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The lateral frontal cortex as a potential substrate of cognitive reserve

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Table of contents

1. Zusammenfassung

Einleitung:

Da die Menschen heutzutage immer älter werden, rücken die Effekte des Alterns, vor allem in Bezug auf das Gedächtnis und auf strukturelle Gehirnveränderungen, immer mehr in den Fokus der Wissenschaft. Diverse Studien haben gezeigt, dass das alternde Gehirn Veränderungen wie bspw. Gehirnatrophie, insbesondere der grauen und weißen Substanz, aufweist. Aufgrund der Abnahme der Gehirnmasse kommt es im Alter zu einer Reduktion der kognitiven Fähigkeiten. Das Ausmaß dieser kognitiven Beeinträchtigung im Alter variiert allerdings stark, was darauf schließen lässt, dass einige Individuen ihre Gedächtnisleistung trotz der Abnahme in der Gehirnintegrität besser aufrechterhalten können als andere. Das Konzept der Reserve, welche als die Fähigkeit definiert ist, altersassoziierte Gehirnveränderungen besser ausgleichen zu können, könnte dieses Phänomen erklären.

Vorherige Studien haben gezeigt, dass Individuen mit höherer schulischer Bildung und höherem IQ die Kognition, sowohl im gesunden Altern als auch bei beginnender Alzheimer Krankheit, besser aufrechterhalten können. Es ist allerdings unklar, welche funktionellen Gehirnveränderungen der Reserve unterliegen, die den protektiven Effekt auf die Gedächtnisleistung im Alter erklären.

Die funktionelle Architektur des Gehirns setzt sich aus mehreren funktionellen Netzwerken zusammen. Hierbei „kommunizieren“ Gehirnregionen innerhalb eines Netzwerkes enger miteinander als Regionen außerhalb des Netzwerkes. Das „kognitive Kontrollnetzwerk“ (CCN) erstreckt sich über fronto-parietale Gehirnregionen und besitzt eine zentrale Rolle bei Prozessen des Gedächtnisses und der Aufmerksamkeit, da es die Aktivität von anderen Netzwerken während diesen kognitiven Prozessen reguliert. Innerhalb dieses Kontrollnetzwerkes stellt eine Region im lateralen Frontalkortex (LFC), das Broca-Areal (BA 44/6), einen zentralen Hub dar, d.h. eine Region, die hochgradig mit anderen Gehirnarealen vernetzt ist.

Um zu messen, wie gut Gehirnregionen miteinander vernetzt sind verwenden wir im Folgenden funktionelle Konnektivität (FK), welche anhand von Korrelationen der Gehirnaktivität zwischen Gehirnarealen, gemessen durch funktionelle MRT im Ruhezustand eines Probanden (rfMRT), quantifiziert werden kann.

Vorstudien konnten zeigen, dass bei Patienten mit der Alzheimer Krankheit (AD) eine höhere rfMRT-gemessene LFC Konnektivität mit geringeren Effekten der Alzheimerpathologie auf die Gedächtnisleitung einherging. Zudem haben bisherige Studien gezeigt, dass die FK des LFC besonders hoch bei Personen mit

hohem IQ und langer schulischer Ausbildung ist. Diese Befunde deuten darauf hin, dass eine hohe LFC-Konnektivität die Reserve erhöhen könnte.

Auch das nicht-pathologische, „normale“ Altern ist mit Gedächtnisverlusten verbunden, wobei Personen mit höherem IQ und längerer Ausbildung häufig eine bessere Gedächtnisperformanz zeigen. Daher stellt sich die Frage, ob potentielle Reservemechanismen, wie die LFC-Konnektivität, mit höherer Gedächtnisperformanz bei Personen mit längerer Ausbildung assoziiert sind.

Daher bestand das Hauptziel dieser Arbeit darin, die Reserve bei älteren, kognitiv gesunden Probanden zu untersuchen. Wir wollten herausfinden, ob eine erhöhte funktionelle Konnektivität des LFC mit protektiven Faktoren wie längerer schulischer Ausbildung einhergeht und ob eine höhere funktionelle Konnektivität des LFC eine bessere Aufrechterhaltung der Gedächtnisleistung, trotz altersbedingter Veränderungen des Gehirns (wie bspw. Hippocampusatrophie), bedingt.

Hypothesen:

1. Eine längere schulische Bildung (als ein approximatives Maß für Kognitive Reserve) ist mit einer höheren globalen funktionellen Konnektivität des LFC während erfolgreichem assoziativem Lernen und Gedächtnisabruf assoziiert.

2. Eine höhere globale funktionelle Konnektivität des LFC im kognitiven Kontrollnetzwerk ist mit einer höheren Performanz während einer Gedächtnisaufgabe, kontrolliert für Hippocampusatrophie, verbunden.

Um diese Hypothesen zu testen haben wir bei älteren kognitiv gesunden Patienten eine fMRT –Untersuchung durchgeführt, während welcher die Probanden eine Gesichter-Namen-Assoziationsaufgabe lösen mussten. Dies erlaubte uns die funktionelle Konnektivität des LFC während des Lernens und des Abrufes von episodischen Gedächtnisinhalten zu bestimmen.

Methoden:

Probanden:

Insgesamt haben wir 37 kognitiv gesunde Probanden eingeschlossen, die in der Gedächtnisambulanz des Institutes für Schlaganfall- und Demenzforschung (ISD) rekrutiert wurden und ein Alter über 60 Jahren (Mittelwert 72.33, SD 5.77) aufwiesen. Weiterhin durften keine Anzeichen für neurologische oder psychiatrische Erkrankungen vorhanden sein. Die Probanden schnitten alle innerhalb von +/- 1.5 SD der alterskorrigierten Normwerte der CERAD-NP-Plus Testbatterie ab und konnten dadurch als kognitiv gesund eingestuft werden.

fMRT Gedächtnisaufgabe:

Die Probanden hatten die Instruktion, während sie im MRT-Gerät lagen eine Gesichter-Namen-Assoziationsaufgabe durchzuführen. Zusammenfassend war die Gedächtnisaufgabe in 14 Lern-Blöcke (Enkodieren), während welcher die Probanden sich ein Gesicht mit zugehörigem Vornamen merken mussten, sowie 14 Gedächtnisabruf-Blöcke (Recognition), in welchen die Probanden zu dem gelernten Gesicht aus zwei darunter stehenden Namen den zugehörigen, richtigen Namen auswählen mussten, unterteilt. Basierend auf korrekt oder falsch erinnerter Namen-Gesichter Paare wurden die Enkodierung der Gesichter-Namen-Paare während des Lernens als erfolgreiches oder inkorrektes Enkodieren klassifiziert. Die Aufgaben-Performanz wurde als die Proportion der Anzahl der erfolgreich abgerufenen Gesichter-Name-Paare in Bezug auf die gesamte Anzahl der Paare gemessen.

Protektive Faktoren und Reserve-Index:

Im Einklang mit vorherigen Studien haben wir die Jahre der schulischen Ausbildung als protektiven Faktor herangezogen.

Gemäß der Definition der Reserve (ein relativ hohes kognitives Leistungsniveau gemessen an dem Grad der Pathologie) haben wir als Reserve-Marker die Gedächtnisleistung, korrigiert für die Hippocampusatrophie, verwendet. In

Anlehnung an die Methode von Reed et al. (2010, Brain) haben wir dazu in einem linearen Regressionsmodel die kompensatorische Kapazität der Probanden gemessen. Die Abweichungen in der Gedächtnisperformanz können teilweise anhand von Pathologie (bspw. Hippocampus-Atrophie), sowie demographischen Maßen (Alter und Geschlecht) erklärt werden. Allerdings verbleibt ein Teil, der durch die genannten Maße nicht erklärbar ist, das Residuum genannt. Das Residuum ist definiert als die Diskrepanz zwischen dem aktuellen Level der Gedächtnisperformanz eines Individuums und dem Level, welches aufgrund von Pathologie und demographischen Maßen vorhergesagt werden kann. Nach dieser Definition haben Individuen mit einer höheren Gedächtnisperformanz als erwartet ein höheres Residuum und damit eine höhere Reserve.

Neuropsychologie:

In der kognitiven Testbatterie CERAD-NP-Plus (48), welche es ermöglicht, eine detaillierte Beurteilung von kortikalen Leistungen und Funktionen sowie des Schweregrads der Beeinträchtigungen und eine Verlaufskontrolle von therapeutischen Maßnahmen zu erfassen, zeigten die Probanden keine Auffälligkeiten.

Statistik:

Psychophysiologische Interaktion (PPI):

Die Psychophysiologische Interaktions-Analyse ist ein statistisches Verfahren, mit welchem man funktionelle Konnektivitätsveränderungen zwischen Gehirnarealen in Abhängigkeit einer Gedächtnisaufgabe untersuchen kann. Wir testeten die Veränderung der funktionellen Konnektivität zwischen dem LFC und restlichen Gehirnarealen während des erfolgreichen Lernens sowie Abrufs von Gesichter-Namenpaaren. Der resultierende PPI-Term repräsentiert das BOLD-Signal des LFC, assoziiert mit erfolgreichem Enkodieren und erfolgreichem Gedächtnisabruf.

In einem ersten Schritt haben wir mittels linearer Regression überprüft, ob eine längere schulische Ausbildung ein größeres Residuum (s.o.) prädiziert. Mit multipler Regression (FK ~ schulische Bildung + Alter + Geschlecht) haben wir dann getestet, ob Probanden mit längerer schulischer Ausbildung eine höhere Aufgaben-assoziierte Gehirnaktivierung zeigen.

Anschließend haben wir unsere Hypothese, ob schulische Bildung mit einer höheren funktionellen Konnektivität des LFC während erfolgreichem Lernen assoziiert ist, überprüft. Dazu haben wir eine voxel-basierte multiple Regressionsanalyse (FK ~ schulische Bildung + Alter + Geschlecht) verwendet.

Als letztes haben wir getestet, ob eine höhere funktionelle Konnektivität des LFC in Bezug auf KR mit einem höheren Residuum assoziiert ist (Kompensatorische Kapazität ~ FK + Alter + Geschlecht).

Ergebnisse:

Während erfolgreichem Enkodieren der Gesichter-Namenpaare konnten wir in fronto-temporalen Gehirnbereichen der linken Hemisphäre eine erhöhte Aktivierung des Gehirns nachweisen. Bei erfolgreichem Gedächtnisabruf haben wir Cluster signifikanter Gehirnaktivierung in beiden Hemisphären, hauptsächlich aber in mittelliniennahen Regionen, gefunden. Ergebnisse unserer PPI-Analyse zeigen, dass während erfolgreichem Enkodieren, sowie während erfolgreichem Abruf, der LFC eine erhöhte funktionelle Konnektivität mit Gehirnarealen, einschließlich temporalen und occipitalen Bereichen, aufweist.

Eine höhere schulische Bildung prädizierte eine erhöhte LFC-Konnektivität, vor allem mit mesiotemporalen Gehirnregionen und während erfolgreichem Enkodieren.

Bei erfolgreichem Abrufen (Recognition) war eine höhere schulische Bildung mit einer erhöhten Konnektivität des LFC mit frontalen Regionen sowie dem Sulcus parieto-occipitalis assoziiert. Eine erhöhte LFC-Konnektivität während der Gedächtnisaufgabe war mit einer erhöhten Gedächtnisperformanz im MRT

Scanner, als auch in neuropsychologischen Tests (CERAD) des freien Abrufs von Wortlisten assoziiert. Dadurch konnten wir zeigen, dass während des Enkodierens und des Abrufs (Recognition) eine höhere LFC-Konnektivität mit einem höheren Residuum der Probanden verbunden ist, diese also eine höhere Reserve besitzen.

Fazit:

Zusammenfassend lässt sich festhalten, dass der LFC (BA 44/6) während verschiedener Gedächtnisaufgaben stark global vernetzt ist. Weiterhin ist während der Gedächtnisaktivierung eine höhere schulische Ausbildung, als Proxy für Reserve, mit einer höheren LFC-Konnektivität assoziiert, was mit einem besserer Gedächtnisleistung relativ zu Alter und Hippocampusatrophie der Probanden einhergeht. Unsere Ergebnisse legen daher nahe, dass eine höhere funktionelle Konnektivität des LFC ein Substrat der Reserve ist und dadurch die Gedächtnisfunktion im Alter stützt, sodass Menschen trotz altersassoziierter Gehirnveränderungen ihre Gedächtnisleistung länger aufrechterhalten können.

2. Abstract

The aging brain undergoes structural changes, such as brain atrophy, especially of the white and grey matter. Due to these changes, the cognition and the memory performance of elderly people decreases, but nevertheless there are considerably large differences in cognitive performance. Why some elderly people are able to maintain their memory performance relatively long despite brain atrophy still remains unclear. A mechanism called reserve is characterized by the phenomenon that a person can preserve a substantial percentage of her cognitive abilities in spite of the presence of age- or disease-related brain changes. It could be shown that in subjects without mental pathology and with similar levels of cognitive performance the degree of reserve (as measured by protective factors such as education or IQ) was associated with the degree of grey matter atrophy. These findings suggest increased compensatory ability in elderly subjects with high reserve, which allows to accrue more age-related grey matter atrophy while still holding up cognitive performance.

Yet, the neural underpinnings of such compensatory effects remain largely unclear. A putative brain network supporting reserve is the cognitive control network (CCN). This particular network is of major importance for the regulation of the activity of other brain networks that are involved in mental processes like memory or attention. Within this control network especially the lateral frontal

cortex (LFC), Brodman-Area 44/6, is a hub-region (a region that is highly connected with other brain regions) with a high degree of functional connectivity (FC, i.e. correlated brain activity) to an array of other brain regions.

In the present study, one of the main goals was the attempt to identify the functional brain mechanisms that underlie reserve in aging subjects, which allow to mitigate the impact of grey matter atrophy on cognitive performance. Specifically, we investigated whether functional MRI assessed LFC connectivity during a memory-task is related to reserve-associated protective factors (IQ, education), and whether high LFC connectivity was associated with better mnestic parameters in relation to the respective level of grey matter atrophy.

The sample consisted of 37 elderly cognitively normal subjects who consulted the memory clinic of the Ludwig-Maximilians-University Munich located at the Institute for Stroke and Dementia Research (ISD). All subjects were over 60 years old and underwent comprehensive neuropsychological testing. To assess brain activation during episodic memory, functional MRI during a face-name association task was acquired. Reserve was operationalized by years of formal education and intelligence quotient (IQ). Grey matter volume was measured within the hippocampus, a key brain region involved in episodic memory, based on volumetric T1 MRI images. Subjects performed a memory task during which

the functional connectivity of the LFC was determined via psychophysiological interaction (PPI) analysis, a useful tool to investigate task-dependent changes in functional connectivity.

Using various linear regression models, we focused on the question if and to what extent the functional LFC connectivity during effective mnestic encoding or recognition may be related to reserve. Reserve was defined as higher educational level and better scores in the memory tasks in relation to the stage of grey matter atrophy.

Our main method was the psychophysiological interaction (PPI) analysis, a useful tool to investigate task-dependent changes in functional connectivity.
The current project uses modern neuroimaging techniques to investigate functional brain mechanisms underlying reserve, which could provide further insight on how the brain manages to sustain higher levels of cognitive abilities and performance despite brain pathology.

Our current findings could show that during memory processes a higher education level was related to higher LFC connectivity, which in turn predicted a

better memory performance relative to the levels of brain atrophy. Higher LFC connectivity may thus be an important factor contributing to reserve.

3. Introduction

3.1 Aging

Since the average life expectancy is continuously rising (1), the effects of aging on brain and on cognition are becoming increasingly relevant. Numerous studies described that aging is linked to major changes of the brain, such as the age-related reduction of the size of the brain, especially of the grey-and white-matter volume (2-4).

At the cognitive level, particularly episodic memory declines in ageing, notably toward age > 70 years (4, 5). The human episodic memory is a neurocognitive ability that allows remembering past and ongoing personal events and daily experiences. Therefore, recognition in episodic memory can be seen as a "mental time travel" through one's past (6). Compared to episodic memory, semantic memory allows remembering general knowledge and facts, but does not include conscious recollection of the experience of the recollected episode.

At the level of age-related brain changes, a global reduction of grey-matter (GM) volume as measured by volumetric MRI has been described. This loss of GM volume is pronounced within the medial temporal lobe and prefrontal cortex (5, 7), brain areas that are crucial for episodic memory.

However, the impact of grey-matter atrophy on memory shows considerable variability among elderly subjects that often exhibit striking discrepancies in the

measured brain changes and the corresponding level of cognitive performance (6). Therefore, the question arises how some elderly people can maintain their memory performance longer than others.

The functional brain mechanisms that support reserve, i.e. the ability to maintain cognition despite brain pathology are, however, still mostly unknown. Identifying brain mechanisms that support reserve was the major goal of the current study.

3.2 Reserve – definition and models

The discrepancy between measured brain pathology and cognitive ability was described early by Katzman et al. (8), who initially discovered a mismatch between brain pathology and cognitive function parameters in patients diagnosed with dementia of the Alzheimer type. Individual's life experiences like educational and intellectual level, and leisure time activities, were found to guard against cognitive decline and were linked to a reduced risk of developing AD dementia (9, 10). Thus, education, IQ and leisure activities (11) are assumed to increase reserve capacity, i.e. the capacity to sustain cognitive functions relatively well with respect to the level of age- or disease related brain changes (see Figure 1).

A core prediction of the reserve concept is that a person with high reserve may not only start with a higher level of cognitive performance before the onset of the disease, but is also able to adequately preserve this level despite age- or disease-related brain changes (9, 12).

In this study we aimed at focusing on reserve and the functional brain changes that may support the concept of reserve upholding memory performance despite brain pathology. Some researchers have posited that reserve may in part stem from modifiable functional brain mechanisms, which are referred to as cognitive reserve (13). Cognitive reserve has been contrasted with a more passive and static concept of reserve, i.e. brain reserve (BR). (14)

Brain reserve

Brain reserve (BR) is defined as a "passive reserve" due to larger brains, more neurons and synapses (15). A typical measure of BR is head circumference, i.e. proxy of premorbid brain volume. Subjects with larger brains show a decreased risk of developing AD dementia (15). The underlying assumption is that subjects with larger brains can tolerate more brain atrophy until reaching a critical threshold of neuronal loss at which cognitive symptoms arise (9, 15). Since functional brain changes (i.e. cognitive reserve) must be interrelated to structural brain changes (i.e. brain reserve), both brain and cognitive reserve

must be related and often been used interchangeably (10). To avoid any confusion, we use the term reserve.

Brain maintenance

A third concept that has been argued to contribute to reserve capacity is brain maintenance (BM), i.e. the persistence of brain integrity throughout one's life (16). The concept focuses on conditions that support the maintenance of structural and functional brain integrity in aging and can be seen as the relative immunity to brain pathology (16).

Figure 1: The concept of reserve

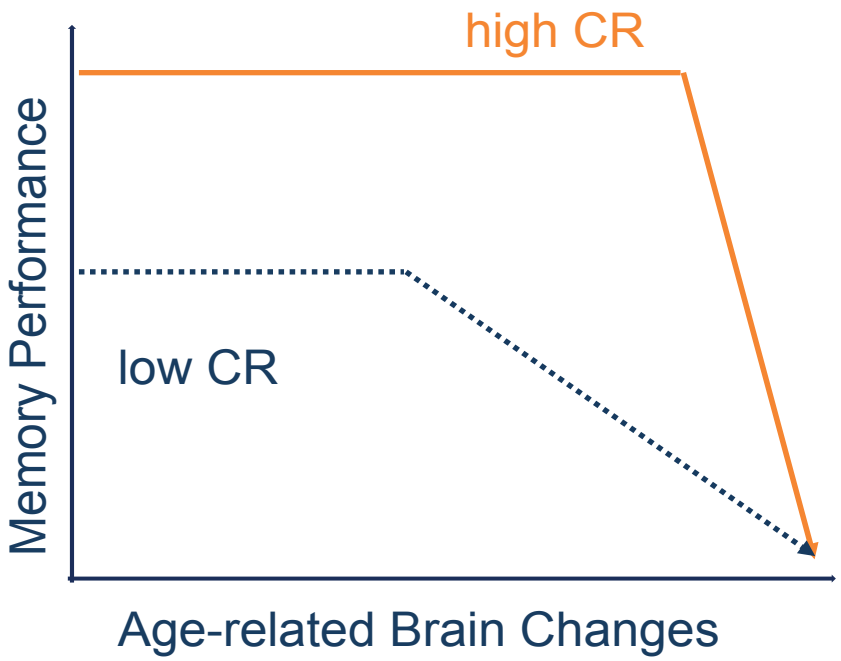

Figure 1: Illustration explaining the concept of reserve – people with high reserve are able to maintain their memory performance relatively well despite age-related brain changes while people with lower reserve develop cognitive decline already in earlier states of age-related brain changes (adapted and modified from 14).

3.3 Functional brain changes

Several functional MRI and PET studies have investigated functional brain changes that may relate to reserve in the face of neuropathology, increased brain atrophy and stronger FDG-PET hypometabolism (17).

Stern et al. proposed that protective factors like educational and intellectual level, are specifically correlated with reserve, i.e. the capacity that relies upon functional brain changes that are presumably modifiable by life time experiences (13). Elderly subjects with higher education were found to have a later onset of memory decline and a lower risk of developing neurodegenerative diseases, such as AD (10, 18), but once the memory impairment appears, the cognitive decline develops more rapidly in subjects with more education in comparison to subjects with lower education (18). Additionally, previous studies showed that elderly subjects with more years of education accumulate more brain pathology, such as FDG-PET hypometabolism, before developing a cognitive decline (19-22). Differences in the brains compensatory capacity of young or old cognitively normal individuals might be explained by the finding that there is a marked inter-individual variance with respect to the processing of memory tasks (23) which may underlie the concept of higher reserve being protective against age-related brain changes (23, 24).

Furthermore, it was found that elderly subjects with preclinical AD showed fronto-parietal hyperactivations during a memory task compared to young healthy subjects (25). This increased neural activation (increased BOLD-signal) during cognitive activity in elderly people with brain pathology or mild cognitive impairment (MCI) in comparison to younger or healthy subjects suggest the fronto-parietal hyperactivation to be compensatory for cognitive decline (26), especially in task-positive regions during memory encoding.

Taken together, all these findings suggest subjects with more years of formal education to develop a reserve capacity during lifetime that enables them to maintain their cognitive performance in ageing relatively well despite age-related brain changes.

3.4 A lateral frontal cortex hub as a potential substrate of reserve

It was recently argued that especially the "cognitive control network" (CCN) (27) that is activated across different cognitive domains (28, 29), may underlie the impact of higher education on cognitive performance in elderly subjects. Due to this "cognitive control network", elderly people can increase their performance during a given task (30, 31).

The frontal lobe is known to be essential for intelligence, memory, language and problem solving. Especially the left frontal cortex (LFC) is an important brain

region that has been associated with higher cognitive control and mental ability (12). The LFC, mainly the Brodman Area 44 of the inferior frontal gyrus that corresponds to the Broca area, is part of the cognitive control network (CCN). Specifically, that LFC region is a hub of the CCN and is globally connected throughout the whole brain. It is assumed to be one of the top 5% of cerebral regions with regard to the number of functional connections to other cerebral regions (31). We refer in the following by "LFC" to this hub region only for the sake of briefness. The CCN consists of flexible hubs (regions that appear to link multiple functional clusters) that regulate different systems such as the visual, limbic or motor system according to a given task (12). Moreover, the CCN is reported to be a network that is crucial for maintaining mental health and due to this being protective against age-related brain changes (12).

In particular, the LFC was reported to be important as a specific control region, due to the finding that individuals with higher global brain connectivity (GBC) of the LFC had greater cognitive control capacity. Regions that show high GBC have an exceedingly high number of connections to the rest of the brain, they are globally connected and thought to use these brain-wide connections as a central mechanism supporting intelligence and cognitive control (31, 32).

Previous studies showed that the LFC as a key region in the CCN has the ability to recollect specific details about past experiences and is involved in retrieval of

episodic memories, increasing the effective performance in cognitively controlled processes (33).

The LFC plays a significant role in numerous mental functions like both working and episodic memory (25), is associated with education and shows a high degree of functional connectivity to other brain regions, facilitating the adaption of brain networks to current task- demands (28).

The LFC modifies its' functional connectivity according to the task and is most active during novel and non-routine tasks. Moreover, it was shown that the LFC-connectivity is related to intelligence (34), higher IQ and memory performance (32). Due to this finding, we hypothesize that higher global LFC functional connectivity may be a potential substrate of reserve. We thus aimed to answer the question whether people with higher reserve may have stronger connections of the LFC to the rest of the brain and if these stronger connections may lead to better memory performance.

4. Theoretical background

4.1BOLD signal & fMRI

Active neurons in the brain need more glucose and oxygen, in response to a demand for information processing, that is rapidly delivered via the blood stream. This process was first shown in 1990 by Ogawa et al. and is called neurovascular coupling (NVC). NVC can be specified as the phenomenon by which the level of neural activity can be estimated by the corresponding level of cerebral blood flow (CBF) (35). The *Blood-oxygen-level-dependent (BOLD) signal* is defined as the magnetic resonance imaging (MRI) contrast of blood deoxyhemoglobin. The change in the oxy- to deoxyhemoglobin-ratio, for example the surplus on local blood oxygen of an active brain area, can be measured with MRI.

Functional MRI (fMRI) gauges brain activity by capturing changes in blood oxygenation and blood flow that emerge as a parameter of neural activity. Since fMRI is a non-invasive examination which does not use radiation and has relatively good spatial and temporal resolution, it shows several advantages in comparison to for example positron emission tomography (PET).

With fMRI we can investigate changes in the brains connectivity and describe the relationship between neuronal activity patterns (36) of an a priori defined seed region and other spatially separated brain regions. The correlated brain activity

of different, functionally linked brain regions is known as functional connectivity (FC).

FC refers to the temporal correlation of the BOLD signal between spatially remote brain regions (37), while structural connectivity refers to directly connected brain regions.

4.2 Resting-State fMRI

Several studies from the past years introduced a method to examine the FC between spatially separated cerebral regions during rest. This approach of resting-state fMRI connectivity (36) is employed to assess the patterns functional communication of different regions of the brain. The level of this resting state brain activity is measured by placing subjects into the scanner and instructing them to close their eyes, to let their mind wander without focusing on special thoughts and to relax, without falling asleep. If the time-series of two spatially separated brain regions show a high correlation, a high level of FC between these brain regions can be assumed. For this technique (RS fMRI) low frequency oscillations (0.01-0.1 HZ) are used.

In 1997, Biswal et al.(38) were the first who could prove that there is a close association between these patterns of spontaneous neural activation of different regions of the brain, suggesting an ongoing information flow and FC

between these regions during rest. Later on, several studies replicated these results, presenting more brain networks where high levels of FC could be found during resting state.

It was shown that during this state a group of functionally and closely linked sub-networks could be detected, which were called resting-state networks. These intrinsic brain networks are spatially separated but during resting state exhibit a high level of FC. One of the most interesting of the eight identified RS networks is the default-mode network (DMN). This network comprises the medial frontal, inferior parietal and temporal regions of the brain as well as the precuneus (36). In comparison to other RS-networks the DMN shows an increase of neural activity during rest and a decrease during task. Moreover, activity and connectivity of the DMN are known to be linked to human cognition and emotional processing and therefore the DMN is of special interest, being related to cognitive dysfunctions, neurological and psychiatric disorders (39), such as a decreased FC of the DMN in AD patients.

Additionally, Tavor et al. could prove that the continuing interaction of the functional networks shows a good match between resting-state and task (40).

4.3 Task based fMRI

To study the brain changes during task processing, fMRI based on BOLD techniques has been widely used (41). In task-based fMRI, subjects perform a given task while lying in the scanner. Thereby, one can determine which brain areas are activated during that task. The differences in brain activation are measured based on regional BOLD signal changes between task and RS (42).

On this basis, a block-model can be created where BOLD images of the whole brain are collected every 1-3 seconds and the BOLD signal can thus be associated with the cognitive task (43). The general linear model (GLM) is then employed to perform the task analysis. For constructing the design matrix for the GLM, the regressor variables are based on the canonical hemodynamic response function (HRF) (see figure 2a).

For task fMRI, it could be shown that within the DMN or "task-negative" networks there is a negative BOLD response (deactivation). On the contrary, task-positive networks get activated during performance tasks (44). Moreover, stronger increases in neural activity during tasks proved to be associated with higher degrees of connectivity to the task-positive brain networks (44).

4.4 Psychophysiological Interaction analysis (PPI)

To measure the changes of connectivity pattern of the LFC during memory processing, we used the Psychophysiological Interaction (PPI) analysis, a useful tool to assess task-specific changes of different brain regions with respect to their FC.

Friston et al. introduced the PPI technique as a method to analyze functional connectivity between brain regions during specific task-demands (45). PPIs are especially suitable to assess how activity in one brain area may predict the activity in another brain area (45).

With the PPI analysis one can identify voxels in the brain in which activity is related to the activity of a specific cerebral region (region of interest = ROI) during a given cognitive task condition. The first step is identifying the seed ROI and extracting the time course of activity from that ROI mask. The condition-specific FC fluctuations between different brain areas (46), the interaction between the task and the ROI BOLD time series, controlled for the main effects, and task related activation were tested in the GLM (see Figure 2b).

Figure 2a: canonical hemodynamic response function (HRF)

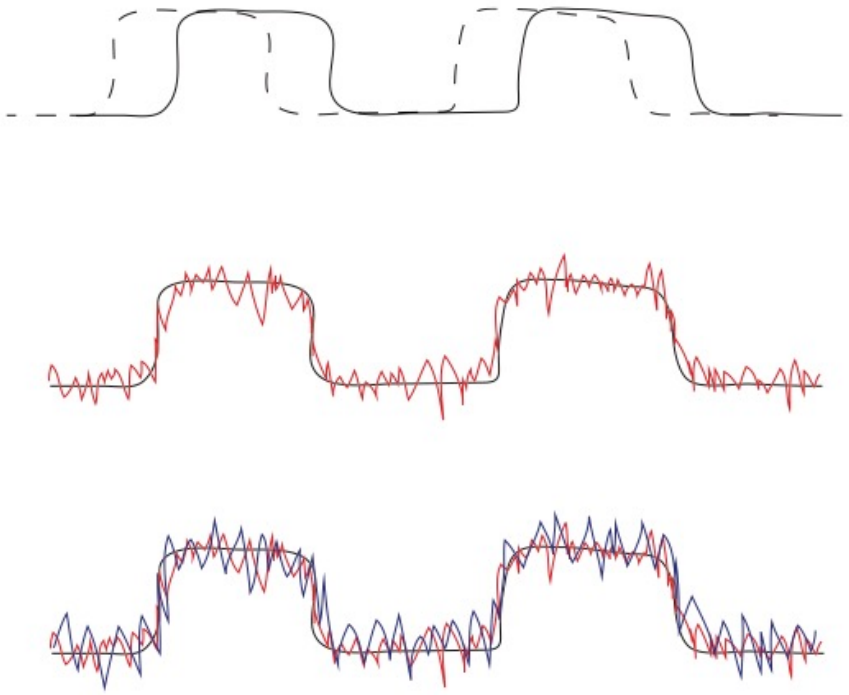

Figure 2a: The illustration shows the association of the BOLD-signal depicted by the hemodynamic-response function (HRF) and the level of neural activity. The HRF represents the change in blood flow that can be attributed to the metabolic demands due to neuronal activity.

Figure 2b: PPI analysis

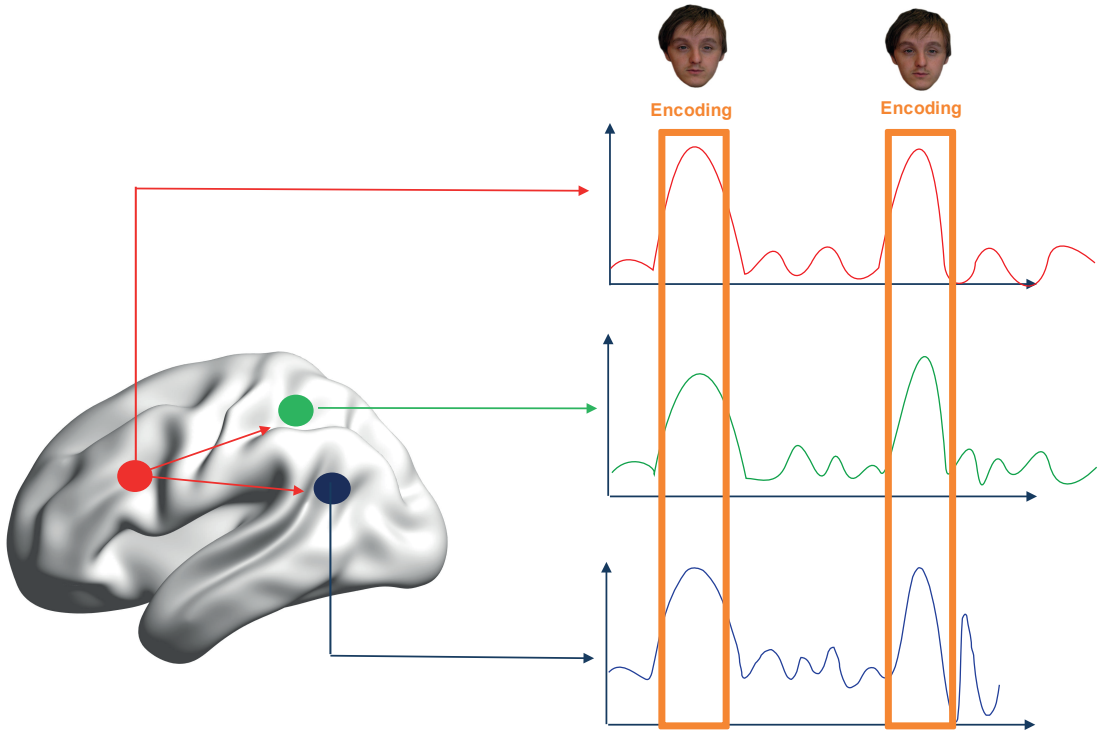

Figure 2b: The execution of PPI analysis which was employed to evaluate. LFC connectivity in the course the processing of mnestic tasks (*encoding* and *recognition*). The illustration shows the calculated LFC time course which in step #1 was deconvolved and multiplied with the task-specific regressor variable (*correct encoding* or *correct recognition*) and then in step #2 reconvolved with a canonical HRF resulting in the PPI interaction terms. Subsequently, for each subject the contrasts *'correct encoding > 0'* and *'correct recognition > 0'* were modeled to compute the degree of connectivity of the LFC in the course of *correct encoding* and *correct recognition*. For the occipital pole and the precuneus, our two control ROIs, equivalent analyses were performed.

Applied to the current study, we used a PPI to assess how the LFC connectivity pattern changes during memory processing in a sample of cognitively normal elderly. It was hypothesized that a greater task-associated connectivity of the LFC during memory encoding and recall corresponds to higher levels of reserve

proxies (e.g. years of education), making it a potential brain area supporting the reserve concept.

5. Methods

The study on which the present thesis is based, was part of a larger research project on the substrate of reserve, conducted at the ISD. For more details on the methods employed, especially the processing of MRI signals, the technical equipment, the task design, and the statistical analyses, please see references 73 and 77.

5.1 Participants

The sample of this study consisted of patients who consulted the memory outpatient clinic of the University Hospital of Munich (Ludwigs-Maximilians-Universität) located at the Institute for Stroke and Dementia Research (ISD). To be eligible for inclusion subjects had to be older than 60 years of age and classified as cognitively normal as measured by the test scores of the CERAD-NP-Plus battery described below. Reasons for exclusion were: the presence of depressive symptoms (as defined by a score above 18 on the geriatric depression scale (47)), indicators of other acute or lifetime neurological and/or psychiatric disorders, MRI contraindications, diabetes mellitus, a premorbid IQ < 85, and any lifetime-history of alcohol or drug abuse. In addition, there were some subjects which we had to exclude because of incomplete fMRI task data or missing

neuropsychological data, or which had a skull deformation due to birth defect. Overall, a total of 37 cognitively healthy subjects could be included in this study.

For the assessment of neuropsychological parameters, the CERAD-NP-Plus battery was used, a well-known testing system for evaluating the cognitive abilities of elderly persons with and without mental impairment (48). To be included in this study the individual scores had to fall in the range of 1,5 SDs of the norms of all subtests of the CERAD-NP-Plus battery, adjusted for education, age, and gender. In line with previous studies (19), we used the educational level (operationalized as years of formal education) as a surrogate marker of reserve. The subjects were assessed during two sessions. On the first day, they underwent physical and neuropsychological examination. On the second day the subjects returned for MRI acquisition, including face-name association task fMRI.

5.2 Ethics, protocol approval, and patient consent

This study was approved by the local ethics committee of the Ludwigs-Maximilians-Universität Munich (LMU). Each participant was informed in detail by a study physician and signed a written declaration of consent prior to the study. The study procedures were performed in concordance with the 164 Helsinki Declaration and its later amendments.

5.3 fMRI Associative Memory Task Design

An event-associated mixed block and design was employed which was adjusted and modified based on previously published fMRI paradigms (49, 50). In brief, the task uses a face-name associative memory paradigm that can assess memory encoding as well as memory recall. As stimuli, images of faces unknown to the scanned individual were used and coupled with the presentation of Christian names. These images were obtained from the 'Glasgow Unfamiliar Face Database' (http://www.abdnfacelab.com) and were chosen on the basis of direct expression, Caucasian ethnicity, neutral look, and no visible jewellery. The Christian names were acquired from the 'Leipzig Corpora Collection' (http://corpora.informatik.uni-leipzig.de) and were selected on the basis of a log-transformed frequency, with a range of five or six letters. In total our subjects had to view 112 different faces (50:50, M: F) and 168 names (50:50, M: F). The task was composed of 14 blocks of face-name encoding and recall where each face-name pair was presented for 5 seconds. Following a randomized inter-trial-interval (ITI) of 1500 – 3000ms, the next pair was shown.

During an encoding block, the subjects were presented 8 faces paired with a name below. In the subsequent recall block, the faces were presented again together with a choice of both names—i.e. the name actually presented vs. a distractor—and subjects were asked to choose the correct name, i.e. the one

that was originally shown with the respective image. In 50% of the recall blocks, the distractor consisted of a new Christian name, while in the remaining 50% a name was presented which had already been shown together with another face. In the recall blocks accurate responses were marked as successful recognition, inaccurate responses as incorrect recognition. Depending on the responses during the recognition block, the previous trials were rated either as accurate encoding or inaccurate encoding. Accordingly, the overall performance of a subject was determined as the percentage of face-name pairs correctly recalled compared to the total number of stimuli presented. In total, there were 14 blocks of encoding and 14 blocks of recall. By employing a similar task on a laptop computer, all subjects underwent a task-specific training session prior to the real fMRI assessment. During this training no answers and no feedback were given. The task was presented via a vision goggle system that allows for individual eyesight correction, responses were recorded using response grips (www.nordicneurolab.com).

5.4 MRI data acquisition

The MRI scans were conducted on a Siemens Verio 3T MRI scanner and a 12-channel head coil. A initial high-resolution structural image was generated by employing a T1-weighted MPRAGE sequence (TR/TE = 1750/2.52 ms, Flip angle

= 9°) with anisotropic voxel size of 1-mm. Task-fMRI was obtained using a T2*-weighted echo-planar imaging (EPI) pulse sequence (TR/TE = 2000/30 ms, flip angle 90 degrees) with an in-plane resolution of 3.4mm, a slice thickness of 3mm and a 1-mm interslice gap. Task fMRI EPIs were recorded divided in 3 runs with the first two runs comprising 320 volumes each, and the third run 260 volumes. The total task-fMRI thus comprised 900 volumes which took approximately 30 minutes to acquire. Before the acquisition of task fMRI data, gradient-echo fieldmaps were registered to control for susceptibility artefacts in T2*-weighted images during preprocessing of fMRI data.

5.5 Preprocessing of MRI data

Structural MRI data were preprocessed with the use of Statistical Parametric Mapping (SPM) 12 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK). In a first analysis, SPM's new segment approach (51) was used to subdivide T1-weighted MPRAGE images into probabilistic maps of cerebrospinal fluid (CSF), white matter (WM), and gray matter (GM). Based on a high-dimensional diffeomorphic registration algorithm, spatial normalization parameters were assessed to warp all individual GM map to an average group-specific GM template which was calculated through an iterative procedure, provided by the SPM DARTEL toolbox (52). The resulting group-specific GM pattern was then

affine registered to a T1 template in MNI space. To normalize a subjects GM image, the non-linear DARTEL flow-fields were combined with the affine transformation parameters and employed on the segmented GM maps. In order to generate a GM mask to restrict the following fMRI analyses to the cortex, these spatially normalized GM maps were subsequently averaged and binarized at a probability value > 0.3.

For preprocessing the fMRI task data, gradient-echo fieldmaps were employed to correct all EPI images interleaved slice-timing acquisition order, motion artifacts, and possible inhomogeneities of the magnetic field using the. In fact, none of the individual motion parameters fell out of the range of 2mm translations or 2° rotations. By applying the combined non-linear DARTEL flow-fields and the affine transformation parameters, the EPI images were subsequently co-registered to the high-resolution T1-weighted images and then normalized to MNI space. To minimize spatial bias, the EPIs were finally smoothed using an 8 mm full width at half maximum Gaussian kernel.

5.6 Hippocampal volume assessment

Hippocampus volume was assessed by employing a well-established and fully automated protocol (53) which has demonstrated its ability to lead to results that are highly similar to the complex manual hippocampal segmentation. For

this protocol, the DARTEL flow-fields obtained during the spatial normalization process were used to normalize the individual grey matter maps to MNI space and then smoothed with an 8mm full width at half maximum Gaussian kernel. To maintain the volume of the images during spatial normalization, Jacobian modulation was applied., After that, the images were masked with a bilateral hippocampus mask drawn from the 'Automatic Anatomic Labeling Atlas' (54) and thus the bilateral hippocampal volume could be extracted.

5.7 Task-fMRI analysis

A fixed-effects general linear model (GLM) was used to analyze task-fMRI data on a subject-level. The GLM is a well-established approach that can be used to make statistical comparisons ranging from unpaired t-tests to linear regression (55). For each subject, the GLM design matrix was formed by including 6 condition regressor variables (*accurate encoding, incorrect encoding, accurate recognition, incorrect recognition, instructions encoding, instructions recognition*) plus 6 movement regressor variables that were derived during EPI preprocessing (3 rotations & 3 translations estimated during EPI preprocessing) to control for motion-induced bias. Each condition was convolved with a canonical hemodynamic response function (HRF) complemented with a

multivariate Taylor expansion accounting for the temporal and dispersion derivatives.

In each measurement a separate covariate—which was time-locked to the stimulus event—was used to model task-related brain activation. Depending on whether the subjects correctly or incorrectly recognized the face-name pair during the subsequent forced-choice recognition test block, the recall trials were coded as events of *successful* or *incorrect recognition performance*. The overall task performance of a subject was defined as the percentage of correctly recognized face-name pairs in relation to the total number of face-name pairs presented.

5.8 Definition of LFC and control regions of interest (ROIs)

For the identification of brain regions that are linked to cognitive control during task-fMRI, the web-based tool NeuroSynth was administered to perform a meta-analysis of published task-fMRI studies. NeuroSynth (http://www.neurosynth.org/) is a meta-analysis tool allowing an entirely automated extraction of coordinates of cerebral activation derived from previous fMRI studies.

Compendiously, the strength of the relation between a specific search term and the corresponding cerebral activation is computed across several studies, thus

resulting in a probabilistic map of the proportion of brain activation that is related to the respective search term (56). As of September 14, 2015, a total of 428 task-fMRI studies could be detected by utilizing the term “cognitive control” (56). Subsequently, the z-score map derived from this procedure was thresholded at $p < 0.01$ (FDR-corrected). Through a visual control, it could be verified that the distribution of brain regions exhibiting high z-scores primarily matched the fronto-parietal cognitive control network, including the LFC. This was taken as evidence that the targeted brain activation locations have been identified. The peak voxel coordinate was sustained within a cluster centered within the LFC, specifically Brodman area 6 (MNI: x = -42, y = 6, z = 28). Centered at that coordinate, an 8-mm spherical binary ROI was constructed and utilized as the seed region for the ensuing PPI analysis (17).

For this study, control ROIs were located in the occipital pole (MNI: x = -19, y = -102, z = -3), and in the precuneus (MNI: x=7, y=-60, z=21). The occipital pole was used because it hosts a unimodal sensory region, which—other than the LFC—does not play a role in higher cognition. On the other hand, the precuneus was chosen for its significance as a functional hub region. Similar to the LFC, the precuneus is universally connected to a wide range of other brain regions (31) and deeply involved in complex cognitive functions including memory (57) .

5.9 Psychophysiological Interaction (PPI) analysis

With the Psychophysiological Interactions (PPI), a seed-based analysis, we aimed to identify changes in the correlation between brain regions under experimental change. In our case this would mean how the interaction between the LFC and the other brain regions changes during the processing of memory tasks. The PPI is a useful tool to evaluate the interaction modes of different brain regions depending on specific tasks and can be seen as an index of condition-specific brain connectivity in task fMRI (task-related connectivity).

First level analysis: We used a generalized PPI (gPPI) in this sample. It was set up to be able to automatically incorporate more than two task conditions in one PPI model. Thus, in our cognitively normal subjects, the context-dependent functional connectivity of the LFC with all other brain voxels during *successful encoding* or *successful recognition* could be computed.

The generalized form of PPIs has been shown to be more sensitive and specific than the standard PPI form as it allows independent modeling of different conditions (58). To accomplish the gPPI, the freely obtainable 'gPPI Toolbox' (http://www.nitrc.org/projects/gppi) was employed. Following a protocol recommended by Gitelman et al. (59), the time course that was deconvolved with a canonical HRF was extracted to transform the BOLD signal into a neural signal. Subsequently, the LFC was pinpointed as a sphere of 8mm around the

peak activation for *successful encoding* greater than *successful recognition*. In a next step, we multiplied the deconvolved LFC time course with the task-specific regression variable (*accurate encoding* vs. *accurate recognition*) and then reconvolved it with a canonical HRF to form the interaction-terms required for the gPPI analysis. Hence, for each subject the resulting PPI terms represent the BOLD signal of the LFC that is associated with *successful encoding* or *successful recognition.*

The gPPI produces a design matrix that contains three different groups of columns per pass: (1) task regressors, generated by combining the task blocks with the canonical HRF; (2) the LFC BOLD signal; and (3) the PPI regressor variables for successful *encoding and successful recognition* which are computed by (a) a separate multiplication with the LFC-BOLD signal, followed by (b) a convolvation with the canonical HRF.

In accordance with our first level GLM analysis, 9 regressors were employed to model the BOLD signal per pass: (1) Encode Correct, (2) Encode Incorrect, (3) Recognition Correct, (4) Recognition Incorrect, (5,6) Instructions for Encode and Recognition, (7,8) Interaction terms for PPIs, (9) time course of the LFC; (10,11) motion parameters. After generating this design matrix, the gPPI Toolbox forms an estimate of the model parameters and calculates linear contrasts. Applying this procedure, the connectivity of the LFC during *correct encoding* and *correct*

recognition was evaluated by modeling these PPI contrasts *successful encoding>0* and *successful recognition>0* for every subject. For the two control ROIs, the precuneus and the occipital pole, identical analyses were carried out.

5.10 Assessment of protective factors and reserve

We assessed reserve based on a previous study (60) that has defined it as the difference between an individuals' factual degree of mnestic performance and the level of performance that can be predicted based on brain pathology and demographic measures (i.e. age, gender & ApoE genotype). According to this definition, those individuals whose given memory performance proves to exceed the expected level of performance that can be deduced from brain pathology and demographics, have a higher reserve (see Figure 3).

A widely used alternative for the evaluation of an individual's level of reserve—which is congruent with numerous previous studies ((61); (19); (18); (62); (63); (9); (64); (65))—is the use of the parameter educational level (i.e. years of formal education) as a readily accessible proxy measure.

Figure 3: Memory performance (adapted from (77)[1])

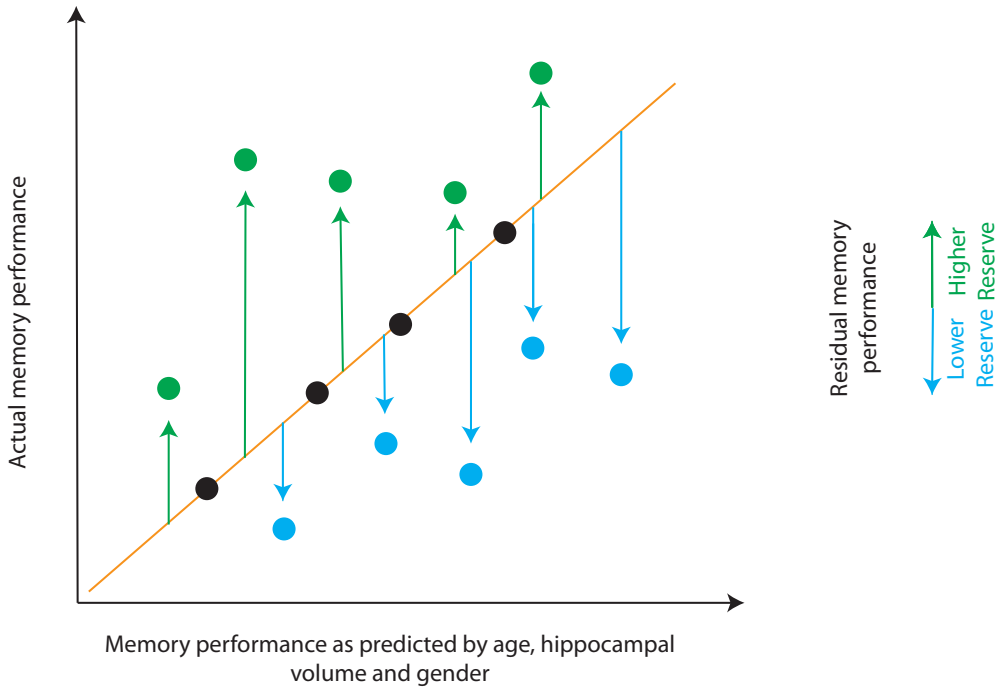

Figure 3: The illustration shows the principle underlying our conceptualization of reserve. The scores of mnestic performance actually measured are plotted against the mnestic performance that could be expected with respect to age, gender, and hippocampal volume. In subjects with high reserve (indicated by green circles), the mnestic performance was better than predicted, while in subjects with lower reserve (indicated by blue circles) the mnestic performance was lower than predicted.

As predictors of memory performance, we used an estimate of brain pathology (hippocampal volume), as well as demographic measures (age, gender & ApoE genotype), similar to an approach previously described (60). The residual variance of episodic memory that is not explained by hippocampal volume, age

[1] The final publication is available at IOS Press through http://dx.doi.org/10.3233/JAD-170360. The permission to reprint this figure was granted by the publisher.

or gender can thus be seen as a scalar indicator of reserve. For computing this residual variance of memory, we used multiple regression analysis after regressing out the amount of variance that can be attributed to hippocampal volume, age and gender.

Reserve was assessed on two different measures of episodic memory. Firstly, we used the mean accuracy in the fMRI memory task where we additionally regressed out variance explained by mean reaction time. This was used as a measure of reserve specific to our fMRI memory task. Secondly, the word list learning score subtest of the CERAD-NP-Plus test battery was used as a memory measure to assess reserve independent of the fMRI memory task paradigm (out-of-scanner-performance). After applying linear regression to fMRI task accuracy and the word list learning score, the residual variances (henceforth referred to as: *fMRI task accuracy – residuals and word list learning – residuals)* were saved and used as estimates of reserve.

6. Aim & Hypotheses

Our aim was to test whether the functional connectivity of the LFC during episodic memory underlies reserve.

The first hypothesis (H1) was if education (as a protective factor related to reserve) is related to higher LFC functional connectivity during successful episodic memory processing. It was tested if a higher level of education (operationalized as number of years of formal education) is related to greater task efficiency (i.e. performance) during memory processing.

Next, we disposed the hypothesis (H2) that greater task-related connectivity of the LFC is a contributing factor to higher reserve.

Finally, we assessed if education is also associated with higher graph-theoretical measures such as the degree of the LFC during correct encoding and correct recognition.

7. Statistical analysis

In a first step we examined via linear regression analysis whether a higher educational level predicted higher reserve. Since we had a clear hypothesis about the directionality between reserve and memory performance (people with higher reserve would have greater memory performance), a one-tailed p-threshold could be applied for classifying an association as statistically significant.

To assess fMRI brain activation during task, the contrasts *accurate encoding > incorrect encoding* and *accurate recognition > incorrect recognition*—both derived at the subject level—were analyzed. Therefore, we used voxel-wise t-tests > 0, controlling for age and gender in each contrast.

Via voxel-wise multiple regression, we assessed, whether subjects with higher education showed higher task-related brain activation in the above-mentioned contrasts, applying an uncorrected voxel threshold of α = 0.001 and a FWE corrected cluster threshold of α = 0.05, controlling for age and gender.

The question whether educational level is related to greater task efficiency during memory processing was tested through a multiple regression analysis. In this analysis, task performance was set as the dependent variable and educational level as the independent variable.

To examine the second hypothesis, whether education is related to a higher degree of the LFC during memory processing, we investigated the connectivity between the LFC and the remaining brain regions during *accurate encoding* and *accurate recognition*. The functional LFC connectivity during the two contrasts was assessed by employing a t-test > 0 on the subject-level contrasts *PPI accurate encoding > 0* and *PPI accurate recognition > 0,* derived during the gPPI analysis. We then applied a voxel-threshold of α = 0.01 FWE, adjusted at the cluster level at α = 0.05 for all voxel-wise functional connectivity analyses. Control variables consisted of gender, age, and task accuracy. These voxel-wise analyses were conducted using SPM12, each confined to a group specific grey matter (GM) mask.

To examine our hypothesis that education is associated with greater functional LFC connectivity during *accurate memory encoding*, we used a voxel-wise multiple regression analysis. The dependent variable here was *PPI successful encoding > 0* maps with the subject level while the independent variable was education, controlling for age and gender. To ensure that the associations between reserve (as measured by education) and LFC functional connectivity were not driven by grey matter differences, the biological parametric mapping toolbox (66) was used to control for the grey matter volume in a voxel-wise manner. In brief, this toolbox implements the inclusion of voxel-wise imaging

covariates in the framework of SPM. For the current analysis, the modulated GM maps of our subjects were smoothed and normalized and entered as covariate images, additionally reducing the sensitivity to outliers by applying a robust regression model (67). Equivalent analyses as described above were conducted for *PPI successful recognition* > 0. For the present analyses, we used a voxel threshold of α= 0.01, but remained the FWE cluster correction at α= 0.05. We saved all clusters that showed a significant effect of education on the LFC connectivity during *successful encoding/rec*ognition as binary ROIs to extract the mean functional connectivity value (henceforth referred to as *education-related LFC connectivity – successful encoding/recognition*) from the corresponding subject level PPI maps.

Next, we extracted the mean value from the subject level PPI maps to then test the hypothesis, that a higher degree of education-linked connectivity of the LFC is related to a better residualized memory performance. In order to do this, we performed a multiple regression analysis with *fMRI task performance* as criterion variable and *education-related LFC-connectivity – successful encoding/recognition* as predictor variable. In this analysis, the variables age and gender were included as control variables. To investigate, whether higher *education-related LFC-connectivity* showed a generalized association with resilience independent of the fMRI memory task, we applied multiple linear

regression using *word list learning – residuals* (for the out-of-scanner-performance) as dependent variable and *education-related LFC-connectivity – correct encoding/recognition* as predictor.

For examining the hypothesis that a higher education-associated connectivity of the LFC is correlated to greater residualized memory performance, the one-tailed p-threshold was set at an $\alpha = 0.05$. The open source statistical software package *R* (68) was used to calculate the multiple linear regression models, where the model assumptions (skewness, kurtosis, heteroscedasticity) were checked with the gvlma function provided by this program. No significant ($\alpha = 0.05$) violations of these assumptions were detected for all models reported.

8. Results

Group demographics and details on neuropsychological characteristics are shown in table 1. The individual scores in the subtest 'word list learning' of the CERAD-NP-Plus battery were correlated with fMRI task accuracy.

Table 1: Group demographics and neuropsychological characteristics:

	Cognitively normal subjects (N=37)
Age (M/SD)	72.33 / 5.77
Gender (m/f)	12 / 25
Years of Education (M/SD)	13.51 / 3.02
fMRI task: Reaction Time (M/SD)	2254.39 / 316.09
fMRI task: Accuracy (M/SD)	0.79 / 0.06
MMSE score (M/SD)	0.37 / 0.99
Word list learning score (M/SD)	22.95 / 2.76
Geriatric depression score (M/SD)	4.46 4.35

8.1 Task-fMRI brain activation during successful encoding

In a first step active brain regions during memory processing were identified related to *successful encoding* > *incorrect encoding*. We found significant clusters

primarily in fronto-temporal brain areas of the left hemisphere (see Figure 4A) and could prove that the LFC is activated during *successful encoding*. See table 2 for more details about statistics and anatomical locations of significant clusters.

Table 2: Local maxima of significant clusters associated with successful encoding

			MNI Coordinates		
Region Name	***Extent***	***t-value***	***x***	***y***	***z***
R Calcarine Gyrus	2367	6.8063	13.5	-91.5	15
L Lingual Gyrus	2367	5.8242	-12	-90	-7.5
L Fusiform Gyrus	2367	4.947	-31.5	-84	-10.5
L IFG (p. Triangularis)	1750	5.8818	-43.5	15	25.5
L Middle Frontal Gyrus	1750	3.9376	-40.5	7.5	46.5
L Middle Frontal Gyrus	1750	3.4286	-37.5	34.5	25.5
R Caudate Nucleus	292	5.5834	22.5	4.5	22.5
L Precentral Gyrus	604	5.0787	-39	-12	42
L Postcentral Gyrus	604	4.6891	-55.5	-10.5	28.5
L Middle Temporal Gyrus	507	4.9735	-55.5	-43.5	-7.5
L Middle Temporal Gyrus	507	4.6466	-58.5	-34.5	12
L Middle Occipital Gyrus	496	4.7605	-27	-70.5	34.5
L Middle Frontal Gyrus	327	4.704	-24	18	43.5
L Superior Frontal Gyrus	650	4.6963	-18	57	24
L Superior Frontal Gyrus	650	4.5152	-13.5	34.5	49.5
L Middle Frontal Gyrus	387	4.4211	-36	40.5	6

In contrast, during *successful recognition* > *incorrect recognition* we discovered bilateral clusters of significant cerebral activation, predominantly in the mediofrontal, posterior-cingulate, as well as the occipital, inferior temporal cortex and the hippocampus (Figure 4). Details about cluster statistics and locations are shown in table 3.

Table 3: Local maxima of significant clusters associated with successful recognition

			MNI Coordinates		
Region Name	***Extent***	***t-value***	***x***	***y***	***z***
R Middle Temporal Gyrus	813	6.6861	42	-70.5	3
L Mid Orbital Gyrus	2527	6.5606	-7.5	46.5	-1.5
R Mid Orbital Gyrus	2527	5.1411	13.5	49.5	-1.5
R Cerebellum (VI)	2748	5.9157	15	-85.5	-13.5
L Cerebellum (Crus 1)	2748	5.5557	-7.5	-85.5	-15
L Fusiform Gyrus	2748	5.2846	-28.5	-66	-4.5
L Hippocampus	271	5.0363	-25.5	-18	-12
R Inferior Temporal Gyrus	292	4.9983	51	-51	-19.5
R Putamen	322	4.9727	33	-13.5	-1.5
R Insula Lobe	322	4.7303	40.5	9	1.5
R Superior Temporal Gyrus	396	4.7121	52.5	-7.5	7.5
R Cuneus	522	4.3585	12	-85.5	27

Figure 4: Brain activation during successful encoding and successful recognition (adapted from 77[2])

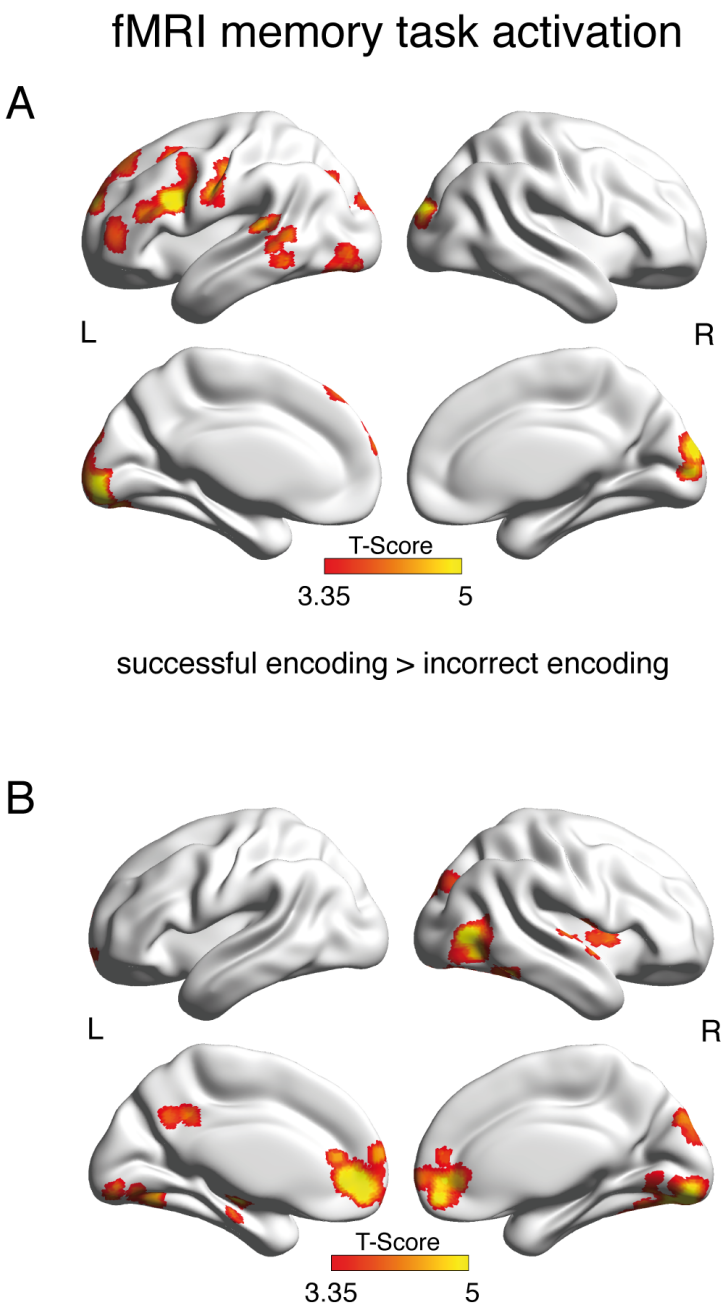

Figure 4: This illustration shows see brain areas where significant activation patterns could be detected in the GLM analysis of the fMRI memory task. Those clusters were highlighted where cerebral activity was significantly higher during accurate versus inaccurate encoding (A) or recognition (B) with a voxel threshold set at an α= 0.001 and a FWE corrected cluster threshold at an α = 0.05.

[2] The final publication is available at IOS Press through http://dx.doi.org/10.3233/JAD-170360. The permission to reprint this figure was granted by the publisher.

We further tested whether educational level (= years of education) was associated with higher levels of cerebral activity. With regard to the *correct encoding* > *incorrect encoding* or *correct recognition* > *incorrect recognition* conditions we found no significant clusters. Also, when applying a more liberal voxel-threshold of $\alpha = 0.01$, at a FWE cluster correction of $\alpha = 0.05$, we found no significant results, indicating that a higher educational level is not related to the degree of brain activity during a memory task.

A further test addressed the question if the average activation level of the LFC-ROI during task-related fMRI (*correct recognition* > *incorrect recognition* and *correct encoding* > *incorrect encoding*) was associated to higher levels of residualized memory. As a matter of fact, no significant association could be detected.

8.2 Reserve, LFC and residualized memory performance

We could show that the LFC entertains global connections during memory processing, both during *accurate encoding* and *accurate recognition,* as shown in Figure 5, left panel, which could be revealed by the use of voxel-wise t-tests on the LFC connectivity.

In a next step, we tested our first hypothesis that higher educational levels are correlated with higher rates of task-related functional LFC connectivity. During

accurate encoding our regression analysis revealed that subjects with greater education showed higher LFC connectivity, especially to inferior frontal, occipital as well as to inferior temporal brain areas. Conversely, during *successful recognition* a higher educational level was associated with greater connectivity of the LFC to the right parieto-occipital sulcus and left inferior frontal gyrus. Figure 5 illustrates the voxel-wise pattern of LFC connectivity, as well as education-related LFC connectivity for successful encoding (Fig 5A, right panel) and successful recognition (Fig 5B, right panel), controlled for age and gender.

In contrast to these results, a higher educational level was **not** significantly related to an increased task-related connectivity of the occipital pole and precuneus regions, our two control ROIs, which can be viewed as indicative of the LFC specificity of the present findings.

Figure 5: LFC connectivity during memory processing (adapted from 77[3])

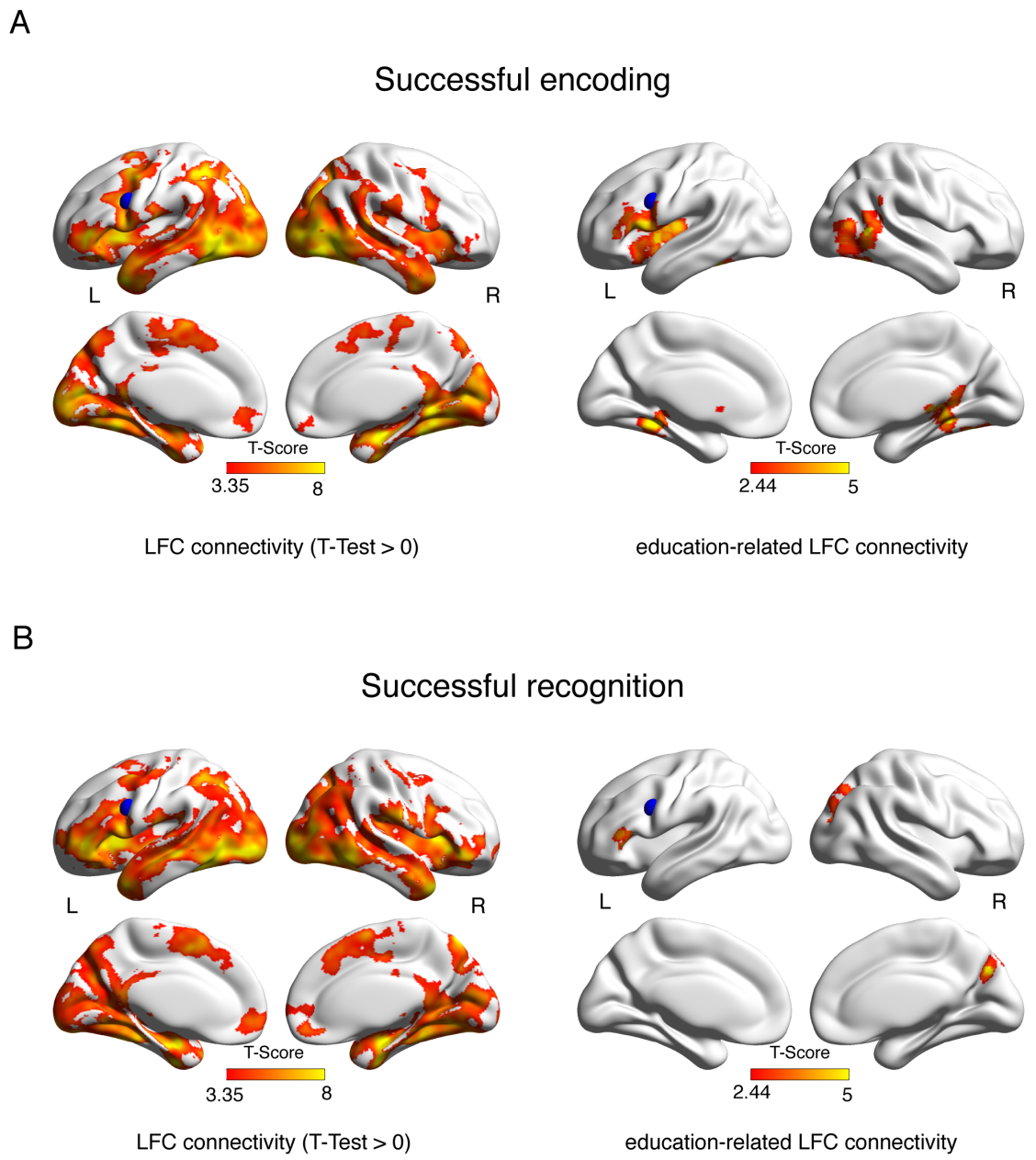

Figure 5: The illustration shows the results of the PPI analysis and the relationship between LFC-connectivity and educational level. In part A clusters of significant LFC connectivity (indicated in blue) during correct encoding are highlighted, while part B shows the respective clusters during successful recognition. Both clusters were computed by voxel-wise *t*-tests against zero, with a voxel threshold of $\alpha = 0.001$ and a FWE-corrected cluster threshold of $\alpha = 0.05$.

[3] The final publication is available at IOS Press through http://dx.doi.org/10.3233/JAD-170360. The permission to reprint this figure was granted by the publisher.

Our second hypothesis focused on the question whether greater task-associated connectivity of the LFC was related to an elevated reserve (residualized memory performance) in the memory domain when age, gender, hippocampal atrophy, and APOE genotype were taken into account. To test this hypothesis, we extracted the mean connectivity value of clusters that were significantly related to *education* and examined whether higher education-related LFC connectivity predicted greater residualized memory performance. Regression analysis showed that greater *education-related LFC connectivity - successful recognition* significantly predicted *fMRI task accuracy – residuals* ($t(35) = 2.161$, $p = 0.019$). For *education-related LFC connectivity – successful encoding* we found an equivalent association to *fMRI task accuracy – residuals* at the trend level ($t(35) = 1.625$, $p = 0.057$). These results support our hypothesis that a better residualized task performance was related to higher functional LFC connectivity during both *correct encoding* and *correct recognition*.

Lastly, we investigated whether this relationship to residualized memory performance showed generalizability to the out of scanner memory performance. Here, both *education-related LFC connectivity – successful encoding* ($t(35) = 1.972$, $p = 0.028$) and *education-related LFC connectivity – successful recognition* ($t(35) = 2.591$, $p = 0.007$) significantly predicted *word list*

learning, residuals. Scatterplots for the relationships between *education-related LFC connectivity – encoding/recognition*, *fMRI task accuracy - residuals* and *word list learning - residuals* are illustrated in Figure 6. This supports the assumption that higher connectivity of the LFC is related to a better reserve in the field of mnestic performance which seems to apply both to normal and pathologically aging brains.

To sum up, no significant correlations between indices of residualized memory performance and connectivity measures of the occipital pole and precuneus regions—which served as our control ROIs— could be detected. This finding can be interpreted as an indicator of the specificity of the current results for the LFC. All findings presented in this context remained virtually unchanged after repeating the analyses with the residualized memory score, even if the MMSE score as an indicator of global cognition was additionally regressed out.

Figure 6: CR-related LFC connectivity during memory processing (adapted from 77[4])

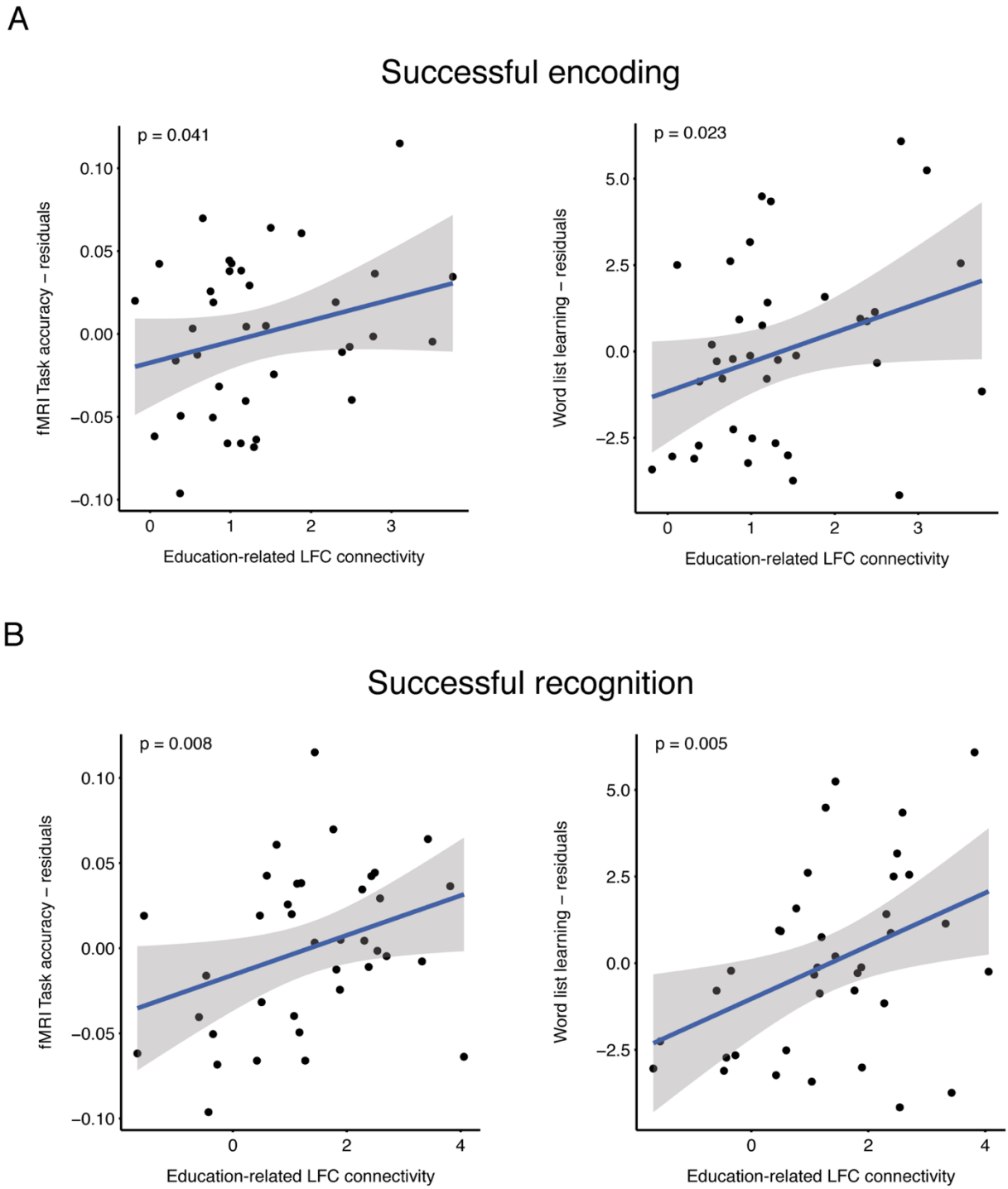

Figure 6: These scatterplots illustrate the relationship between educational level (operationalized as years of education) and connectivity of the LFC (defined as connectivity averaged across significant voxels as depicted in figure 5) during accurate encoding (panels A) and accurate recognition (panels B).

[4] The final publication is available at IOS Press through http://dx.doi.org/10.3233/JAD-170360. The permission to reprint this figure was granted by the publisher.

9. Discussion

The main goal of the present study was to evaluate whether the functional connectivity (FC) of the lateral frontal cortex (LFC) during episodic memory processing supports reserve i.e. relatively well-preserved cognition compared to the level of brain pathology. We hypothesized that higher education (as a protective factor) is related to increased LFC functional connectivity during effective processing of episodic memory and that greater education-related LFC connectivity attenuates the effects of age-related brain changes on cognition.

The main results of the current study indicate that during successful memory encoding the LFC hub was strongly and universally connected with other brain regions and functional networks. Furthermore, it was found that (1) people with higher education show higher functional LFC connectivity during both memory encoding and recognition and that (2) there is a positive correlation between connectivity and mnestic abilities, i.e. the higher the LFC connectivity, the higher the memory performance.

Furthermore, our findings endorse and broaden earlier results pertaining to LFC-connectivity and reserve in mild cognitive impairment (MCI; (17)) assessed by resting-state fMRI, such as that during a memory task the brain-wide connectivity of the LFC hub facilitates reserve.

The current findings thus support our hypothesis that—in normal as well as in pathological aging—the global FC of the LFC, which is considered a central hub region of the fronto-parietal control network, supports reserve and helps maintaining memory performance.

To better understand why some elderly people are able to maintain their memory performance, we investigated the concept of the LFC as a potential substrate of reserve. For this purpose, reserve was defined as the residualized memory performance or more precisely as the discrepancy between the factually observed mnestic task performance and the level of performance which could be expected considering gender, age, hippocampal volume, and ApoE genotype (60). This concept of measuring reserve bears the advantage that it addresses a dynamic aspect of reserve (69) since one can observe changes in the residual variable over time, which probably represent a substrate of cognitive resilience to pathological cerebral processes.

The results of this study are in agreement with the conceptual model of reserve which was introduced by Stern et al. (13): Patients with higher reserve (education) showed better performance in memory tasks., This underlines the notion of a dynamic mechanism through which persons with more years of education are able to compensate for brain pathology or age-related brain changes.

Previous studies showed that in elderly subjects, higher residualized memory performance was associated with higher education, higher IQ, slower memory decline and a reduced risk of developing AD (69, 70). Moreover, it was found that the residual memory variance functions as a moderator variable for the mnestic performance that can be explained by brain variables and subsequent changes in executive functioning and language (60, 69).

Our results endorse the consideration that higher resting-state connectivity of the LFC is related to higher levels of fluid intelligence—a well-known protective factor with respect to the cognitive performance of elderly people. Interestingly, this association could also be detected in younger adults (32).

Overall, our findings support the presumption that connectivity of the LFC may be a brain feature that bears a plasticity with respect to environmental variables like education, and enables a person to compensate for pathological changes during diseases like AD. This confirms a concept of reserve as a dynamic capacity which can be modified and enhanced in the course of life.(9).

The LFC can be seen as a brain region that is highly qualified to support reserve capacity in aging (32), because it serves as a hub region of the fronto-parietal control network which is known to be essential for cognitive control, it. On the one hand, it belongs to the top 5% of cerebral regions with respect to the

number of connections, and on the other hand, it is also a central hub connecting various functional brain networks (71), allowing it to regulate the activity of other major networks in the brain (72).

In aging, the LFC in particular and together with the whole fronto-parietal control network may be responsible for an enhanced efficiency of major brain networks during cognitive processes, due to the finding that better education-based LFC connectivity to networks that are essential for memory processes is related to a better network efficiency (73). Therefore, the relatively spared LFC hub probably plays a central role with regard to the education-associated variability of network efficiency and seems to be well-suited to be conducive to the maintenance of cognitive abilities during the course of brain pathology like Alzheimer's disease.

Moreover, the definition of the posterior-anterior shift theory of aging (PASA) underlines the importance of the frontal lobe in aging as it refers to an age-related reduction of occipito-temporal brain activity together with an age-related frontal hyperactivation (74). According to the PASA theory an additional recruitment of education-related LFC connectivity allows elderly people to perform relatively well despite age-related cognitive decline (74) and therefore the frontal lobe is seen to be increasingly important to maintain cognitive

performance in aging (75). Several studies showed that the PASA theory can be found across a variety of cognitive functions including encoding and recognition and that an age-related reduction in functional connectivity involving posterior brain regions is associated with an increase of education-related LFC connectivity (76).

In addition, in older adults a hemispheric asymmetry reduction was described by several studies, a phenomenon addressed by the HAROLD theory. Due to HAROLD, an increased bilaterality, especially a recruitment of bilateral frontal regions during memory tasks in the aging brain, could help countervail neurocognitive deficits (76).

Even if we did not explicitly test the PASA or HAROLD theories and did not observe a compensatory increase in LFC connectivity with aging our findings thus support the importance of the frontal lobe, proving the LFC might be a substrate of reserve that helps maintaining memory performance in aging.

In a previous study it was shown that LFC functional connectivity was unmodified in prodromal AD patients and therefore an increase of LFC functional connectivity in aging may compensate for posterior parietal FDG-PET hypometabolism (77). This is also underlining our hypothesis of higher LFC connectivity as a protective and beneficial factor which strengthens mnestic functions in face of neurodegeneration. In addition, it seems to act as an

attenuator in terms of the negative impact of the parietal glucose hypometabolism on memory caused by Alzheimer's disease.

Limitations

There are several limitations to our study that should be taken into account. Firstly, a hypothesis-based approach was adopted which focused on the LFC as a potential substrate of reserve, thereby reducing the risk of random false positive findings. Due to this strategy, relevant changes in the connectivity of brain regions different from the LFC hub may have been missed.

However, we did analyse several control regions in the brain, including the precuneus (a region of higher cognitive abilities including memory), as well as the occipital pole (harbouring primary sensory areas) and could not detect any significant association with educational level or residualized mnestic performance. This finding endorses the specificity of our results with respect to the LFC as a potential substrate of reserve. Nevertheless, as it cannot be ruled out that other brain regions are also involved in reserve, more research is required to address these aspects.

Next, we focused on healthy elderly subjects. Application of the current findings to subjects with neurodegenerative disease is desirable. In fact, in extension to the current study (which was not part of the MD thesis), we applied the same

analysis scheme to face-name task obtained in patients with MCI (73). In this clientele, just like in the cognitively normal subjects evaluated in this study, it could also be found that the LFC supports memory performance due to a rapid and resource-efficient information processing in connected networks.

One further caveat that must be taken into consideration is the fact that in our sample of cognitively normal subjects there were carriers of the ApoE e4 allele, which could increase the probability of a beginning AD pathology. As a consequence, the variable ApoE genotype was included in the calculation of the residualized memory score, thus controlling for this genetic AD risk during the calculation of the individual reserve levels.

We caution against suggesting that education may act as a general protective factor, often called a proxy measure of reserve, that is correlated with variables like intelligence level, socioeconomic and health status, and risk of disease (64). The same level of formal education most likely does not signify that these people share the same lifetime experiences(78), (79). It rather could vary in groups with the same level of ability (80) and lead to test-taking strategies that can increase "test-wiseness" and thus let test bias occur. Education may be a life experience unspecific to reserve, lacking a causative influence on reserve. Thus, education should neither be taken as a measure of reserve nor as a causative event, but

rather as an environmental protective factor associated with maintaining memory performance despite cognitive decline in aging.

Outlook

To summarize our findings, we conclude that the LFC has global connections to other brain regions during memory tasks. We could prove that during mnestic processes a better educational level is associated with higher connectivity of the LFC, which in turn predicts better task-performance in our memory paradigm, as well as in the word list learning test. High LFC connectivity may thus be an important facilitator of the effects of aging on the brain. We further argue that greater reserve-related functional connectivity of the LFC is compensatory for age-related hippocampal atrophy and the LFC can thus be seen as a substrate of reserve.

In terms of their clinical implications, the results of the present study strongly support the feasibility of a more sophisticated elucidation of the opportunities of the LFC-connectivity as a potential therapeutic target. Examples include using transcranial direct current stimulation (tDCS) of the LFC to enhance learning processes (shown in post-stroke patients) and maintain the working memory in aging (81). Also, cognitive training may improve memory performance and LFC function in both normal aging and mild cognitive impairment.

Even though some new studies questioned the concept of reserve and the hypothesis that more years of education could be compensatory for age-related decline (82), the fact that some elderly people maintain their memory performance better than others in the face of neurodegeneration remains to be further elucidated and with it the search for compensatory brain mechanisms. Finally, it would be interesting to see if our findings can be replicated in patients with neurodegenerative diseases other than AD, where functional connectivity of the LFC may also act as an indicator in pharmacological or psychological intervention trials.

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11. Appendix

11.1. Declaration

I declare that this thesis was composed by myself, that the work contained herein is my own except where explicitly stated otherwise in the text, and that this work has not been submitted for any other degree or qualification except as specified.

Parts of this work have been published in the ‘Alzheimer’s Research & Therapy’ Journal and the ‘Journal of Alzheimer’s Disease’.

11.2 Acknowledgements

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11.3 Eidesstattliche Versicherung

Hartmann, Julia Clarissa

Ich erkläre hiermit an Eides statt,

dass ich die vorliegende Dissertation mit dem Titel

„The lateral frontal cortex as a potential substrate of cognitive reserve“

selbstständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht habe und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, 25.04.2021 Julia Clarissa Hartmann