyloid PET and comprehensive neuropsychological test scores. Amyloid beta (Aβ) levels in the brain were determined based on a global measure of [18-F] AV-45 PET binding, which is provided by the ADNI PET core as a summary measure of several cortical ROIs that have been described previously (Landau et al., 2013). Specifically, an abnormally high Aβ level was defined according to an a priori established cutoff value (Landau et al., 2013), i.e., a global AV-45 PET binding (SUVR) $\geq$1.11 (Aβ+, n = 44 for MCI; n = 13 for HC). Normal low Aβ levels (AV-45 PET binding [SUVR] <1.11, Aβ−) were present in 32 MCI and 23 HC.

In the ISD study, MCI was also diagnosed according to the Petersen (Petersen, 2004) criteria. MCI was defined as a score 1.5 SD below the norm (adjusted for age, education) on at least one of the memory subtests (word list or figure learning/recall) of the CERAD-Plus battery (Luck et al., 2009). All MCI patients underwent resting-state fMRI, T1-weighted MRI, and comprehensive neuropsychological testing. Additional inclusion criteria consisted of age >55 years, absence of symptoms of depression, other neurological disorders, uncontrolled arterial hypertension or diabetes mellitus or a history of alcohol or drug abuse. The ISD-MCI patients had been recruited for a cognitive intervention trial at the ISD [registered at www.clinicaltrials.gov as NCT01525368 as "Outcome Predictors of a Cognitive Intervention in aMCI"; see (Franzmeier et al., 2016) for details]. However, for the present study, we used only baseline data that were assessed before the cognitive intervention.

2.2. Standard protocol approvals, patient consents, and registration

For the ADNI sample, ethical approval was obtained by the ADNI investigators (for details see: http://www.adni-info.org/pdfs/adni_protocol_9_19_08.pdf). Recruitment of the ISD sample was approved by the ethics committee of the Ludwig Maximilian University Munich. All procedures were conducted in accordance with the Helsinki Declaration of 1975 and the applicable revisions at the time of the investigation. Written informed consent was obtained from all patients for being included in the study.

2.3. Neuropsychological assessment

To estimate memory performance, we used the ADNI-MEM score, a composite measure of episodic memory based on a broad battery of neuropsychological memory tests, as described previously for the ADNI study (Crane et al., 2012). Briefly, the ADNI-MEM score takes into account scores of the Rey Auditory Verbal Learning Test, AD Assessment Scale—Cognitive Subscale, word recall (3 words) of the MMSE and the Wechsler Logical Memory Scale II.

For the ISD-Munich sample, we generated a memory composite score via a similar approach that was used for the ADNI-MEM score (Crane et al., 2012). Here, we selected cognitive tests that are similar regarding test construction and measure the same neuropsychological construct (i.e., memory). To this end, we used the verbal memory subtests of the CERAD-Plus battery (Luck et al., 2009), the learning and recall subscales of the German version of the California Verbal Learning Test (Woods et al., 2006), and the word list learning and recall subtest of the AD Assessment Scale (Rozzini et al., 2008). Next, we applied maximum-likelihood confirmatory factor analysis to these memory tests, using a single factor model. The analysis yielded factor weights for each memory test loading on a principal factor with an eigenvalue of 9.14, indicating that the composite score captures considerably more variance than a single measure. For each

subject, the factor score was computed and z-score transformed to be used as a summary memory index in the subsequent analyses.

2.4. CR assessment

For the ADNI study, we employed years of formal education and premorbid verbal IQ [as assessed via the American national adult reading test; ANART (Bright et al., 2002)] as commonly used CR proxies (Stern, 2012). For the ISD study, we applied the premorbid verbal IQ assessed via the German multiple vocabulary test (Hessler et al., 2013; Valenzuela and Sachdev, 2006). We did not use years of education in the ISD sample because many older patients in Germany experienced their educational years during or shortly after World War II, which did compromise the educational system and may limit the reliability of the number of years of education as a proxy of CR. Thus, we focused on IQ as a CR proxy, whose scoring procedure is independent of the number of years of education. Since both education and IQ are frequently used proxies of CR and have been shown to be correlated (Nucci et al., 2012; Tucker and Stern, 2011), they both relate to CR. Hence, the interpretation of results should be similar.

2.5. Data acquisition

In the ADNI study, scanning was performed on Philips 3T MRI scanners, using an 8-channel head matrix coil. T1-weighted anatomical images were acquired using a 3-dimensional (3D) MPRAGE sequence, with whole brain coverage and $1 \times 1 \times 1.2$ mm voxel resolution. Resting-state fMRI images were recorded using a single shot T2*-weighted echo planer imaging (EPI) pulse sequence in transverse slice orientation, with a repetition time of 3000 ms, a flip angle of 80°, and 3.3-mm isotropic voxel resolution. The resting-state fMRI sequence comprised a total number of 140 volumes.

In the ISD study, scanning was performed on a Siemens 3T Magnetom Verio Scanner with a 12-channel head matrix coil. T1-weighted anatomical images were acquired using a 3D MPRAGE sequence with whole brain coverage and an isotropic voxel resolution of 1 mm. Resting-state fMRI images were acquired using a T2*-weighted EPI pulse sequence in transverse slice orientation with a repetition time of 3000 ms, a flip angle of 80°, 3-mm isotropic voxel resolution, and a total number of 120 volumes.

2.6. Preprocessing and spatial normalization of resting state fMRI data

All preprocessing steps were conducted using SPM 12 (Wellcome Trust Centre for Neuroimaging, University College London). The same preprocessing protocol, if not otherwise noted, was applied to the resting-state fMRI scans from ADNI and ISD. For each subject, the first 10 volumes of the fMRI time series were discarded because of known instabilities of the MR signal at the beginning of the fMRI acquisition. The remaining volumes were realigned to the first volume, motion corrected, and coregistered to native space 3D T1-weighted images and smoothed using a Gaussian kernel with a full width at half maximum of 8 mm. Preprocessed resting-state fMRI images were then spatially normalized using DARTEL (Ashburner, 2007), where the spatial normalization parameters and the creation of customized gray matter templates were done separately for the ADNI and ISD groups to avoid biases due to scanner differences between both studies. However, the same, spatial normalization protocol was used for both ADNI and ISD. In a first step, high-resolution 3D T1-weighted images were segmented in gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) maps, using SPM's new-segment approach (Ashburner and Friston, 2005). Based on the segmentations, we applied a diffeomorphic high-dimensional registration algorithm to warp individual subject brains to a common space that is defined in an iterative procedure, as implemented in the SPM 12 toolbox DARTEL (Ashburner, 2007). The resulting gray matter group template was then affine registered to the Montreal Neurological Institute (MNI) template of T1 images implemented in DARTEL.

The DARTEL flow fields and affine registration transformation matrix were subsequently combined and applied to each subjects' coregistered fMRI volumes for spatial normalization to the MNI template.

To remove noise from the EPI images, the spatially normalized resting-state fMRI images were detrended and band-pass filtered with a frequency band of 0.01–0.08 Hz. In addition, we regressed out the 6 motion parameters and the BOLD signal averaged across the WM and CSF. Since we were specifically interested in anti-correlations between DMN and DAN, we did not perform global signal regression, which may artificially introduce anti-correlations between resting-state fMRI signal changes of the DMN and DAN (Carbonell et al., 2014; Chai et al., 2012; Murphy et al., 2009; Spreng et al., 2016). To create GM masks, we averaged spatially normalized but unmodulated GM maps, followed by binarization (voxel value >0.3), which was conducted separately within the ADNI and the ISD groups.

For the extraction of GM volume, we additionally created spatially normalized GM maps for each subject, that were smoothed with an 8-mm full width at half maximum Gaussian kernel, following a previously described approach (Mak et al., 2011). During the normalization step, modulation was applied so that local concentrations of gray matter are preserved after warping the image to template space.

2.7. Resting-state fMRI data analysis

2.7.1. Independent component analysis

Spatial group ICA (Calhoun and Adali, 2012) on preprocessed resting-state fMRI data was performed using the Infomax Algorithm implemented in the GIFT-Toolbox (http://mialab.mrn.org/software/gift). The ICAs of resting-state fMRI scans were run separately for the ADNI and ISD samples. The number of independent components (ICs) to extract was a priori set to 20, which has previously been shown to robustly identify the DMN and DAN (Di and Biswal, 2014). To estimate the reliability of the resulting IC decomposition, the Infomax Algorithm was repeated 10 times in ICASSO (http://research.ics.aalto.fi/ica/icasso). All components showed stability indices greater than 0.95 in both groups suggesting that the components extracted by the group ICA algorithm show a high reliability. In line with earlier studies (Damoiseaux et al., 2012; Di and Biswal, 2014; Jones et al., 2011, 2012; Smith et al., 2009), we found the DMN to be subdivided into an anterior (aDMN) and a posterior (pDMN) component in both ADNI and ISD samples (see Fig. 1). The identification of the networks was confirmed by spatial regression matching the group ICA maps to the IC templates of major resting state networks (Laird et al., 2011). After group ICA, subject-specific IC maps and time courses (TCs) for the aDMN, pDMN, and DAN were back-reconstructed using GICA3 algorithm (Erhardt et al., 2011).

2.7.2. Sliding time window analysis of network time courses

We applied sliding time window analysis on the ICA derived component time courses to estimate peaks of anti-correlation between the aDMN versus DAN pair and the pDMN versus DAN pair (See Fig. 2 for illustration of the analysis). To this end, we used the GIFT-Toolbox (Allen et al., 2014), applying a sliding time window with a width of 30 repetition time (TR)'s (equivalent to 90 seconds of MRI acquisition) shifted in steps of 1 TR on the time courses of the 3 ICs. In line with previous studies, the rectangular time

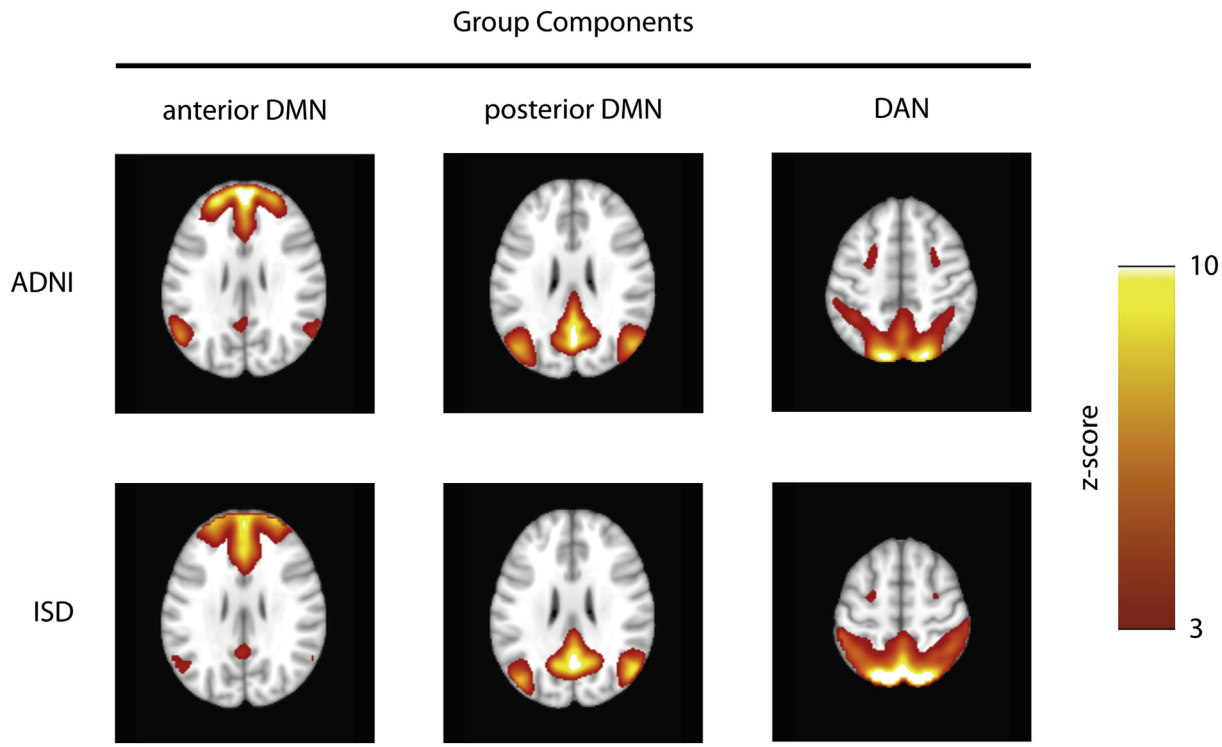

Fig. 1. ICA results. Resting-state networks identified via group independent component analysis (depicted in radiological convention). Group components for both study samples (ADNI and ISD) are superimposed on an MNI template and thresholded at a z-score >3. Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; DAN, dorsal attention network; DMN, default mode network; ICA, independent component analysis; ISD, Institute for Stroke and Dementia Research.

window was convolved with a Gaussian sigma of 3 TRs to achieve tapering near the edges (Allen et al., 2014). Within each time window, we computed the Pearson moment correlation between the ICA time courses of each DMN component and the DAN. Sliding the window successively yielded a continuous graph reflecting internetwork correlations over the entire duration of the resting-state scan for each subject (Fig. 2). As a measure of peak anti-correlation between the networks, we computed the mean correlation coefficient across those consecutive 10 time windows (equivalent to 40 TR's or 120 seconds of MRI acquisition) that surrounded the time window showing the highest anti-correlation between the networks' time courses. To test the impact of time window selection on our findings, we conducted all analyses thrice, using the mean of the 5 or 15 time windows (equivalent to 105 and 135 seconds of resting-state fMRI) showing the highest negative correlations. Window selection did not change the result pattern of our statistical analyses testing our hypothesis as reported in the following. We further aimed to assess whether changes in peak functional connectivity were confounded by spontaneous head motion (Power et al., 2012). To this end, we computed the framewise displacement (FD) for each subjects' resting-state scan, following a previously described approach (Power et al., 2012). In brief, the FD indexes the relative head movement between subsequent EPI volumes and is calculated as the sum of the absolute values of the differentiated realignment estimates at every timepoint. Subsequently, we computed the overall mean FD, the mean FD within those time windows encompassing the peak anti-correlations as well as the mean FD of all remaining time windows.

2.7.3. Assessment of static within- and between-network functional connectivity (FC)

As a validation measure to the peak anti-correlation assessed via the sliding time window approach, we computed the more common between-network connectivity averaged across the whole resting-state scan similar to previous studies (Fox et al., 2005; Uddin et al., 2009). To this end, we assessed the Pearson moment correlation between the ICA-derived component whole-scan time courses of each DMN component and the DAN component. To later address confounding effects of head motion, we also computed the mean FD averaged across the whole resting-state scan. To extract the specific mean stationary FC within the network components for each individual, we binarized the group component maps of the aDMN, pDMN, and DAN at a threshold of z-score > 3. The binarized IC masks were then superimposed onto each individuals' respective IC map to compute a mean z-score transformed independent component value for each network and individual, reflecting intranetwork FC.

2.8. GM volumetric assessment

To control for potentially confounding effects of GM atrophy in the analysis of the resting-state anti-correlation between a(p)DMN and DAN, we computed the gray matter volume within the spatial intersection between the binary GM mask and binarized (threshold $z > 3$) aDMN-DAN and pDMN-DAN maps. Specifically, we extracted the aDMN-DAN and pDMN-DAN GM volume for each subject from the modulated, smoothed, and normalized GM maps that were created during the preprocessing of structural MRI images. All volumetric measures were subsequently adjusted to intracranial volume (i.e., the sum of CSF, WM, and GM maps).

2.9. Statistical analysis

Demographics between all study groups were compared using *t* tests for continuous variables and chi-squared test for categorical variables. Next, we assessed in the ADNI sample, whether the peak

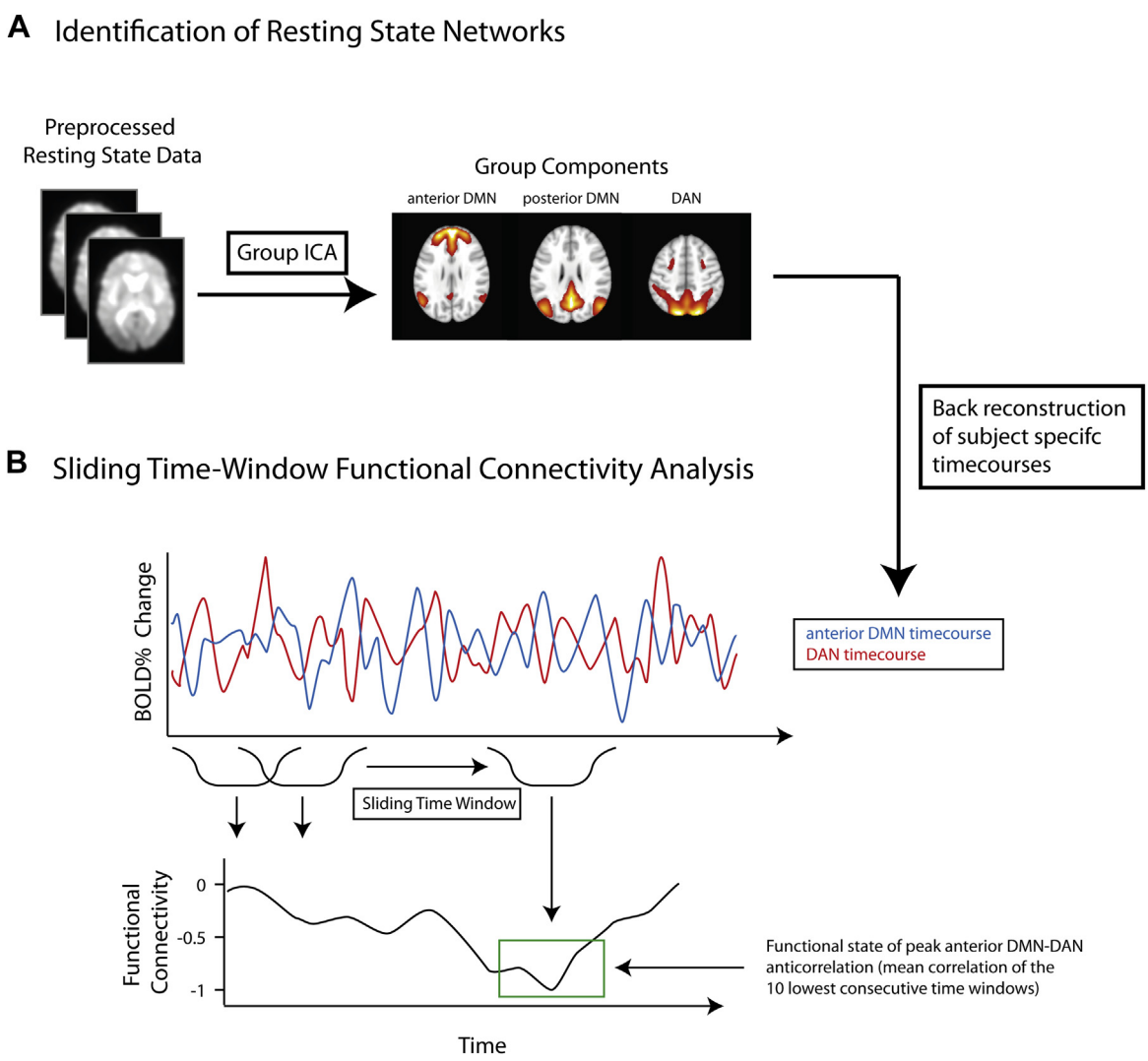

Fig. 2. Illustration of the sliding time window correlation analysis. (A) Networks of interest were identified by analyzing preprocessed resting state data via group ICA. Component time courses were back-reconstructed on subject level and subsequently entered in the sliding time window correlation analysis. (B) Example of a sliding time window correlation analysis for the anterior DMN and the DAN. The upper graph illustrates the time courses of both networks for a single subject over a whole resting state scanning session. A time window of 30 TRs is applied and subsequently shifted in steps of 1 TR over the whole time course of resting-state fMRI, and within each time window, the correlation coefficient between both network time courses is computed. Shown in the lower graph is the correlation of both networks across the resting-state fMRI scan as assessed via this sliding time window approach. The green box highlights an episode of peak anticorrelation between both networks indicating a transient state of high internetwork competitiveness. Abbreviations: DAN, dorsal attention network; DMN, default mode network; ICA, independent component analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

aDMN-DAN or pDMN-DAN anti-correlations (henceforth referred to as a(p)DMN-DAN anti-correlation) were pathologically reduced in MCI, using analysis of covariance with group (MCI vs. HC) as independent variable, controlling for age, gender, and education.

To address our main hypothesis that CR proxies moderate the relationship between the a(p)DMN-DAN anti-correlation and memory, we applied all regression analyses described below separately for the peak aDMN-DAN and peak pDMN-DAN anti-correlations. In all interaction models, CR proxies and the peak aDMN-DAN anti-correlation were entered as continuous measures. For illustrational purposes, interactions are, however, visualized by binarizing CR groups via median split.

For the ADNI sample, we tested the main and interaction effect of CR × peak a(p)DMN-DAN anti-correlation on ADNI-MEM (memory composite), with additional covariates including age, gender, AV-45 PET status (Aβ+ vs Aβ−), a(p)DMN-DAN GM volume and mean FD within the time windows of peak a(p)DMN-DAN anti-correlation. To investigate whether moderating effects of CR were different for Aβ positive or negative MCI patients, we also tested the 3-way interaction effect of AV-45 PET status × peak a(p)DMN-DAN anti-correlation × CR on the ADNI-MEM score, controlling for age and gender and a(p)DMN-DAN GM volume and mean FD within the time windows of peak a(p)DMN-DAN anti-correlation. To assess whether results were specific for peak functional connectivity, we conducted confirmatory analyses using the static whole time course instead of the peak a(p)DMN-DAN anti-correlation. For cross-validation purposes, we applied the same regression analyses to the MCI patients of the ISD study. Although Aβ levels were not assessed in the ISD sample, we included the Apolipoprotein (*APOE*) genotype (i.e., ε4 allele carrier vs. non-carrier) as a covariate indexing an individuals' risk of presence of AD pathology.

To assess whether stronger reductions in the peak a(p)DMN-DAN anti-correlation were driven by AD-specific brain changes

Table 1
Average (and standard deviation) of demographic variables, global cognitive scores, ApoE genotype, between-network correlations, and cognitive reserve surrogates for the ADNI and ISD samples

	ADNI-HC	ADNI-MCI	ISD-MCI
Sample size	36	76	93
Age	75 (6.3)	71 (7.5)[a]	73.8 (5.7)
Gender f/m	21/15	36/40	43/50
MMSE	28.8 (1.2)	27.9 (1.8)	27.3 (1.8)
MCI subtype			
Amnestic single-/multiple-domain	n.a.	67/9[b]	35/58
APOE status			
ε4 carriers/noncarriers	12/24	33/43	50/43
AV-45 status			
Aβ−/Aβ+	23/13	32/44[a]	n.a.
DMN-DAN correlation			
aDMN-DAN	−0.48 (0.5)	−0.48 (0.4)	−0.41 (0.4)
aDMN-DAN (age adjusted)	−0.51 (0.5)	−0.47 (0.4)	n.a.
pDMN-DAN	−0.60 (0.4)	−0.58 (0.4)	−0.57 (0.4)
pDMN-DAN (age adjusted)	−0.61 (0.4)	−0.59 (0.4)	n.a.
Cognitive reserve surrogate			
Years of education	16.19 (2.1)	16.39 (2.6)	n.a.
ANART (number of errors)	7.56 (5.48)	12.83 (9.7)[a]	n.a.
MWT-B (IQ)	n.a.	n.a.	116.68 (13.7)

Key: aDMN, default mode network; ADNI, Alzheimer's Disease Neuroimaging Initiative; ANART, American national adult reading test; DAN, dorsal attention network; f, female; HC, healthy controls; m, male; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; MWT-B, multiple vocabulary test; n.a., not assessed; pDMN, posterior default mode network.
[a] Significantly different from ADNI-HC ($p < 0.05$).
[b] Significantly different from ISD-MCI.

(i.e., Aβ deposition), we applied linear regression analyses, including the peak a(p)DMN-DAN anti-correlation as the dependent variable, and global AV-45 PET uptake as the predictor, controlling for age, gender, and education. Finally, we tested in linear regression analyses the association between the peak a(p)DMN-DAN anti-correlation and the mean (stationary) within-network functional connectivity, to assess whether the relationship between-network connectivity was influenced by the within-network integrity. To this end, we included the peak a(p)DMN-DAN anti-correlation as the dependent measure, and the CR proxy, mean within-network functional connectivity of the a(p)DMN and DAN as predictors, controlling for the memory composite score, age, gender the AV-45 PET status (ADNI sample) or the *APOE* genotype (ISD sample).

To eliminate methodological concerns, we tested whether head motion was in- or decreased during episodes of peak a(p)DMN-DAN anti-correlation versus the remaining resting-state scan. To this end, we applied Wilcoxon tests (due to nonnormal distribution of mean FD), testing differences between mean FD within time windows of peak a(p)DMN-DAN anti-correlation against mean FD within the remaining time windows. We further tested whether the peak a(p)DMN-DAN anti-correlation correlated with mean FD in that time windows.

Linear model assumptions were tested using the gvlma package in R. For all models reported, no significant deviations for linear model assumptions were found (alpha threshold = 0.05). All statistical analyses were conducted in R statistical software (Version 2.13.2; *R* Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Sample characteristics

Demographics, cognitive measures, and the a(p)DMN-DAN correlation coefficients for the ADNI and ISD samples are depicted in Table 1. In the ADNI sample, MCI patients were significantly younger than the HC subjects [$t(110) = 2.80$, $p = 0.006$].

3.2. Comparison of peak a(p)DMN-DAN anticorrelation between HC and MCI subjects

In the ADNI sample, we tested whether MCI patients differed from HC regarding the a(p)DMN-DAN anti-correlation or within network FC measures. We found no differences in the a(p)DMN-DAN anti-correlation between HC and MCI. There were also

Table 2
Regression models for the interaction between peak aDMN-DAN anti-correlation and CR on composite memory scores, controlled for age, gender, and aDMN-DAN gray matter volume and mean FD

Sample, model terms	ADNI-HC B (SE)	*p*-value	ADNI-MCI B (SE)	*p*-value	ISD-MCI B (SE)	*p*-value
CR proxy: IQ						
Intercept	2.60 (0.85)	0.005	2.00 (0.75)	0.009	2.36 (0.70)	0.001
IQ X aDMN-DAN anticorrelation	0.01 (0.03)	0.701	−0.03 (0.02)	0.030	0.01 (0.01)	0.015
IQ	0.01 (0.02)	0.977	−0.02 (0.01)	0.017	0.27 (0.12)	0.031
aDMN-DAN anticorrelation	−0.04 (0.29)	0.887	0.14 (0.22)	0.533	−0.70 (0.33)	0.036
CR proxy: years of education						
Intercept	2.85 (1.38)	0.049	0.25 (0.83)	0.776	n.a	n.a
Education X aDMN-DAN anticorrelation	−0.03 (0.10)	0.733	0.14 (0.04)	0.002	n.a	n.a
Education	−0.01 (0.07)	0.873	0.10 (0.03)	0.001	n.a	n.a
aDMN-DAN anticorrelation	0.62 (1.61)	0.705	−2.65 (0.77)	0.001	n.a	n.a

In the ADNI sample, we additionally controlled for AV45 uptake. In the ISD sample, we controlled for *APOE* carrier status (ε4 vs. other).
Key: aDMN, anterior Default Mode Network; CR, cognitive reserve (years of education for ADNI, IQ for ISD sample); DAN, dorsal attention network; mean FD = mean framewise displacement (during the time windows of peak aDMN-DAN anti-correlation); n.a., not assessed.

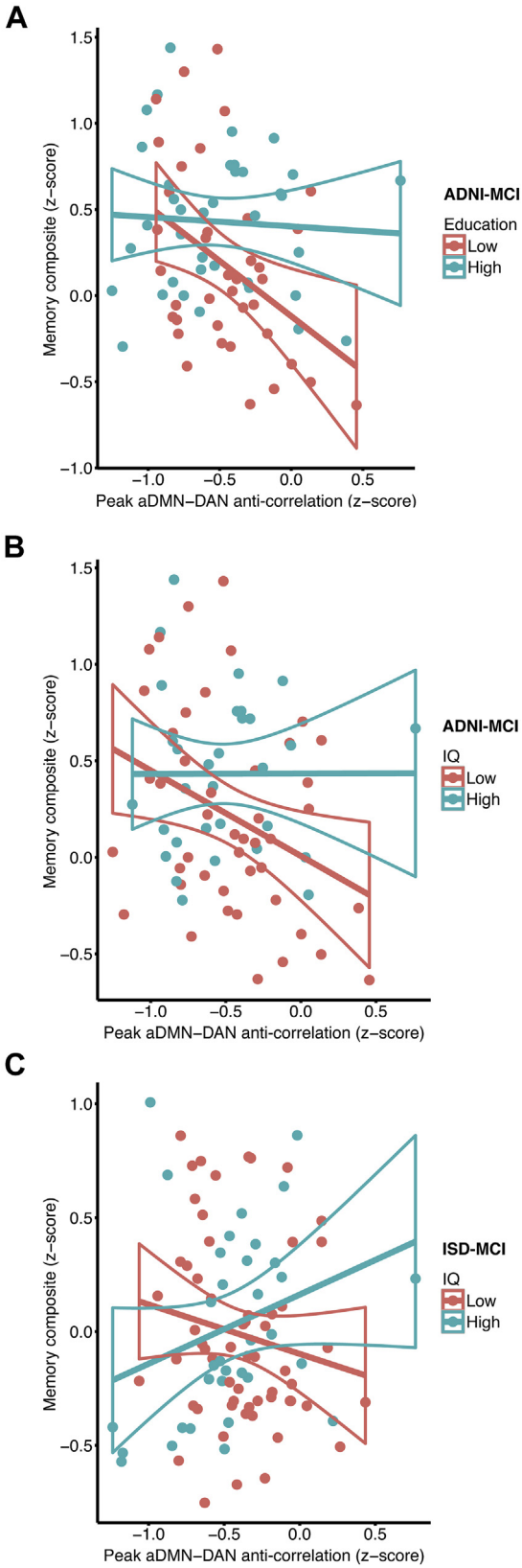

Fig. 3. Scatterplot for the interaction between peak aDMN-DAN anti-correlation and education (A) and IQ (B) for predicting the composite memory score in the ADNI-MCI sample. The correlation between the aDMN and the DAN is plotted against the composite memory score. Regression lines plus the 95% CIs are plotted for high and low CR (education or IQ) groups that were defined via median split for illustrational purposes. (C) Scatterplot for the interaction between IQ and peak aDMN-DAN anti-correlation for predicting the composite memory score in the ISD-MCI sample. The correlation between the aDMN and the DAN is plotted against the composite memory score. For illustrational purposes, regression lines plus the 95% CIs are plotted for high IQ and low IQ groups that were again defined via median split. Abbreviations: aDMN, anterior default mode network; CR, cognitive reserve; DAN, dorsal attention network; ISD, Institute for Stroke and Dementia Research; MCI, mild cognitive impairment.

no observed differences, when MCI Aβ+ and MCI Aβ− groups were separately compared to HC, or to HC Aβ− only. Since MCI patients were significantly younger than HC, we manually adjusted the a(p)DMN-DAN anti-correlations for age (see Table 1; details on the adjustment procedure can be found in the Supplementary data). Here, the a(p)DMN-DAN anti-correlation was numerically but not significantly decreased in MCI when compared to HC.

3.3. CR as moderator of the association between a(p)DMN-DAN anticorrelation and memory performance in MCI

For the ADNI study, the interaction effect of CR × peak aDMN-DAN anti-correlation on the memory composite score was significant in MCI patients for different CR proxies [education: $t(67) = 3.176$, $B = 0.14$, $SE = 0.04$, $p = 0.002$; IQ: $t(67) = -2.213$, $B = -0.03$, $SE = 0.02$, $p = 0.030$]. Fig. 3A and B show that a decrease in the peak aDMN-DAN anti-correlation was associated with lower episodic memory composite scores in the low CR but not the high CR patients (groups are split at the median for illustrational purposes). Controlling for *APOE* genotype rather than Aβ− status in the MCI patients did not change the result pattern. Congruent effects were found when entering static whole time course aDMN-DAN anti-correlation in the interaction term [education: $t(67) = 3.384$, $B = 0.18$, $SE = 0.05$, $p = 0.001$; IQ: $t(67) = -2.083$, $B = -0.03$, $SE = 0.01$, $p = 0.041$]. For the pDMN, the interaction effect of education × peak pDMN-DAN anti-correlation on the memory composite was not significant for both peak as well as static FC in MCI. When tested in the HC group, we found no main effect of peak a(p)DMN-DAN anti-correlation on the memory composite nor was the interaction education or IQ × peak a(p)DMN-DAN anti-correlation significant (see Supplementary Fig. 1), suggesting reduced levels of peak aDMN-DAN anti-correlation to impact memory first at the level of MCI. Cross-validation analysis in the ISD sample confirmed a significant interaction effect of IQ × peak aDMN-DAN anti-correlation on the memory composite score in MCI [$t(84) = 2.477$, $B = 0.01$, $SE = 0.01$, $p = 0.015$; see Fig. 3C]. Consistent with the results obtained in the ADNI study, a reduced peak aDMN-DAN anti-correlation was associated with lower episodic memory composite scores at lower levels of IQ. A congruent interaction effect was found when using static whole time course aDMN-DAN anti-correlation [$t(84) = 2.498$, B 0.02, $SE = 0.008$, $p = 0.014$]. Again, no significant interaction effect was observed between the IQ × peak pDMN-DAN anti-correlation on the composite memory score. For detailed regression statistics on interaction models please see Table 2.

Neither education (ADNI sample) nor IQ (ISD-sample) were correlated with the level of peak aDMN-DAN anti-correlation (ADNI: $r = -0.08$, $p = 0.483$; ISD: $r = -0.03$, $p = 0.79$), or pDMN-DAN anti-correlation (ADNI: $r = -0.19$, $p = 0.15$; ISD: $r = -0.08$, $p = 0.45$) suggesting that CR does not alter the a(p)DMN-DAN anti-correlation itself.

3.4. Aβ-status, education, and peak aDMN-DAN anti-correlation in MCI (ADNI)

We next tested whether (1) greater Aβ deposition was related to decreased levels of peak aDMN-DAN anti-correlation, or

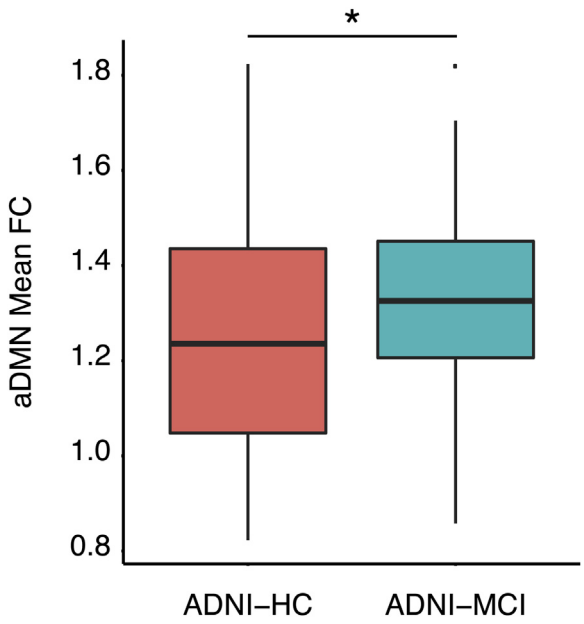

Fig. 4. Group comparison of the mean aDMN-FC between HC and MCI subjects of the ADNI sample. The group difference is significant at $^{*}p < 0.05$. Abbreviations: aDMN, anterior default mode network; ADNI, Alzheimer's Disease Neuroimaging Initiative; FC, functional connectivity; HC, healthy controls; MCI, mild cognitive impairment.

(2) whether the interaction CR × peak aDMN-DAN anti-correlation was different with regard to Aβ-status. In a linear regression model, global AV-45 PET levels did not predict peak aDMN-DAN anti-correlation [t(73) = 0.806, B = 0.17, SE = 0.21, $p = 0.423$]. There were no differences in the effect of education × peak aDMN-DAN anti-correlation on memory between the MCI Aβ+ and MCI Aβ− groups, suggesting that the moderating effect of CR on the association between peak aDMN-DAN anti-correlation and memory performance was not influenced by Aβ status [3-way interaction: education: t(64) = −1.383, B = −0.26, SE = 0.11, $p = 0.17$; IQ: t(64) = −0.5, B = −0.013, SE = 0.027, $p = 0.618$].

3.5. Group differences in stationary within-network functional connectivity and its association with peak a(p)DMN-DAN anti-correlation

When comparing the mean stationary functional connectivity within the networks (aDMN, pDMN, DAN) between MCI and HC of the ADNI sample, we found an increased aDMN-functional connectivity in ADNI-MCI compared to ADNI-HC [t(110) = −2.42; $p = 0.017$; see Fig. 4], but no differences in functional connectivity within the pDMN or DAN. Levels of within-network functional connectivity (DAN, aDMN, pDMN) were neither associated with the level of between-network anti-correlation nor with CR proxies in either sample.

3.6. Peak aDMN-DAN anti-correlation and head motion

To rule out that the possibility that our results were driven by excessive head motion, we first tested, whether head motion was different between time windows of peak aDMN-DAN anti-correlation and remaining time windows. In both samples, we found no significant differences between mean FD in the 10 time windows representing peak aDMN-DAN anti-correlation and mean FD in the remaining time windows (ADNI-MCI: $p = 0.86$, ADNI-HC: $p = 0.47$, ISD-MCI: $p = 0.12$). This suggests that head motion is not increased during episodes of peak aDMN-DAN anti-correlation. When testing whether the mean FD during peak aDMN-DAN anti-correlation was associated with the level of anti-correlation, we found no significant correlations (ADNI-MCI: r = 0.01, $p = 0.92$, ADNI-HC: r = 0.1, $p = 0.55$, ISD-MCI: r = 0.15, $p = 0.17$). There were no significant differences in mean FD between HC and MCI patients in the ADNI sample ($p = 0.63$). MCI patients of the ISD sample showed significantly less head motion (i.e., smaller mean FD) than MCI patients of the ADNI sample (U = 5464, $p < 0.001$).

4. Discussion

The major finding of the present study was that in amnestic MCI, higher levels of CR proxies alleviated the association between lower aDMN-DAN anti-correlation and lower episodic memory performance. This effect was consistently detected in 2 independent samples of MCI patients, using different proxy measures for CR (education or IQ). Our findings suggest that higher levels of CR are associated with protective effects at the functional network level in MCI and allow maintenance of relatively high memory performance at low levels of aDMN-DAN crosstalk.

In line with our findings, protective effects of education and IQ in nondemented older adults have been suggested by several lines of research. First, older adults with higher levels of education and IQ show at any level of cognitive performance relatively more severe levels of gray matter atrophy (Bastin et al., 2012; Solé-Padullés et al., 2009), temporoparietal glucose hypometabolism (Bastin et al., 2012; Ewers et al., 2013; Morbelli et al., 2013), or white matter hyperintensities (Brickman et al., 2011; Teipel et al., 2009), suggesting that those with higher CR proxy levels can cope better with brain pathology. Second, higher levels of education and IQ are associated with a delayed onset of cognitive decline (Amieva et al., 2014; Hall et al., 2007; Vemuri et al., 2011) and conversion from MCI to AD dementia (Dekhtyar et al., 2015; Querbes et al., 2009), suggesting that individuals with higher CR show prolonged maintenance of preserved levels of cognitive performance. Consistent with these previous results, our current findings reveal protective effects of education and IQ at the functional network level in MCI, where education and IQ consistently moderate the effect of lower levels of aDMN-DAN anti-correlation on episodic memory.

We found in both MCI samples that the DMN contains subcomponents including and anterior and posterior part of the DMN (Damoiseaux et al., 2006, 2012; Di and Biswal, 2014; Jones et al., 2011, 2012). Interestingly, the anti-correlation between the aDMN-DMN rather than pDMN-DAN was associated with memory performance. Previous studies including voxel-based functional connectivity analyses reported the aDMN to be predominantly connected to the parietal regions of the DAN, but the pDMN to be primarily connected to the premotor cortex (Uddin et al., 2009). Thus, it is predominantly the aDMN which is associated with those brain regions of the DAN that are known to be involved in memory and attention (Kim, 2015; Kim et al., 2010; Vossel et al., 2014). Therefore, the interaction effect of CR × DMN-DAN anti-correlation on memory was selectively found for the aDMN component probably due to its stronger connectivity to memory-supporting brain structures.

The opposing activity pattern of the DAN and DMN has previously been proposed to subserve an adaptive mechanism to increase attention to external stimuli presented during a cognitive task and to reduce the interference from irrelevant processes (Andrews-Hanna et al., 2010; Fox et al., 2005; Fransson, 2005; Keller et al., 2015; Spreng et al., 2016). This DMN-DAN anti-correlation has been shown to be pathologically reduced in AD dementia but not yet at the stage of MCI (Wang et al., 2007; Zhu et al., 2016). Consistent with those results, we found a numerical but not

significant reduction of the DMN-DAN anti-correlation in MCI when compared to HC. Together with our finding that at low levels of CR, weaker DMN-DAN anti-correlations are coupled to reduced memory performance only in MCI, the current results suggest that the DMN-DAN anti-correlation becomes critical to sustain memory at a fragile state of the brain, such as observed in MCI at low levels of CR. During cognitive processes, such as successful memory performance, task-positive networks including the DAN are critically involved (Spreng et al., 2010; Whitfield-Gabrieli and Ford, 2012) and are thought to orchestrate efficient network activation in the brain during task performance (Fox et al., 2005). Especially in MCI, where medial temporal lobe structures become functionally isolated (Pasquini et al., 2015; Tahmasian et al., 2015), memory performance requires coordinated coupling of the DMN and DAN (Celone et al., 2006). Thus, in the presence of regionally circumscribed brain alterations in MCI, the role of the anti-correlated DMN-DAN activity may become especially important to maintain brain processes of successful memory performance. Our finding of the interaction between CR proxies and aDMN-DAN anti-correlation suggests that higher levels of CR buffer the effects of relatively low anti-correlation of DAN and aDMN on memory at the stage of MCI.

Our results raise the question which functional brain changes underlie CR. In the current study, intranetwork connectivity of the aDMN was increased, consistent with previous findings of increased frontal connectivity in MCI and AD (Jones et al., 2011; McCarthy et al., 2014). Increased frontal connectivity and activation in MCI and AD has been previously considered as a mechanism of compensatory nature (Barulli and Stern, 2013; Jones et al., 2011; Zhou et al., 2010). However, in the present study, no association between aDMN and CR or the aDMN-DAN anti-correlation was found. Alternatively, the increased aDMN functional connectivity may reflect dedifferentiation of frontal lobe function in aging and neurodegenerative diseases (Dennis and Cabeza, 2011; Jones et al., 2011). Several previous studies have investigated the effect of CR on brain connectivity or task-related brain activation (Arenaza-Urquijo et al., 2013; Bosch et al., 2010; Marques et al., 2016; Stern et al., 2008) [for a review see (Arenaza-Urquijo et al., 2015; Stern, 2012)]. Higher CR proxies have been reported to be associated with higher temporal and parietal brain activation during a memory encoding task in AD (Solé-Padullés et al., 2009), and higher resting state frontal connectivity and parietal functional segregation in cognitively healthy subjects (Arenaza-Urquijo et al., 2013; Marques et al., 2016). Still, compensatory functional brain changes of CR that support memory performance in MCI are unknown. The current findings may provide a reference standard for the search of functional mechanisms that account for the moderating effects of CR in MCI, i.e., the alleviated association between lower levels of the peak aDMN-DAN anti-correlation and memory impairment.

The present study included MCI subjects both with and without elevated risk for AD. Importantly, we found no effect of Aβ status or ApoE4 carrier-status on the relationship between peak aDMN-DAN anti-correlation, CR proxies and memory performance. The DMN-DAN anti-correlation is a fundamental feature of network interaction that is associated with cognition. The DMN-DAN has been found to be altered in many neurodegenerative and psychiatric disease and may thus not be specific to AD (Anticevic et al., 2012; Baggio et al., 2015). The current results in amnestic MCI suggest that lower levels of the aDMN-DAN anti-correlation are associated with memory impairment, which is alleviated by CR, regardless of the presence of AD pathology.

Further, our samples included subjects with both single and multiple domain MCI. It is an open question whether the MCI subtype influences the effects of CR proxies on the association between peak aDMN-DAN anti-correlation and memory. We did not assess this in the present study since a restriction of our sample to single or multiple domain MCI would have drastically reduced statistical power and thus limited the sensitivity to detect the hypothesized effects. We encourage future studies to test a possible effect of the MCI subtype in larger samples of single and multiple domain MCI patients.

For the present study, we used sliding time window analysis to capture states of peak aDMN-DAN anti-correlations. However, sliding time window functional connectivity analysis in resting-state fMRI is a relatively new method (Allen et al., 2014), and no standardized index to characterize dynamics of between-network connectivity has been yet established [for review see (Hutchison et al., 2013b)]. In the present study, we used the peak anti-correlation of ICA derived time courses of the DMN components and DAN to measure states of high between-network anti-correlations. Alternative measures include the analysis of recurring patterns of functional connectivity derived from ROI-to-ROI analyses or ICA which have been previously interpreted as mental states or modes of functional connectivity (Allen et al., 2014). However, the anti-correlation of the DMN components and DAN can be observed in multiple of such modes (Damaraju et al., 2014; Meskaldji et al., 2016). In the present study, the peak anti-correlation was therefore considered the index of choice. A previous study that analyzed such peak anti-correlations between DMN and DAN brain regions during resting-state has shown that this measure is a strong predictor of memory performance in MCI (Meskaldji et al., 2016). To assure that the index was not dependent on an arbitrary decision, such as the length of time intervals across which peak correlations were identified, we varied the interval length, observing virtually no change in the results. To assess whether our results were specific to our peak functional connectivity measure, we also computed the static whole time course aDMN-DAN anti-correlation, following the methodology of previous studies (Fox et al., 2005; Uddin et al., 2009). Here, we found consistent results, i.e., an interaction of aDMN-DAN anti-correlation × CR proxies on memory performance across samples. These observations support the robustness of the current findings and that moderating effects of CR can be detected across methods.

It is important to keep in mind that the assessment of the anti-correlation between the DAN and DMN is sensitive to preprocessing steps including global signal regression (Murphy et al., 2009; Spreng et al., 2016; Weissenbacher et al., 2009) as well as physiological noise, which has been shown for both static and sliding time window functional connectivity analysis (Birn et al., 2014; Nikolaou et al., 2016). In the present study, we regressed out the signal of CSF and WM, without global signal removal from the BOLD signal time series. Regression-based removal of the CSF and WM signal fluctuation was previously shown as an effective control when compared against the standard of noise removal based on monitored breathing and cardiac activities (Chai et al., 2012; Chang and Glover, 2009). To further control for potential influence of movement, we could show that states of peak aDMN-DAN anti-correlation were not associated with larger head motion. Moreover, we demonstrated that the anti-correlation between the aDMN and DAN was associated with memory performance in 2 independent MCI samples, rendering it unlikely that the levels of anti-correlation stemmed from nonneural sources. Supporting this notion, a previous resting-state EEG-fMRI study has shown changes in the BOLD DMN-DAN anti-correlation to be associated with simultaneous changes in EEG alpha band power (Chang et al., 2013). We caution, however, that the present study remains correlational in nature so that a clear cause and effect relationship cannot be discerned.

5. Conclusions

In summary, the present study suggests that higher levels of education and IQ confer protective effects in MCI, moderating the association between lower levels of aDMN-DAN anti-correlation and memory. The results provide a crucial support for the CR hypothesis in that we show a cognitive benefit through altered association between functional network changes and cognitive outcome. Based on these results, questions on the search for compensatory brain mechanisms and therapeutic interventions to stimulate the moderating effects of CR at the functional level can be addressed in future studies.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2016.11.013.

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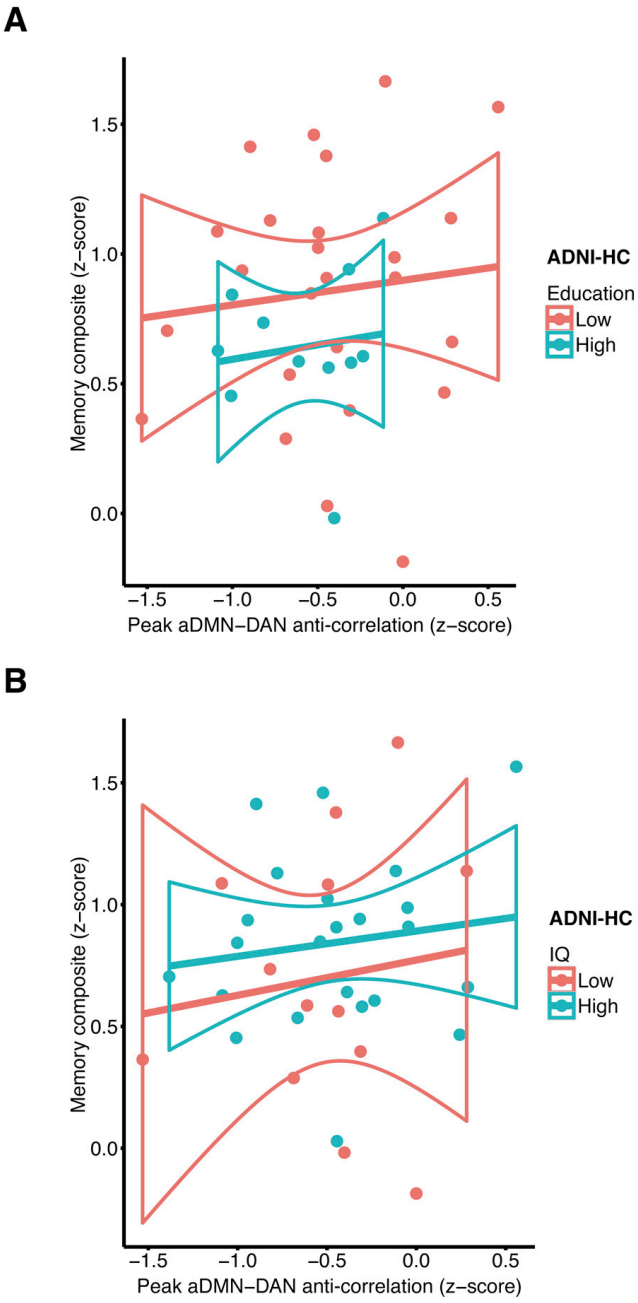
Supplementary

Methods:

The a(p)DMN-DAN anti-correlation values were age-adjusted for each subject according to the mean age of the according group (i.e. ADNI-HC vs. ADNI-MCI). Specifically, the influence of age on a(p)DMN-DAN anti-correlation and age was estimated with a linear regression model of the form: a(p)DMN-DAN anti-correlation ~ β_{age} + *intercept*. Next, the anti-correlation value for each subject j was adjusted by the extent to which a subject's age deviated from the mean age of the group mean age (μ_{age}) multiplied by the β_{age} coefficient of the influence of age on memory. This was done by applying the adjustment according to the equation: *adjusted* a(p)DMN-DAN anti-correlation$_j$ = a(p)DMN-DAN anti-correlation $_j$ – β_{age}(age_j - μ_{age}. For example, if a subject is 10 years older than the group average and with higher age the anti-correlation is decreased, then that subject's aDMN-DAN anti-correlation would be enhanced by the factor β_{age} x 10. In brief, this equation centers the a(p)DMN-DAN anti-correlation values at the mean age of the group μ_{age}. We have added this section explaining the manual adjustment procedure to the supplementary.

Figure:


A
1.5
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Memory composite (z−score)
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Peak aDMN−DAN anti-correlation (z−score)
ADNI-HC
Education
Low
High
B
1.5
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0.0
Memory composite (z−score)
−1.5
−1.0
−0.5
0.0
0.5
Peak aDMN−DAN anti-correlation (z−score)
ADNI-HC
IQ
Low
High

3 | A Fronto-Parietal Control Network Hub as a Substrate of Cognitive Reserve

3.1. Summary

In the second study, we applied our newly developed research criteria (see paragraph 1.6) to test the fronto-parietal control network model of cognitive reserve (see paragraph 1.7. and Figure 4B). Specifically, we assessed in a sample of MCI patients with abnormal amyloid beta levels (i.e. prodromal AD) whether greater global connectivity of the LFC is associated with more years of education as a protective factor (i.e. criterion of face validity) and better tolerance of AD pathology (i.e. criterion of cognitive benefit). We specifically focused on the LFC as it is relatively unaffected by AD pathology (Buckner et al., 2005), among the top 5% of globally connected regions and associated with protective factors (i.e. IQ & education) in healthy individuals (Cole et al., 2012) and patients with MCI (Serra et al., 2016). Following a previously described approach, we determined the hubness of the LFC using resting-state fMRI global functional connectivity (Cole et al., 2012). This measure of global connectivity quantifies the level of interconnectedness between the LFC and the rest of the brain and is assumed to reflect the level of control a given brain region can exert on other functional networks. As a measure of AD pathology we used FDG-PET, which assesses brain glucose metabolism and acts as a proxy for AD-related synaptic dysfunction. Supporting the fronto-parietal control network model of cognitive reserve, we could show that 1) more years of education were associated with greater global LFC connectivity (i.e. criterion of face validity), and 2) that at a given level of posterior parietal FDG-PET hypotmetabolism, greater global LFC connectivity was

associated with better memory memory (i.e. criterion of cognitive benefit). The results of this hypothesis driven study provide for the first time systematic evidence that the LFC hub of the fronto-parietal control network may constitute a neural substrate of cognitive reserve in AD.

3.2. Reference

This work was carried out under the supervision of Michael Ewers; N.F. and M.E. designed research and wrote the manuscript; N.F. analyzed the data; M.Düring, M.Dichgans & M.W. critically revised the manuscript.

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Left frontal cortex connectivity underlies cognitive reserve in prodromal Alzheimer disease

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ABSTRACT

Objective: To test whether higher global functional connectivity of the left frontal cortex (LFC) in Alzheimer disease (AD) is associated with more years of education (a proxy of cognitive reserve [CR]) and mitigates the association between AD-related fluorodeoxyglucose (FDG)-PET hypometabolism and episodic memory.

Methods: Forty-four amyloid-PET–positive patients with amnestic mild cognitive impairment (MCI-Aβ+) and 24 amyloid-PET–negative healthy controls (HC) were included. Voxel-based linear regression analyses were used to test the association between years of education and FDG-PET in MCI-Aβ+, controlled for episodic memory performance. Global LFC (gLFC) connectivity was computed through seed-based resting-state fMRI correlations between the LFC (seed) and each voxel in the gray matter. In linear regression analyses, education as a predictor of gLFC connectivity and the interaction of gLFC connectivity × FDG-PET hypometabolism on episodic memory were tested.

Results: FDG-PET metabolism in the precuneus was reduced in MCI-Aβ+ compared to HC ($p = 0.028$), with stronger reductions observed in MCI-Aβ+ with more years of education ($p = 0.006$). In MCI-Aβ+, higher gLFC connectivity was associated with more years of education ($p = 0.021$). At higher levels of gLFC connectivity, the association between precuneus FDG-PET hypometabolism and lower memory performance was attenuated ($p = 0.027$).

Conclusions: Higher gLFC connectivity is a functional substrate of CR that helps to maintain episodic memory relatively well in the face of emerging FDG-PET hypometabolism in early-stage AD. ***Neurology*® 2017;88:1054–1061**

GLOSSARY

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **BNT** = Boston Naming Test; **CR** = cognitive reserve; **EPI** = echo-planar imaging; **FDG** = fluorodeoxyglucose; **gLFC** = global left frontal cortex; **GM** = gray matter; **HC** = healthy controls; **LFC** = left frontal cortex; **MCI** = mild cognitive impairment; **MEM** = episodic memory composite score; **OP** = occipital pole; **ROI** = region of interest; **SUVR** = standardized uptake value ratio; **TMT-B** = Trail-Making Test B.

Cognitive reserve (CR) is defined as the ability to maintain cognition relatively well in the presence of brain pathology[1] and is assessed mainly via proxies such as years of education or IQ. Neuroimaging studies in Alzheimer disease (AD) have shown that higher CR is associated with exacerbated temporoparietal fluorodeoxyglucose (FDG)-PET hypometabolism at a given level of cognitive performance,[2–4] suggesting that CR allows the patient to better cope with AD pathology.[1,5] The neural mechanisms underlying CR, however, are largely unknown. Previous resting-state fMRI studies suggest that global functional connectivity of the left frontal cortex (LFC) might support CR because it is associated with IQ (CR proxy) and cognitive performance in young individuals.[6] As a major cortical hub within the cognitive control network, the LFC supports cognitive performance at a task-invariant level,[7] which sets it apart from other task-specific changes that may relate to CR.[8–12] Because the LFC is relatively spared in AD,[13]

Supplemental data at Neurology.org

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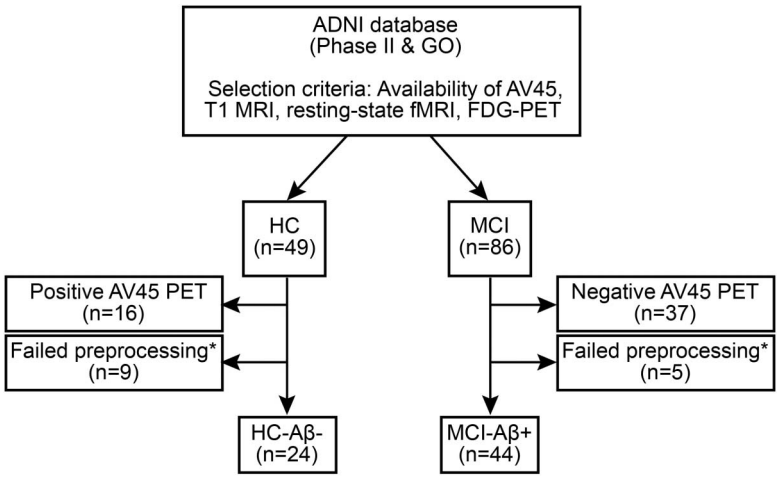
we hypothesized that higher LFC functional integrity as measured by global LFC (gLFC) connectivity underlies CR in prodromal AD. In a first step, we aimed to confirm previous findings of the ability of patients with AD with higher CR (education) to maintain cognitive performance relatively well despite parietal FDG-PET hypometabolism.[2,14] Second, we examined whether gLFC connectivity underlies CR, i.e., the increased ability to tolerate FDG-PET hypometabolism. Therefore, we tested whether in patients with prodromal AD higher gLFC connectivity is associated with more years of education (criterion of face validity) and attenuates the association between FDG-PET hypometabolism and memory impairment (criterion of cognitive benefit).

METHODS

Participants. All participants were recruited within the Alzheimer's Disease Neuroimaging Initiative (ADNI; recruitment phases GO and II) and were selected on the basis of the availability of AV45-PET scans to assess β-amyloid (Aβ) levels, T1-weighted MRI, resting-state fMRI, FDG-PET, and cognitive testing. The final sample (see figure 1 for a flowchart) included 24 healthy controls (HC) and 44 patients with amnestic mild cognitive impairment (MCI) with elevated Aβ levels meeting research criteria for prodromal AD. MCI was diagnosed according to the Petersen[15] criteria. With the use of pre-established cutoff values[16] applied to the global AV45-PET standardized uptake value ratio (SUVR), participants were characterized as having abnormally high amyloid deposition (SUVR ≥ 1.11, MCI-Aβ+, n = 44). HC showed normal cognitive performance and normal AV45-PET SUVR values (SUVR < 1.11, n = 24). For details on PET acquisition, see appendix e-1 at Neurology.org.

Figure 1 Participant selection flowchart



*Excluded because of excessive motion or failed segmentation, coregistration, or normalization. Aβ = β-amyloid; ADNI = Alzheimer's Disease Neuroimaging Initiative; FDG = fluorodeoxyglucose; HC = healthy controls; MCI = mild cognitive impairment.

Standard protocol approvals, registrations, and patient consents. Ethics approval was obtained by the ADNI investigators. All study participants provided written informed consent.

Neuropsychological assessment and CR. Episodic memory was measured through a previously described episodic memory composite score (ADNI-MEM) composite score.[17] The ADNI-MEM score is a weighted factor score based on neuropsychological memory tests, including the Rey Auditory Verbal Learning Test, the Alzheimer's Disease Assessment Scale, the Wechsler Logical Memory I and II, and the word recall of the Mini-Mental State Examination. We expanded our analysis of gLFC connectivity on secondary nonmemory domains, including language function (Boston Naming Test [BNT]) and executive functions (Trail-Making Test B [TMT-B]). The TMT-B was chosen because we previously found this test to be affected early in AD.[18] Consistent with our previous study[2] and others (for a review, see reference 19), we used years of education as a CR proxy. Education is highly correlated with other CR proxies, including IQ[20] or occupational attainment,[21] and is to date the best established CR proxy.[19]

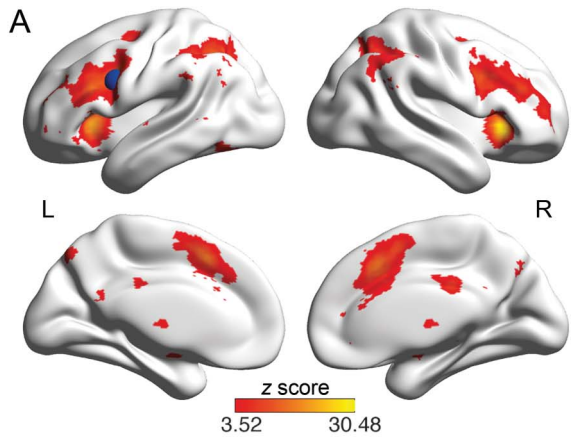
MRI acquisition. MRI scans were performed on Philips 3T MRI scanners using an 8-channel coil. T1-weighted images were acquired with a 3-dimensional magnetization-prepared rapid gradient-echo sequence, with whole-brain coverage at a voxel resolution of 1 × 1 × 1.2 mm. Resting-state fMRI images were acquired with a single-shot T2*-weighted echo-planar imaging (EPI) sequence in transverse slice orientation (repetition time = 3,000 milliseconds, flip angle of 80°, 3.3-mm isotropic voxel resolution). Overall, 140 EPI volumes were acquired during which participants were instructed to keep their eyes open.

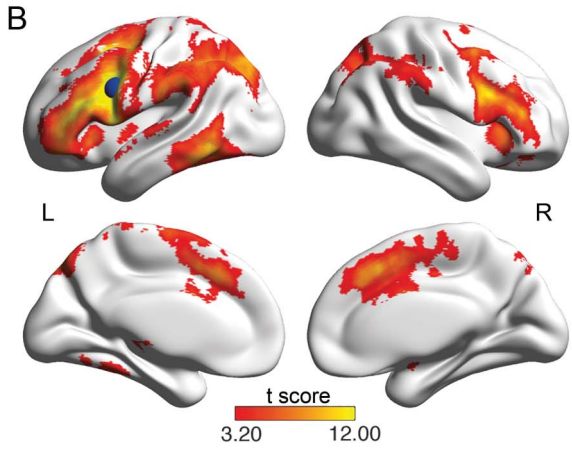
Preprocessing of FDG-PET data. Preprocessing was conducted with SPM8 (Wellcome Trust Centre for Neuroimaging, University College London). Spatial normalization of FDG-PET images was performed with DARTEL,[22] a nonlinear registration algorithm implemented in SPM8 (for details, see appendix e-2). All FDG-PET images were subsequently smoothed (8-mm full-width half-maximum gaussian kernel) and adjusted to the individual mean signal of the pons and cerebellar vermis to address interindividual differences.

Preprocessing of resting-state fMRI data. The first 10 EPI volumes were discarded because of equilibration effects of the magnetic field. The remaining 130 volumes were realigned to the first volume, motion-corrected, registered to T1-weighted images, and smoothed (6-mm full-width half-maximum gaussian kernel). The DARTEL flow fields and affine transformation matrix were combined and applied to the registered EPI volumes for normalization to Montreal Neurological Institute space. To remove noise, all spatially normalized EPI images were detrended and band-pass filtered (0.01–0.08 Hz). Additionally, we regressed out the 6 motion parameters and the blood oxygen level–dependent signal averaged across the white matter and CSF.

Assessment of gLFC connectivity. gLFC connectivity was determined through seed-based functional connectivity following a previously described protocol.[6] The LFC seed (BA 6/44; Montreal Neurological Institute: x = −42, y = 6, z = 28) was determined as the peak coordinate of meta-analytically detected brain activation associated with cognitive control (for further details, see appendix e-3).[23] We created an 8-mm sphere centered around the LFC coordinate (figure 2A), which was used as a seed for subsequent connectivity analyses. Using voxel-wise one-sample *t* tests, we explored the pattern of significant ($p < 0.001$) positive LFC functional connectivity in MCI-Aβ+, which was found preferentially, although not exclusively, to frontoparietal brain

Figure 2 Meta-analysis of brain activation related to cognitive control





(A) Meta-analytical map of activation peaks across task fMRI studies that were associated with cognitive control (false discovery rate corrected at $p < 0.01$). Colors indicate z scores. Superimposed in blue is an 8-mm spherical region of interest (ROI) centered around the peak voxel of the left frontal cortex (LFC) cluster of the z map. The ROI was used as the seed region in the seed-based functional connectivity analysis to obtain global LFC connectivity in the resting-state fMRI scans. (B) Spatial pattern of positive LFC seed-based connectivity (t test against zero $p < 0.001$, family-wise error corrected at the cluster threshold $p < 0.05$). The analysis was restricted to voxels falling within the gray matter mask. ADNI = Alzheimer's Disease Neuroimaging Initiative; MCI = mild cognitive impairment.

areas belonging to the cognitive control network (figure 2B). For the assessment of gLFC connectivity, the LFC region of interest (ROI) was superimposed onto the preprocessed and gray matter (GM)–masked resting-state scans to extract the mean LFC time series. Next, we calculated the Pearson-moment correlations between the LFC time series and each GM voxel. The resulting voxel-based correlations were Fisher z-transformed, and all positive voxel values were averaged to yield gLFC connectivity for each participant.[6,24] The gLFC connectivity values were log-transformed and centered to achieve a gaussian distribution. Global connectivity was further assessed for 2 control ROIs (occipital pole [OP] and precuneus) to test the specificity of the LFC as a substrate of CR (for details, see appendix e-4).

Statistical analysis. Continuous measures of demographics were compared between groups with 2-sample t tests; sex was compared with a χ^2 test. To test whether more years of education allow the patient to cope better with FDG-PET hypometabolism in MCI-Aβ+,[2] we applied voxel-wise regression including FDG-PET as the dependent variable and years of education (CR proxy) as the independent variable, controlling for age, sex, and ADNI-MEM. The voxel-wise analysis was restricted to the group-specific GM mask, and the resulting t statistics map was thresholded at the voxel level at $\alpha = 0.01$ and corrected at the cluster level at $\alpha = 0.01$. The FDG-PET value averaged across voxels within clusters of significant effects of education (a single cluster within the left precuneus; see Results) was computed for each participant and used as a marker of FDG-PET hypometabolism in MCI-Aβ+ in the subsequent analyses. In addition, the mean FDG-PET metabolism in the precuneus was extracted in HC. To test whether precuneus FDG-PET was decreased in MCI-Aβ+, we conducted an analysis of covariance, with group (HC vs MCI-Aβ+) as the predictor, controlling for age and sex. For testing our first hypothesis, i.e., that higher gLFC connectivity is associated with more years of education in MCI-Aβ+, we used linear regression analysis including gLFC connectivity as the dependent variable and education, age, and sex as independent variables. For testing our second hypothesis, i.e., that higher gLFC connectivity attenuates the association between FDG-PET hypometabolism and episodic memory impairment, we tested in a linear regression analysis the interaction of gLFC connectivity × FDG-PET (precuneus cluster) on ADNI-MEM, controlled for age and sex in MCI-Aβ+. Because our second hypothesis clearly specifies a directionality of the effects, i.e., detriments in memory performance associated with FDG-PET hypometabolism are worse at lower compared to higher levels of gLFC connectivity, we applied a one-tailed significance threshold to test this hypotheses ($p < 0.05$). Hypothesis 2 was also tested for secondary cognitive outcome measures, including BNT and TMT-B. To test the specificity of the gLFC connectivity as a substrate of CR, we conducted control analyses testing global connectivity of the OP and precuneus instead of the LFC. To this end, all regression analyses were repeated in an analogous way, this time replacing gLFC connectivity by global connectivity of the OP or precuneus. For each regression model, gaussianity of the distribution of the residuals was tested with the Shapiro-Wilk test, where none of the models showed significant deviation ($\alpha = 0.05$). The variance inflation factor was <10 for all models tested, indicating that there was no multicollinearity among predictors.

Voxel-wise regression analyses were computed with SPM8. Further analyses were computed with the R statistical software package (r-project.org).[25] Regression parameters of log-transformed regressors were back-transformed to ensure interpretability.

RESULTS Descriptive statistics for each group are displayed in the table. Two-sample t tests showed that HC performed significantly better than MCI-Aβ+ on all cognitive measures.

Association between years of education and FDG-PET in MCI-Aβ+. Voxel-wise multiple regression analysis of FDG-PET data showed that more years of education were associated with lower FDG-PET metabolism within a single cluster within the left precuneus ($B = -0.025$, $SE = 0.006$, $t\,[39] = 2.43$, $p = 0.006$), controlled for ADNI-MEM, age, and sex (figure 3A). The association between education and the average FDG-PET within the precuneus cluster is plotted in figure 3B.

Results of the analysis of covariance showed that FDG-PET within the precuneus cluster was significantly

Table Demographics and neuropsychological characteristics of HC and MCI-Aβ+ participants

	HC	MCI-Aβ+
Sample size, n	24	44
Age, y	74.6 (6.4)	72.4 (6.5)
Sex, F/M	18/6	26/18
Education, y	15.8 (2.1)	16.1 (2.6)
ADNI-MEM[a]	0.82 (0.5)	0.2 (0.5)
MMSE[a]	28.9 (1.3)	27.4 (1.7)
BNT[a]	28.8 (1.3)	26.7 (3.8)
TMT-B[b]	78.5 (43.1)	107.5 (59.0)

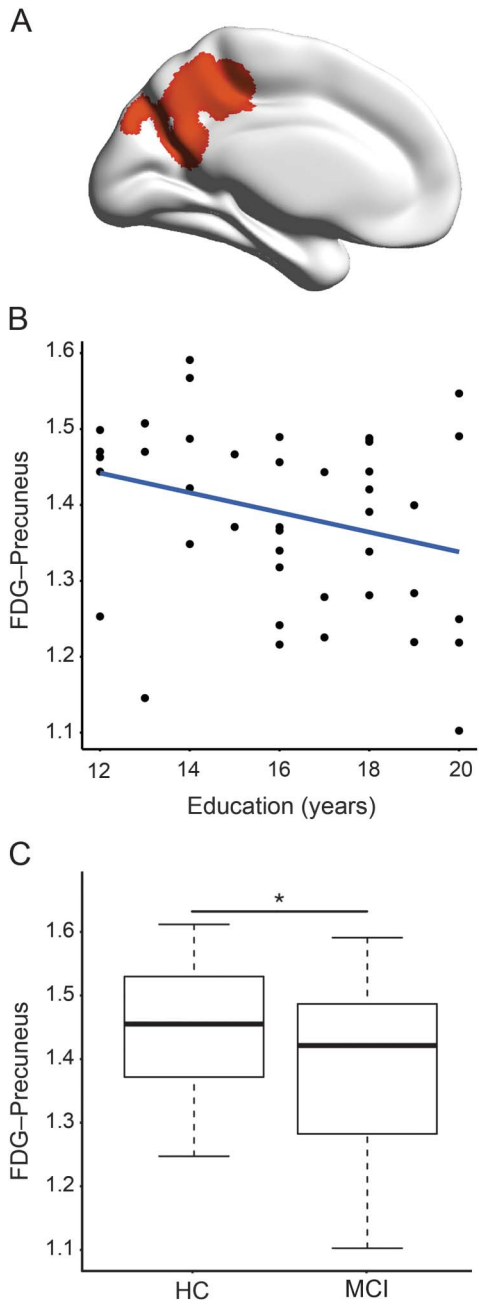
Abbreviations: ADNI-MEM = Alzheimer's Disease Neuroimaging Initiative episodic memory composite score; BNT = Boston Naming Test; MCI-Aβ+ = amyloid-PET–positive with amnestic mild cognitive impairment; MMSE = Mini-Mental State Examination; TMT-B = Trail Making Test B.
[a] HC > MCI ($p < 0.05$).
[b] HC < MCI ($p < 0.05$).

reduced in the MCI-Aβ+ compared to HC ($F_{62} = 5.056$, $p = 0.028$), controlled for age and sex (figure 3C), suggesting that precuneus FDG-PET was pathologically reduced in MCI-Aβ+.

Association among gLFC connectivity, education, and precuneus FDG-PET in MCI-Aβ+. Next, we tested our hypothesis that gLFC connectivity is associated with more years of education (CR proxy) in MCI-Aβ+ (criterion of face validity). More years of education predicted higher gLFC connectivity, controlled for age and sex in the MCI-Aβ+ (B = 0.07, SE = 0.03, t [40] = 2.401, $p = 0.021$; figure 4A) but not in HC ($p = 0.49$). gLFC connectivity was not associated with precuneus FDG-PET metabolism in HC ($p = 0.25$) or MCI-Aβ+ participants ($p = 0.12$).

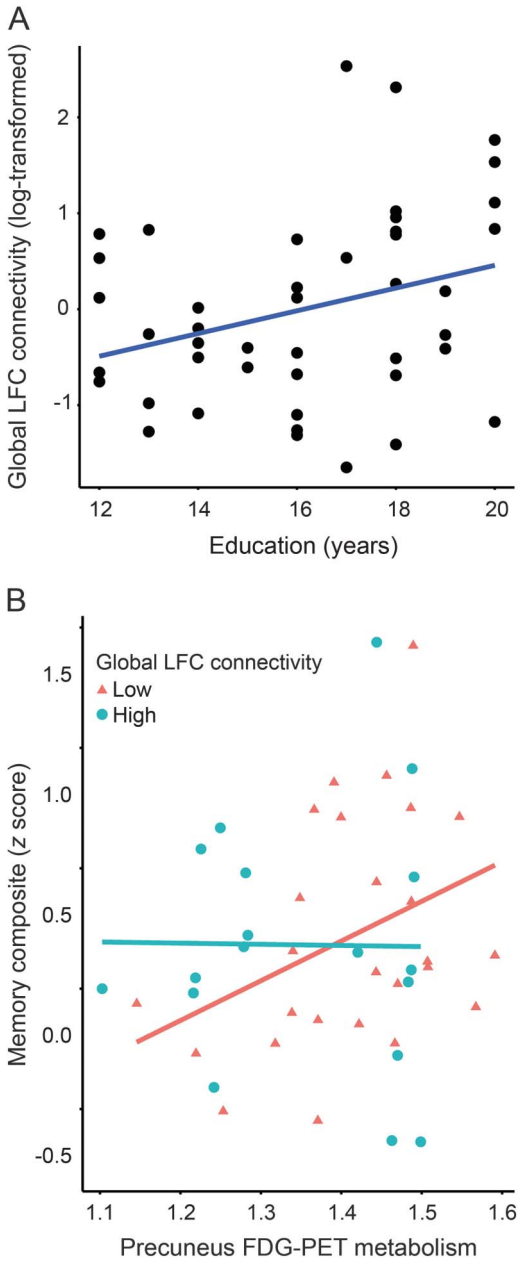
Addressing our main hypothesis, we assessed whether higher gLFC connectivity is associated with an attenuated effect of precuneus FDG-PET hypometabolism on memory in MCI-Aβ+ (criterion of cognitive benefit). The interaction effect gLFC connectivity × precuneus FDG-PET on ADNI-MEM was significant (B = −10.43, SE = 2.62, t [38] = −1.988, $p = 0.027$, hypothesis-free 2-tailed $p = 0.054$). Figure 4B shows that at low levels of gLFC connectivity, lower precuneus FDG-PET metabolism was associated with worse memory performance, whereas at higher levels of gLFC connectivity, the association between precuneus FDG-PET metabolism and ADNI-MEM was not observed. These results suggest that in the presence of higher gLFC connectivity, the detrimental effect of AD-related precuneus FDG-PET hypometabolism on memory is reduced. We detected no significant interaction effects on secondary cognitive measures, including BNT ($p = 0.78$) and TMT-B ($p = 0.12$). Control

Figure 3 Voxel-wise regression for education predicting FDG-PET controlling for memory performance in MCI-Aβ+



(A) Location of the precuneus cluster in the left hemisphere, where amyloid-PET–positive patients with amnestic mild cognitive impairment (MCI-Aβ+) with more years of education showed lower fluorodeoxyglucose (FDG)-PET metabolism when controlling for memory performance, age, and sex ($p < 0.01$ corrected at the cluster threshold at $p < 0.01$). (B) Scatterplot for the regression model of education on the average precuneus FDG-PET metabolism in MCI-Aβ+. (C) Box plot for the group comparison (MCI-Aβ+ vs healthy controls [HC]) in precuneus FDG-PET metabolism. Precuneus FDG-PET metabolism was significantly reduced in MCI-Aβ+, controlled for age and sex ($p = 0.028$).

Figure 4 Scatterplot for the interaction of gLFC connectivity × precuneus FDG-PET metabolism on memory performance in MCI-Aβ+



Association among education, global left frontal cortex (gLFC) connectivity, and precuneus fluorodeoxyglucose (FDG)-PET metabolism in amyloid-PET–positive patients with amnestic mild cognitive impairment (MCI-Aβ+). (A) Scatterplot of the association between years of education and gLFC connectivity. (B) Scatterplot for the interaction gLFC connectivity × precuneus FDG-PET metabolism on memory performance in MCI-Aβ+. Precuneus FDG-PET metabolism is plotted against the Alzheimer's Disease Neuroimaging Initiative memory score for participants with high and low gLFC connectivity. For illustrational purposes, groups of high and low gLFC connectivity (defined via median split) are plotted separately.

analyses including global connectivity of the OP or precuneus showed no significant associations with education (OP $p = 0.34$; precuneus $p = 0.51$) or precuneus FDG-PET metabolism (OP $p = 0.33$; precuneus $p = 0.23$). The interaction effect including ROI global connectivity × precuneus FDG-PET metabolism on ADNI-MEM was significant for none of the control ROIs (OP $p = 0.58$; precuneus $p = 0.67$).

DISCUSSION Our major findings were that in prodromal AD, more years of education (CR proxy) allowed the patient to better cope with precuneus FDG-PET hypometabolism, higher gLFC connectivity was associated with more years of education (CR proxy; criterion of face validity), and higher gLFC connectivity was associated with milder effects of precuneus FDG-PET hypometabolism on memory performance (criterion of cognitive benefit). Together, these findings suggest that higher gLFC connectivity met major a priori defined criteria as a substrate of CR, including the association with a common CR proxy (education) and a beneficial effect that moderated the association between AD core pathology (precuneus FDG-PET hypometabolism) and the level of memory impairment. No association with education was found for global functional connectivity of 2 control ROIs (OP and precuneus), suggesting that our findings are specific to gLFC connectivity.

First, we showed that in MCI-Aβ+ more years of education were associated with stronger precuneus FDG-PET hypometabolism when controlling for memory performance. These findings are consistent with results of previous studies showing an association between higher CR proxies and lower parietal FDG-PET or perfusion in AD,[2,5,26,27] providing indirect evidence for an enhanced ability in patients with AD with greater education to cope better with brain pathology than those patients with lower education.

Next, we tested in a series of analyses whether gLFC connectivity may subserve protective effects in MCI-Aβ+. First, we showed an association between years of education and gLFC connectivity (criterion of face validity). This is in agreement with previous studies in healthy individuals in which more years of education were associated with increased frontal lobe function, i.e., higher anterior cingulate FDG-PET metabolism and fMRI functional connectivity.[28] Similarly, more years of education are associated with higher frontal FDG-PET metabolism in prodromal AD.[3] We found that higher gLFC connectivity was associated with more years of education in MCI-Aβ+ but not in HC. Higher LFC connectivity is most likely a functional difference associated with higher education that existed before the onset of MCI, in line with the idea of neural reserve.[29] Ceiling effects, reduced interindividual variability of gLFC connectivity in HC, and a small sample size of 24 may have reduced the power to detect an association between education and gLFC connectivity. We

caution that the primary focus of the current study was on CR in MCI. gLFC connectivity as a putative substrate of CR in elderly HC participants should be assessed in larger future studies.

For our second a priori defined criterion of CR-related brain differences, we postulated that any putative brain substrate of CR should be associated with higher levels of cognitive performance in the face of brain pathology (criterion of cognitive benefit).[30,31] Consistent with this hypothesis, we showed that gLFC connectivity not only was associated with a CR proxy (education) but also was beneficial with regard to memory performance in the presence of brain pathology (precuneus FDG-PET hypometabolism). Our finding is reminiscent of a previous study in AD showing that at higher levels of CR (as measured by IQ), the association between precuneus Aβ deposition and memory impairment was attenuated.[32] Our results suggest that gLFC connectivity may underlie such compensatory effects. Here, we found an interaction between gLFC connectivity and precuneus FDG-PET only on memory but not on secondary cognitive measures, including BNT and TMT-B. A possible explanation is that deficits in BNT or TMT-B are related to frontal and temporal FDG-PET hypometabolism rather than precuneus FDG-PET hypometabolism, as shown previously.[33,34] Thus, it is possible that FDG-PET hypometabolism in areas other than the precuneus may have shown an interaction with gLFC connectivity on these nonmemory domains.

It is unclear how gLFC connectivity may support cognition in prodromal AD. One possibility is that because of its widespread connectedness, the LFC interacts with and regulates the activity of functional networks. According to the flexible-hub theory, the LFC shows adaptive functional connectivity to other brain regions during cognitive processes.[35] A recent fMRI study testing different cognitive tasks showed that the LFC dynamically shifts connectivity to different networks across cognitive tasks.[36] Previous resting-state fMRI studies reported that the LFC is characterized by a high participation coefficient with regard to its connectivity to major networks in the brain.[37] At the cognitive level, increased gLFC connectivity was shown to be associated with increased cognitive control, higher IQ, and higher cognitive performance in young individuals.[6] Together, these studies suggest that the LFC, possessing high global connectivity, may flexibly orchestrate the activation of specific networks during cognitive tasks and may thus enhance cognitive performance. Applied to the current findings, this means that high gLFC connectivity may be linked to greater flexibility in neural network activation to compensate for local neurodegeneration (i.e., precuneus FDG-PET hypometabolism) in patients with prodromal AD. Another possibility is that the LFC exerts a beneficial effect on cognitive performance particularly through its association with the frontoparietal control network, also called the task-positive network.[38] Our spatial mapping of significant LFC connectivity supports particularly high functional connectivity with frontoparietal brain areas belonging to the control network, consistent with previous findings.[6,7]

In cognitively normal elderly with abnormal levels of amyloid PET, increased activation of the control network during memory encoding was associated with increased memory performance.[39] These results suggest that increased frontoparietal activation may play a compensatory and beneficial role during memory performance in the early stage of AD. Future studies may investigate whether, in patients with AD with high CR, increased gLFC connectivity may support such increased frontoparietal activation and thus support cognitive function. While the exact compensatory mechanism of the LFC needs to be confirmed in future studies, the current results suggest that the LFC is associated with CR and may moderate the association between AD pathology and cognitive impairment.

For the interpretation of the current results, several caveats should be considered. First, we examined gLFC connectivity during resting-state fMRI, which may not necessarily translate into increased connectivity or activation during cognitive tasks because the association between connectivity and task-related brain activation can be complex.[40] However, a previous study showed that during working memory task fMRI, the LFC connectivity increased in a task-related manner, suggesting a direct role of LFC connectivity during task performance.[7] We specifically chose resting-state gLFC connectivity as a candidate neural marker of CR that can be readily assessed in patients with cognitive deficits and does not depend on a particular cognitive task. However, future studies should assess to what extent gLFC connectivity supports compensatory task-related brain activation in AD. Second, we examined only MCI-Aβ+ patients in the stage of prodromal AD. Thus, the generalization to other stages of AD and cognitive functions remains open. Because in AD the frontal lobe function is relatively spared until a late stage, the gLFC connectivity may be a prime candidate to show a generalized cognitive performance-enhancing function in AD. Overall, gLFC connectivity is a promising candidate marker of CR in AD that may play a compensatory and cognitively beneficial role when AD pathology emerges. The identification of the locus of functional brain mechanisms related to CR opens up the possibility to specifically train and stimulate such brain mechanisms through neurofeedback, transcranial direct current stimulation, or drugs to

enhance compensatory brain mechanisms and to slow down the cognitive decline in AD.

AUTHOR CONTRIBUTIONS

N. Franzmeier: study concept and design, statistical analysis, interpretation of the data, drafting the manuscript. M. Duering: interpretation of the data, revising the manuscript. M. Weiner and M. Dichgans: revising the manuscript. M. Ewers: study concept and design, interpretation of the data, drafting the manuscript.

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DISCLOSURE

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Left frontal cortex connectivity underlies cognitive reserve in prodromal Alzheimer disease

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Supplementary

Appendix e-1:

AV45-PET:

[^{18}F] AV-45 Florbetapir PET scans were assessed during four 300 second time frames measured 50 minutes after intravenous injection of the tracer (http://adni.loni.usc.edu/wp-content/uploads/2010/05/ADNI2_PET_Tech_Manual_0142011.pdf). Global AV-45 Florbetapir PET uptake was assessed as a summary measure of the SUVR in several cortical ROIs that have been described previously.[1] Details on the preprocessing of the AV-45 PET images are available at the ADNI study website (http://adni.loni.usc.edu/data-samples/pet/).

FDG-PET acquisition:

FDG-PET scans were acquired on different PET scanners (Siemens, GE and Philips). Dynamic 3D scans were recorded in 6 x 300 seconds time frames measured 30 minutes after an intravenous injection of the tracer. Each frame was coregistered to the first time frame of the raw image file. Each subject's co-registered, averaged images were then reoriented into a standard image grid that is parallel to the AC-PC line. An averaged image was generated from the "AC-PC" coregistered frames and then intensity normalized so PET data from different scanner models can be compared more easily. Details on the ADNI protocol of FDG-PET acquisition can be found online at http://adni.loni.usc.edu/wp-content/uploads/2010/05/ADNI2_PET_Tech_Manual_0142011.pdf.

e-References:

1. Landau SM, Breault C, Joshi AD, et al. Amyloid-beta imaging with Pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2013;54:70-77.

Appendix e-2:

Spatial-normalization of FDG-PET images:

FDG-PET images were first registered to the T1-weigthed images. For spatial normalization, T1-weighted images were segmented in gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) maps.[1] Spatial normalization parameters were estimated based on a high-dimensional registration algorithm to warp each participant's GM map to an average GM template that was defined in an iterative procedure, as implemented in the SPM DARTEL toolbox.[2] The resulting group template was subsequently registered to the T1-MNI template implemented in DARTEL, estimating affine transformation parameters. Next, the the non-linear DARTEL flow-fields and affine transformation parameters were combined and applied to the segmented GM maps and the coregistered FDG-PET images. The spatially normalized GM maps were averaged and binarized at a voxel value > 0.3 to create a GM mask for functional connectivity analyses.

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2. Ashburner J. A fast diffeomorphic image registration algorithm. NeuroImage 2007;38:95-113.

Appendix e-3:

Definition of LFC ROI:The seed coordinate was determined as the peak coordinate of brain activation associated with cognitive control processes during task-fMRI. We determined the seed-coordinate independent from the current data set, in order to avoid a group-specific bias in our sample. To this end, we conducted a meta-analysis of previous task-fMRI studies using the software Neurosynth as described previously. The software NeuroSynth is a web-based meta-analysis tool for fully automated extraction of brain activation coordinates from published fMRI studies (http://www.neurosynth.org/). In brief, the strength of the association between a cognitive ability (entered as a search term in Neurosynth) and the activation in any brain location is analyzed across studies, yielding a probabilistic map of the brain activation that is associated with a particular cognitive state [1]. For the current study, a total of 428 task-fMRI studies were identified using the search-term "cognitive control" (as of September 14, 2015).[1] The resulting z-score map was thresholded at $p < 0.01$ (FDR-corrected). Visual inspection confirmed that the distribution of brain regions with high z-scores matched predominantly the fronto-parietal cognitive control network that included the LFC, providing confidence that relevant brain activation locations were identified (Figure 2A). We obtained the peak voxel coordinate within a cluster that was centered within the LFC, i.e. Brodman area 6 (MNI: x = -42, y = 6, z = 28), and created a 8-mm spherical binary ROI centered at that coordinate (see figure 2A). This ROI was used as the seed region in the subsequent functional connectivity analysis (see figure 2B).

e-References:

1. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. Large-scale automated synthesis of human functional neuroimaging data. Nature methods 2011;8:665-670.

Appendix e-4:

Selection of control ROIs:

As a first control region, we used the occipital pole (OP; MNI: x = -19, y = -102, z = -3), based on the rationale that the OP is – in contrast to the LFC - involved in early visual processing but not in higher cognitive functions such as memory or executive functions. As a second control region, we used the precuneus (MNI: x = 7, y = -60, z = 21) following the rationale that it is – similar to the LFC –involved in higher cognitive functions such as memory,[1] and a highly connected hub.[2]

e-References:

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2. Cole MW, Pathak S, Schneider W. Identifying the brain's most globally connected regions. NeuroImage 2010;49:3132-3148.

4 | An Imaging-based Marker of Cognitive Reserve

4.1. Summary

With the third study, we aimed to translate the previous findings on the fronto-parietal control network model of cognitive reserve to a clinically useful neuroimaging marker of reserve. The rationale for this study was to develop a measure that directly assesses neural mechanisms that relate to cognitive reserve. In contrast to static measures like education an IQ, such a neuroimaging measure may allow dynamically assess changes in neural mechanisms of cognitive reserve across the course of AD. Specifically, we aimed to capture the hubness of the fronto-parietal control network that is related to protective factors (i.e. criterion of face validity). In line with our second study, we quantified hubness using resting-state fMRI assessed global functional connectivity, this time in a voxel-wise manner for each voxel of the brain. Next, we compared the distribution of global functional connectivity within the fronto-parietal control network between MCI patients and healthy controls stratified by high and low education. First, we could confirm previous evidence (Cole et al., 2010) that fronto-parietal control network regions show among the highest global connectivity in the brain. We found that MCI patients with greater education (i.e. protective factor) showed higher global functional connectivity of the fronto-parietal control network as compared to healthy controls, whereas this pattern was inverted in individuals with low levels of education. In line with the second study included in this thesis, this suggests that protective factors are associated with relatively high global functional connectivity of fronto-parietal control network hubs at the stage of

MCI. We developed a data driven algorithm that captures this pattern of education-related global connectivity in MCI patients within a single scalar index. This index shows strong positive associations with protective factors including years of education and a more complex questionnaire based cognitive reserve proxy and was fully validated in two independent cohorts. This imaging-based global functional connectivity reserve (GFC-R) index could be adopted by future studies to test how cognitive reserve mechanisms change during AD progression and whether they can be fostered by pharmacological or cognitive interventions.

4.2. Reference

This work was carried out under the supervision of Michael Ewers; N.F. and M.E. designed research and wrote the manuscript; N.F. analyzed the data; N.F., M.A.A.C., A.N.W.T., L.S.V., K.B., C.M., C.C., D.J., E.B. and B.G. collected the data; B.E.W. and M.D. critically revised the manuscript.

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SI: RESILIENCE/RESERVE IN AD

Resting-state global functional connectivity as a biomarker of cognitive reserve in mild cognitive impairment

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Abstract Cognitive reserve (CR) shows protective effects in Alzheimer's disease (AD) and reduces the risk of dementia. Despite the clinical significance of CR, a clinically useful diagnostic biomarker of brain changes underlying CR in AD is not available yet. Our aim was to develop a fully-automated approach applied to fMRI to produce a biomarker associated with CR in subjects at increased risk of AD. We computed resting-state global functional connectivity (GFC), i.e. the average connectivity strength, for each voxel within the cognitive control network, which may sustain CR due to its central role in higher cognitive function. In a training sample including 43 mild cognitive impairment (MCI) subjects and 24 healthy controls (HC), we found that MCI subjects with high CR (> median of years of education, CR+) showed increased frequency of high GFC values compared to MCI-CR- and HC. A summary index capturing such a surplus frequency of high GFC was computed (called GFC reserve (GFC-R) index). GFC-R discriminated MCI-CR+ vs. MCI-CR-, with the area under the ROC = 0.84. Cross-validation in an independently recruited test sample of 23 MCI subjects showed that higher levels of the GFC-R index predicted higher years of education and an alternative questionnaire-based proxy of CR, controlled for memory performance, gray matter of the cognitive control network, white matter hyperintensities, age, and gender. In conclusion, the GFC-R index that captures GFC changes within the cognitive control network provides a biomarker candidate of functional brain changes of CR in patients at increased risk of AD.

Keywords Cognitive reserve · Biomarker · Mild cognitive impairment · Alzheimer's disease · Global functional connectivity · Resting-state fMRI

Introduction

Cognitive reserve (CR) refers to the ability to cognitively perform relatively well in the presence of brain pathology (Stern 2002, 2009). Life-time experiences - such as education and occupational attainment – or IQ are commonly used as proxy measures of CR (Stern 2009). In Alzheimer's disease (AD), higher levels of such CR proxies are associated with higher cognitive performance relative to the level of brain damage, such as measured by cerebral FDG-PET hypometabolism or impaired blood flow (Bastin et al. 2012; Boots et al. 2015; Ewers et al. 2014; Scarmeas et al. 2003; Stern et al. 1992, 1995), grey matter atrophy (Bastin et al. 2012; Boots et al.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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2015), white matter damage (Brickman et al. 2011), and primary pathologies including amyloid-beta (Aβ) and tau (Rentz et al. 2010; Vemuri et al. 2011, 2015). These results suggest that higher levels of CR as measured by education and other proxies are associated with a higher ability to cope with brain pathology in AD.

Compensatory functional brain changes that may underlie CR have been investigated in a number of task-related fMRI studies (Stern et al. 2005, 2008) or resting-state fMRI studies in HC subjects (Arenaza-Urquijo et al. 2013). Task-related fMRI studies in MCI and AD revealed an association between increased CR proxies (education, occupation) and higher brain activation (Bosch et al. 2010; Solé-Padullés et al. 2009). However, task-fMRI is often difficult to perform for cognitively impaired patients, and may thus not be suitable for clinical use to assess CR in AD. From a clinical point of view, a major question is whether simple measures of basic brain function are indicative of CR, and thus could be used as a marker of CR-related brain changes in AD. The need of a biomarker of CR-related brain changes is urgent in view of a growing number of clinical trials that target protective brain mechanisms in AD, such as cognitive training or meditation (Buschert et al. 2011; Reijnders et al. 2013; Schultz et al. 2015; Wells et al. 2013).

The overall goal of the current study was to develop a neuroimaging-based diagnostic biomarker of functional brain changes underlying CR in subjects with mild cognitive impairment (MCI). We specifically chose a sample of MCI subjects since CR-related functional brain changes may most likely become apparent at a stage of emerging brain pathology, such as in MCI (Stern 2002). We focused on resting-state global functional connectivity (GFC, also known as weighted degree centrality) within the cognitive control network as a measure of functional brain processes of CR. The rationale for selecting the cognitive control network to subserve CR is based on its' link to CR proxies (Cole et al. 2012), its' task-invariant role in cognition (Cole et al. 2013), and its' suggested compensatory function in early AD (Elman et al. 2014; Oh et al. 2015). The cognitive control network includes major brain hubs with high GFC (Cole et al. 2010), where greater GFC has been previously associated with higher IQ, i.e. a proxy of CR, in young subjects. In the current study, CR was measured by the proxy of years of education, which is the best validated CR proxy measure to date in AD (Stern 2012).

Using a cross-validation approach, we compared the frequency distribution of GFC values within the cognitive control network between MCI subjects with high CR (more years of education) to MCI with low CR (lower years of education) and HC groups. A newly developed summary index that detects GFC frequency differences between MCI subjects with low and MCI subjects with high CR, henceforth called GFC reserve (GFC-R) index, was tested as a marker of CR in an independent validation sample of MCI subjects. We hypothesized firstly that MCI subjects with more years of education show an increased number of relatively high GFC values within the cognitive control network compared to MCI subjects with less years of education. Secondly, we hypothesized that higher levels of the GFC-R index are predictive of more years of education and a second questionnaire based CR proxy in the validation sample of MCI subjects. Thirdly, we hypothesized that the GFC-R index is specifically related to CR proxies and not driven by pathological brain changes such as amyloid-beta deposition, cerebral small vessel disease or grey matter atrophy.

Methods

Subjects

We included two independent samples each of amnestic MCI and HC subjects to cross-validate our findings. The training sample included 24 amyloid-PET negative (Aβ-) HC subjects and 43 Amyloid-PET positive (Aβ+) patients with amnestic MCI. Amyloid PET status was defined based on pre-established cut-off values of global [^{18}F] AV-45 PET standardized uptake value ratio (for Aß- = global AV-45 PET SUVR < 1.11) (Landau et al. 2013). All data were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, freely accessible for researchers (http://adni.loni.usc.edu/). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure and predict the progression of MCI and early AD (www.adni-info.org).

The test sample comprised 32 HC subjects as well as 23 subjects with amnestic MCI, recruited between 2014 and 2015 at the memory clinic of the Institute for Stroke and Dementia Research (ISD) at the Klinikum der Universitaet Muenchen in Germany.

For the ISD study, the inclusion criteria were defined as follows: 1) age >60 years, 2) no signs of depression, 3) no presence or history of neurological or psychiatric disorders (except for MCI), 4) no presence or history of alcohol or drug abuse, 5) no diabetes mellitus, 6) no MRI contraindications. All subjects underwent structural MRI, resting-state fMRI and cognitive testing using the CERAD-Plus test battery (Luck et al. 2009). A subject was defined as HC, when reporting no subjective memory complaints and scoring within 1.5 standard deviations (SD) of the age, gender and education adjusted norms in all subtests of the CERAD-Plus battery (Luck et al. 2009). MCI was diagnosed according to the Petersen criteria (Petersen 2004), when scoring 1.5 SD below the age, gender and education adjusted norms in at least one of the learning or recall subtests of the CERAD-Plus battery.

For the training sample (ADNI), details about the inclusion can be found online (https://adni.loni.usc.edu/wp-content/uploads/2008/07/adni2-procedures-manual.pdf). Similar to the diagnosis of MCI in the ISD sample, MCI was diagnosed in ADNI according to the Petersen criteria (Petersen 2004).

Cognitive reserve and neuropsychological assessment

The number of years of formal education was used as a proxy for CR in both samples. In the test sample (ISD) we additionally used the cognitive reserve index questionnaire (Nucci et al. 2012) as a second proxy of CR. The CRIq is a standardized questionnaire based measure for the assessment of CR that combines information about education, working activity and leisure time. For neuropsychological assessments, memory performance was assessed using memory tests that were comparable between the ADNI and the ISD sample. As a measure of episodic memory performance, the total score of the CERAD word list learning tests was assessed in the ISD sample (Luck et al. 2009), and the total score of the Rey Auditory Verbal Learning Test (RAVLT) in the ADNI sample (Schoenberg et al. 2006). Both tests are designed as list-learning paradigms in which the patient is read a list of words by the examiner in several trials (CERAD: 10 words in 3 trials; RAVLT: 15 words in 5 trials) and is asked to recall as many words from the list as possible after each trial. The total score reflects the number of words correctly remembered cumulated across trials.

MRI acquisition

Training sample (ADNI)

All MRI scans were performed on Philips 3 T MRI scanners, using an 8-channel head matrix coil. High-resolution T1-weighted scans were acquired using a 3D MP-RAGE sequence, with whole brain coverage and a voxel resolution of $1 \times 1 \times 1.2$ mm. Fluid attenuated inverse recovery (FLAIR) scans were obtained with a voxel resolution of $0.86 \times 0.86 \times 5$ mm. Resting-state-fMRI images were acquired using a single shot T2*-weighted EPI sequence collecting 140 volumes, with a TR of 3000 ms, a flip angle of 80° and 3.3 mm isotropic voxel resolution. Prior to the resting-state scan, subjects were instructed to keep their eyes open.

Test sample (ISD)

All MRI scans were performed on a Siemens Verio 3 T MRI scanner using a 32-channel head coil. For each subject a structural image was obtained using a high-resolution 3D MPRAGE T1-weighted sequence with 1 mm isotropic voxel resolution. Using the same field of view and voxel dimensions FLAIR images were recorded. Functional resting-state images were acquired using a T2*-weighted echo-planar imaging (EPI) pulse sequence collecting 180 volumes with a TR = 2580 ms, flip angle = 80° and 3.5 mm isotropic voxel resolution. Prior to the resting-state scan the subjects were instructed to keep their eyes closed and not to fall asleep during the scanning procedure. Using the same field of view as the functional resting-state images, field maps were acquired (TE = 7.38/4.92 ms, TR = 675 ms) to correct for susceptibility artifacts and inhomogeneity of the magnetic field during preprocessing of the resting-state data.

Spatial normalization of MRI scans

The spatial normalization of the MRI scans was done separately for both samples, following the same protocol of image processing based on SPM 12 (Wellcome Trust Centre for Neuroimaging, University College London, United Kingdom: www.fil.ion.ucl.ac.uk/spm). T1-weighted images were segmented into probabilistic maps of grey matter, white matter and cerebrospinal fluid maps through the SPM's new-segment approach (Ashburner and Friston 2005). Next, the spatial normalization parameters were estimated using a high-dimensional diffeomorphic registration algorithm to warp each subjects' grey matter map to a group-specific grey matter template that was defined in an iterative procedure, as implemented in SPM's DARTEL toolbox (Ashburner 2007). Subsequently, the group-specific template was registered to the MNI template in order to estimate the affine transformation parameters. Next, the non-linear (DARTEL flow-fields) and the affine transformation parameters were combined and applied to the segmented grey matter maps, so that all grey matter images were spatially normalized to the MNI space. The spatially-normalized grey matter maps were averaged and binarized at a voxel value >0.3 to create a group-specific grey matter mask for later fMRI functional connectivity analyses. Similarly, we averaged and binarized the spatially-normalized white-matter (binarized at threshold >0.9) and cerebrospinal-fluid (binarized at threshold >0.7) that were used during preprocessing of the resting-state fMRI data. For later extraction of grey matter volume, we created spatially normalized grey matter maps for each subject, that were smoothed with a 8-mm full-width at half-maximum (FWHM) Gaussian kernel and modulated to preserve the volume of the images.

WMH volume assessement

The assessement of WMH volume was conducted separately for both samples but following the same protocol. In a first step, FLAIR images were registered to the T1-weighted images and segmented into three tissue-probability maps. Subsequently, a histogram-segmentation (Otsu 1979) was conducted to separate WMH from confounding cerebrospinal

fluid voxels. The resulting WMH segmentations were manually edited by two independent raters in order to remove voxels that were misclassified as WMH. The inter-rater reliability of the WMH assessment yielded a Dice coefficient of 0.98. For each subject, WMH volume was computed as the volume of WMH divided by the total brain volume.

Preprocessing of resting-state fMRI

The preprocessing of both samples was done separately, but following the same protocol. The first 10 volumes of each subjects' resting-state scan were discarded to allow for equilibration of the magnetic field. All remaining volumes were realigned to the first volume to correct for motion, coregistered to native-space T1-weighted images and smoothed using an 8 mm FWHM Gaussian kernel. None of the subjects' motion parameters exceeded 2 mm translations or 2° rotations. For the ISD-sample, there was additional slice-timing and field map correction. Next, the DARTEL flow-fields and affine registration parameters that were estimated during preprocessing of the T1-weighted images were combined and applied to all resting-state fMRI volumes to spatially normalize the images to MNI space. The spatially normalized fMRI images were further detrended and band-pass filtered, using a frequency band of 0.01–0.08 Hz. In a second step we regressed out the 6 motion parameters (3 translations, 3 rotations) and the BOLD signal averaged across the white matter and cerebrospinal fluid masks that were created during preprocessing of the T1-weighted images.

Assessment of GFC

For each subject, GFC was determined based on the preprocessed and spatially normalized resting-state fMRI scans, following a previously established protocol (Cole et al. 2012). For each voxel in the grey matter, the GFC was determined by computing seed-based Pearson-Moment correlations of the BOLD signal changes between the seed voxel and each of the other voxels within the grey matter (as defined by the customized grey matter mask). For each seed voxel, only Pearson-Moment correlation coefficients with r >0 were retained, Fisher z-transformed and averaged across the voxels within the grey-matter-mask space to obtain the GFC coefficient. This resulted in a 3D brain map of GFC coefficients for each subject. Note that we included only positive correlation coefficients for computing the GFC, because positive and negative correlations may cancel each other out when averaging the correlation coefficients. More precisely, if a voxel shows high positive connectivity to brain area A and high negative connectivity to brain area B, averaging both values would result in a small if not zero correlation coefficient, which would be falsely interpreted as low connectivity. Thus, in line with a previous study (Cole et al. 2012), we focused on positive connectivity values only.

Spatial maps of resting-state networks

The cognitive control network covers the anterior cingulate cortex, dorsolateral prefrontal cortex, anterior insular cortex, dorsal premotor cortex and posterior parietal cortex (Cole et al. 2013, 2014a; Cole and Schneider 2007). For the current study, we determined the spatial boundaries of the cognitive control network based on an a-priori conducted meta-analysis in order to avoid a sample specific bias in the spatial definition of the network. The meta-analysis was conducted using NeuroSynth, a web-based tool for fully automated detection of brain activation coordinates from published task-fMRI data (http://www.neurosynth.org). By entering a search term in the NeuroSynth database, brain activation associated with the search term entered is analyzed across studies, yielding a probabilistic map of brain activation related to that term (Yarkoni et al. 2011). For the current study, we used "cognitive control" as a search term, yielding a z-scored probability map based on 428 task-fMRI studies (as of September 14, 2015). In order to obtain a reliable map of the cognitive control network we applied a false discovery rate corrected p-threshold of p(FDR) <0.01 (see Fig. 1). The spatial map of the cognitive control network was additionally masked with the group-specific grey matter masks for each sample separately in order to restrict all further analyses to voxels that had a high likelihood of falling within the grey matter. We performed control analyses on 7 major brain networks (Yeo et al. 2011), to test whether a relationship between CR and GFC was specific to the cognitive control network. Accordingly, we downloaded the 7 network parcellations that are freely available online

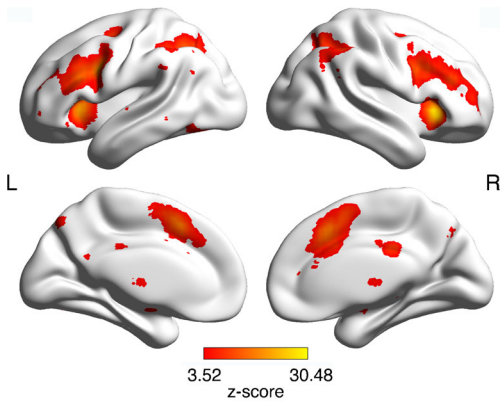

Fig. 1 Meta-analytical activation map across 428 task-fMRI studies that were associated with search term "cognitive control" (FDR-corrected at $p < 0.01$) in NeuroSynth, projected on a brain surface. Colors indicate z-scores

(ftp://surfer.nmr.mgh.harvard.edu/pub/data/Yeo_JNeurophysiol11_MNI152.zip). Again, all 7 networks were additionally masked with the group specific grey matter masks for each sample. To control for potentially confounding effects of brain atrophy, we extracted the grey matter volume within the network masks for each subject, applied to the modulated smoothed and normalized grey matter images that were created during the preprocessing of structural MRI images.

Generation of GFC index related to CR (GFC-R index)

Study design

Our aim was to develop a summary index to quantify GFC frequency changes within the cognitive control network that were associated with the CR proxy years of education in patients with MCI. In brief, the ADNI sample served as a training sample to create the GFC-R index that is related to our CR proxy *education*. Subsequently, we tested the validity of this GFC based index as a predictor of the CR proxy years of education and the CR-questionnaire (CRIq) composite score in the ISD sample, which served as an independent test sample. A Flow diagram illustrating the individual steps to create the GFC-reserve index is shown in Fig. 2.

Dichotomization of subjects according to CR

The HC and MCI groups were each dichotomized into groups of low and high CR (CR− vs CR+), split at the median of years of education within the entire sample. The groups were dichotomized separately within the ISD (CR+: > median education = 13) and the ADNI sample (CR+: > median education = 16).

Histogram analysis of GFC

For each diagnostic group (MCI vs. HC) within the CR+ and CR- subjects, we plotted a histogram of the GFC frequencies across voxels of the cognitive control network (Fig. 2a and b). Visual inspection of the histograms in the training sample (ADNI) revealed, that the GFC histogram of the MCI CR- subjects showed an overall shift to the left of the HC subjects, with a decreased frequency of relatively high GFC values, but an increase of lower GFC values compared to the HC CR- group (Fig. 2b). Conversely, the GFC histogram of the MCI CR+ subjects showed a shift to the right of the HC CR+ group.

In a next step, we binned the GFC voxel values for each subject at intervals of 0.01 from z = 0 to z = 0.6 resulting in a total of 60 bins, each containing the number of voxels (i.e. the GFC frequency) falling within that bin. To quantify changes in GFC frequency in MCI with respect to the HC group, we bin-wise subtracted each MCI CR+ subject's GFC frequencies from the averaged GFC frequencies in the HC CR+ group. The analogous subtraction was done for the MCI CR-, where each MCI subject's histogram was subtracted from the average histogram of the HC CR- group. Thus, for each MCI CR group, alterations of GFC frequencies (called GFC-Diff, Fig. 2c) were obtained according to the following equation.

$$GFC\text{-}Diff_{ijk} = GFC frequency(MCI)_{ijk} - Mean\,GFC frequency(HC)_{ik} \quad (1)$$

where, i = CR group (CR + or CR-), j = MCI subject, k = GFC bin (1–60).

In bins where a MCI subject had a higher GFC frequency than the HC group, GFC-Diff values were positive (green shaded area in Fig. 2c–e). Conversely, in bins where a MCI subject showed a lower GFC frequency compared to the HC group, the GFC-Diff score was negative (red shaded area in Fig. 2c–e). To identify GFC bins where MCI CR+ and MCI CR- subjects showed different GFC frequency changes, we compared GFC-Diff scores between the CR groups for each of the 60 bins, using two-sample t-tests with the significance threshold being $\alpha = 0.05$ for each t-test (Fig. 2d). We did not correct for multiple testing at this stage, since the analysis was an intermediate step, exclusively done in order to select bins where MCI CR- and MCI CR+ groups differed in terms of GFC-Diff.

The results of the t-tests showed that GFC-Diff scores were greater (i.e. more positive) in MCI CR+ compared to MCI CR- in the range from 0.34 to 0.5, suggesting that MCI CR+ had significantly increased frequencies of relatively high GFC values (henceforth referred to as $GFC\text{-}Diff_{CR+>CR-}$) relative to MCI CR- subjects. In contrast, GFC-Diff scores were increased in MCI CR- compared to MCI CR+ subjects in a range from 0.2 to 0.26, suggesting that MCI CR- subjects had a higher frequency of relatively low GFC values (henceforth referred to as $GFC\text{-}Diff_{CR+<CR-}$) compared to MCI CR+ subjects. In order to create a subject-specific summary score of GFC frequency differences indicative of CR+ status, we subtracted the sum of GFC-Diff values in the $GFC\text{-}Diff_{CR+<CR-}$ from the sum of GFC-Diff values in the $GFC\text{-}Diff_{CR+>CR-}$. Finally, this differences was divided by the total number of voxels in the cognitive control network mask to standardize it to a range between −1 and 1 (Fig. 2e and f, Eq. 2).

$$GFC\text{-}R\,index_j = \frac{\sum GFC\text{-}Diff_{CR+>CR-} - \sum GFC\text{-}Diff_{CR+<CR-}}{Number\ of\ voxels\ in\ mask} \quad (2)$$

where j = subject

This coefficient was then used as our GFC-R index. A negative GFC-R index indicates an increased GFC frequency in $GFC\text{-}Diff_{CR+<CR-}$ and a simultaneous decrease in $GFC\text{-}Diff_{CR+>CR-}$, i.e. a MCI CR- characteristic pattern. Conversely a positive GFC-reserve indicates an increased GFC frequency in $GFC\text{-}Diff_{CR+>CR-}$ and a decreased frequency in $GFC\text{-}Diff_{CR+<CR-}$, a pattern that was typically seen in MCI CR+.

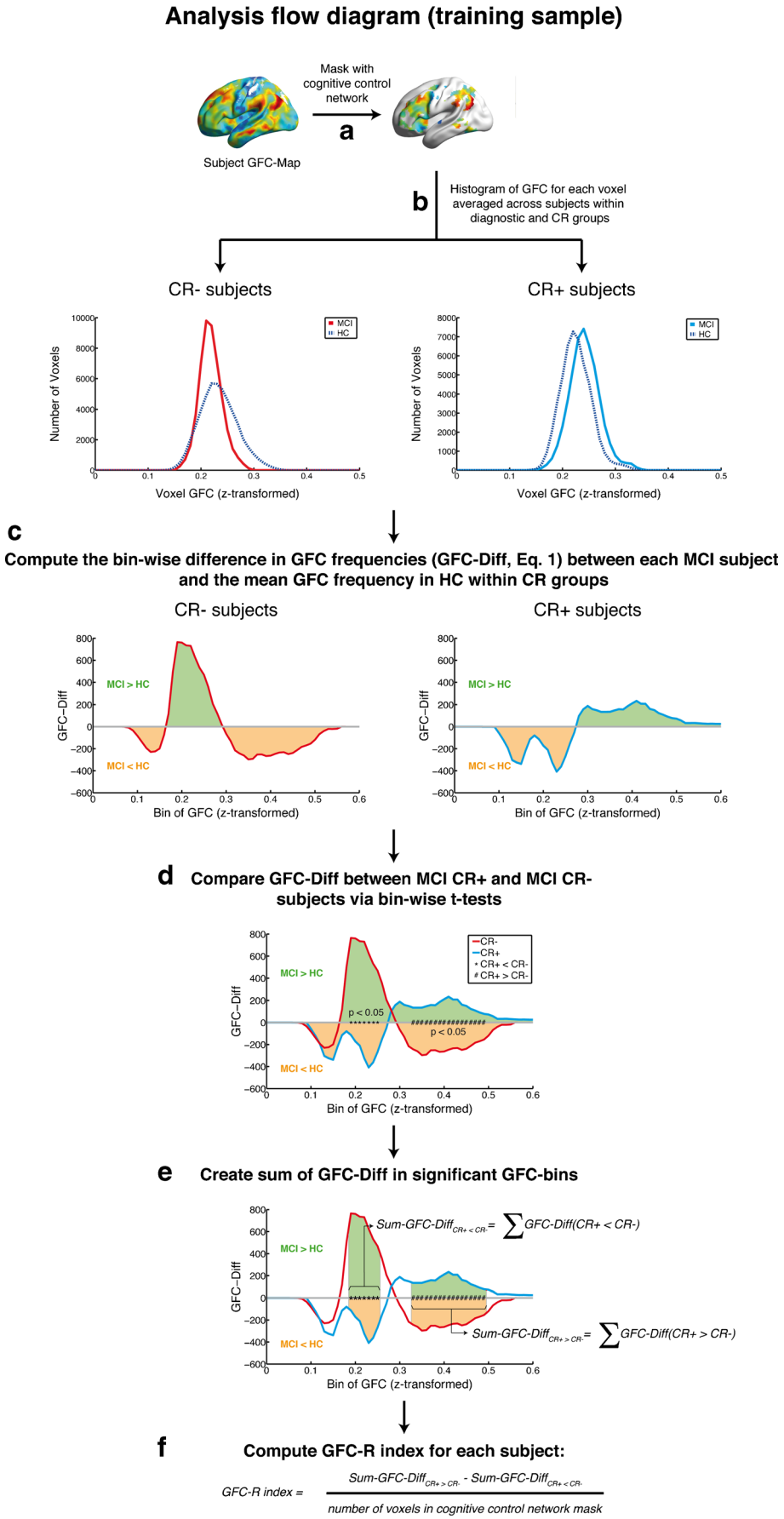

Fig. 2 Analysis flow diagram, illustrating the steps of GFC-R index computation. **a** Voxel-wise GFC is computed based on preprocessed resting-state fMRI for each subject and masked with the binarized cognitive control network map. **b** The GFC frequency distribution within the cognitive control network is plotted for groups split by diagnosis (HC & MCI) and CR status (CR− & CR+). **c** GFC within the cognitive control network is binned in intervals of 0.01 for each subject. Within each CR group, the difference in GFC differences (GFC-Diff) between each MCI subject and the average GFC within the HCs group is are computed. Colored areas indicate whether MCI subjects showed lower (*red*) or higher (*green*) GFC frequency than the HC subjects. **d** GFC-Diff scores are compared between MCI CR+ and MCI CR- groups via bin-wise two-sample t-tests. **e** GFC-Diff scores are summed up across the selected bins for each MCI subject. In order to create a subject-specific summary score of GFC frequency differences indicative of CR+ status, the sum of GFC-Diff values in the $\text{GFC-Diff}_{CR+<CR-}$ was subtracted from the sum of GFC-Diff values in the $\text{GFC-Diff}_{CR+>CR-}$. **f** This differences was divided by the total number of voxels in the cognitive control network mask to standardize it to a range between −1 and 1 to derive the GFC-R index for each MCI subject

All steps described above were conducted also for the test sample (ISD). Supplementary Figure 1 is showing – equivalent to Fig. 2b - the distribution of GFC voxels averaged across subjects within CR and diagnostic (MCI vs. HC) groups. When conducting the t-tests to compare the GFC-Diff values between MCI CR+ and MCI CR-, we found GFC-$Diff_{CR+<CR-}$ in a range from 0.2 to 0.22 (vs. 0.2–0.26 in the training sample) and the GFC-$Diff_{CR+>CR-}$ in a range from 0.29 to 0.41 (vs. 0.34–0.5 in the training sample). The GFC-$Diff_{CR+<CR-}$ fully overlapped between both samples, whereas the GFC-$Diff_{CR+>CR-}$ only partly overlapped. For our validation analysis, we used the GFC-$Diff_{CR+>CR-}$ and GFC-$Diff_{CR+<CR-}$ ranges derived from the training sample to compute the GFC-R index in the test sample. All above delineated steps were conducted accordingly for 7 major brain networks derived from a previous publication to control whether a relationship between CR and GFC was specific for the cognitive control network. Again, GFC-$Diff_{CR+>CR-}$ and GFC-$Diff_{CR+<CR-}$ ranges were assessed in the training sample and used to create the GFC-R index in the test sample. The histogram analysis was conducted fully-automated using in-house MATLAB scripts.

Statistical analysis

Demographic variables were compared between groups using t-tests for continuous variables and χ^2-test for gender.

In order to test whether the GFC-R index differed between MCI CR+ vs. MCI CR- groups in the training sample, we conducted an ANCOVA, with group as the predictor, and age, gender, the global AV45 uptake, the grey matter volume within the cognitive control network, WMH volume and the learning score of the RAVLT as covariates. To evaluate how accurately the GFC-R index classified between MCI CR+ and MCI CR- subjects we performed a Receiver Operating Characteristic (ROC) Curve analysis. Prediction accuracy was quantified using the area under the curve (AUC). The 95 % Confidence interval (CI) for each ROC was computed with 2000 stratified bootstrap replicates for each ROC analysis. Equivalent models were run in the test sample, with the exception of AV45 PET uptake, which was not available in the ISD test sample.

Lastly, we tested whether the GFC-R index predicted the CR proxies (years of education, CRIq) in the MCI subjects of the test sample (pooled across CR+ and CR-). To this end we conducted a multiple regression analysis, with the GFC–R index as a predictor of years of education or the CRIq, controlled for age, gender, WMH volume, the learning score of the CERAD and the total grey matter volume within the cognitive control network. For the ADNI sample, the association between the continuous AV-45 PET measure, WMH volume and GFC-R was tested in the MCI subjects (who were by definition of the inclusion criteria all AV-45 PET positive). We conducted a linear regression analysis, with WMH volume and AV45 uptake as independent variable and the GFC-R index as dependent variable, and age, gender, the RAVLT learning score and grey matter volume as nuisance covariates. An equivalent model was run for the ISD sample with the exception that AV45 was not available and that the CERAD word list learning score was entered as a covariate. To test whether the GFC-R index was related to cognitive performance, we applied linear regression, with the RAVLT learning score (ADNI) or the CERAD word list learning score (ISD) as a dependent variable and the GFC-R index as an independent variable, controlling for age, gender, as well as WMH volume and grey matter volume of the cognitive control network. Next, we tested whether our findings on the GFC-R for the prediction of years of education were specific for the cognitive control network. Thus, the regression analyses on GFC-R were repeated for each GFC-R index derived on the GFC frequencies in one of 7 major functional brain networks (i.e. Default Mode Network (DMN), Visual Network, Somatomotor Network, Dorsal Attention Network (DAN), Ventral Attention Network (VAN), Limbic Network, Frontoparietal Network (FPAN)) (Yeo et al. 2011).

All statistical analyses were conducted using the statistical software package *R* (R Development Core Team 2013). Linear models were computed using the lm command in *R*. Linear model assumptions (skewness, kurtosis, heteroscedasticity) were tested using the gvlma function implemented in *R*. For all models reported, no significant ($\alpha = 0.05$) violations of linear model assumptions were found.

Results

Demographics, cognitive measures and the mean GFC-R index values for the training and test sample are depicted in Table 1. The GFC-R index was not related to age in both samples.

GFC distribution

Figure 3 shows the spatial distribution of significant GFC values in the brain displayed in percentiles for the training (ADNI) and the test sample (ISD). We found a high spatial correspondence of significant GFC values between both samples with a correlation coefficient of $r = 0.84$, $p < 0.001$. The highest GFC values were observed predominantly within the frontal cortex, lateral parietal cortex, and areas of the medial brain surface. Those brain areas are known to be part of the DMN and the cognitive control network as reported previously (Cole et al. 2010).

Table 1 Demographics and neuropsychological characteristics of the study samples subjects split by Diagnosis and CR group

Training sample (ADNI)				
	HC CR− ($n = 13$)	HC CR+ ($n = 11$)	MCI CR− ($n = 24$)	MCI CR+ ($n = 19$)
Age (years)[a]	75.12 ± 5.85	74.30 ± 7.56	74.90 ± 5.87	69.10 ± 6.16
Gender (female/male)	3/10	5/6	14/10	12/7
Education[b,c]	15.15 ± 1.41	18.64 ± 1.12	14.17 ± 1.58	18.58 ± 1.02
Global AV45 Uptake	0.99 ± 0.45	0.98 ± 0.04	1.4 ± 0.18	1.37 0.15
MMSE[a,c]	29.12 ± 0.91	27.91 ± 1.45	26.71 ± 1.63	28.16 ± 1.34
RAVLT Learning[b]	45 ± 13.46	43.74 ± 7.81	31.71 ± 9.40	38.70 ± 8.91
Test sample (ISD)				
	HC CR− ($n = 17$)	HC CR+ ($n = 15$)	MCI CR− ($n = 13$)	MCI CR+ ($n = 10$)
Age (years)	70.17 ± 3.94	72.52 ± 6.33	77.02 ± 3.63	73.87 ± 4.23
Gender[d] (female/male)	13/4	5/10	11/2	8/2
Education[b,c]	11.59 ± 1.33	16.6 ± 2.1	10.92 ± 1.98	17.1 ± 2.08
MMSE[b]	29.53 ± 0.87	29.33 ± 0.72	25.15 ± 1.52	27.9 ± 2.33
CERAD Word List Learning[b]	23 2.6	24.07 3.24	13.3 2.84	18.9 3.14

[a] MCI CR+ < MCI CR−

[b] MCI CR+ > MCI CR−

[c] HC CR+ > HC CR−

[d] HC CR+ < HC CR−

The GFC-reserve index is decreased in MCI CR- as compared to MCI CR+

MCI CR- showed significantly lower GFC-R index values than the MCI CR+ subjects in the training sample ($F(7,35) = 17.82$, $p = 0.0001$; see Fig. 4a) and the test sample ($F(6,16) = 7.50$, $p = 0.015$). In an exploratory regression analysis in the training sample, we tested the association between the global AV45 uptake, WMH volume and the GFC-R index of the cognitive control network with age, gender, grey matter volume of the cognitive control network and the RAVLT learning score as covariates of no interest. The model showed no significant relationship between AV45 and the GFC-R index or between WMH volume and the GFC-R index. Similarly, in the test sample, WMH volume did not predict the GFC-R index, controlling for age, gender, CERAD word list learning and grey matter volume of the cognitive control network.

ROC analysis

Using a ROC analysis, we evaluated how accurate the GFC-reserve index discriminated between MCI CR+ and MCI CR- subjects (Fig. 4b). The AUC was 0.840 with the 95 % CI ranging between 0.72 and 0.95 within the training sample. Similarly, in the test sample, we found a AUC of 0.79 with the CI ranging from 0.60 to 0.99.

The GFC-reserve index is a predictor of CR proxies in the ISD test sample

Using linear regression, we tested whether the GFC-R index predicted CR proxies in the test sample, when controlling for age, gender, the word list learning score of the CERAD battery, WHM volume and grey matter volume of the cognitive control network. For years of education, the regression model was significant ($F(6,16) = 10.12$, $p = 0.0001$) with an adjusted R^2 of 0.71, showing that a higher GFC-R index significantly predicted higher years of education ($t(16) = 2.225$, $p = 0.041$). For the CRIq score, a higher GFC-R index predicted a higher CRIq score ($t(16) = 2.581$, $p = 0.020$, overall model fit: $F(6,16) = 3.498$, $p = 0.021$, adjusted R^2 0.41). The relationship between the GFC-R index and the CR proxies is illustrated in Fig. 5. When testing the Pearson-moment correlation between the GFC-R index and our CR proxies, the correlation was significant for both years of education ($r = 0.46$, $p = 0.026$) and the CRIq ($r = 0.6$, $p = 0.0024$).

The GFC-reserve index is specific to CR proxies

In linear regression analyses, we tested whether the GFC-R index is associated with better cognitive performance. We did not find the GFC-R index to predict RAVLT learning (ADNI), CERAD word list learning (ISD), or MMSE (ADNI & ISD) scores, controlling for age, gender, WMH volume and grey matter volume of the cognitive control network.

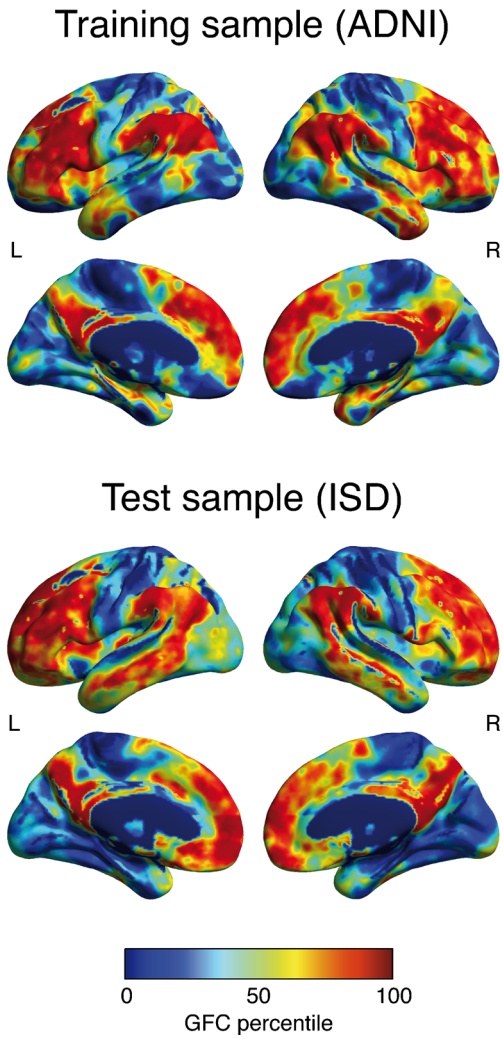

Fig. 3 Distribution of significant GFC values in the brain. T-values of voxel wise one-sample t-tests of the GFC among the pooled HC and MCI subjects (FWE corrected at the voxel level at $\alpha = 0.001$) were converted to percentiles to facilitate visual group comparison between both samples

Control analyses in other brain networks

In order to test, whether our findings on the prediction of years of education by GFC-R index were specific for the cognitive control network, we repeated the regression analysis for GFC-R index derived from each of seven other major cortical networks (Yeo et al. 2011). For none of the other networks, the GFC-R index predicted years of education or the CRIq ($p > 0.05$, Table 2). This suggests that the relationship between GFC changes and education is specific for the cognitive control network.

Discussion

The first major finding of the current study was that MCI subjects with high CR (as measured by years of education) had an increased frequency of high GFC values within the cognitive control network compared to MCI subjects with lower years of education. Secondly, a newly derived summary measure of abnormal GFC frequencies within the cognitive control network, the GFC-R index, showed a linear association with more years of education and a higher CRIq score, a composite measure of CR, in an independent cross-validation sample of MCI patients. The predictive value of GFC-R index was independent of demographic variables including age and gender, episodic memory performance, grey matter volume of the cognitive control network or WMH volume as a proxy of cerebral small vessel disease. These results suggest that the GFC-R index constitutes a biomarker candidate of CR-related functional brain changes in MCI.

For our first major finding, MCI CR+ showed a right-ward shift of the GFC histogram to that in HC CR+, i.e. MCI CR+ showed an increased frequency of relatively high GFC values. In contrast, there was a left-ward shift of the GFC histogram in the MCI CR- group, i.e. an increased frequency of lower GFC values. A previous study on GFC changes in MCI reported decreased GFC in the frontal, parietal, and temporal cortices in MCI (J. Wang et al. 2013). That latter study, however, did not assess the impact of years of education on GFC differences. Our results extend those previous results showing that the levels of CR are an important modifying factor, where MCI CR- subjects show a decrease in GFC but MCI CR+ subjects show an increase in GFC within the cognitive control network.

The increase in the frequency of high GFC values in MCI CR+ may reflect either pre-existing high levels of GFC before the development of MCI or, alternatively, a compensatory increase in GFC during the development of MCI, or thirdly, a dedifferentiation of functional connectivity that is related to pathological brain changes (Cabeza et al. 2002; Jones et al. 2011). Previous studies showed that higher IQ is associated with higher GFC within the left frontal core region of the cognitive control network in young subjects (Cole et al. 2012). Given that years of education and IQ are correlated (Matarazzo and Hermann 1984), it is possible that MCI CR+ subjects had already higher levels of GFC before disease onset, thus possessing higher brain reserve. However, the fact that MCI CR+ subjects showed abnormally increased frequency of high GFC values when compared to HC CR+, i.e. at similarly high levels of education, suggests a compensatory increase of GFC in MCI. Such an interpretation of compensatory increase of GFC in MCI is consistent with several previous studies showing increased resting-state functional connectivity in MCI and AD compared to HC (K. Wang et al. 2007), that is attributable to higher levels of education (Bozzali et al. 2015). On the other hand, the lacking relationship between the GFC-R index and cognitive performance partly challenge the notion that GFC increases are compensatory. A third possible explanation for an increase in GFC is a dedifferentiation of

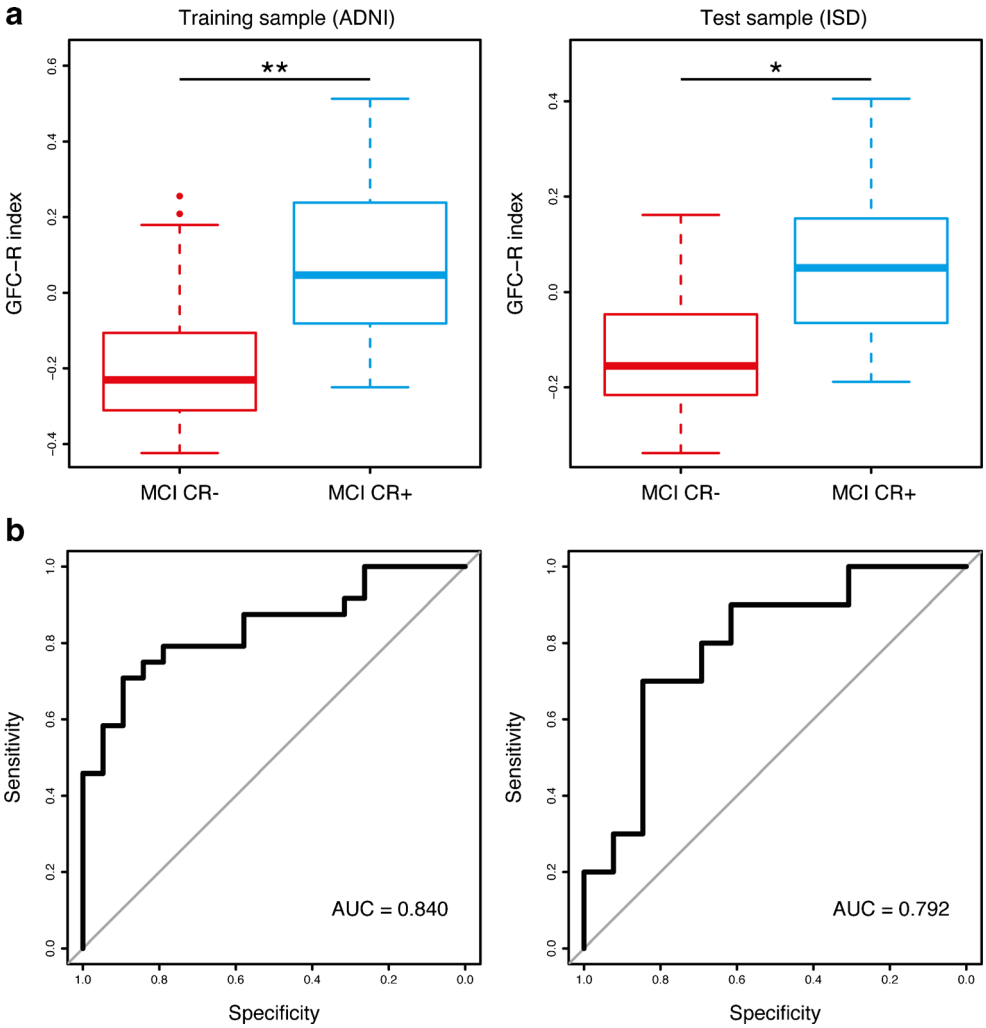

Fig. 4 **a** Boxplots of the GFC-R index split by CR group for the training and the test sample. MCI CR- subjects show significantly lower GFC-CR values as MCI CR+ subjects in both samples. **b** shows the ROC curves with the specificity on the x- and the sensitivity on the y-axis. *AUC* Area under the curve, * = $p < 0.05$, ** = $p < 0.001$

functional connectivity due to pathological brain changes as suggested previously (Cabeza et al. 2002; Jones et al. 2011). However, we did not find GFC increases to be related to grey matter atrophy, WMH volume or amyloid deposition. Thus, our results indicate that the observed increase in GFC is unlikely to reflect pathology-driven dedifferentiation of functional connectivity. In summary, the MCI CR+ subjects specifically show increased frequency of high GFC values within the cognitive control network, which could reflect compensatory changes in MCI, however this needs to be further investigated by future studies.

For our second major finding, we could show in a cross-validation approach that higher levels of the GFC-R index allow accurate point prediction of higher levels of education

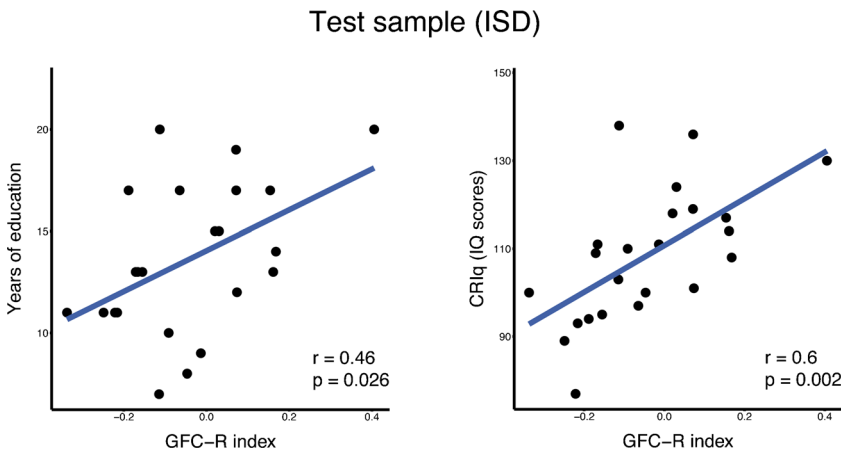

Fig. 5 Scatterplot for the relationship between the GFC-R index and the CR proxies (years of education & CRIq) in the test sample

Table 2 Control analyses of the GFC-R index as a predictor of CR proxies in major brain networks

Functional network	Training sample (ADNI)		Test sample (ISD)			
	GFC-Diff		GFC-CR as a predictor of education in MCI CR+ and CR− pooled[1]		GFC-CR as a predictor of CRIq in MCI CR+ and CR− pooled[1]	
	CR+ < CR−	CR+ > CR−	T	p	T	p
Cognitive control	0.2–0.26	0.34–0.5	2.225	0.041	2.581	0.020
Default mode	0.2–0.27	0.37–0.52	0.631	0.537	1.324	0.204
Dorsal attention	0.22–0.28	0.41–0.51	0.998	0.333	0.934	0.364
Ventral attention	0.19–0.23	0.3–0.5	0.885	0.389	1.767	0.096
Frontoparietal	0.2–0.27	0.35–0.52	1.284	0.216	1.635	0.122
Limbic	0.25	0.36–0.46	0.644	0.529	0.577	0.572
Visual	0.22–0.28	0.43–0.53	0.255	0.801	1.526	0.147
Somatomotor	0.21–0.28	0.32–0.46	1.078	0.30	0.995	0.335

[1] Models controlled for age, gender, WMH volume, grey matter volume of the tested network, CERAD Word list learning score

and CRIq in MCI and could well separate high vs. low education groups in MCI as shown by the ROC analysis, with an AUC of 0.79. Note however that sensitivity and specificity is not of primary clinical significance in the context of CR, which is likely to be continuously distributed. More importantly, the GFC-R index showed a significant linear relationship with two different CR proxies in the validation sample. The point prediction is difficult but clinically important as previous studies showed that with each additional year of education, the onset of dementia is delayed by 0.21 years (Hall et al. 2007) and the risk of AD dementia is reduced (Sando et al. 2008; Stern et al. 1994). A critical test in the future will be whether the GFC-R index predicts slower cognitive decline in subjects with preclinical AD or MCI as has been reported for years of education as a proxy of CR (Soldan et al. 2015). The advantage of using fMRI based CR biomarkers such as GFC-R in such prediction models is that GFC-R could be used as a measure to track CR changes over time. CR may be reduced as the disease progresses since brain pathology may eventually use up the reserve (Members et al. 2010). In contrast, proxies of CR such as education or occupational attainment are time-invariant.

We found that only the GFC-R index derived from GFC values within the cognitive control network but not within any of the other major resting-state networks did significantly predict years of education or CRIq. For the ventral attention network, we found a trend level association between the GFC-R index and the CRIq, suggesting that the ventral attention network is to a certain extent associated with CR-related GFC increases. From a functional viewpoint, the ventral attention network is hypothesized to be involved in attentional control via coupling with other networks such as the dorsal attention or cognitive control network (Vossel et al. 2014). Similar to the cognitive control network, the ventral attention network shows task-related hyperactivations in MCI and AD, as revealed by a recent meta-analysis of task-fMRI studies (Li et al. 2015). This suggests, that the ventral attention network is potentially involved in compensatory brain changes in MCI and AD. However, given that there was only a trend level association with one of the two CR proxies tested, we think that the role of the ventral attention network for the assessment of CR-related brain changes is questionable and requires further validation in future studies. Our results are broadly consistent with previous findings showing that higher GFC of brain regions in the cognitive control network but not the default mode network were predictive of higher IQ in healthy subjects (Cole et al. 2012). A possible explanation includes that the cognitive control network has a unique role in the brain, such that it is highly connected with the other networks and may orchestrate the activation of other networks during cognitive tasks (Cole et al. 2013, 2014b). Brain regions with increased connectedness in the brain have previously shown to be more resilient to targeted attacks as shown in graph theoretical analysis of resting-state fMRI (Achard et al. 2006). Higher GFC of the cognitive control network may enable to more flexibly activate different networks during cognitive processing (Cole et al. 2013), which in neurodegenerative disease may render a more flexible coping with local damage of specific neural networks such as the DMN (Greicius et al. 2004; Mevel et al. 2011), thus increasing CR. This will need to be tested in future combined resting-state and task-related fMRI studies.

We used years of education as our primary outcome measure, i.e. the gold standard, since educational attainment has been recommended as the best validated indicator of cognitive reserve (Stern 2012). Years of education has been tested as a CR proxy in numerous studies in AD (for review see (Stern 2012)) and is robustly associated with reduced risk of AD

dementia across studies (Meng and D'Arcy 2012; Valenzuela and Sachdev 2006). Alternative proxy measures of CR include assessments such as occupational attainment, premorbid IQ or leisure activities. Since we used international cross-validation samples, equivalent measures of such variables were not available in both samples in the current study. However, in the test sample, we found a significant positive association between the GFC-R index and the CRIq (Nucci et al. 2012) an alternative CR proxy that takes into account education, working and leisure activities, supporting criterion validity of the GFC-R index.

A promising alternative marker of CR has been recently proposed, consisting of the residual episodic memory variability after accounting for brain atrophy and demographic variables (Reed et al. 2010; Zahodne et al. 2013, 2015). Such a measure captures well CR as the discrepancy between the level of cognitive performance and brain pathology, but is non-informative about any structural or functional brain changes that may underlie CR. The current GFC-R index captures functional brain changes related to CR in MCI and would thus be complimentary to such memory-variance based marker or any of the standard proxy measures of CR.

For the interpretation of the current results several caveats need to be taken into account. It is important to note that the GFC-R index is not a biomarker candidate of CR per se, rather it is a biomarker of functional brain changes that are associated with CR in subjects with MCI. Ideally, the primary outcome parameter for the validation of the current biomarker constitute specific functional mechanisms that cause CR in MCI. Although several task fMRI studies have attempted to extract specific functional brain changes of CR in subjects with MCI and AD, no core mechanism, however, has yet emerged (for review see (Barulli and Stern 2013)). Thus, more work is needed to disentangle the functional brain processes that underlie CR, which could then provide a point of reference for the validation of functional biomarkers of CR in MCI. Still, years of education has been validated in numerous studies as a marker of CR and may thus constitute the best primary outcome as a reference measures for the validation of functional biomarkers of CR at this point.

It should be also taken into account that the reliability of GFC assessment is an important factor for the utility of GFC-R as a CR biomarker in MCI. Previous studies showed that GFC exhibits a fair to excellent test-retest reliability and its retest reliability ranks among the highest of resting-state fMRI functional connectivity measures (Liao et al. 2013; J. H. Wang et al. 2011). Multicenter variability of resting-state fMRI is an active field of research and needs still to be established for the various connectivity indices including that of GFC. However, the current cross-validation of the GFC-R between different samples suggest robustness of the current findings (Feis et al. 2015). Moreover, both samples were scanned on different scanners with different scanner protocols, but still results were highly comparable. This favors the use of the GFC-R index as a fMRI-based marker of CR in MCI that can be validly assessed across sites and scanners. Summary indices that average across a large number of voxels such as the GFC-R index may be more robust to multicenter variability than measures focusing on small ROIs (Ewers et al. 2006). Still, the test-retest and multicenter variability of the GFC-R index needs to be established in future studies, however, our analysis renders the GFC-R index a promising candidate marker of CR that can be robustly assessed across different scanner protocols.

A strength of the current approach is the fully automated way to extract GFC frequency changes in MCI based on resting-state fMRI. Thus, functional MRI data can be assessed without reliance on a task and data processing can be done without manual intervention, which provides a high attractiveness to be used in clinical praxis. Possible clinical applications of the GFC-R index as diagnostic biomarker candidate include the use as an outcome measure in clinical trials such as cognitive training, physical training that target compensatory brain mechanisms to prevent conversion from MCI to AD dementia (Suo et al. 2016). Secondly, the GFC-R index could be used to track changes in CR during the progression of the disease. Future longitudinal studies may address these next steps.

Compliance with ethical standards The study at the ISD was approved by the ethics committee of the Ludwig Maximilian University of Munich. For the ADNI-sample ethical approval was obtained by the ADNI investigators. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All study participants provided written, informed consent to the study.

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Conflict of interest The authors declare that they have no conflict of interest

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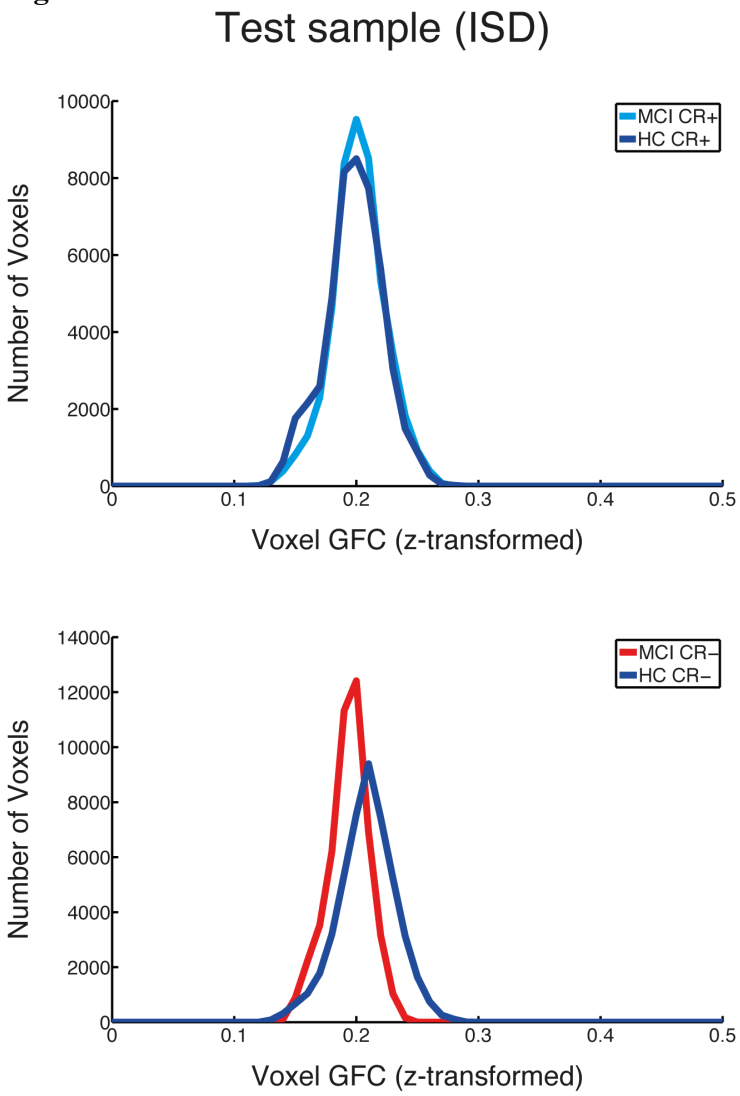
Supplementary

Figure:



5 | Discussion and Conclusion

The major findings of the current thesis were that 1) education and IQ were associated with an attenuated effect of lower resting-state DMN-DAN anti-correlation on episodic memory in MCI 2) higher global connectivity of the LFC, a major hub of the fronto-parietal control network was associated with higher education and attenuated effects of posterior parietal FDG-PET hypometabolism on episodic memory in prodromal AD, and 3) a summary index of the global connectivity of the fronto-parietal control network was a predictor of the protective factors in MCI.

These findings suggest that higher education moderates the effects of posterior parietal dysfunction (measured by DMN-DAN anti-correlation or posterior parietal FDG-PET) on memory. Thus, subjects with higher reserve (as indexed by education) may be able to cope better with core AD pathological brain changes, and maintain episodic memory relatively well in the course of AD. Whereas posterior parietal networks may be afflicted in AD, it is higher connectivity of the fronto-parietal control network, in particular the hub in the LFC, more specifically the inferior frontal lobe (Brodmann area 6/44), which may support higher reserve. The LFC and fronto-parietal control network regions are relatively spared in mild stages of AD (Buckner et al., 2009; Buckner et al., 2005), and may thus be well posed to support cognitive function at least in the prodromal stage of AD. Thus, we showed that functional connectivity alterations can be subject to pathological alterations in AD (DMN-DMN anti-correlation) whereas connectivity of other networks (fronto-parietal control network) may support higher reserve in AD. Protective factors such as education may ameliorate the impact of posterior parietal functional abnormalities on memory.

Higher global connectivity of fronto-parietal control network hubs such as the LFC may underlie such protective effects of education on memory in AD.

5.1. Cognitive Reserve in Alzheimer's disease

In the first study, we assessed whether protective factors that are commonly related to cognitive reserve (education, IQ) are associated with better tolerance of posterior functional network changes on memory performance. We focused on the antagonistic (i.e. anti-correlated) activity between the DMN and the DAN, two key functional networks whose anti-correlated activity pattern during both resting-state and task demands is critical for cognition including memory (Chai, Ofen, Gabrieli, & Whitfield-Gabrieli, 2014; Fox et al., 2005; Huijbers et al., 2013). Importantly, the anti-correlation between both networks is decreased in the course of AD as shown by task and resting-state fMRI studies, what has been linked to poorer memory performance (Meskaldji et al., 2016; Pihlajamaki & Sperling, 2009; Sperling et al., 2009). In line with these previous findings, we could show that patients with amnestic MCI show more severe memory dysfunction with stronger reductions in the DMN-DAN anti-correlation, confirming the notion that the the functional antagonism between the DMN and the DAN is fundamental for cognition (Chai et al., 2014; Meskaldji et al., 2016). Supporting the concept of cognitive reserve, we could show that detrimental effects of a reduced DMN-DAN anti-correlation were attenuated in MCI patients with more years of education or higher IQ, which was independently validated across two samples. This finding critically supports the notion that protective factors like education and IQ are associated with increased cognitive reserve, which renders individuals less susceptible to pathological brain changes. Furthermore, this study shows to our knowledge for the first time beneficial effects of education and IQ with regard to dysfunctional resting-state fMRI assessed functional network changes, i.e. a

reduced DMN-DAN anti-correlation. These results also raise the question whether the detected associations can be translated to task fMRI, since a reduced DMN-DAN antagonism during a memory encoding task has been shown detrimental for memory in AD (Pihlajamaki & Sperling, 2009). Future task-fMRI studies may thus investigate whether greater education or IQ are associated with attenuated effects of a reduced DMN-DAN antagonism on memory while actively engaging in a memory task.

Further supporting the cognitive reserve concept, our second study (Franzmeier, Duering, et al., 2017) revealed protective effects of education on the impact of AD-related posterior parietal FDG-PET hypometabolism on cognition in MCI patients. FDG-PET hypometabolism is a surrogate for synaptic dysfunction where especially posterior parietal FDG-PET hypometabolism is a hallmark of early AD (Bailly et al., 2015; Buckner et al., 2005) that co-develops with memory deficits (Mosconi & McHugh, 2011; Mosconi, Pupi, & De Leon, 2008). It was previously shown that in preclinical AD, subjects with higher education could maintain normal cognition at more severe levels of temporo-parietal FDG-PET hypometabolism than subjects with lower levels of education (Ewers et al., 2013). Here, we could replicate those findings in prodromal AD, where at a given level of cognitive performance, patients with greater education showed stronger reductions in precuneus glucose metabolism (i.e. a medial parietal region that harbors a key hub of the DMN) than less educated individuals, thus providing indirect evidence that more highly educated individuals possess higher cognitive reserve. These findings are consistent with previous studies, showing that protective factors including education, IQ and occupational attainment are associated with better tolerance of FDG-PET hypometabolism or hypoperfusion in healthy elderly (Bastin et al., 2012) as well as in preclinical and clinical stages of AD (Carapelle et al., 2017; Ewers et al., 2013; Morbelli & Nobili, 2014; Stern et al., 1995). In the current thesis, we took the crucial next step to identify those functional

brain changes that may explain such higher education-related tolerance of FDG-PET hypometabolism, i.e. we explored whether functional properties of the fronto-parietal control network can indeed explain the link between protective factors like education and better tolerance of brain pathology. This question was for the first time systematically addressed in the second study of this thesis based on a sample of MCI patients with abnormal levels of Amyloid-beta deposition (i.e. prodromal AD).

5.2. Connectivity of Fronto-Parietal Control Network Hubs as a Neural Substrate of Cognitive Reserve

In order to test whether global connectivity of the LFC hub is a neural substrate of cognitive reserve we stipulated two criteria that we have introduced in paragraph 1.6. First, any putative functional brain feature of cognitive reserve should be associated with commonly established protective factors (i.e. criterion of face validity). Secondly, the functional brain feature of cognitive reserve should be associated with an attenuated effect of brain pathology on cognitive performance (i.e. criterion of cognitive benefit). Here, we could show that greater education was associated with higher global connectivity of the LFC – a key hub of the fronto-parietal control network. Second, and most importantly, we could show that greater global LFC connectivity moderated the effects of posterior parietal FDG-PET hypometabolism on memory: Specifically, at a given level of FDG-PET hypometabolism, patients with higher global LFC connectivity showed relatively high memory performance compared to those with lower global LFC connectivity. Put another way, highly educated patients had greater global connectivity of the LFC which was associated with relatively preserved memory performance despite AD pathology. Together, the results of this study confirm both criteria of face validity and cognitive benefit and provide for the first time systematic and hypothesis driven evidence of a

neural mechanism of cognitive reserve that may explain the association between protective factors like education and better tolerance of brain pathology in AD. We have recently studied the role of the LFC as a substrate of reserve in two larger samples of patients with sporadic and autosomal dominantly inherited AD. Here, we could confirm our findings, that greater resting-state fMRI assessed global connectivity of the LFC is associated with greater education (i.e. criterion of face validity) and attenuated effects of AD pathology on memory performance (i.e. criterion of face validity) across the spectrum of preclinical and clinical AD (Franzmeier et al., Manuscript in preparation).

A critical question is, why the hubness (i.e. global connectivity) of the LFC is a substrate of reserve. Global connectivity is based on graph-theory and represents the level of interconnectedness between a given brain region and the rest of the brain and is thus hypothesized to reflect the level of control a given brain region can exert on the remaining networks (Cole et al., 2012). The LFC has been previously shown to belong to the most globally connected brain hubs (Cole et al., 2010), which was confirmed in two independent samples by our voxel-wise mapping of global connectivity as included in our third study (Franzmeier et al., 2016). Connectivity changes in highly connected brain hubs have a strong impact on brain and cognitive function, compared to connectivity changes in other brain regions (Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006; Alstott, Breakspear, Hagmann, Cammoun, & Sporns, 2009) and disruptions of functional hubs have been previously associated with neurodegenerative or neuropsychiatric diseases (Buckner et al., 2009; Crossley et al., 2014). In contrast, higher hub connectivity was linked to better cognition (Cole et al., 2012; Liu et al., 2016). Since previous studies have shown that AD affects predominantly posterior parietal hubs mainly included in the DMN, whereas frontal hubs such as the LFC are relatively spared (Buckner et al., 2009; Buckner et al., 2005; Engels et al., 2015) it is possible that connectivity of key fronto-parietal

control network hubs like the LFC is important for sustaining cognition relatively well when developing AD.

The exact mechanisms by which the LFC supports cognitive reserve in the face of AD pathology remains, however, unanswered by our current studies thus requiring further investigation. The flexible hub theory suggests, that fronto-parietal control network hubs like the LFC exert control on other networks where they can dynamically shift their connectivity across different cognitive tasks to help adapt functional brain architecture to current task demands (Cole et al., 2013). In line with this notion, the LFC has been shown to be a key connector hub that mediates information exchange across different networks (Cole et al., 2015). In a follow up study that is not part of this thesis, we applied a face-name memory task fMRI in a sample of cognitively normal elderly and MCI patients (Franzmeier et al., submitted). In agreement with our resting-state fMRI findings, we found greater education to predict higher global LFC connectivity during successful face-name learning (i.e. criterion of face validity), which in turn predicted greater memory performance relative to the level of age and hippocampal atrophy (i.e. criterion of cognitive benefit). Together, this confirms the notion that fronto-parietal control network hubs like the LFC underlie cognitive reserve. Due to its high intrinsic global connectivity the LFC hub may help increase the efficiency of and communication among other networks during task demands and thereby support cognitive performance (Cole et al., 2013). In the face of emerging brain pathology, greater global LFC connectivity could thus help to more efficiently recruit brain regions that are stressed by pathology, or help recruit alternative brain regions to compensate the dropout of critical brain regions. While this remains speculative, it would be congruent with the initial idea that cognitive reserve is conferred by more efficient or more flexible brain networks (Barulli & Stern, 2013), and may explain previous reports on associations between protective factors and localized

brain activation differences which we have summarized in paragraph 1.5 (Bosch et al., 2010; Scarmeas et al., 2004; Sole-Padulles et al., 2009). Together, these results support the fronto-parietal control network model of cognitive reserve and may constitute a starting point to guide future research to further disentangle the neural mechanisms of cognitive reserve.

Since higher cognitive reserve – as indexed by education and IQ – is important for individual risk prediction of cognitive decline in AD (Barulli & Stern, 2013; Soldan et al., 2015), we aimed to translate our findings to a clinical useful index that captures neural mechanisms of cognitive reserve. The rationale for such a measure is, that an imaging-based index of cognitive reserve might be better suited to capturing the underlying construct of reserve relative to using protective factors like education or IQ. Hence our third study (Franzmeier et al., 2016) proposes a novel-imaging based marker of cognitive reserve mechanisms, where we focused on education-related hubness (i.e. global connectivity) of the fronto-parietal control network. When mapping the global connectivity distribution across the cortex in a voxel-wise manner, we could confirm previous evidence (Cole et al., 2010) that hubs with the greatest global connectivity can be found among fronto-parietal control network regions including the LFC. This supports the view that the fronto-parietal control network is a central coordinating system that is highly interconnected with the rest of the brain (Cole et al., 2013; Cole et al., 2012). In two independent samples, we could show that highly educated patients with MCI show relatively high global connectivity of fronto-parietal control network hubs when compared to MCI patients with lower levels of education. Based on this result pattern we have established a fully automated algorithm that summarizes individual distributions of fronto-parietal control network global connectivity in a single scalar measure termed global

functional connectivity reserve index (GFC-R). This GFC-R index showed strong associations with protective factors including years of education and a more complex cognitive reserve index questionnaire, which takes into account education, occupational complexity, and leisure time activities (Nucci, Mapelli, & Mondini, 2012). Apart from the fronto-parietal control network, we also derived this GFC-R index from 7 other major functional networks including the DMN and DAN. However, for none of these 7 other networks a significant association between the GFC-R index and protective factors like education or the cognitive reserve index questionnaire was found. These results support a specific role of the fronto-parietal control network as a neural substrate of cognitive reserve. We argue, that the GFC-R index may hold several advantages when compared to conventional indicators of reserve like education and IQ. Both education and IQ are relatively static measures that show no (i.e. education) or little (i.e. IQ) change in old age or when developing AD, however, cognitive reserve mechanisms are assumed to be rather dynamic as they may be fostered by pharmacological, physical or cognitive intervention or decline with aging or AD progression (Xu et al., 2015). Thus, an imaging-based measure that captures individual cognitive reserve mechanisms may be especially well-suited to track changes in cognitive reserve during the disease course or in response to intervention. From a technical perspective, the GFC-R index showed strong and congruent associations with education across different scanner protocols and different samples. This favors the use off the GFC-R index as a fMRI-based marker that can be validly used across sites and scanners. However, its' multicenter variability and test re-test reliability remains to be empirically tested by future studies.

5.3. Limitations

For the interpretation of the current findings, several caveats should to considered. First, all studies included in this thesis are based on resting-state fMRI, hence a generalization of our findings to task fMRI remains open. With regard to our first study (Franzmeier, Buerger, et al., 2017) it is an open question 1) whether a reduced DMN-DAN anti-correlation at rest is associated with a reduced DMN-DAN anti-correlation during cognitive demands (i.e. during memory task fMRI) and 2) whether higher education or IQ are associated with less strong reductions in memory performance in the face of a reduced task-related DMN-DAN anti-correlation. For our second study (Franzmeier, Duering, et al., 2017), it remains to be tested whether resting-state global connectivity of the LFC translates into greater connectivity during task demands and thus better task performance. Here, the results of our follow-up study using memory task-fMRI show a similar association between education, task-related global LFC connectivity and memory in healthy elderly and MCI subjects, however these results are still under review and thus not included in this thesis (Franzmeier et al., submitted).

A further limitation is that the results of this thesis were exclusively assessed on patients at the stage of MCI, who are at risk of developing AD dementia, hence a generalization of our findings to preclinical or dementia stages of AD remains open. Also, measures of AD pathology (i.e. amyloid levels) were not assessed in all MCI patients of study 1 & 3, hence it remains open, whether our findings were specific for patients with underlying AD pathology. A crucial next step here will be to test whether the fronto-parietal control network and especially the LFC hub support cognitive reserve across biomarker-characterized cohorts covering the entire preclinical and clinical spectrum of AD. Since beneficial effects of cognitive reserve have been described across preclinical and clinical AD stages (Ewers et al., 2013; Rentz et al., 2010; Roe, Xiong, Miller, Cairns, & Morris,

2008) and given that frontal lobe function is relatively spared in later stages of AD (Buckner et al., 2009; Buckner et al., 2005), it is likely that the LFC supports cognitive reserve consistently across different AD stages. As stated in paragraph 5.2., we have preliminary results in two samples of autosomal dominant and sporadic AD that support this view (Franzmeier et al., in preparation), however these data are not included in the current thesis.

When testing neural mechanisms of cognitive reserve, we have employed a hypothesis driven approach focusing on the fronto-parietal control network (Franzmeier et al., 2016) and in particular on its hub in the LFC (Franzmeier, Duering, et al., 2017). While a priori focusing on a specific brain network or region decreases the risk of false-positive findings this in turn increases the risk of missing other brain regions that are potentially implicated in cognitive reserve. However, we have included control analyses on other brain regions and networks in our studies 2 & 3, showing that associations between education, global connectivity and memory performance were specific for the fronto-parietal control network and the LFC respectively (Franzmeier et al., 2016; Franzmeier, Duering, et al., 2017). While these control analyses support specificity of our findings, a potential role of other brain regions in cognitive reserve can currently not be ruled out.

5.4. Outlook & Concluding Remarks

In summary, the results of this thesis support the cognitive reserve concept in AD and provide systematic evidence that the fronto-parietal control network – in particular the LFC hub - may be a long sought-after neural substrate of cognitive reserve. We provide a theoretical framework on how the fronto-parietal control network may implement its beneficial effects on cognition in the face of AD pathology. Further, our novel research criteria can be adopted by future task and resting-state fMRI studies to elucidate the

detailed functional mechanisms by which fronto-parietal control network hubs such as the LFC help better tolerate AD pathology and we encourage future studies to test the generalizability of the fronto-parietal control network model of cognitive reserve to different stages of the disease.

Importantly, different lines of research have emphasized that cognitive reserve effects are not restricted to the memory domain or to AD: Rather, protective effects of education or IQ on cognitive performance in the face of brain pathology have been reported in numerous neurological conditions such as small-vessel disease (Zieren et al., 2013), stroke and traumatic brain injury (Nunnari, Bramanti, & Marino, 2014), multiple sclerosis (Sumowski & Leavitt, 2013), fronto-temporal dementia (Premi et al., 2013) or Parkinson's disease (Hindle, Martyr, & Clare, 2014). Thus, the current findings may be a starting point for future studies to test whether the fronto-parietal control network is a substrate of cognitive reserve consistently across different neurological conditions and cognitive domains by applying our novel research criteria.

Our findings may also help investigate how neural mechanisms of cognitive reserve change in the course of AD and whether they predict conversion to dementia or can be promoted using cognitive trainings (Buschert et al., 2011), non-invasive brain stimulation (Drumond Marra et al., 2015) or pharmacological interventions (Dhanjal & Wise, 2014). In this context, especially the GFC-R index may provide a useful tool for longitudinal assessment. If modifiable, fostering fronto-parietal control network global connectivity and thus cognitive reserve may ultimately hold potential for secondary prevention to delay the development of AD dementia in our aging society.

6 | References

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Curriculum Vitae

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Honors and Awards

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Publications

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Franzmeier, N., Unterauer, E., Ewers, M., Düring, M., Mueller, C., ... Buerger, K. (2016) Effects of Age, APOE ε4, Cognitive Reserve and Hippocampal Volume on Cognitive Intervention Outcome in Amnestic Mild Cognitive Impairment. *J Alzheimers Dis Parkinsonism,* 6: 246. doi:10.4172/2161-0460.1000246

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Teipel, S., Grothe, M.J., Metzger, C.D., Grimmer, T., Sorg, C., Ewers, M., **Franzmeier, N.**, Meisenzahl, E., Kloeppel, S., Borchardt, V., Walter, M., Dyrba, M. (2017). Robust Detection of Impaired Resting State Functional Connectivity Networks in Alzheimer's Disease Using Elastic Net Regularized Regression. *Front Aging Neurosci, 8*, 318. doi:10.3389/fnagi.2016.00318

Selected Conference Presentations

2017:

Human Amyloid Imaging Conference, Miami, United States: Left frontal global connectivity is a substrate of cognitive reserve in mild cognitively impaired patients with a high amyloid burden.

2016:

Alzheimer's Association International Conference, Toronto, Canada: Left Prefrontal Global Connectivity Enhances Cognitive Reserve in Alzheimer's Disease.

Brain Connectivity Conference, Vienna, Austria: Global connectivity of the left frontal cortex enhances cognitive reserve in prodromal Alzheimer's disease

Brain Connectivity Conference, Vienna, Austria: Resting-state global functional connectivity as a biomarker of cognitive reserve in mild cognitive impairment

2015:

Alzheimer's Association International Conference, Washington, United States: Abnormally reduced anti-correlation between resting-state default mode and fronto-parietal networks is associated with memory impairment in MCI

Eidesstattliche Erklärung/Affidavit

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation *„Neural Mechanisms of Cognitive Reserve in Alzheimer's Disease"* selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation *„Neural Mechanisms of Cognitive Reserve in Alzheimer's Disease"* is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

Munich, 2nd of June Nicolai Franzmeier

Declaration of Author Contributions

Cognitive reserve moderates the association between functional network anti-correlations and memory in MCI.
Franzmeier, N., Buerger, K., Teipel, S., Stern, Y., Dichgans, M., Ewers, M., & Alzheimer's Disease Neuroimaging, I. (2017). Neurobiology of Aging.

The author of this thesis is the first author of the manuscript. N.F. and M.E. designed research and wrote the manuscript, N.F. analyzed the data, K.B. and NF collected the data, Y.S., S.T., K.B. and M.D. critically revised the manuscript.

Left frontal cortex connectivity underlies cognitive reserve in prodromal Alzheimer disease.
Franzmeier, N., Duering, M., Weiner, M., Dichgans, M., Ewers, M., & Alzheimer's Disease Neuroimaging, I. (2017). Neurology.

The author of this thesis is the first author of the manuscript. N.F. and M.E. designed research and wrote the manuscript, N.F. analyzed the data, M.Duering, M.Dichgans & M.W. critically revised the manuscript.

Resting-state global functional connectivity as a biomarker of cognitive reserve in mild cognitive impairment.
Franzmeier, N., Caballero, M. Á. A., Taylor, A. N. W., Simon-Vermot, L., Buerger, K., Ertl-Wagner, B., Mueller, C., Catak, C., Janowitz, D., Baykara, E., Gesierich, B., Duering., M., Ewers, M. (2016). Brain Imaging and Behavior

The author of this thesis is the first author of the manuscript. N.F. and M.E. designed research and wrote the manuscript; N.F. analyzed the data; N.F., M.A.A.C., A.N.W.T., L.S.V., K.B., C.M., C.C., D.J., E.B. and B.G. collected the data; B.E.W. and M.D. critically revised the manuscript.

Hereby confirms the first supervisor the listed contributions of Nicolai Franzmeier to the publications included in this thesis

Munich, 2nd of June Michael Ewers