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The influence of age and cognitive status on large-scale brain networks in episodic memory

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MY CONTRIBUTION TO THE PUBLICATIONS

I, Christiane Sophie Helene Oedekoven, drafted and wrote all abstracts, manuscripts and articles relevant to this dissertation. I contributed to a large degree to the hypotheses and aims followed in this work. Furthermore, I constructed and adapted all three face-name memory tasks used for the study, using Presentation. All appointments with patients and participants were completed by me, conducting the MRI sessions as well as the neuropsychological tests. Data were analyzed by me, using SPM and SPSS. I summarized all data and linked it to the existing literature. All publications relevant to this dissertation were written by me and I presented the results at various scientific conferences.

CONTENT

ABSTRACT

The present synopsis summarizes three scientific articles published or submitted to international scientific journals. All three articles relevant to this dissertation are tied by the question to what extent healthy aging and cognitive impairment influence brain activation in regard to episodic memory encoding and retrieval. Here, our interest focuses on the role of parietal lobe and changes occurring within underlying large-scale brain networks. The data in all articles consist of the same groups of participants, healthy young, healthy elderly and patients with mild cognitive impairment (MCI). We adapted the memory tasks for our fMRI study to control for age-related changes in memory function. This allowed us to consider the differences in activation with a given standardized performance level. We were interested in the differences and overlaps in activation concerning memory encoding (Paper #3), face memory retrieval (Paper #1) and associative memory retrieval (Paper #2). While Paper #1 focuses on healthy participants and the effects of aging on participating networks, Paper #2 and Paper #3 are concerned with age-related effects as well as effects of MCI, an at-risk state for Alzheimer's dementia (AD). Furthermore, in Paper #1 and Paper #2, we also focused on functional connectivity, examining interactions and correlations between relevant brain regions. We were especially interested in the connections of parietal lobe and hippocampus, since these are two brain regions essential for episodic memory. Our main goal was to distinguish changes occurring in healthy elderly and MCI patients regarding their activation in large-scale brain networks involving parietal lobe.

In all three episodic memory tasks we found overlapping patterns of activation across groups, indicating participation of similar networks regardless of age and cognitive decline. Changes were seen regarding magnitude of activations within these networks. The networks involved were two large-scale brain networks relevant for episodic memory: a frontoparietal task positive network (TPN) and the default mode network (DMN), which is a task negative network.

Our results demonstrate that DMN regions such as lateral and medial parietal as well as prefrontal regions show deactivation during encoding and activation during retrieval, which constitutes an encoding/retrieval flip. Only hippocampus, as part of the DMN, was activated during both encoding and retrieval. Spatial extent and magnitude of DMN deactivation during encoding was related to age

and cognitive status. Young showed more deactivation in posteromedial cortex and inferior parietal lobe than healthy elderly, whereas only healthy elderly showed additional activation of hippocampus and posterior DMN regions. In retrieval tasks, healthy elderly showed more activation in DMN regions, whereas MCI patients showed lower hippocampal activation during a face-name recognition task, corresponding to lower associative memory performance. Moreover, age-related DMN impairment was reflected in functional connectivity measures. Analyses of functional connectivity revealed fewer correlations of parietal DMN brain regions for healthy elderly than young. In contrast, there were more correlations with a hippocampal seed in healthy elderly than young, indicating a more extensive network with age involving hippocampus and striatal regions.

Regarding TPN activation, spatial extent and magnitude of activation was increased in all older adults compared to young. In all three episodic memory tasks healthy elderly and MCI - regardless of memory status - showed increased activation within TPN regions. Especially pre- and postcentral as well as striatal regions were involved.

In conclusion, we were able to distinguish age-related effects from changes occurring with MCI in large-scale-brain networks involving parietal lobe. Even in healthy aging we found functional connectivity of parietal lobe to be impaired in comparison to young. For the first time, changes in large-scale brain networks DMN and TPN were described for MCI. Healthy elderly and MCI may be distinguished by their activation patterns in DMN regions. The overrecruitment of DMN regions suggests compensatory processes present in healthy elderly but not in MCI. Since connectivity analysis of posterior DMN regions imply impaired connectivity with age, increased DMN activation may indicate a compensatory process for a less extensive functional network in healthy elderly. Furthermore, healthy elderly and MCI can be distinguished by their hippocampal DMN activation, MCI generally showing less hippocampal activation in accordance with an impaired memory performance. During associative retrieval, healthy elderly and MCI patients showed different patterns of functional connectivity to a hippocampal seed. TPN overrecruitment was present in both healthy elderly and MCI, thus indicating dedifferentiation processes with age. By distinguishing healthy elderly and MCI based on their activation within large-scale brain networks, our study facilitates early recognition of dementia.

DEUTSCHE ZUSAMMENFASSUNG

Die vorliegende Synopsis fasst drei wissenschaftliche Artikel zusammen, die in Fachzeitschriften veröffentlicht wurden oder werden. Alle drei Artikel dieser Dissertation sind durch die Frage verbunden, inwiefern gesundes Altern und kognitive Beeinträchtigung die Hirnaktivierung bei Lernphase und Abruf episodischer Gedächtnisinhalte beeinflussen. Hier interessierten wir uns insbesondere für die Rolle des Parietalkortex und deren mögliche Veränderungen in zugrunde liegenden Hirnnetzwerken. Die Daten in allen drei Artikeln basieren auf denselben Stichproben junger Erwachsener, gesunder Älterer und Patienten mit Mild Cognitive Impairment (MCI).

Für unsere fMRT-Studie passten wir die Gedächtnisaufgaben für die älteren Probanden an, um altersbedingte Veränderungen der Gedächtnisfunktionen zu berücksichtigen. Dies ermöglichte uns, die Aktivierungsunterschiede vor dem Hintergrund einer standardisierten Leistung zu bewerten. Wir untersuchten die Unterschiede und Überschneidungen der aktivierten Regionen während der Enkodierung neuer Gedächtnisinhalte (Artikel #3), dem Abruf von Gesichtern (Artikel #1) und assoziativem Gedächtnisabruf (Artikel #2). Während sich Artikel #1 mit gesunden Probanden befasst und den Einfluss des Alterns auf die beteiligten Netzwerke beschreibt, befassen sich Artikel #2 und Artikel #3 darüber hinaus mit den Auswirkungen von MCI, einer Vorstufe der Alzheimer Demenz (AD). Ein weiterer Fokus der beiden Artikel #1 und Artikel #2 lag insbesondere auf der Untersuchung der funktionellen Konnektivität, wobei wir die Interaktionen und Korrelationen zwischen relevanten Hirnregionen untersuchten. Wir interessierten uns insbesondere für die funktionelle Konnektivität des Parietalkortex und des Hippocampus, da diese beiden Hirnregionen eine wichtige Rolle für das episodische Gedächtnis spielen. Ziel der Studie war, die Veränderungen in gesunden Älteren und MCI-Patienten hinsichtlich ihrer Aktivierungen in Hirnnetzwerken, die den Parietalkortex einschließen, zu beschreiben und zu unterscheiden.

In allen Aufgaben zum episodischen Gedächtnis fanden wir überlappende Aktivierungen über die Gruppen hinweg, was auf eine Beteiligung ähnlicher Netzwerke, unabhängig von Alter oder kognitiver Beeinträchtigung, hinweist. Es zeigten sich Veränderungen hinsichtlich der Intensität der Aktivierungen in den beteiligten Netzwerken. Zwei Hirnnetzwerke sind beteiligt am episodischen

Gedächtnis: Ein frontoparietales Task Positive Network (TPN) und ein Task Negative Network, das Default Mode Network (DMN).
Unsere Ergebnisse zeigen, dass DMN-Regionen wie der laterale und mediale Parietalkortex, sowie präfrontale Regionen während der Enkodierung neuer Gedächtnisinhalte deaktiviert und während der Abrufphase aktiviert sind, was einen Encoding/Retrieval Flip, einen Wechsel von Deaktivierung und Aktivierung im DMN darstellt. Einzig der Hippocampus als Teil des DMN zeigte sich aktiviert während beider Aufgaben. Die räumliche Ausbreitung und die Stärke der DMN-Deaktivierung während der Enkodierung werden durch Alter und kognitiven Status beeinflusst. Junge Probanden zeigten eine stärkere Deaktivierung im posteromedialen Kortex und im inferioren Parietalkortex als gesunde Ältere, wohingegen nur die gesunden Älteren zusätzliche Aktivierung im Hippocampus und in posterioren DMN-Regionen zeigten. In den Abrufphasen zeigten gesunde Ältere eine stärkere Aktivierung der DMN-Regionen, während MCI-Patienten beim Wiedererkennen von Namen und Gesichtern weniger hippocampale Aktivierung zeigten. Diese verringerte hippocampale Aktivierung hing mit einer verminderten assoziativen Gedächtnisleistung zusammen. Darüber hinaus ließen sich altersbedingte Veränderungen des DMN im Hinblick auf die funktionelle Konnektivität finden. Eine Analyse der funktionellen Konnektivität offenbarte weniger Korrelationen von parietalen DMN-Regionen für gesunde Ältere im Vergleich zu jungen Probanden. Dagegen wiesen gesunde Ältere stärkere Korrelationen zwischen Hippocampus und striatalen Regionen auf als junge Probanden.
Im Hinblick auf TPN-Regionen ließ sich eine Zunahme der räumlichen Ausdehnung und der Intensität der Aktivierungen in beiden älteren Gruppen im Vergleich zu jungen Probanden finden. In allen Aufgaben zum episodischen Gedächtnis - Enkodierung, Abruf und assoziativem Abruf - zeigten gesunde Ältere und MCI-Patienten erhöhte Aktivierung in TPN-Regionen, unabhängig vom kognitiven Status. Insbesondere zeigten sich zusätzliche Aktivierungen in prä- und postzentralen sowie in striatalen Regionen.

Abschließend lässt sich sagen, dass wir altersbedingte Veränderungen und Auswirkungen von MCI auf Hirnnetzwerke, die den Parietalkortex einschließen, unterscheiden konnten. Auch in gesunden Älteren finden wir die funktionelle Konnektivität des Parietalkortex beeinträchtigt. Zum ersten Mal beschreiben wir

die Auswirkungen von MCI auf die beiden Hirnnetzwerke DMN und TPN. Gesunde Ältere und MCI-Patienten lassen sich anhand ihrer Aktivierungen in DMN-Regionen unterscheiden, wobei die zusätzliche Aktivierung in DMN-Regionen auf kompensatorische Prozesse hindeutet, die in gesunden Älteren stattfinden, allerdings nicht in MCI-Patienten. Da Konnektivitätsanalysen der posterioren DMN-Regionen eine beeinträchtigte funktionelle Konnektivität mit dem Alter zeigen, könnte die zusätzliche Aktivierung der DMN-Regionen eine Kompensation für ein weniger umfangreiches Netzwerk bedeuten. Darüber hinaus lassen sich ältere Gesunde und MCI-Patienten anhand ihrer hippocampalen Aktivierung unterscheiden, wobei MCI-Patienten generell weniger hippocampale Aktivierung zeigten, in Übereinstimmung mit einer beeinträchtigten Gedächtnisleistung. Während des assoziativen Abrufs zeigten gesunde Ältere und MCI-Patienten unterschiedliche funktionelle Konnektivität im Hippocampus.

Dagegen zeigten sich zusätzliche Aktivierungen der TPN-Regionen in gesunden Älteren und MCI-Patienten, unabhängig vom kognitiven Status. Daraus lässt sich schließen, dass die zusätzliche TPN-Aktivierung keine kompensatorische Funktion hatte, sondern eher auf Dedifferenzierungsprozesse im Hirn hindeutet. Durch die Unterscheidung gesunder Älterer und MCI anhand ihrer Aktivierung in den Hirnnetzwerken DMN und TPN, erleichtert unsere Studie die Früherkennung von Demenz.

ABBREVIATIONS

ACC = Anterior cingulate cortex
AD = Alzheimer's disease
BOLD = Blood oxygenation level dependent
DMN = Default mode network
fMRI = Functional magnetic resonance imaging
IPL = Inferior parietal lobe
IPS = Intraparietal sulcus
MCI = Mild cognitive impairment
MTL = Medial temporal lobe
PMC = Posteromedial cortex
SPL = Superior parietal lobe
TPN = Task positive network

SYNOPSIS

1. INTRODUCTION

In our aging society dementia is a growing area of public and medical concern. While the probability for dementia is below 1% in 60-year-olds, this probability rises to 24-33% in 85-year-olds (Blennow, De Leon, & Zetterberg, 2006). Despite intense research, causes for Alzheimer's disease (AD) as the most common form of dementia, remain unclear (Bateman et al., 2012). The possibility to treat this condition depends on our ability to distinguish individuals who will maintain cognitive function from individuals at-risk for dementia. Common age-related effects and changes with at-risk states for AD occur on a behavioral level as well as in large-scale functional brain networks. Mild cognitive impairment (MCI) is a transitional at-risk state for AD. This stage includes subjective and objective memory impairment without fulfilling criteria for dementia (Albert et al., 2011). MCI patients have an increased probability of 12% to convert to AD within the next year, in comparison to 1-2% in healthy elderly (Petersen, 2004). Our main goal was to distinguish changes occurring in healthy elderly and MCI patients on a neural level, regarding their activation in large-scale brain networks involving parietal lobe.

To accomplish this, we used functional magnetic resonance imaging (fMRI). With fMRI, magnetic properties of deoxygenated and oxygenated blood can be distinguished. The resulting blood oxygenation level dependent (BOLD) signal is the basis for measurement of brain activation with fMRI. Increased blood flow, the hemodynamic response, is assumed to represent increased neural activation (for more information on fMRI see Poldrack, Mumford, & Nichols, 2011). Differences in activation across conditions are discerned by contrasting events, such as faces vs. baseline or old faces vs. new faces.

We investigated changes within two large-scale brain networks with age and cognitive status: the default mode network (DMN) and the task positive network (TPN). The DMN includes medial and lateral parietal, medial prefrontal regions and hippocampus (Fox et al., 2005; Toro, Fox, & Paus, 2008). It is deactivated during tasks that require attention to external stimuli. Successful encoding of episodic memory is externally oriented and therefore requires a suppressed DMN, whereas successful memory retrieval requires an involvement of internal attention, so DMN is activated (Huijbers, Pennartz, Cabeza, & Daselaar, 2011;

Kim, Daselaar, & Cabeza, 2010). This is described as encoding/retrieval flip (Daselaar et al., 2009). A decrease of deactivation in DMN indicates more cognitive demand, such as an increased effort or more attention to external details (Harrison et al., 2008). The TPN or frontoparietal network (Fox et al., 2005; Toro et al., 2008) supports processing of externally presented information and cognitive control (Cole & Schneider, 2007; Kim et al., 2010; Salami, Eriksson, & Nyberg, 2012). It consists of prefrontal, precentral and sensorimotor areas as well as insulae and lateral parietal regions anterior and superior to DMN regions (Fox et al., 2005; Toro et al., 2008).

In previous studies, older adults showed less deactivation in DMN than younger adults, pointing towards a compensatory recruitment of DMN regions in order to maintain the same level of performance (Lustig et al., 2003; Miller et al., 2008). At the same time, many studies report overrecruitment of frontal and other TPN regions in older adults (Grady, 2008; Grady et al., 2010; Miller et al., 2008; Park & Reuter-Lorenz, 2009). The increasing activation of TPN regions in addition to less accuracy in performance indicates the need for more cognitive control with age. While young show more deactivation in DMN, older adults show more activation of TPN, effectively leading to a simultaneous decrease of DMN and an expansion of TPN with age (Grady et al., 2010). Since DMN and TPN are both involved in episodic memory encoding and retrieval, we were interested how the involvement of relevant network regions, such as parietal lobe and hippocampus, changes with age and cognitive decline.

Neuroimaging literature has found parietal lobe to play an important role in episodic memory retrieval (Hutchinson, Uncapher, & Wagner, 2009; Vilberg & Rugg, 2008). Parietal lobe is especially relevant for “retrieval success”, which describes the distinction of hits and correct rejections, i.e. correctly identified known items and correctly identified new items. In a recent meta-analysis of regions involved in retrieval success, the main cluster consisted of left posterior parietal lobe (Spaniol et al., 2009). Within posterior parietal lobe, one has to distinguish between 1) a dorsal part which includes superior parietal lobe (SPL), intraparietal sulcus (IPS) and precuneus and 2) a ventral part which includes inferior parietal lobe (IPL) and subregions (supramarginal gyrus, temporoparietal junction and angular gyrus) (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008). In regard to memory retrieval, the dorsal part is thought to be important for the recognition of single context-free items (single faces before

a neutral background) (Nelson et al. 2010; Vilberg & Rugg, 2008). In contrast, the ventral part of parietal lobe is activated in associations (e.g. face-name pairs) (Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Wheeler & Buckner, 2004). Posterior parietal lobe is divided concerning affiliation to DMN and TPN (Kim et al., 2010).

Hippocampus is another important neural correlate of episodic memory. It is part of the medial temporal lobe (MTL) and essential for associative memory, such as the combination of faces and names (Dickerson & Eichenbaum 2010; Tsukiura et al., 2011; Wais, 2008). Hippocampus is considered part of the DMN (Huijbers et al., 2011).

Episodic memory is defined as memory of events in one's past within a spatio-temporal context (Tulving, 1985; Viard, Desgranges, Eustache, & Piolino, 2012). Linking several components is a fundamental feature of episodic memory, such as associating faces and corresponding names. In neuroimaging studies, episodic memory retrieval is typically investigated by memory encoding and recognition tasks. Face-name associative tasks are a popular measure to investigate associative episodic memory while using a relevant everyday task, since binding a specific name to a specific face resembles everyday associations (Irish, Lawlor, Coen, & O'Mara, 2011; Naveh-Benjamin, Guez, Kilb, & Reedy, 2004). Previous behavioral studies have investigated associative memory of MCI patients and found face-name tasks to discriminate well between healthy elderly and MCI (Irish et al., 2011; Pike et al., 2012).

In aging, episodic memory impairment and memory complaints are common, especially regarding the inability to remember faces and names (Pires et al., 2012). Older adults have trouble binding pieces of information into complex memories, indicating an overall age-related associative deficit (Old & Naveh-Benjamin, 2008). This deficit is thought to stem from age-related declines in perception, attention and memory in elderly (Craik & Rose, 2011). In order to be able to compare activations across age groups, we adjusted episodic memory task difficulty throughout the study. This is a well established strategy to allow interpretation of differential brain activation (Price & Friston, 1999).

Patients with MCI show cognitive decline particularly in associative episodic memory (Irish et al., 2011), as well as changes regarding brain structure and function. Especially hippocampus plays a major role in the pathogenesis of AD, since the earliest structural changes in the course of MCI and AD have been

found in MTL regions (Dickerson & Eichenbaum, 2010). MCI patients show less hippocampal activation during episodic memory tasks (Johnson et al., 2006; Mandzia, McAndrews, Grady, Graham, & Black, 2009; O'Brien et al., 2010), whereas young and healthy elderly show similar hippocampal activation (Miller et al., 2008).

Structural and functional connections between brain regions are essential for communication within large-scale networks. Since our focus was on memory related regions, we investigated correlations within networks with seed voxel functional connectivity analysis, choosing parietal lobe and hippocampus as seed regions (Paper #1 and #2). Thus, an analysis is conducted of temporal correlations of the chosen seed regions with all other regions of the brain. Several studies have shown that aging has a disruptive influence on connectivity within brain networks, which in turn influences performance in episodic memory retrieval (Andrews-Hanna et al., 2007; Wang et al., 2010). Connectivity studies with fMRI reveal an altered hippocampal network in older adults in comparison to young, involving primarily frontal and striatal regions rather than posterior regions (Grady et al., 2010). Adding to these effects of age, AD is thought to be a disconnection syndrome where large-scale functional network correlations become dysfunctional in AD and at-risk states (Bokde, Ewers, & Hampel, 2009). There are changes of functional connectivity with MCI and AD in comparison to healthy elderly, particularly regarding attenuated functional connectivity of hippocampus to frontal regions (Bokde et al., 2009). Less is known about functional connectivity of parietal lobe, especially regarding its participation in different networks.

In order to investigate episodic memory in all three groups, we used three memory tasks, including encoding (Paper #3), face retrieval (Paper #1) and associative retrieval (Paper #2). During the encoding task, participants were asked to memorize faces and names, which were presented repeatedly (1-3 times). During the face retrieval task, only faces were shown and participants were asked to judge whether they had seen the face during the preceding encoding phase. During the associative retrieval task, face-names combinations were shown and participants were asked which of two names were shown with the face beforehand. We adjusted task difficulty for older adults, in order to allow similar memory performance in young and healthy elderly (Price & Friston,

1999). All older adults saw less faces which were presented for a longer time, during encoding as well as face retrieval.

To our knowledge, our fMRI study is the first to compare healthy young, healthy elderly and MCI patients who differed in age (young/older) and cognitive status (healthy/MCI), while investigating episodic memory with the same face-name tasks. This design allows us to distinguish brain activation of individuals who will maintain cognitive function with age from those with cognitive decline (MCI). Furthermore, while earlier studies used MTL regions of interest, we take large-scale functional brain networks into account (Johnson et al., 2006; Lustig et al., 2003; Pihlajamäki, O'Keefe, O'Brien, Blacker, & Sperling, 2011). Additionally, we matched performance level for young and elderly by adjusting the episodic memory tasks for age-related decline, allowing a direct comparison of activation levels across groups (Price & Friston, 1999). We were interested how large-scale brain networks and specific brain regions relevant for episodic memory encoding and retrieval interact in young, healthy elderly and MCI. Due to their involvement in episodic memory, we focused on DMN and TPN, and parietal and hippocampal regions. To our knowledge, no previous study has investigated the influence of MCI on DMN and TPN activation. By including MCI patients, we aimed to investigate whether loss of DMN functionality and overrecruitment of TPN is also seen with decline of cognitive status (Grady et al., 2010, Paper #3). Age-related alterations of the connections of parietal DMN regions were investigated in Paper #1. We expected to find age-related changes in parietal activations, when comparing young and elderly participants with the same episodic memory retrieval task (Paper #1). Regarding associative memory, we expected a change in hippocampal activation with age and a decrease in hippocampal activation with decline of cognitive status (Paper #2). Concerning functional connectivity, we expected a decrease of hippocampal connectivity with memory decline in MCI (Paper #2).

The present synopsis summarizes the current results of our project “Functional and structural imaging of the parietal lobe depending on memory performance – An approach to early recognition of Alzheimer's disease” (Funktionell und strukturell bildgebende Untersuchung des Parietalkortex in Abhängigkeit von der Gedächtnisleistung - Ein möglicher Ansatz zur Früherkennung der Alzheimer-Erkrankung). This study was conducted in the past three years at the

Philipps University Marburg. All neuropsychological and fMRI-data were accumulated at the Department of Psychiatry and Psychotherapy in Marburg between August 2010 and September 2011 by the author. The personal contributions of the author of this dissertation compile all aspects of scientific study: formulating hypotheses, design of functional tasks, and accumulation of data, data analysis and writing of all three scientific articles as well as presenting the results at various scientific conferences.

2. RESULTS

In this section, the results of episodic memory encoding (Paper #3), face memory retrieval (Paper #1) and associative memory retrieval (Paper #2) are summarized. Hypotheses and results are presented by topic. Figures and tables refer to the attached manuscripts.

Episodic memory performance

Based on the literature, we expected MCI patients to perform worse in episodic memory tasks than young and healthy elderly (Irish et al., 2011). In order to allow a similar memory performance in young and healthy elderly, we adjusted the difficulty of the encoding and the face retrieval task by presenting less faces for an increased time (Price & Friston, 1999). This adaptation of task difficulty is discussed below (see Discussion).

1) **We expected MCI patients to show an impaired memory performance in comparison to both young and healthy elderly, whereas young and healthy elderly should show a similar performance, due to the adjusted memory task difficulty (Paper #1, Paper #2, Paper #3). MCI patients were expected to be especially impaired regarding associative episodic memory (Paper #2).**

As expected, young and healthy elderly showed a similar performance level in face retrieval, judging which faces they had seen before (hits and correct rejections) (see Table 1, Paper #1) and associative retrieval, deciding on one of two names to belong to a face (see Table 1, Paper #2). This indicates a successful adaptation of episodic memory tasks (encoding and face retrieval).
Unexpectedly, all three groups including MCI, showed a similar performance regarding previously seen faces (hits) (see Table 1, Paper #3). Nevertheless, MCI patients were impaired in episodic memory performance in both retrieval tasks. Regarding face retrieval, MCI judged significantly less new faces correctly identified as new (correct rejections). Furthermore, in associative face-name recognition, MCI patients recognized less face-name combinations (see Table 1, Paper #2).

Similarities in large-scale network activation across groups

According to the literature, DMN is deactivated during tasks that require an external focus of attention and it is activated during internal tasks (Kim et al., 2010). TPN activation is required for external tasks, possibly allowing for cognitive control. While young generally show more deactivation in DMN, older adults show more activation of TPN, effectively leading to a simultaneous decrease of DMN and an expansion of TPN with age (Grady et al., 2010). Despite these changes in magnitude of activation, we expected these networks to be found in every group.

2) Despite age-related changes regarding magnitude of activation, we expected activations in large-scale brain networks DMN and TPN to cover similar brain regions in young and healthy elderly (Paper #1, Paper #2, Paper #3).

In all three memory tasks, we found similar network structures, despite aging and cognitive impairment.

DMN

First we examined similarities in DMN regions across groups: In Paper #1, the retrieval success network was similar across young and healthy elderly, involving mostly activation of lateral and medial parietal (posteromedial cortex, PMC) regions, focused on posterior DMN regions. Parietal regions involved were SPL, IPS, precuneus and middle cingulate (see Fig 1 and Table 2, Paper #1). In Paper #3, common deactivation of DMN regions across groups during face-name encoding included anterior cingulate cortex (ACC) and IPL (see Fig 1 and Table 2, Paper #3).

TPN

Regarding TPN regions, we also found overlaps across groups. In Paper #2, a conjunction analysis across the three groups, young, healthy elderly and MCI indicated common activation in TPN regions during associative face-name recognition, involving prefrontal, precentral and sensorimotor areas, insulae and lateral parietal regions (anterior and superior to DMN regions), as well as fusiform gyri, which are associated with TPN (Grady et al., 2010; see Fig 1 and

Table 2, Paper #2). Similarly, in Paper #3, we found TPN regions activated in all three groups during encoding of face-name pairs, again involving precentral regions and lateral parietal regions, as well as insulae and fusiform gyri (see Table 3, Paper #3).
Together, these results further corroborate the existence of independent large-scale networks that remain in place despite age-related changes.

Differences in activation in large-scale networks

Inherently, healthy elderly and MCI can be distinguished by their performance in memory tasks, as shown above. However, our main aim was to differentiate healthy elderly and MCI by means of patterns and magnitude of activation in DMN and TPN during the episodic memory tasks. While similar networks were involved, we expected spatial extent and magnitude of brain activation to vary. To our knowledge, no previous studies have investigated changes occurring with MCI in these networks.

DMN

3) **Regarding DMN regions, we expected less DMN deactivation in healthy elderly and changes in MCI in comparison to young. We expected to see age-related changes in parietal activations, when comparing young and elderly participants with the same episodic memory retrieval task. (Paper #1). In regard to MCI we were interested if loss of DMN functionality is also seen with decline of cognitive status (Paper #3). Regarding hippocampus, we expected a change in hippocampal activation with age and a decrease with change of cognitive status (Paper #2).**

In Paper #1, we found increased effort with age, which was demonstrated in the overall larger activation in healthy elderly across all conditions of face retrieval, regardless of correct identification or previous knowledge of the stimuli (Old/New) (see Fig 2, Paper #1).
In addition to the similarities found in DMN during encoding in Paper #3, there were decreases in magnitude of deactivations with increasing age. Increased age was related to less deactivation, especially in posterior DMN regions. But DMN activity was also influenced by memory status, since overrecruitment (less

deactivation) of posterior DMN regions, such as PMC and IPL was especially prominent in healthy elderly, whereas MCI did not exhibit overrecruitment of posterior DMN regions (see Fig 1 and Table 2 & 4, Paper #3). Hippocampus as the only DMN region activated during both encoding and retrieval showed similar results, indicating less hippocampal activation in MCI during encoding (see Fig 2, Paper #3).

In Paper #2 we found associative memory performance to be linked primarily to activation in the left hippocampal region. MCI were impaired in regard to associative memory performance and showed decreased hippocampal activation in comparison to healthy elderly and young, whereas healthy elderly and young showed similar associative memory performance and hippocampal activation (see Fig 3, Paper #2). During encoding, hippocampal activation was increased in healthy elderly, but not in MCI (see Fig 2, Paper #3).

Interestingly, we observed different reactions in hippocampus depending on the task. Healthy elderly and young showed similar hippocampal activation during the associative face-name retrieval (Paper #2), whereas MCI patients showed decreased hippocampal activation in line with less memory accuracy. However, during encoding, hippocampal activation was increased in healthy elderly in comparison to both young and MCI (Paper #3). The observed overrecruitment of parietal and hippocampal DMN regions in healthy elderly may indicate stronger compensational processes not available in MCI.

TPN

4) Regarding TPN activation, we expected increases with age and further changes with MCI. We were interested if the overrecruitment of TPN present in healthy elderly is also seen with decline of cognitive status (Paper #3).

Interestingly, results for overrecruitment of TPN regions were very similar across all three episodic memory tasks, indicating increased magnitude and spatial extent of TPN in both older groups.

In Paper #1 we found age-related changes in pre- and postcentral TPN regions (see Fig 3, Paper #1). Additional TPN activation in parietal as well as precentral regions was found in Paper #2, where older age and memory impairment were related to increased activation in brain regions associated with TPN, such as

precentral regions, striatal regions and IPL (see Fig 2 and Table 3, Paper #2). Consistently, in Paper #3, direct group comparisons showed overrecruitment of pre- and postcentral TPN regions in older participants, regardless of memory status (see Fig 3 and Table 4, Paper #3). Since the additional activation in TPN regions is present in both healthy elderly and MCI, this might suggest dedifferentiation processes with age, rather than compensation.

Functional Connectivity

When analyzing functional connectivity regarding correlations across brain regions, we used seed voxel analysis. In Paper #1 the seed for functional connectivity analysis was placed in left IPS, which is part of the dorsal parietal lobe. Since parietal lobe is divided in regard to DMN/TPN affiliation, and dorsal parietal lobe may indeed be a part of TPN rather than DMN, the results will have to be discussed further (see Discussion). We assumed our seed region to be part of DMN. Regarding hippocampus as a DMN region, in Paper #2 a seed was placed in left hippocampus during associative memory retrieval. Since both seeds were placed in DMN regions and DMN deactivation is expected to decrease with age (Andrews-Hanna et al., 2007), we expected functional connectivity within DMN regions to decrease with age.

5) We expected a decrease in functional connectivity with age and further changes of functional connectivity to occur with MCI. Age-related alterations of the connections between DMN regions were investigated in Paper #1. Concerning functional connectivity in MCI, we expected a decrease of hippocampal connectivity with memory decline (Paper #2).

Based on the seed in left IPS (Paper #1), we found a less extensive network in healthy elderly than in young. In young, the network included correlations with lateral and medial parietal regions, middle temporal and frontal areas, whereas healthy elderly had strongest correlations with parietal areas only, such as right SPL, bilateral precunei and bilateral IPL (see Fig 4, Paper #1). Correlations with these DMN regions indicated our seed to be part of DMN. Adding to a higher activation in healthy elderly in these regions (see Differences in activation), there were weaker correlations of the seed in left posterior parietal lobe to other

cortical regions in healthy elderly.

In Paper #2, we observed the network based on the seed in left hippocampus during associative memory retrieval. Similar to the activation patterns, we found a common network of functional connectivity in all groups, including mostly medial and lateral temporal regions. Older adults (healthy elderly and MCI) showed additional correlations to task-positive and striatal regions (see Fig 4 and Table 4, Paper #2). For healthy elderly, there were stronger correlations of the hippocampal seed and bilateral frontal regions, bilateral temporal regions as well as bilateral putamen in comparison to young. For MCI patients there were increased correlations of bilateral caudate nuclei in comparison to young.

Summary of results

For the first time, our study investigating young, healthy elderly and MCI in one episodic memory task allowed a direct comparison of activations and underlying large-scale networks. This enables us to differentiate healthy elderly and MCI by patterns of activation in the episodic memory tasks.

This allowed some major new revelations, especially regarding large-scale brain network activation in older adults. For the first time, these networks were investigated in MCI patients. Regarding DMN, we found large differences in activation patterns and magnitude for healthy elderly and MCI. While both groups showed less deactivation than young, healthy elderly showed additional activation of DMN regions, such as PMC, IPL and hippocampus. Activation of these brain regions may be compensational, allowing for a similar memory performance in healthy elderly and young, since MCI patients did not show the additional activation.

In regard to TPN, it was of major interest to note that both older groups showed additional activation of pre- and postcentral TPN regions in all episodic memory tasks, since this effect has not been reported for patients with MCI. Since the additional activation in TPN regions is present in both older groups, this might suggest dedifferentiation processes with age, rather than compensation.

3. DISCUSSION

Our main goal was to distinguish changes occurring in healthy elderly and MCI patients on a neural level, regarding their activation in large-scale brain networks involving parietal lobe. By including MCI patients in our study, we aimed to investigate if loss of DMN functionality and overrecruitment of TPN is also seen with decline of cognitive status (Grady et al., 2010, Paper #3). Our study is the first to detect the distinct activation patterns in DMN when observing healthy aging and cognitive decline. Furthermore, the similarities regarding TPN activation in healthy elderly and MCI have not been described before. Together, these results represent an important step in differentiating healthy elderly and MCI regarding their large-scale brain network activation in episodic memory. Healthy elderly and MCI can be distinguished by patterns of activation in large-scale brain networks during episodic memory tasks.

Moreover, our interest in the involvement of parietal lobe and hippocampus in episodic memory was justified. We expected to see age-related changes in parietal activations, when comparing young and elderly participants with the same episodic memory retrieval task (Paper #1). Parietal lobe represents a versatile brain structure segmented regarding its participation in large-scale networks and with varying functions in regard to episodic memory.

Regarding hippocampal activation we expected age-related changes and a decrease with decline cognitive status (Paper #2). We found a decrease of hippocampal activation in relation to impaired memory performance. Concerning functional connectivity, we expected changes in DMN with age and MCI (Paper #1, Paper #2) and these differed between the two older groups.

The discussion of the presented results shall start by an overview of the results sorted by the influence of healthy aging and MCI. Furthermore, in regard to limitations I present some of several much debated points in the study. This is followed by a brief outlook on future studies.

Influence of healthy aging on episodic memory and underlying networks

Healthy elderly showed a similar memory performance to young in all episodic memory tasks (Paper #1, Paper #2, Paper #3), indicating a successful adaptation of memory task difficulty. This is an important step towards interpretation of brain activation based on similar performance often missing in

fMRI studies (Price & Friston, 1999).

In agreement with the hypotheses regarding the role of parietal lobe in episodic memory, we found age-related differences in activation (Paper #1). While young and healthy elderly activated similar parietal regions, there was an additional activation of parietal DMN regions in healthy elderly, regardless of condition. This result fits well to previous studies finding additional parietal activation in elderly to be associated with better memory performance (Huang et al., 2012). In contrast to our interpretation of this additional activation in the discussion of Paper #1, the subsequent results of our study point to a compensatory function (Paper #3). Overrecruitment of parietal DMN regions might be an attempt to compensate for a decrease in functional connectivity. As expected, functional connectivity of posterior DMN regions was reduced in healthy elderly, similar to a study by Andrews-Hanna and colleagues (Paper #1; Andrews-Hanna et al., 2007). The findings of Paper #1 mainly support earlier findings, and expand knowledge of the function of parietal lobe in healthy elderly.

In associative face-name retrieval, there was no difference between young and healthy elderly in hippocampal activation (Paper #2). However, there was increased activation in putamen and TPN regions in healthy elderly. On the whole, these results support recent results by Grady and colleagues who demonstrated the TPN and striatal regions to be more active in older adults (Grady et al., 2010). The additional activation of putamen was associated with better memory performance in our study, implying compensatory processes (Langenecker, Briceno, Hamid, & Nielson, 2007). Compensational processes or dedifferentiation can co-occur in older adults during retrieval (Grady, 2008; Zarahn, Rakitin, Abela, Flynn, & Stern 2007); therefore, we interpreted the additional pre- and postcentral TPN activation to be caused by dedifferentiation. While we expected functional connectivity to change with age, we found an augmented network based on a hippocampal seed. In contrast to Paper #1, which showed reduced functional connectivity based on a parietal seed, an analysis of correlations with a hippocampal DMN seed showed an increased network for healthy elderly in comparison to young, involving primarily frontal and striatal regions, rather than posterior regions (Paper #2; Grady et al., 2010). This might be due to the additional activation in striatal regions with age (Langenecker et al., 2007).

During the encoding phase healthy elderly showed additional activation of DMN

regions deactivated in young adults (Paper #3). These results are consistent with the findings of earlier studies (Lustig et al., 2003; Miller et al., 2008). We attributed the additional activation in PMC, IPL and hippocampus to increased effort in healthy elderly and suggest a compensatory function.

Taking together the findings from all three articles, we repeatedly found additional age-related activation in DMN as well as TPN regions. Overall, healthy elderly showed more activation, indicating compensatory as well as dedifferentiation processes. Together, these results further corroborate findings of increased effort and cognitive control in healthy elderly (Grady, 2008; Park & Reuter-Lorenz, 2009).

Influence of MCI on episodic memory and underlying brain networks

As expected, MCI showed impaired performance regarding correct rejections and associative memory (Paper #2).

There are studies investigating the influence of age on large-scale networks (Andrews-Hanna et al., 2007; Grady et al., 2010), but to our knowledge we were the first to investigate the influence of MCI on large-scale networks.

In regard to hippocampus as part of DMN, it was shown that MCI in contrast to healthy elderly show less activation of hippocampal regions and this is related to impaired associative memory performance (Paper #2). This is in line with earlier studies (Johnson et al., 2006); however some studies have found additional hippocampus activation in MCI (Dickerson et al., 2005). During the encoding phase, MCI showed impaired DMN deactivation, but no additional activation of DMN regions (Paper #3). This may indicate that MCI fail to put up the additional resources needed to compensate their age-related decline.

Moreover, in associative memory performance MCI showed increased IPL activation in comparison to young (Paper #2). In view of the division of parietal lobe regarding network affiliation, this was interpreted as a larger demand on cognitive control (TPN). Despite the impaired memory performance, MCI showed increased activation in pre- and postcentral TPN regions similar to healthy elderly. This was likewise interpreted as increased demand indicating dedifferentiation processes (Paper #2, Paper #3). Overall, these findings support the notion of similar dedifferentiation processes in TPN for healthy aging and MCI (Grady, 2008).

Limitations

Adaptation of task

We adapted the encoding (Paper #3) and face retrieval task (Paper #1), showing fewer faces, more often and longer for all older adults. The reasoning behind this is described well by Price and Friston (1999): If a participant "cannot perform the task, the corresponding neuronal system cannot be activated, and it is not possible to tell whether the abnormal neural processing is a consequence of the performance deficit or whether the performance deficit is a consequence of the abnormal neural processing" (p.102). Evidence supporting these assumptions was found in all three episodic memory tasks. In all tasks, the similarities in the activated networks in young and healthy elderly in line with similar memory performance proved the efficiency of our adaptation.

While task adaptation enabled a similar episodic memory performance for healthy elderly, it was not unequivocally so for MCI. Similar to previous studies, simultaneous adaptation of task difficulty for age and cognitive decline proved challenging (same accuracy and RT in elderly and MCI, but not with reference group) (Johnson et al., 2006). MCI patients showed a similar percentage of subsequent hits (Paper #3), but were impaired regarding recognition of new faces (correct rejections) and associations of faces and names (Paper #2). A task providing similar performance in MCI would most likely cause ceiling performance in young, leading to different problems regarding interpretation (boredom, distraction).

Categorization of MCI patients

Our goal was to describe differences in activation in order to discern healthy aging and MCI, but depending on the study, the categorization of MCI differs. In contrast to previous studies our healthy elderly group showed additional DMN activation, especially regarding hippocampus, while MCI patients showed a decline in hippocampal activation (Paper #3, Paper #2). Several earlier studies using encoding paradigms, have found an increase in hippocampal activation with MCI which have mostly been labeled compensatory hyperactivations (Celone et al., 2006; Dickerson et al., 2005). These studies have shown an inverse u-shape pattern to peak in MCI and decline with further conversion to AD, whereas in our study activation peaked in healthy elderly and declined with

MCI (Paper #3). In comparison to Dickerson (2005) our MCI patients were rather more impaired regarding memory functions, and their MCI patients were close in performance to our healthy elderly, where we also found the hyperactivation of hippocampus. Despite the fact that we used established criteria for the categorization of our MCI patients (Petersen, 2004), MCI remains a transient at-risk category for AD with ill-defined borders.

Affiliation of parietal lobe to DMN and TPN

The problem of broad categorization of brain regions as well as contradicting affiliations to brain networks is present in many studies using fMRI.

In order to investigate functional connectivity within DMN, we placed a seed in left IPS to see which brain regions correlated with this seed (Paper #1). Since the network correlated with this seed consisted of DMN regions, we assume the seed region to be part of DMN. Nevertheless, the exact affiliation of parietal lobe to brain networks is difficult to discern. Broad descriptions such as „lateral parietal cortex“ considered to be part of DMN (Fox et al., 2005; Toro et al., 2008) or „dorsal parietal lobe“ considered to be part of TPN (Kim et al., 2010) complicate the attribution of brain regions to networks. For instance, Fox and colleagues used a seed in left IPS to describe connectivity across TPN, but their seed is at a different coordinate further left from our seed (x -25, x -57, z 46) (Fox et al., 2005). Furthermore, IPL is also divided regarding affiliation to DMN and TPN. While Fox describes IPL to be part of TPN (Fox et al., 2005), the angular gyrus as part of IPL is also described as part of DMN (Kim et al., 2010). These contradicting descriptions of affiliations to brain networks aggravate comparisons across fMRI studies.

Group effects

We interpreted the additional activation of DMN regions to be attempts at compensation in healthy elderly, and TPN overrecruitment in both older groups as dedifferentiation. Nevertheless, there are other interpretations possible. On the one hand, the additional activation in TPN seen in all tasks could be caused by the increased reaction time in older adults. Due to the fact that a longer reaction time might affect the hemodynamic response, the fMRI measurement might sample the BOLD-signal at a different time point. We tried to control for the difference in reaction time by introducing it as covariate in our analysis

(Paper #1).

On the other hand, the additional activation shown by healthy elderly might be caused by an additional matching process with previously learned faces. The longer life span might lead more experience and a greater number of known faces to be matched. Furthermore, brain regions activated in healthy elderly match those found in mirror neuron studies (Cattaneo & Rizzolatti, 2009). Therefore, their activation might be caused by observational learning and face perception in general.

Outlook

The presented research has been able to show that healthy aging and MCI show different effects on large-scale brain network activation in episodic memory tasks. For the first time, the direct comparison of age-related effects and influence of MCI revealed differences in DMN and similarities in TPN activation. Regarding DMN, healthy elderly show additional activation of DMN regions, possibly allowing for a similar memory performance in healthy elderly and young. Interestingly, both older groups show additional activation of TPN regions in all episodic memory tasks. This might suggest dedifferentiation processes with age, since the additional activation in TPN regions is present in healthy elderly as well as MCI.

In future studies this information may be used to distinguish healthy and MCI based on their brain activation. Even more enticing is the possibility to actively influence brain activation in the aging brain. Using neurofeedback, future studies may be able to enhance activation magnitude in DMN regions in MCI. This additional activation was shown in healthy elderly in our study and an increase might have compensatory function in order to increase memory performance in MCI. Furthermore it might be possible to influence the observed overrecruitment of TPN shown in all older adults. There are various imaging techniques which allow simultaneous observation of activation as well as neurofeedback, such as real-time fMRI or electroencephalography (EEG).

By distinguishing healthy elderly and MCI based on their activation within large-scale brain networks, our study facilitates early recognition of dementia. Future research should consider the described differences in large-scale network activation due to age and MCI.

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Brakemeier

DANKSAGUNG

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So, don't forget the bigger picture: Keep pushing. (Matt Might)

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Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin Marburg zur Promotionsprüfung eingereichte Arbeit mit dem Titel „The influence of age and cognitive status on large-scale brain networks in episodic memory" in der Klinik für Psychiatrie und Psychotherapie unter Leitung von PD Dr. Dirk Leube mit Unterstützung durch Prof. Dr. Andreas Jansen und Prof. Dr. Tilo Kircher ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation aufgeführten Hilfsmittel benutzt habe. Ich habe bisher an keinem in- oder ausländischen Medizinischen Fachbereich ein Gesuch um Zulassung zur Promotion eingereicht, noch die vorliegende oder eine andere Arbeit als Dissertation vorgelegt.

Ort, Datum, Unterschrift

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Folgende Arbeiten wurden (oder werden) in internationalen Fachzeitschriften (peer-review) veröffentlicht:

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MANUSCRIPTS

Paper #1: Age-related changes in parietal lobe activation during an episodic memory retrieval task

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Age-related changes in parietal lobe activation during an episodic memory retrieval task

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Abstract

The crucial role of lateral parietal regions in episodic memory has been confirmed in previous studies. While aging has an influence on retrieval of episodic memory, it remains to be examined how the involvement of lateral parietal regions in episodic memory changes with age. We investigated episodic memory retrieval in two age groups, using faces as stimuli and retrieval success as a measure of episodic memory. Young and elderly participants showed activation within a similar network, including lateral and medial parietal as well as prefrontal regions, but elderly showed a higher level of brain activation regardless of condition. Furthermore, we examined functional connectivity in the two age groups and found a more extensive network in the young group, including correlations of parietal and prefrontal regions. In the elderly, the overall stronger activation related to memory performance may indicate a compensatory process for a less extensive functional network.

Keywords: Aging, Parietal cortex, Episodic memory retrieval, Functional connectivity

Introduction

It is well known that aging influences memory, especially in regard to episodic memory. Episodic memory is defined as memory of events in one's past within a spatio-temporal context (McDermott et al. 2009; Tulving 1985; Viard et al. 2012). In neuroimaging studies, episodic memory retrieval is typically investigated by memory recognition tasks, comparing old and new events. In aging, episodic memory impairment and memory complaints are common (Craik and Rose 2012; Jonker et al. 2000). This development is often accompanied by increases in brain activation with age (Grady et al. 2006) although decreases in brain activation have been reported as well (Duarte et al. 2008). This influence is attributed to structural changes (e.g. atrophy, disruption of white matter) as well as changes in functional connections. Several studies have shown that aging has a disruptive influence on connectivity within brain networks which in turn influence performance in episodic memory retrieval (Andrews-Hanna et al. 2007; Wang et al. 2010).

While most studies have focused on age-related changes in prefrontal regions (Reuter-Lorenz and Park 2010), less attention has been paid to activation differences in parietal regions, despite the fact that recent neuroimaging literature has found posterior parietal lobe to play an important role in episodic memory retrieval. Several studies have identified a network of corresponding areas involved in episodic memory retrieval, consisting of parietal, medial temporal and prefrontal regions (for reviews see McDermott et al. 2009; Spaniol et al. 2009; Vilberg and Rugg 2008). A puzzling aspect of parietal activation in episodic memory has been the apparent irrelevance of lesions in parietal regions to memory retrieval, in contrast to lesions in medial temporal lobe (Haramati et al. 2008; Simons et al. 2008). Only when using more detailed analyses, it became apparent that parietal lesions cause more subtle memory deficits, concerning details and vividness of the remembered material (Berryhill et al. 2007).

While some imaging studies have associated parietal lobe involvement with established parietal functions such as spatial orientation, motor intention and working memory (Andersen and Buneo 2002; Cabeza and Nyberg 2000), more recent studies have also linked activation of posterior parietal lobe to attentional

processes (Corbetta and Shulman 2002).

Data supporting parietal involvement in episodic memory retrieval were mainly derived from functional magnetic resonance imaging studies (fMRI; for reviews see Hutchinson et al. 2009; Vilberg and Rugg 2008). In retrieval paradigms used in studies examining episodic memory, it is shown that parietal lobe functionality is a main factor of “retrieval success", which is measured as the contrast of hits > correct rejections (hits: correctly identified learned items; correct rejections: correctly identified new items). The difference between hits and correct rejections is commonly referred to as the parietal “retrieval success effect”. While some studies used verbal material, others have used faces and names as stimuli, increasing everyday relevancy (Grady et al. 2002; Ishai and Yago 2006; Leube et al. 2003; Miller et al. 2008; Stevens et al. 2008; Vannini et al. 2011). Faces and names play an important part in everyday life and forgetting them constitutes a major complaint with increasing age (Craik and Rose 2012). In a recent meta-analysis of regions involved in retrieval success, the main cluster found consisted of left posterior parietal lobe (Spaniol et al. 2009). Moreover, the activation for this contrast is mostly left lateralized, regardless of the nature of the stimuli (Vilberg and Rugg 2008).

Within posterior parietal lobe, one has to distinguish between 1) a dorsal part which includes superior parietal lobe (SPL), intraparietal sulcus (IPS) and precuneus and 2) a ventral part which includes inferior parietal lobe (IPL) and subregions (supramarginal gyrus, temporoparietal junction and angular gyrus) (Cabeza, et al. 2008). In regard to memory retrieval, the dorsal part is thought to be important for the recognition of single context-free items (single faces before a neutral background) and triggers familiarity judgments which have been shown to concentrate in left intraparietal sulcus (IPS) (Nelson et al. 2010; Vilberg and Rugg 2008). In contrast, the ventral part of parietal lobe is activated in the framework of recollection of associations (e.g. face-name pairs) (Henson et al. 1999; Wheeler and Buckner 2004).

In respect to its role in episodic memory, the Attention to Memory model (AtoM) links previous findings regarding attentional processes in parietal lobe to episodic memory (Cabeza et al. 2008; Ciaramelli et al. 2008). The AtoM model is based on the concept, that the dorsal part generates goal-oriented attention in a top-down fashion, whereas the ventral part works through a bottom-up

principle by creating associations between incoming sensory stimuli and retrieved memory information bits. Involvement of the dorsal part implies an effortful process, whereas the ventral part represents reflexive action.
Despite the attentional processes involved in episodic memory retrieval, parietal involvement is not fully explained by them (Shannon and Buckner 2004). In a recent meta-analysis Hutchinson and colleagues found memory retrieval areas to be more lateral than attention areas within parietal lobe (Hutchinson et al. 2009).

In regard to large-scale brain networks, medial and lateral parietal regions are believed to be part of the "default mode network" (DMN). The DMN is thought to monitor introspective processes and is thus involved in memory retrieval but not encoding (Daselaar et al. 2009; Grady et al. 2009; Wang et al. 2010).
With aging, activations in DMN as well as connections within DMN regions show deteriorations (Andrews-Hanna et al. 2007; Koch et al. 2012). Elderly adults show less deactivation in DMN than younger adults, pointing towards an increased effort during tasks (Grady et al. 2006; Lustig et al. 2003). Andrews-Hanna and colleagues found positive relations between functional connectivity within DMN and memory performance in elderly adults (Andrews-Hanna et al. 2007). These findings indicate a compensatory recruitment of DMN regions in elderly in order to maintain the same level of performance (for a review see Reuter-Lorenz and Park 2010).

In our study we aim to investigate if there is a compensatory recruitment of the parietal DMN regions in episodic memory retrieval with age. We expect to see age-related changes in parietal activations, when comparing young and elderly participants with the same episodic memory retrieval task.
The second aim of this study is to investigate the age-related alterations of the connections between DMN regions, focusing on memory retrieval. Therefore, we examined the differences in functional connectivity of parietal regions to other cortical areas across two age groups. We expect a disruption within the network including parietal lobe and other brain regions with age.

Methods

Participants

In total, 21 healthy young participants (female: 11) between the age of 18 – 35 years (mean age ± SD: 24.6 ± 3.6) and 33 healthy elderly participants (female: 16) between the age of 50-89 years (mean age ± SD: 63.4 ± 10.6) took part in this study. Groups are referred to as Young and Elderly. All participants were right handed native German speakers and had normal or corrected-to-normal vision. A medical screening interview was used to exclude participants with any psychiatric or neurological illness.

Elderly participants were screened for cognitive deficits and classified as healthy, using the CERAD-Plus neuropsychological test battery (German version; available at Memory Clinic, Basel, Switzerland, http://www.memoryclinic.ch). The study was approved by the local ethics committee and all participants provided written informed consent.

Stimuli

A face recognition task was used to examine episodic memory retrieval. Retrieval task difficulty was adjusted for Elderly in order to allow a similar level of memory performance. For Elderly, less faces were presented and faces were shown for an increased duration (adjustments shown in parentheses). A total of 120 faces (80 faces) from an online face database were presented (Minear and Park 2004), which were balanced according to age and gender and shown in a pseudo-randomized order. During encoding we used a face-name memory task, where faces were repeatedly presented with a fictional first name in order to facilitate encoding. Participants were asked to memorize faces and names. In the retrieval session, half of the faces shown during the preceding face-name encoding session were repeated (“Old”) the other 60 (40) were novel faces (“New”). No names were shown during the retrieval phase. Although participants were scanned during both encoding and retrieval, the present study focuses on data collected at retrieval.

Design

During retrieval we used a rapid event related design. The task was programmed using Presentation (Neurobehavioral Systems, Albany, CA, USA).

Faces were shown for 2 seconds (3 seconds) and a further 60 null-events were shown for 2 seconds (3 seconds), displaying a scrambled face. Participants were asked to respond within the time the face was shown. Presentation time was adjusted for Elderly in order to allow for longer reaction times, which occur with increasing age (Craik and Rose 2012; Lustig et al. 2003). All events were followed by a jitter of 1-2 seconds, continuing the scrambled face.
For retrieval, participants were instructed to decide whether they had seen the face before. To answer, participants pushed one of two buttons to indicate their response on a custom-made response box.

fMRI procedures

Participants were scanned using a Trio Magnetom 3-T scanner (Siemens, Erlangen, Germany) with a twelve-channel head coil. Functional images were acquired using an echo-planar imaging (EPI) sequence (repetition time = 2250 ms (TR), echo time = 30 (TE), flip angle = 90, FOV = 230 mm, slice order: ascending) Thirty-six slices were acquired in an oblique axial orientation (voxel dimensions, 3.6 x 3.6 x 3.6 mm).

Data analysis

Functional data were analyzed using statistical parametric mapping (SPM8, Wellcome Trust Centre of Neuroimaging, UK). Pre-processing included realignment of head motion, slice timing to account for time differences in image acquisition and normalization to MNI template space. Afterwards, images were smoothed with a Gaussian kernel of 8 mm.
To identify task-related hemodynamic responses on the subject-level, four regressors were included, modeling memory accuracy (hits, correct rejections, misses, false alarms). Furthermore, six regressors modeling head movement parameters of each participant were implemented. Categorizing of memory accuracy, resulted in individual scores of correctly identified old faces (hits), correctly identified new faces (correct rejections) and errors (misses, false alarms). D-prime (d') was calculated to identify a corrected score of memory accuracy (d' = z (hit rate) – z (false alarm rate)). Memory performance for each participant was evaluated with the contrast of retrieval success (hits > correct rejections). For group level analysis, we used subject level contrasts of retrieval success (hits > correct rejections) in a two sample t-test, using reaction time and

d' as covariates. To better estimate effects across groups and conditions, we used a full factorial model in SPM8 (ANOVA), comparing groups (Young, Elderly) and trial types (hits, correct rejections, misses, false alarms) in a 2 x 4 design, using reaction time and d' as covariates.

Functional connectivity analysis

In order to examine correlations of regions involved in episodic memory retrieval, an analysis of functional connectivity was conducted, using seed voxel analysis.

A seed time series was extracted for each participant in left IPS. For each participant, the time series was extracted from 5 mm diameter spheric volumes centered on foci based on strongest activation during the contrast of retrieval success. Individual seeds were chosen, using Wake Forest Pick Atlas toolbox for SPM 8 (http://fmri.wfubmc.edu). Individual time series were corrected for task effects and noise and processed using a MATLAB-Toolbox for functional connectivity analyses (Bedenbender et al. 2011). The extracted seed time series were then correlated with each voxel in the brain to produce spatial correlation maps. Correlations were compared across groups using t-statistics.

Results

Behavioral data

Performance measures are summarized in Table 1. Data from one young participant were excluded after scanning due to anomalously large ventricles. Data from one elderly participant were excluded due to a physical inability to press the response buttons. Thus, behavioral and fMRI measures were analyzed for 20 healthy young participants (female: 11) between the age of 18 – 35 years (mean age ± SD: 24.5 ± 3.7) and 32 healthy elderly participants (female: 15) between the age of 50-89 years (mean age ± SD: 62.9 ± 9.7).

Overall memory performance was similar in Young and Elderly. In the retrieval task Young and Elderly performed similarly regarding percentage of hits, correct rejections and memory accuracy (d') (Table 1). Age was a predictor of memory performance within the group of Elderly ($r = .47$, $p < .01$) but not in Young ($r =$

.01, p = .97). Reaction time differed between groups and was controlled for in second level analysis. Elderly were slower to respond than Young in all four conditions (F (1,51)= 6.795, p < .001).

fMRI results

To determine activation in episodic memory within a group, we compared activation maps for the contrast of retrieval success in Young and Elderly using t-statistics (hits > correct rejections). Young and Elderly showed activation within a similar network. For coordinates see Table 2. No differences in activation were found when contrasting retrieval success in Young > Elderly and Elderly > Young using a two-sample t-test (T = 3.26, unc. p < .001). We compared brain activation across groups and trial types using a 2 x 4 ANOVA (group (Young, Elderly) x trial type (hits, correct rejections, misses, false alarms)). There were no interactions of group x trial type to reveal group differences regarding activations. Given the broad age range in Elderly, a subdivision of the Elderly group (median split: 15 participants (50-60 years) and 17 participants (61-89 years)) resulted in the comparison of three groups (Young, Elderly, Old). Between the resulting three groups, no activation differences were revealed in the network activated in retrieval success, even when comparing the two extreme groups Young and Old with t-statistics. This was confirmed in an additional 3 x 4 ANOVA (group (Young, Elderly, Old) x trial type (hits, correct rejections, misses, false alarms)). No group x trial type interactions were found.

Instead, Young and Elderly showed overlapping activation within the same network (see Fig. 1). Joint activation was mostly left lateralized, showing strongest activation in left IPS, left precuneus, right SPL and left calcarine gyrus (hits > correct rejections, FWE p < .05, see activation map in Fig. 2a). There was a main effect of group, showing an overall stronger activation in Elderly for all conditions (see plots in figure 2b of regions relevant to retrieval success). This effect was mainly located in lateral parietal regions (left SPL, bilateral IPL) as well as pre- and postcentral gyri (F (1, 197) = 23.44, FWE p < .05, see Fig. 3). The stronger activation was also present in Old, when considering the three groups of Young, Elderly and Old.

Since overall strongest activation for retrieval success was found in left IPS, we assumed cluster size of activation to be correlated with memory accuracy (d').

Cluster size of left SPL (including IPS) predicted memory accuracy in Elderly ($r = .361$, $p < .05$) but not in Young ($r = .293$, $p = .21$). To evaluate the contribution of hippocampus to retrieval success, we drew a bilateral ROI using Wake Forest Pick Atlas. The hippocampal ROI showed joint activation of both age groups for retrieval success ($T = 3.13$, FWE $p < .05$).

Functional connectivity

A whole brain analysis based on the seed in left IPS showed a similar network activated in Young and Elderly concerning correlations within parietal regions. In Young the network included correlations within parietal, middle temporal and frontal areas, whereas Elderly had strongest correlations only within parietal areas such as right SPL, bilateral precunei and bilateral IPL ($T = 8.83$; FWE $p < 10^{-6}$; see Fig. 4). In a two sample t-test, whole brain analysis uncorrected for multiple comparisons showed a more local pattern in Elderly with stronger correlations than Young in bilateral precunei and supramarginal gyri, whereas Young had stronger correlations than Elderly in a more extensive network involving bilateral middle temporal gyri ($T = 3.28$, $p < .001$).

Discussion

In this study, we examined memory retrieval in two different age groups to evaluate the influence of aging on the involvement of parietal cortex in episodic memory. There were three main findings: Firstly, Young and Elderly showed activation within a similar network. Unlike previous studies we did not find age-related changes regarding the regions involved in episodic memory retrieval (Grady et al. 2009). Instead, Young and Elderly showed activation within one network, involving lateral and medial parietal regions, with strongest activation found in left IPS. The mostly left lateralized activation corresponds well to previous findings regarding activation during retrieval success (McDermott et al. 2009; Spaniol et al. 2009; Vilberg and Rugg 2008). Joint peak activation of Young and Elderly in left IPS matches results of segmentations of parietal lobe into retrieval-sensitive (IPS, IPL and angular gyrus) and retrieval-insensitive regions (SPL and supramarginal gyrus) (Nelson et al. 2010; Vilberg and Rugg

2008). Furthermore, the dorsal parietal activation of the current study complements the more ventral parietal activation in IPL found in our previous study (Leube et al. 2003). In the previous study, young participants had to remember 30 faces, whereas Young and Elderly in the current study had to remember 60 (40) faces. Therefore the activation of dorsal parietal lobe in the current study could indicate an increasing effort in episodic memory retrieval with greater number of faces, in accordance with the AtoM model (Cabeza et al. 2008; Ciaramelli et al. 2008).

Adding to this, we found an increased effort in with age, which is demonstrated in the overall larger activation in Elderly across conditions. This increase in activation enclosed all four conditions of retrieval, regardless of correct identification or previous knowledge of the stimuli (Old/New) and is in accordance with previous studies, finding task related increases of activation in Elderly compared to Young (for a review see Grady 2008). This may be partly due to a greater engagement of top-down attentional processes, involving dorsal parietal regions, required in a more effortful memory search (Cabeza et al. 2008). Our findings of additional parietal activation correspond well to recent findings of Huang and colleagues who found more parietal activation in elderly to be associated with better performance (Huang et al. 2012).

Overrecruitment of activation in Elderly is thought to be the neuronal expression of an age-related process. This might be part of a compensatory process, activating additional brain regions in order to reach a similar performance level (Grady 2008). However, the increase in parietal activation in Elderly compared to young could also be evidence of a dedifferentiation process (Cabeza et al. 2002; Craik and Rose 2012). Dedifferentiation signifies the less efficient use of resources in Elderly and is expressed by a less focused activation in different brain regions (Reuter-Lorenz and Park 2010). In her review Grady (2008) described the various explanations for age-related changes in brain activation. Additional activation in the same brain regions, in case of the Elderly left SPL and bilateral IPL, is thought to be a sign of inefficiency, whereas additional activation of new brain regions in Elderly (pre-and postcentral gyri) might be evidence for a compensatory process (Grady 2008).

Speculating on the effects of training, we expect a reduction in overrecruitment of parietal regions, since retrieval success effects are influenced by retrieval demand (Shannon and Buckner 2004). To that effect, activation levels are

expected to decrease to a similar level to Young, if activation is indeed indicator of a compensatory process. If it was instead part of a dedifferentiation process, parietal overrecruitment should not decrease with training (Voss et al. 2010).
The overrecruitment of parietal areas corresponds well to our third main finding: the less extensive network in the Elderly found in the functional connectivity analysis. Similar to other studies we found functional connectivity to be reduced with age (Andrews-Hanna et al. 2007; Grady et al. 2009). Despite a higher activation in Elderly, there were weaker correlations of parietal DMN regions to other cortical regions in Elderly. Instead, our results suggest that the overall stronger activation in Elderly might be a compensatory attempt to counteract disruption of the network involved in episodic memory retrieval. The disruption of the network might be the underlying reason for the overrecruitment. Regions correlated with successful retrieval are part of the DMN (Daselaar et al. 2009) and disruptions of the DMN are common with age and often result in an increase of activation with age (Lustig et al. 2003; Grady et al. 2006; Grady et al. 2009, Stevens et al. 2008).

There are limitations to this study. Firstly, while matching memory performance level in Young and Elderly facilitates the comparability of design matrices and allows an immediate comparison of performance across groups, it also inhibits the possibility to compare memory accuracy (d') under the same conditions. Previous knowledge of longer response time and memory deficits with age were the reasons for this alteration. To compare groups in regard to activation during performance, it is essential to enable the same level of performance, even if this results in adapting the task (Price and Friston 1999). Since we were interested in the age-related changes in activation of parietal cortex, it was required to keep performance level similar.
Secondly, the group effect revealed a generally higher level of activation in the Elderly, which may have inhibited the detection of significant differences between groups in retrieval success, since activation is more intense in hits as well as correct rejections. The significant main effect of group (Elderly > Young) may have overshadowed more subtle interactions/differences between age groups.
Since we expect additional activation to be eliminated by further training in Elderly, further studies are required.

Thirdly, we did find Elderly to react slower in all conditions. Reaction time differences between Elderly and Young do not represent an effect of increased difficulty – both groups show a similar memory accuracy (d') corrected for number of events - but are instead a deceleration of mental operations is part of the aging process (Craik and Rose 2012; Hedden and Gabrieli 2004; Reuter-Lorenz and Park 2010).

Conclusions

Our data reveal age-related changes in episodic memory retrieval and parietal lobe activation. While both age groups activate similar regions during the contrast of retrieval success, there are differences regarding intensity and correlations within the network. Elderly show an overall higher activation regardless of condition and a disruption of connections between the parietal lobe and other cortical areas. The extent of parietal activation and memory performance in the elderly may indicate a compensatory effect of the overrecruitment of parietal regions.

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Table 1 Memory Performance and Reaction Times, Mean ± SD

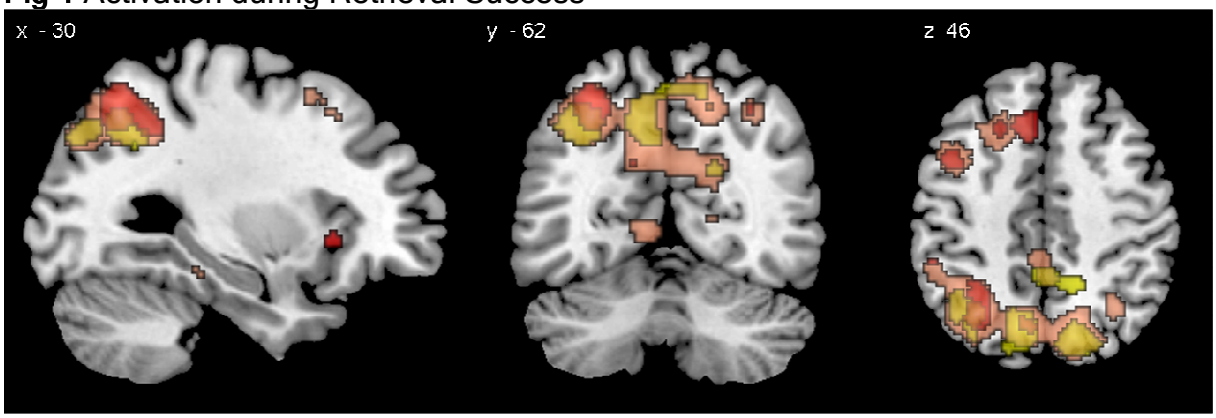
	Young	Elderly	p
Memory Performance			
Hits (%)	75.9 ± 10.9	78.9 ± 11.6	.350
Correct Rejections (%)	73.4 ± 13.8	68.9 ± 17.6	.343
Memory accuracy d'	1.54 ± 0.72	1.49 ± 0.81	.833
Reaction Time (sec)			
Hits	1.169 ± 0.12	1.307 ± 0.22	< .005
Correct Rejections	1.293 ± 0.17	1.594 ± 0.29	< .005
Misses	1.367 ± 0.19	1.858 ± 0.38	< .005
False Alarms	1.349 ± .019	1.607 ± 0.38	< .005

Table 2 Brain Regions activated in Retrieval Success

	Hemisphere	x	y	z	T
Young					
Precuneus	L	- 4	- 66	30	5.78[a]
Inferior Frontal	L	- 38	16	28	5.55[a]
Middle Frontal	L	- 22	20	48	5.54[a]
Intraparietal Sulcus	L	- 32	- 66	48	5.37[a]
Superior Parietal	R	18	- 68	52	4.84
Middle Temporal Gyrus	L	- 58	- 44	10	4.79
Lingual Gyrus	L	-14	- 80	- 6	4.72
Middle Cingulate	L	- 6	- 32	38	4.35
Elderly					
Calcarine Gyrus	L	- 8	- 84	0	4.73
Cuneus	L	- 8	- 70	24	4.61
Superior Parietal	R	20	- 74	50	4.45
Cuneus	R	14	- 86	24	4.19
Precuneus	R	4	- 44	50	3.78

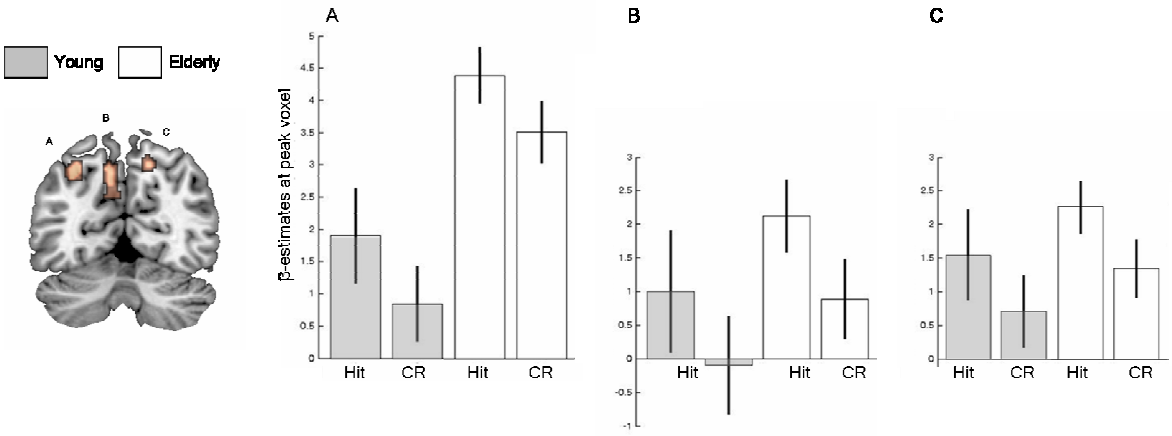
Contrast for each group in second level t-test. L = left, R = right, x,y,z = peak voxels in MNI coordinates FWE cluster corrected $p < .05$, [a] = FWE peak corrected $p < .05$

Fig 1 Activation during Retrieval Success



Red: Young; Yellow: Elderly; Coral: Joint activation (unc., p < .001)

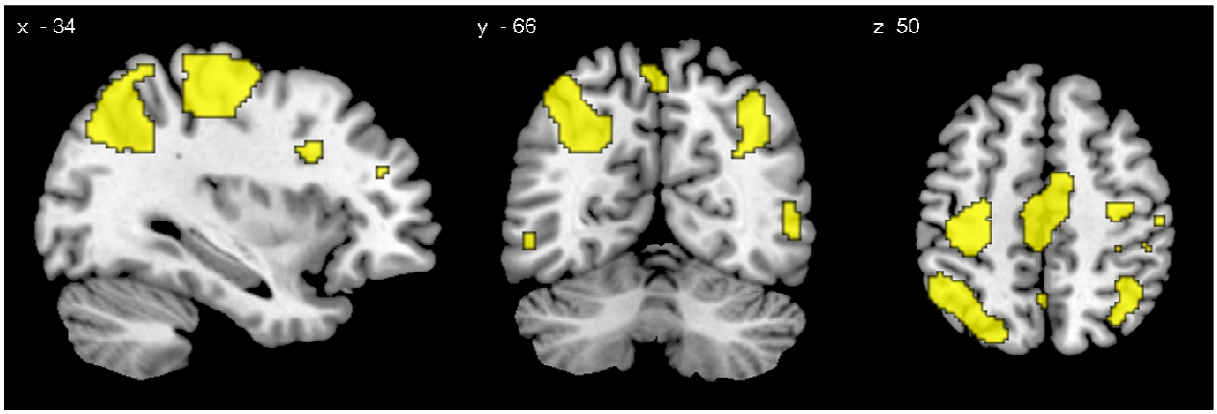
Fig 2 Joint Parietal Activation during Retrieval Success



Bar graphs indicate peak voxel activation in parietal areas for Young and Elderly during the contrast of retrieval success (FWE, p < .05). Activation levels (betas) indicate a group effect: a generally higher activation level in Elderly. Error bars represent 90% confidence interval.

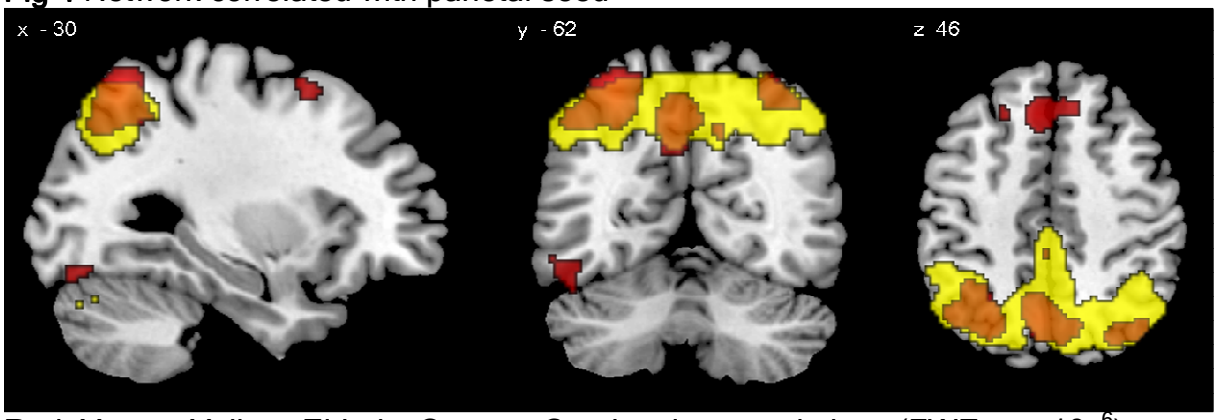
Coordinates in MNI space. A: left intraparietal sulcus -30 -62 46, B: left precuneus -8 -68 48, C: right superior parietal lobe 14 -68 52

Fig 3 Main effect of Group



Yellow: Activation in Elderly > Young across trial types (FWE, $p < 0.05$)

Fig 4 Network correlated with parietal seed



Red: Young; Yellow: Elderly; Orange: Overlapping correlations (FWE, $p < 10^{-6}$)

Paper #2: Changes with age and MCI in associative memory performance and underlying brain networks

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Changes with age and MCI in associative memory performance and underlying brain networks

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Abstract

Associative memory is relevant for everyday activities, such as the binding of faces and corresponding names to form single bits of information. This ability is impaired in elderly and a typical complaint with increasing age. The most important neural correlate of associative memory is the hippocampus, a structure that is crucially implicated in the pathogenesis of Alzheimer's disease (AD). The aim of this study was to compare neural changes with aging and mild cognitive impairment (MCI), an at-risk state for AD, regarding associative memory. Using fMRI, we observed lower hippocampal activation in MCI patients during a face-name recognition task, corresponding to lower associative memory performance. Moreover, spatial extent and magnitude of activation was increased in elderly compared to young, especially in frontal and striatal regions, indicating a stronger involvement of the task positive network (TPN) with age. Functional connectivity analysis revealed an augmented network in healthy elderly in comparison to young. Compensatory processes may involve additional striatal activation, while dedifferentiation may be linked to an increase of TPN activation.

Keywords: Aging, Mild cognitive impairment (MCI), Hippocampus, Task positive network (TPN), Functional connectivity

Introduction

In our aging society dementia is a growing area of public and medical concern. The possibility to treat this condition will depend on our ability to distinguish individuals who will maintain cognitive function from individuals at risk for dementia. Alzheimer's disease (AD) is the most common form of dementia. Common age-related effects and changes with at-risk states for AD occur on a behavioral level as well as in large-scale functional brain networks. Our study aims to distinguish age-related effects and changes with mild cognitive impairment (MCI) on a neural level.

MCI is a transitional at-risk state for AD. This stage includes subjective and objective memory impairment without fulfilling criteria for dementia[1,2]. MCI patients have an increased probability of 12% to convert to AD within the next year, in comparison to 1-2% in healthy elderly[2]. Patients with MCI show cognitive decline particularly in associative memory [3,4], as well as changes regarding brain structure and function. Associative memory includes binding of several pieces of information in one memory trace. Linking of several components is a fundamental feature of episodic memory, such as linking faces and corresponding names[5]. The earliest structural changes in the course of MCI and AD have been found in medial temporal lobe (MTL) regions, which comprise hippocampus, parahippocampal, perirhinal and enthorhinal regions[6,7]. Structural changes due to age or disease include neuropathological changes as well as atrophy within MTL regions. This is especially interesting, since hippocampal structures are believed to play an essential role in the formation and retrieval of associative memory[8,9]. Regarding functional changes, consistent deficits have been found in activation of MTL in mild AD during episodic memory retrieval[10].

Associative memory is often investigated using face-name tasks [4,5,11-17], since recognition of faces and names is an essential part of everyday memory and at the same time represents the spontaneous binding of two arbitrary pieces of information. Remembering names and faces is one of the most common complaints in older adults regardless of memory status and this ability shows impairment with increasing age[18]. Moreover, with age there is a larger impairment in associative recognition than in simple item recognition[19]. When comparing recognition of single items (faces, names) and associative items

(face-name combinations) Naveh-Benjamin and colleagues found specific deficits for associative memory in older adults [20,21]. Based on these results, their associative deficit hypothesis claims that older adults show a deficit in binding single pieces of information to form and later retrieve coherent associative memories[22].

On the neural level, studies find activation in hippocampal regions in tasks for associative memory[12,16,17,23]. While hippocampus and its neighboring MTL structures are thought to be activated during encoding and retrieval of associative memories, fewer studies exist for retrieval[24]. There are various theories describing hippocampus as an integration site for binding memories. Especially between-domain memory associations are thought to be processed in distant neocortical areas and combined in hippocampus[8,9,25]. Hippocampal structures are also critical for recognition memory in general[26]. Episodic memory encoding and retrieval of personal events are supported by hippocampus and surrounding MTL regions[6,14]. While hippocampal structures are essential for associative memory, hippocampal binding is impaired with age[9,19]. Connectivity studies with fMRI reveal an altered hippocampal network in older adults in comparison to young subjects, involving primarily frontal and striatal regions rather than posterior regions[27,28,29]. Adding to these effects of age, AD is thought to be a disconnection syndrome where large scale functional network correlations become dysfunctional in AD and at-risk states[30]. There are changes of functional connectivity with MCI and AD in comparison to healthy elderly, especially regarding attenuated functional connectivity of hippocampus to frontal regions[30,31].

Previous studies have investigated associative memory of MCI patients and found face-name tasks to discriminate well between healthy elderly and MCI[4,5,15,32]. Less is known about underlying brain networks since only two of these studies investigated associative memory and its underlying networks with fMRI, observing decreased hippocampal activation with declining memory status[15,32].

Few studies have compared young, healthy elderly and MCI or AD patients in the same study with the same task[3,33,34]. Of these, only Johnson and colleagues investigated encoding and retrieval in MCI and healthy elderly and young within the same study. Using MTL and posterior cingulate (PC) regions of interest, they found less hippocampal and PC activation in MCI[33].

The present report focuses on recognition retrieval, while in the majority of studies only encoding was scanned. To our knowledge, our fMRI study is the first to compare healthy young, healthy elderly and MCI patients who differed in age (young/older) and memory status (healthy/MCI), while investigating associative memory with the same face-name recognition task. This design allows us to distinguish individuals who will maintain cognitive function with age from those with cognitive decline (MCI). Furthermore, while earlier studies used MTL regions of interest, we take large-scale functional brain networks into account. We use a face-name recognition task to investigate associative memory in young, healthy elderly and MCI patients. Since the combination of faces and names needs associative binding, we expect activation in hippocampal regions. We expect to see changes in hippocampal activation mirroring the difficulties with associative face-name memory in healthy elderly and especially MCI. Regarding functional connectivity, we expect a decrease of hippocampal connectivity with memory decline in MCI.

Methods

Participants

Twenty-one healthy young participants (female: 11) with a mean age of 24.6 (± SD 3.6) years (range: 18 – 35), 34 healthy elderly participants (female: 18) with a mean age of 63.0 (± 10.0) years (range: 50-89) and 24 MCI patients (female: 12) with a mean age of 65.9 (± 9.6) years (range: 50-86) took part in this study. All participants were right-handed native German speakers and had normal or corrected-to-normal vision. A medical screening interview was used to exclude participants with any psychiatric or neurological illness.

All older participants were screened for cognitive deficits using the CERAD-Plus neuropsychological test battery which enables a comparison of subtests considering age- and education-adjusted norms (German version; available at Memory Clinic, Basel, Switzerland, http://www.memoryclinic.ch). MCI patients were classified according to the Mayo criteria for MCI which are based on a subjective cognitive complaint and an objective memory impairment in a standardized test (performing at least 1.5 standard deviations below norm in at

least one relevant subtest of the CERAD-Plus test battery (z < -1.5 in Total Word List, Delayed Recall Word/Figures, MMSE)), relatively preserved general cognition and essentially intact activities of daily living, no dementia[2]. Recently developed clinical criteria regarding MCI due to AD are also applicable for our participants[1]. In critical cases, the decision was based on multidisciplinary clinical judgment and consensus. The study was approved by the ethics committee of the Medical Faculty of the University of Marburg. All participants provided written informed consent and were paid for participation.

Experimental design

All participants were scanned during face-name encoding, face retrieval and face-name recognition. The face retrieval phase is described in a previous publication[35]. The present report focuses on data collected at the face-name recognition task which was used to examine associative episodic memory retrieval. A total of 40 faces from an online face database were presented[36], which were balanced according to age and gender and shown in a pseudo-randomized order.

For the preceding encoding phase, we used a face-name learning task, where faces were repeatedly presented with a fictional first name. First names were taken from a listing of the most common German names for each decade and were matched to the age of the person pictured. Participants were asked to memorize faces and names. Encoding task difficulty was adjusted in order to allow a similar level of memory performance for young and healthy elderly[37]. For older participants (healthy elderly and MCI), less faces were presented (80 vs 120) and faces were shown for an increased duration (3000ms vs 2000ms). This allowed us to control for effort when comparing healthy participants (young and elderly), assuming that face-name recognition is influenced by encoding success. The face-name recognition task followed approximately 30 minutes after the completion of the encoding phase.

During the face-name recognition task we used an event related design. The task was programmed using Presentation (Neurobehavioral Systems, Albany, CA, USA).

Faces were shown with a choice of two names printed below and participants were asked to choose the name the face was presented with during the preceding encoding phase. Faces and names were shown for 5000 ms and

participants were asked to choose one of the names within the time frame. To answer, participants pushed one of two buttons using the index and middle finger of the right hand to indicate their response on a custom-made response box. An additional 20 null-events were shown for 5000 ms each, displaying a scrambled face. All events were followed by a jitter of 1-2 seconds, displaying the scrambled face.

Data acquisition

Participants were scanned at the Philipps University Marburg with a Trio Tim Magnetom 3-T scanner (Siemens, Erlangen, Germany) and a twelve-channel head coil. Functional images were collected with a T2*-weighted echo planar imaging sequence (EPI) (64 x 64 matrix, FOV 230 mm, TR = 2200ms, TE = 30 ms, flip angle 90°, slice order: ascending). Thirty-six slices were acquired in an oblique axial orientation (voxel dimensions 3.6 x 3.6 x 3.6 mm). After discarding five initial volumes, 185 scans were included in the analyses.

Data analysis

Behavioral data and participant statistics were analyzed using SPSS for Windows 15.0 (SPSS Inc., Chicago, USA).

Functional MRI data were analyzed using statistical parametric mapping SPM8 (Wellcome Trust Centre of Neuroimaging, UK) based on Matlab 7.7.0 (Version R2008b, The Mathworks, MA, USA). Data pre-processing consisted of realignment of head motion, slice timing to account for time differences in image acquisition and normalization to SPM8's MNI EPI template (resulting voxel size 2 x 2 x 2 mm). Images were smoothed with a Gaussian kernel of 8 mm full width half maximum.

To identify task-related hemodynamic responses on the subject-level, one regressor modeling face-name events convolved with a canonical hemodynamic response function and six regressors modeling head movement parameters were included. For group level analysis, we used subject level contrasts of face-name events vs baseline. Baseline included nullevents and jitters. We conducted a full factorial model in SPM8 (ANCOVA) to compare groups (young, healthy elderly, MCI), using individual memory performance as covariate (percentage of correctly chosen names). A group level conjunction analysis was

calculated to localize a common associative memory network in all participants across groups. In order to identify activation differences between the groups, group-level t-contrasts were used. Memory performance was expected to depend on hippocampal activation. To investigate the relation between memory performance and hippocampal activation, a regression analysis was conducted across groups. All analyses refer to whole brain results and anatomical locations were determined using the Anatomy Toolbox[38] .

To examine correlations of regions involved in associative face-name recognition, functional connectivity was analyzed using a seed region approach. Based on peak activation regarding memory performance during the face-name recognition task, left hippocampus was selected as seed region (MNI: x -22, y -26 z -16). To restrict individual seed voxels to left hippocampus, a hippocampal mask was created using Wake Forest Pick Atlas toolbox for SPM 8 (http://fmri.wfubmc.edu). Starting at peak activation, an individual seed was chosen for each participant based on the next local maximum within the left hippocampus mask. Individual seeds were based on a threshold of $p < .1$ within the mask. Time series were extracted for each participant as the first eigenvariate in SPM in a sphere of 6 mm radius[39] . To account for noise, two additional time series were extracted for each participant within CBF and WM masks. Subject level analysis included the extracted seed time series of left hippocampus, two time series for noise, the regressor modeling face-name events and six regressors modeling head movement. To remove task-related variance, the F-contrast was placed on the six regressors modeling head movement. Time series were analyzed for 16 young, 29 healthy elderly and 16 MCI, since no activation within left hippocampus was found for the other participants. To compare correlations across groups, a full factorial (ANOVA) was conducted in SPM8, comparing networks of correlations to hippocampus for young, healthy elderly and MCI.

Results

Behavioral data

Data of one young participant were excluded after scanning due to anomalously large ventricles. Data of one healthy elderly participant were excluded due to a physical inability to press the response buttons. Data of one healthy elderly and two MCI patients were excluded due to missing data for the face-name task. Data of one MCI patient were excluded due to a high GDS score. Thus, behavioral and fMRI measures were analyzed for 20 young participants, 32 healthy elderly participants and 21 MCI patients. Participant statistics and memory performance of the included subjects are summarized in Table 1.

MCI patients were impaired in face-name recognition in comparison to young and healthy elderly ($F(2, 70) = 11.8$, $p < .001$). There was no impairment in healthy elderly in comparison to young, indicating the adjustment of face-name learning task difficulty was successful. Within the group of healthy elderly, there was a correlation of memory performance and age, representing a decline of associative memory performance with age ($r = -.37$, $p < .05$).

Reaction time varied with age and memory impairment. In a repeated measure ANOVA (within: RT hits, RT misses; between: young, healthy elderly, MCI) we found a main effect for RT type: participants of all groups were slower to respond when making a wrong recognition than a correct association ($F(1, 70) = 38.1$, $p < .001$). We also found a main effect for group: MCI were slower to respond than young ($F(2, 70) = 6.5$, $p < .001$). There was no difference in RT when comparing young and healthy elderly, indicating RT to vary only with memory performance.

fMRI data

Results are reported whole brain FWE cluster corrected ($p < .05$) unless otherwise specified. All coordinates refer to MNI space as used in SPM8.

We compared brain activation during the face-name recognition task across groups with an ANCOVA, regarding individual memory performance as covariate (percentage of correctly chosen names). The conjunction analysis indicated a common network activated in response to the face-name recognition task in all three groups, involving bilateral fusiform gyri, bilateral insulae, left

parietal lobe, left frontal regions and left calcarine gyrus (Fig 1, FWE peak corrected, p <.05; for coordinates see Table 2). For varying magnitude of activations in individual groups with age and memory status see Fig 1. To illustrate, sum of activated voxels across groups were 5946 in young, 34,737 in healthy elderly and 12,860 in MCI, suggesting an inverse u-shape of activation magnitude across groups.

When comparing activations between groups, there was a main effect of group. Group-level t-tests indicated that healthy elderly and MCI showed increased activation in comparison to young. Healthy elderly displayed increased activation in bilateral precentral regions and bilateral putamen (Fig 2a) and MCI showed stronger activation in bilateral precentral regions as well as bilateral inferior parietal cortex (IPL) (Fig 2b). Thus, both older groups showed increased activation in precentral areas. For coordinates see Table 3. No additional activation was found in young (Young > Elderly, Young > MCI) or when comparing older groups (Elderly > MCI or MCI > Elderly).

When considering memory performance during the face-name recognition task, peak activation was predominantly in left hippocampal and parahippocampal regions (T (67) = 4.63, Fig 3). The hippocampal cluster was the only activation related to memory performance. In the regression analysis, increased hippocampal activation was correlated to better memory performance in the face-name recognition task (r = .51, p < .001; Fig 3). This correlation was still valid when correcting for age (r = .48, p < .001). Similar results were found with a regression across both older groups (r = .58, p < .001). Even when correcting for age, increased activation of left hippocampus was correlated to better face-name recognition (r = .52, p < .001), signifying a change of hippocampal activation with associative memory performance. MCI patients showed the lowest hippocampal activation in comparison to the other groups.

We analyzed correlations of the peak hippocampal seed (-22, -26, -16) across the whole brain using an ANOVA for group analysis. All groups showed correlations of the hippocampal seed across medial and lateral temporal regions (Elderly > Young > MCI). When comparing groups, there was stronger correlation of the hippocampal seed and bilateral frontal regions, bilateral temporal regions as well as bilateral putamen in healthy elderly in comparison to young (Fig 4a, for coordinates see Table 4). For MCI patients there was

increased correlation of bilateral caudate nuclei in comparison to young (Fig 4b, Table 4). Thus, increased connectivity to striatal areas (putamen, caudate nucleus) was present in both older groups, while correlations to frontal and temporal regions were only present in healthy elderly. No other contrasts showed differences in correlations with the hippocampal seed (FWE cluster corrected $p > .05$).

Discussion

In the present study we investigated the effects of age and MCI on associative memory. We examined behavioral differences, pattern of activations and corresponding networks in response to an associative face-name recognition task. There were four main findings. MCI patients were impaired regarding associative memory performance. While there was a common network activated in young, healthy elderly and MCI, older age and memory impairment were related to increased activation in brain regions associated with TPN, such as precentral regions, striatal regions and parietal lobes. Moreover, we found associative memory performance to be linked primarily to activation in the left hippocampal region. Similar to the activation patterns, we found a common network of functional connectivity in all groups, but older adults (healthy elderly and MCI) showed additional correlations within task-positive and striatal regions.

Behavioral effects

Between the three groups significant differences were found in associative memory accuracy and reaction time. As expected, we found associative memory impairment for face-name recognition in MCI patients compared to healthy elderly. While impaired face-name recognition in comparison to young could be an effect of the adjusted encoding task, the attenuated memory performance of MCI patients in comparison to healthy elderly is valid. Consistent with previous studies using face-name recognition in MCI, we confirmed associative memory deficits in MCI patients that exceeded deficits occurring with age[4,5].

In contrast to studies reporting associative deficits in healthy elderly, we did not find healthy elderly to recognize less face-name combinations than young[19,20,23]. While the face-name recognition task was the same for all three groups in our study, we adjusted the preceding face-name learning phase difficulty to enable similar task performance. During the encoding phase, healthy elderly and MCI patients saw less faces and had more time to react (see 2.2 Experimental design). The similar associative memory performance in young and healthy elderly indicates a successful adjustment of encoding phase difficulty. We have reported the comparison of memory for faces within the same sample of young and healthy elderly and we found both groups to perform similar in our face retrieval task as well[35]. This is in line with findings of recent fMRI studies which, when adjusting task difficulty, did not find differences in memory performance between young and older participants[14,40]. At the same time, we did observe a loss of associative memory performance with increasing age within the group of healthy elderly; a decline in face-name memory performance was inversely related to increasing age. When task difficulty is not adjusted, recognition of face-name combinations has repeatedly been shown to be impaired in older adults[20,23]. Rather, our behavioral results emphasize a deficit in associative memory for MCI patients, while also showing a decrease of associative memory performance with increasing age.

Age-related effects and changes with MCI in pattern of activations

When looking at underlying neural patterns, we found a common network activated in all three groups, consisting of fusiform gyri and parietal regions. Altogether, we were successful in adapting face-name task difficulty to elderly participants, since performance level and location of the activated network were similar in young and healthy elderly. At the same time our findings confirm previous studies reporting many similarities in the patterns of activation in young and healthy elderly[41] and a common network activated in MCI and healthy elderly during retrieval[42].

However, neural correlates of memory impairment were observed. We observed differences in activation magnitude across the three groups. The sum of activated voxels in the three groups suggests an inverted u-shape for changes in the underlying network in face-name recognition across age and memory status. Healthy elderly showed a marked increase in network activation in

comparison to young, which was again reduced in MCI patients. This indicates a possible compensational mechanism in healthy elderly, which deteriorates with loss of memory performance and results in reduced activation in the functional network. To address the issue of an inverted u-shape curve accompanying alterations in memory performance, we did direct group comparisons.

In direct group comparisons, we found increased activation in healthy elderly and MCI in precentral regions and IPL, which are regions involved in the fronto-parietal network or task positive network (TPN)[43,44]. In addition, we found increased activation in putamen in healthy elderly. On the whole, these results support recent results by Grady and colleagues who demonstrated the TPN and striatal regions to be more active in older adults[29].

The TPN is a large-scale functional brain network implicated in cognitive control and attention [43,44]. This network including frontal and parietal regions is engaged in encoding and retrieval of face-name associations[45]. Precentral regions of TPN are active in encoding and retrieval[46] and together with IPL part of the cognitive control network[47]. Pre- and postcentral gyrus activation has been observed in healthy elderly and MCI during retrieval[42], while contradicting results have been found in regard to its influence on memory performance[48,49].

When investigating episodic memory, increased activation in healthy elderly are typical findings, especially in frontal and parietal regions which are part of the TPN[40,41,50,51]. Overrecruitment of these regions with age is often explained with strategic processes and increased reliance on cognitive control[10,41,45]. We encountered a similar pattern in bilateral pre- and postcentral regions as well as parietal regions, when investigating memory with a face retrieval task in our sample[35]. There, healthy elderly showed more activation in precentral areas regardless of condition (old/new or correct/incorrect). Various explanations exist for the observed increase in brain activation with age: compensational processes or dedifferentiation, which can also co-occur in older adults during retrieval[41,52].

In general, dedifferentiation signifies reduced efficiency in the use of resources with age and is expressed by less focused activation in different brain regions[53], whereas compensation indicates the use of additional brain regions in order to reach a similar performance level despite deteriorating brain circuitry function[41]. The additional precentral activations in our study occurred in healthy elderly and

MCI patients and therefore might be indicators of dedifferentiation rather than compensational processes, since there is supposedly no advantage for memory performance with increased activation in these areas. This is in line with the idea of age related changes in neural efficiency, where older adults show overrecruitment for a similar level of memory accuracy[40,41]. On the other hand, there remains the possibility of an attempt at compensational reorganization, which is not sufficient to boost performance in MCI patients [52].

Despite the similar performance level of young and healthy elderly in our study, healthy elderly showed additional bilateral striatal activation in comparison to young. The striatum is implicated in a memory network underlying declarative memory in thalamo-striatal-cortical circuits[54] and greater activation of elderly in comparison to young has been observed[55]. This additional activation of healthy elderly was associated with better memory performance, implying compensatory processes[48,55], which supports our findings of additional putamen activation associated with better memory performance.

In contrast to this, MCI patients showed an increase in bilateral inferior parietal activation in comparison to young, confirming findings of hyperactivation in IPL in subjects at-risk and patients with AD[10,32]. The additional activation of IPL is related to poorer performance, implicating dedifferentiation processes in MCI and might reflect greater demand on cognitive control[29].

In conclusion, judging from the better results in face-name recognition in healthy elderly participants in comparison to MCI patients, the extra putamen activation might serve a compensational effect, while the additional TPN activation in both groups might be an indicator of dedifferentiation.

Hippocampal activation and correlation to memory performance

When looking at activation patterns regarding associative memory performance during face-name recognition, we found primarily left hippocampal activation. The hippocampal cluster was the only activation related to memory performance.

Previous studies have shown increased activation for associative memory in hippocampal regions, mostly during encoding tasks[12,16,17,23]. We showed further evidence that hippocampal activation is also increased during recognition of associative information. Our finding is in line with recent studies finding activation of hippocampal areas in encoding and during retrieval of associative

memories especially for the combination of faces and names[14,32,45,56] In addition to the finding that the hippocampal cluster was the only activation found in relation to memory performance, we also found magnitude of hippocampal activation to be correlated to memory performance in the face-name recognition task.

Consequently, MCI patients showed lower memory performance and hippocampal activation whereas increased performance was related to a higher level of activation in left hippocampus, similar to previous studies (for a review see[26]). Concluding, we found a reduction in hippocampal activation with memory status. MCI patients were impaired in memory performance and hippocampal activation, even when controlling for age. Across age groups we did not find hippocampal activation to be decreased in the healthy elderly group, which is in agreement with recent studies[14,27], whereas others have found decreased hippocampal activation with age when comparing healthy young and elderly[23]. However, we adjusted the preceding encoding phase in our study, so memory performance across healthy groups was similar and underlying hippocampal activation as well.

In healthy elderly, activation of left hippocampus is often linked to successful retrieval[50,57] and between-domain associations which involve hippocampal binding, are impaired with age[9,19]. More extended activation within hippocampus has been found for combination of names and faces, than for faces or names alone[56], which fits to the associative deficits Naveh-Benjamin and colleagues found in elderly for the association of both stimuli in comparison to one[20]. Memory performance was decreased in MCI and consistently, hippocampal activation was reduced as well.

Studies have reported reduced activation of left hippocampal region in memory retrieval for AD and populations at-risk for AD[15,58-60]. In contrast to retrieval, several studies using encoding paradigms, have found an increase in hippocampal activation with MCI which have mostly been labeled compensatory hyperactivations[61-63]. On the contrary, other encoding studies have found attenuated hippocampal activation in MCI[16,33,64] or no change in activation[11,24]. The few studies examining episodic encoding and retrieval with the same task in MCI and healthy consistently reported reduced hippocampal activation in retrieval[15,32]. Concordant to these results, we found reduced hippocampal activation in MCI, even when controlling for memory performance.

To conclude, the finding of left hippocampal activation during face-name recognition which is related to memory performance and is impaired in at-risk states for AD, bears further evidence that the hippocampus is critically involved in relational binding during retrieval of associative information[8,9]. Recent longitudinal studies provide evidence that hippocampal activation decreases with clinical decline in memory studies and tests of associative memory are best to differentiate effects of age and MCI[5,13].

Correlations of networks with hippocampal seed

To determine the neural underpinnings of associative memory a description of activations and their connections within large-scale functional networks are essential. Starting from a hippocampal seed, the network of positively correlated brain activation included primarily MTL regions in all groups. These were as expected, quite symmetric across hemispheres and included mostly temporal areas, similar to a hippocampal network found in an earlier study[65,66].

We chose the left hippocampal seed, since it was the location of strongest activation related to memory performance. Accordingly, left hippocampus is part of a network (including caudate nucleus, temporal gyri) that underlies autobiographical, episodic and semantic memory retrieval[6710)].

Consistent with the pattern of increased activation in healthy elderly described above, we found stronger correlations of the hippocampal seed to bilateral middle frontal, temporal gyri and bilateral putamen. This is in line with previous results, which describe an altered hippocampal network in elderly in comparison to young, involving frontal and striatal regions [27,28,29]. This is a further indication of a stronger functional connectivity within the TPN network in healthy elderly in response to increased cognitive demand[29].

While we found increased functional connections to putamen in healthy elderly, we also found stronger connections to caudate nucleus in MCI patients. Putamen and caudate nucleus are part of the striatum. Studies have found increased connectivity to caudate nucleus in at risk population for AD[11] and poorer performance associated with additional caudate activation[55], while regarding it as compensatory effort. To conclude, older participants regardless of memory status demonstrated stronger connections to striatum. One explanation could be a dysfunctional connection to caudate nucleus, while suggesting a beneficial connection to putamen. The hippocampal-putamen

connection is thought to be compensatory, since young and healthy elderly show the same associative memory performance level, and putamen is the only additional activation and hippocampal link that differs between young and healthy elderly and is not present in MCI patients.

In conclusion, our study shows that MCI patients are impaired in recognition of associative information and this is reflected in underlying neural networks. While activating a similar network in response to face-name recognition, magnitude of activation suggests an inverse u-shape in TPN and striatal regions across young, healthy elderly and MCI patients. In contrast to healthy elderly, MCI patients do not seem able to compensate for deficits with additional neural activation. Moreover, hippocampal activation is decreased in MCI patients, mirroring their difficulties with associative face-name memory. Across groups, less hippocampal activation is related to impaired memory performance. The underlying network shows stronger connections to frontal and striatal regions in healthy elderly in response to increased cognitive demand and connections decrease with MCI. Compensatory processes seem to involve additional striatal activation, while dedifferentiation may be linked to an increase of TPN activation. Our study reveals how cognitive aging and decline of memory performance with an at-risk state for AD is reflected in neural networks.

Disclosure statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Table 1: Participant statistics and memory performance

	Young	Elderly	MCI
Participant statistics			
n	20	32	21
Age	24.5 ± 3.7	62.2 ± 9.2	65.6 ± 8.5
Sex ratio F/M	11/9	16/16	10/11
Education	16.4 ± 2.1	15.2 ± 3.2	14.1 ± 3.5
GDS score*		1.8 ± 1.7	3.2 ± 1.9
Face-name task			
Hits %*** [a]	74.0 ± 10.7	65.6 ± 14.0	55.1 ± 11.5
Misses %*** [a]	26.0 ± 10.7	34.4 ± 14.0	44.9 ± 11.5
Reaction time hits** [a]	2.12 ± 0.4	2.41 ± 0.4	2.70 ± 0.5
Reaction time misses** [a]	2.34 ± 0.5	2.57 ± 0.6	2.82 ± 0.5
Selected CERAD scores			
MMSE***		29.2 ± 0.8	26.7 ± 1.5
Total CERAD score***		91.8 ± 4.0	80.3 ± 8.7
Total word list***		24.8 ± 2.6	19.5 ± 3.8
Delayed world list***		9.0 ± 1.1	6.1 ± 2.0

Means ± Standard Deviations; *p<0.05; **p<0.01 *** p <0.001.
[a] difference between MCI < healthy participants (Young and Elderly)

Table 2: Common network activated during associative face-name recognition

	Hemisphere	x	y	z	T
Conjunction Analysis					
Fusiform Gyrus	R	38	- 56	- 16	8.33
Fusiform Gyrus	L	- 40	- 60	- 14	8.00
Precuneus	R	20	- 66	40	7.04
Frontal/SMA	L	- 6	8	50	7.00
Superior Parietal Lobe	L	- 26	- 62	46	6.33
Insula Lobe	R	32	24	- 2	6.29
Inferior Parietal Lobe	L	- 34	- 46	44	6.23
Insula Lobe	L	- 30	22	2	6.02
Precentral Gyrus	L	- 36	- 22	58	5.75
Inferior Frontal Gyrus	L	- 40	8	28	5.51
Precuneus	L	- 14	- 68	36	5.44
Calcarine Gyrus	L	- 8	- 80	4	5.31

Conjunction analyses across young, healthy elderly and MCI
MNI coordinates; FWE corrected $p < .05$ (peak-level)

Table 3: Group effects in face-name recognition

	Hemisphere	x	y	z	T
Elderly > Young					
Putamen	R	30	- 12	0	5.75
Putamen	L	- 30	- 14	2	5.71
Middle Temporal Gyrus	R	46	- 70	2	5.32
Precentral Gyrus	L	- 24	- 16	60	4.67
Precentral Gyrus	R	20	- 18	64	4.52
Cerebellum	R	20	- 66	- 34	4.45
MCI > Young					
Superior Frontal Gyrus	R	22	- 10	64	5.16
Supramarginal Gyrus	R	56	- 34	44	5.06
Precentral Gyrus	L	- 22	- 26	64	4.85
Supramarginal Gyrus	L	- 50	- 28	24	4.79
Angular Gyrus	L	- 30	- 50	34	4.14

MNI coordinates; FWE corrected $p < .05$ (cluster-level)

Table 4: Group effects in connectivity

	Hemisphere	x	y	z	T
Elderly > Young					
Middle Frontal Gyrus	L	- 42	14	54	5.31
Middle Frontal Gyrus	R	42	- 4	64	5.23
Superior Temporal Gyrus	L	- 52	- 16	- 4	5.18
Superior Temporal Gyrus	R	58	- 12	0	5.13
Putamen	L	- 26	- 8	14	5.11
Middle Temporal Gyrus	R	52	- 4	- 26	4.83
Putamen	R	24	10	10	4.75
MCI > Young					
Caudate Nucleus	R	18	16	12	5.42
Caudate Nucleus	L	- 18	16	10	5.04

MNI coordinates; FWE corrected, $p < .05$ (cluster-level)

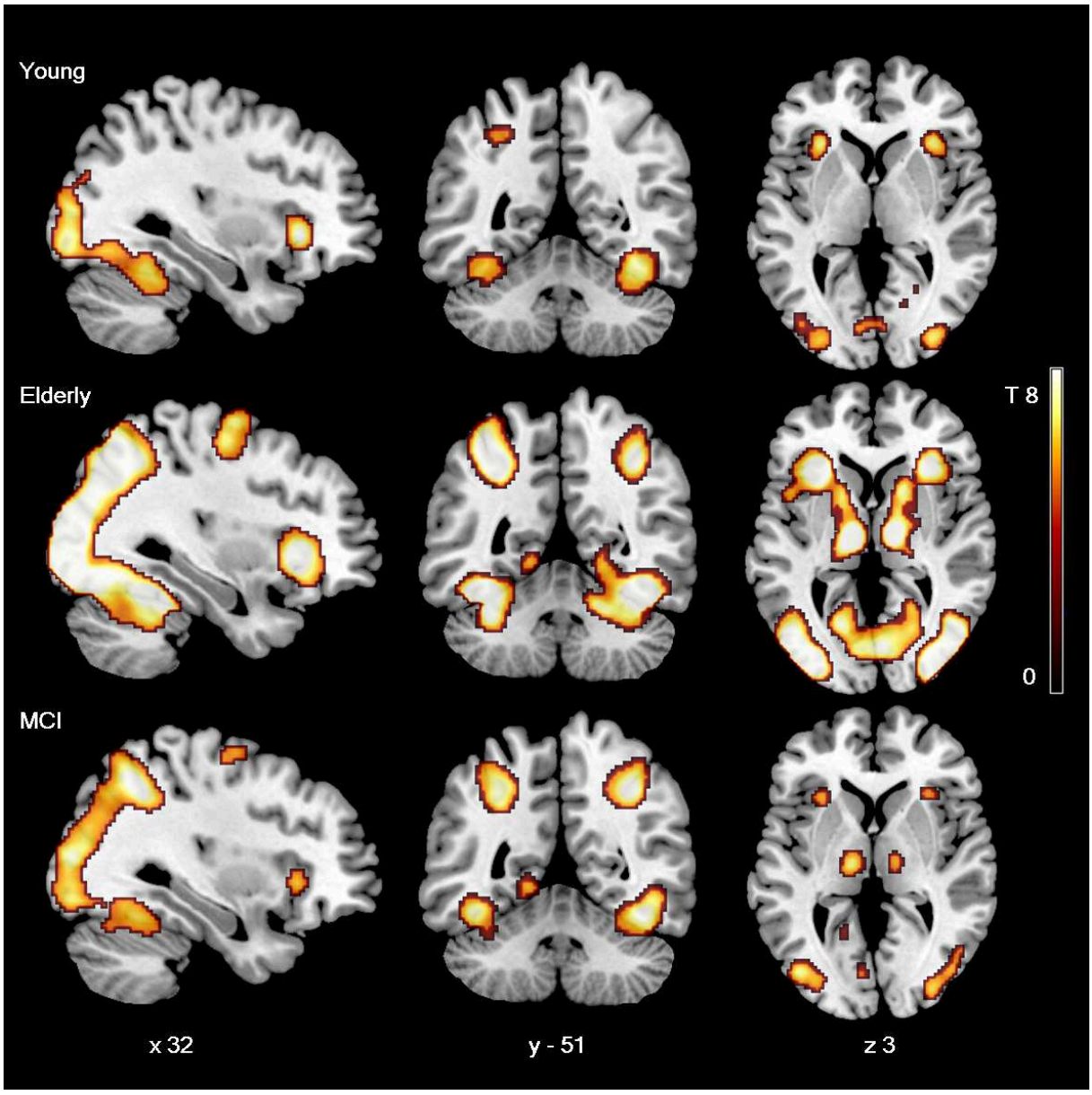

Fig 1: Activation in groups during face-name recognition task in young, healthy elderly and MCI. For coordinates see Table 2. FWE corrected $p < .05$ (cluster-level)

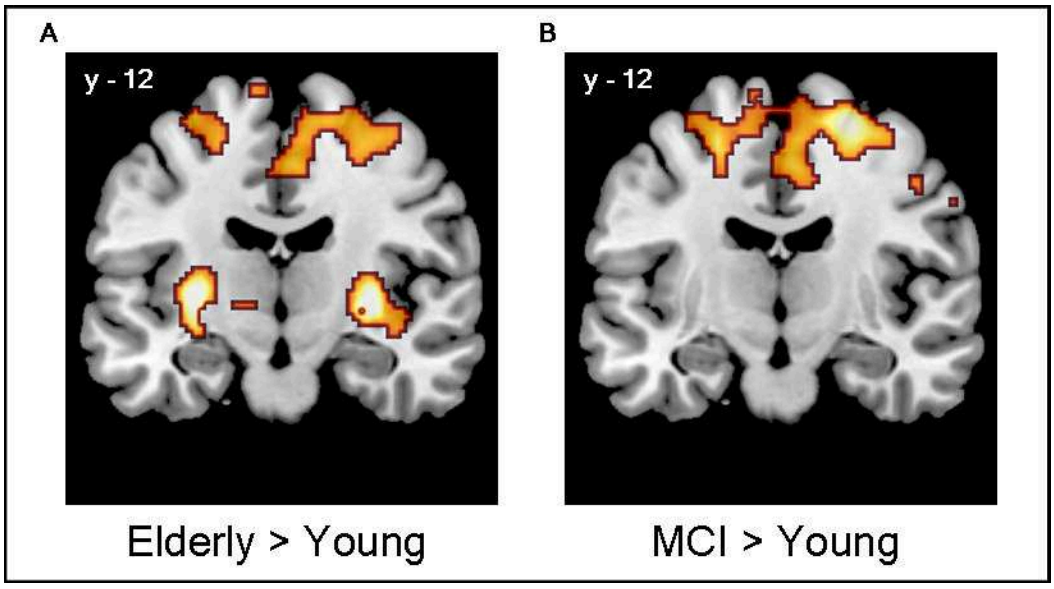

Fig 2: Activation in group contrasts during face-name recognition (t-tests). For coordinates see Table 3. FWE corrected $p < .05$ (cluster-level)

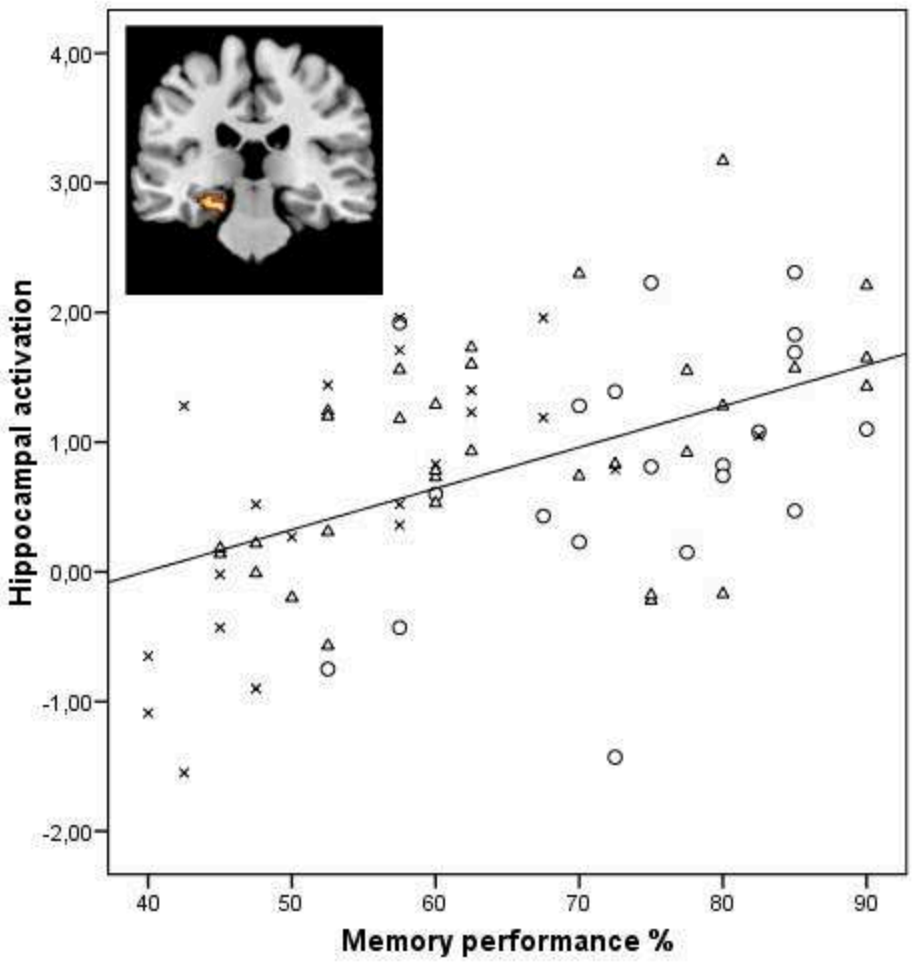

Fig 3: Hippocampal activation in relation to memory performance across groups. Contrast on memory performance. With hippocampal/ parahippocampal ROI mask for visualization. FWE corrected $p < .05$ (cluster-level).Correlation of memory performance and hippocampal activation (ß-estimates) across groups. Δ = Young, o = Elderly, x = MCI

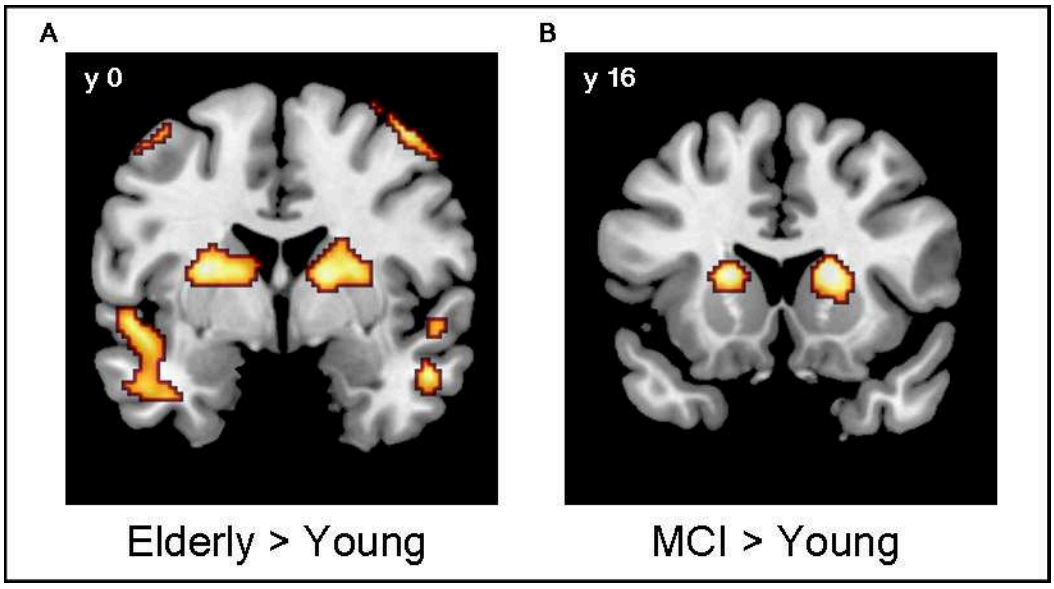

Fig 4: Functional Connectivity increased in older groups. For coordinates see Table 4. FWE corrected $p < .05$ (cluster-level)

Paper #3: Changes in large-scale network activation during face-name encoding in young, healthy elderly and MCI – an fMRI study

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Changes in large-scale network activation during face-name encoding in young, healthy elderly and MCI – an fMRI study

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Abstract

Previously, it has been shown that encoding is supported by deactivation of the default mode network (DMN) and activation of the task positive network (TPN). Using functional magnetic resonance imaging (fMRI), we investigated changes within these large-scale brain networks in relation to age and cognitive status. Twenty healthy young, 31 healthy elderly and 23 MCI patients took part in a face-name encoding task. During the encoding task, magnitude of DMN deactivation was related to age and cognitive status. Young showed more deactivation in posteromedial cortex and inferior parietal lobe than older adults, whereas only healthy elderly showed additional activation of hippocampus. TPN activation increased with age, showing no effect of cognitive status. Both healthy elderly and MCI patients showed increased activation in pre- and postcentral TPN regions in comparison to young. In conclusion, DMN deactivation decreased with age, suggesting compensation in healthy elderly but not in MCI, while TPN overrecruitment was present in both healthy elderly and MCI, indicating dedifferentiation processes with age.

Keywords: Aging, Mild Cognitive Impairment (MCI), Default Mode Network (DMN), Task Positive Network (TPN)

1. Introduction

The inability to remember names is the most commonly reported memory failure in healthy older adults, especially in elderly visiting memory clinics (Irish, Lawlor, Coen, & O'Mara, 2011; Pires et al., 2012). Older adults have trouble binding pieces of information into complex memories, indicating an overall age-related associative deficit (Old & Naveh-Benjamin, 2008). The encoding deficit is thought to stem from age-related declines in perception, attention and memory in elderly (Craik & Rose, 2011). Moreover, the ability to form face-name associations represents an important everyday function and is a potential predictor of subsequent conversion to Alzheimer's disease (AD) (Irish et al., 2011). Face-name associative encoding tasks are a popular measure to investigate associative episodic encoding in healthy elderly and at-risk patients for AD while using a relevant everyday task, since binding a specific name to a specific face resembles everyday associations (Kirwan & Stark, 2004; Sperling et al., 2010; Zeineh, Engel, Thompson, & Bookheimer, 2003).

Encoding of new episodic memories requires an extensive neural network centering on hippocampus, which is part of the medial temporal lobe (MTL) (Dickerson & Eichenbaum, 2010; Wais, 2008). During subsequent memory success, this encoding network found in young adults includes activation of hippocampus and deactivation of frontal and temporal regions, inferior parietal cortex (IPL) and posteromedial cortex (PMC) (Daselaar et al., 2009; Miller et al., 2008; Pihlajamäki et al., 2009). The hippocampal structure is an essential part of this network and formation of new memories relies on it, especially encoding of associative memory in order to bind several pieces of information into one memory (De Rover et al., 2011; Greicius et al., 2003; Kirwan & Stark, 2004; Zeineh et al., 2003). Hippocampus supports encoding as well as retrieval of episodic memories (Dickerson & Eichenbaum, 2010; Wais, 2008). Cognitive decline present in AD leads to attenuated activation in hippocampus during memory encoding compared to healthy elderly (Machulda et al., 2003; Schwindt & Black, 2009; Sperling et al.; 2003). This has been confirmed in studies with patients, who suffer from Mild Cognitive Impairment (MCI). These at-risk patients for AD show less hippocampal activation during episodic memory tasks (Johnson et al., 2006; Mandzia, McAndrews, Grady, Graham, & Black, 2009; O'Brien et al., 2010; Oedekoven, Jansen, Kircher, & Leube, submitted),

whereas young and healthy elderly show similar hippocampal activation (Miller et al., 2008).

The network supporting episodic memory encoding has been also been described in resting state research. In recent years, fMRI research has increasingly focused on brain activation during resting state. Here, the default mode network (DMN) has been described, which is activated during "cognitive idleness" in resting state and is thought to monitor internal states. It is deactivated during tasks that require attention to external stimuli. The DMN is thought to be a core network involved in various processes such as rest, theory of mind and memory (Harrison et al., 2008; Spreng, Mar, & Kim, 2009).

It is one of two complementary, anticorrelated large-scale brain networks, a task-negative (DMN) and a task-positive network (TPN) (Fox et al., 2005). The DMN includes PMC (including posterior cingulate and precuneus), bilateral IPL (including angular gyrus), medial prefrontal cortex (including anterior cingulate cortex (ACC)) and MTL regions (including hippocampus) (Daselaar et al., 2009; Fox et al., 2005; Huijbers et al., 2011; Spreng et al., 2009; Toro, Fox, & Paus, 2008). The task-positive network (TPN) (Fox et al., 2005) or frontoparietal network (Toro et al., 2008) supports processing of externally presented information and cognitive control (Cole & Schneider, 2007; Kim, Daselaar, & Cabeza, 2010; Salami, Eriksson, & Nyberg, 2012). The TPN consists of dorsolateral prefrontal cortex, precentral and sensorimotor areas, insulae and lateral parietal regions anterior to DMN regions (Fox et al., 2005; Toro et al., 2008).

Episodic memory functions involve both task-positive and task-negative networks of brain activation. Encoding success is based on deactivation of the internally oriented DMN and activation of the task positive network (TPN) which supports externally oriented processing (Daselaar et al., 2009; Kim et al., 2010). Deactivation of DMN regions is essential for encoding success. Successful encoding is externally oriented and therefore requires a suppressed DMN network, while successful retrieval requires an involvement of internal attention and DMN is activated. Hippocampus is described as the only part of the DMN, which is activated during encoding as well as retrieval (Huijbers et al., 2011). An activation of DMN regions indicates cognitive demand, such as an increased effort or more attention to external details (Harrison et al., 2008). Deactivation is defined as decrease of the BOLD response when measuring task-related

activation in comparison to a control baseline (Gould, Brown, Owen, Bullmore, & Howard, 2006). Studies analyzing encoding success described activation as contrast of subsequent hits > baseline and deactivation as baseline < subsequent hits (Gould et al., 2005; Kennedy et al., 2012; Kircher et al., 2007; Vannini et al. 2011). Greater deactivation of DMN regions during encoding is related to greater activation during successful retrieval (Vannini et al., 2011).

Both large-scale brain networks, DMN and TPN, change with age. While young generally show more deactivation in DMN, older adults show more activation of TPN, effectively leading to a simultaneous decrease of DMN and an expansion of TPN with age (Grady et al., 2010). While DMN is usually deactivated during cognitive tasks, this deactivation is less pronounced in older adults relative to younger adults, older adults even showing activation in posterior DMN regions (Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Lustig et al., 2003; Miller et al., 2008; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007). Especially in PMC, level of deactivation is essential to discriminate elderly and young, since older adults show less deactivation in PMC with increasing age (Miller et al., 2008, Lustig et al., 2003). Furthermore, PMC activation is related to decreased memory performance (Miller et al., 2008; Pihlajamäki et al., 2009). Based on the literature, we expect alterations in magnitude and spatial extent of DMN deactivation with age and cognitive status.

At the same time, many studies report overrecruitment of frontal and other TPN regions in older adults (Grady, 2008; Grady et al., 2010; Miller et al., 2008; Park & Reuter-Lorenz, 2009). This overrecruitment of TPN regions is thought to be either a compensational attempt or inefficiency of neural resources leading to a greater extent of TPN in old in lateral and medial frontal cortices (Grady et al., 2010). The increasing activation of TPN regions simultaneously with less accuracy in tasks indicates the need for more cognitive control with age. To our knowledge, no study has investigated the influence of MCI on DMN and TPN activation. By including MCI patients in the encoding task, we aim to investigate if loss of DMN functionality and overrecruitment of TPN is also seen with decline of cognitive status, independent of age (Grady et al., 2010). Few other studies have compared young, elderly and at-risk states for AD with the same task, and these have focused exclusively on MTL or other regions of interest (Johnson et al., 2006; Lustig et al., 2003; Pihlajamäki, O'Keefe; O'Brien, Blacker, & Sperling, 2011; Sperling et al., 2003).To our knowledge, this study is the first to compare

young, healthy elderly and MCI patients using whole brain fMRI analysis during face-name encoding. Furthermore, we matched performance level for young and elderly by adjusting the encoding task for older adults. In our study we investigate the neural correlates of the formation of new episodic memories in young, healthy elderly and MCI subjects. Whole brain analysis allows us to distinguish age effects and influence of cognitive status across large-scale brain networks.

2. Materials and methods

2.1 Participants

Twenty-one healthy young participants (female: 11) with a mean age of 24.6 (± 3.6) years (± SD) (range: 18 – 35), 34 healthy elderly participants (female: 18) with a mean age of 63.0 (± 10.0) years (range: 50-89) and 24 MCI patients (female: 12) with a mean age of 65.9 (± 9.6) years (range: 50-86) took part in this study. All participants were right handed native German speakers and had normal or corrected-to-normal vision. A medical screening interview was used to exclude participants with any psychiatric or neurological illness.

All older participants were screened for cognitive deficits using the CERAD-Plus neuropsychological test battery which enables a comparison of subtests considering age- and education-adjusted norms (German version; available at Memory Clinic, Basel, Switzerland, http://www.memoryclinic.ch). MCI patients were classified according to the Mayo criteria for MCI which are based on a subjective cognitive complaint and an objective memory impairment in a standardized test (performing at least 1.5 standard deviations below norm in at least one relevant subtest of the CERAD-Plus test battery ($z < -1.5$ in Total Word List, Delayed Recall Word/Figures, MMSE)). Further criteria include relatively preserved general cognition and essentially intact activities of daily living, not demented (Petersen, 2004). Recently developed clinical MCI criteria are also applicable (Albert et al., 2011). The study was approved by the ethics committee of the Medical Faculty of the University of Marburg. All participants provided written informed consent and were paid for participation.

2.2 Experimental Design

A face-name encoding task was used to examine associative episodic memory learning. We used an event related design. The task was programmed using Presentation (Neurobehavioral Systems, Albany, CA, USA). During encoding, faces were presented repeatedly with a fictional first name. Faces were taken from an online face database (Minear &Park, 2004) and were balanced according to age and gender and shown in a pseudo-randomized order. First names were taken from a listing of the most common German names for each decade and were matched to the age of the person pictured. Participants were asked to judge whether the name “fit” the face, as well as to memorize faces and names. To answer, participants pushed one of two buttons using the index and middle finger of the right hand to indicate their response on a custom-made response box. An additional one third of events were null-events, displaying a scrambled face. All events were followed by a jitter of 1-2 seconds, displaying the scrambled face.

Encoding task difficulty was adjusted for older participants allowing for a similar level of memory performance in young and healthy elderly (Price & Friston, 1999). For all older participants, less face-name pairs were presented (80 vs 120) and stimuli were shown for an increased duration (3000ms vs 2000ms). Face-name pairs were repeatedly shown. For young participants, the whole encoding phase took place in the scanner, 60 face-name pairs were shown only once and 60 were shown three times. For all older participants (healthy elderly and MCI), the first two repetitions of 80 face-name pairs were presented outside the scanner, one repetition of the 80 faces inside the scanner, the 80 faces were thus shown three times.

Following the face-name encoding task, participants took part two further experiments, face retrieval and an associative face-name retrieval task. Participants were scanned during encoding and retrieval phases. The present study focuses on data collected at the face-name encoding task. The face retrieval phase is described in Oedekoven et al. (2012) and the face-name recognition task is described in Oedekoven et al (submitted).

2.3 FMRI data acquisition

Participants were scanned at the at the Philipps University Marburg using a Trio Tim Magnetom 3-T scanner (Siemens, Erlangen, Germany) with a twelve-

channel head coil. Functional images were collected with a T2*-weighted echo planar imaging sequence (EPI) (64 x 64 matrix, FOV 230 mm, TR = 2200ms, TE = 30 ms, flip angle 90°, slice order: ascending). Thirty-six slices were acquired in an oblique axial orientation (voxel dimensions 3.6 x 3.6 x 3.6 mm).

2.4 Data analysis

Behavioral data and descriptive statistics were analyzed using SPSS for Windows 15.0 (SPSS Inc., Chicago, USA). Functional data were analyzed using statistical parametric mapping SPM8 (Wellcome Trust Centre of Neuroimaging, UK) based on Matlab 7.7.0 (Version R2008b, The Mathworks, MA, USA). Data pre-processing consisted of realignment of head motion, slice timing to account for time differences in image acquisition and normalization to SPM8's MNI EPI template (resulting voxel size 2 x 2 x 2 mm). Images were smoothed with a Gaussian kernel of 8 mm full width half maximum.

To identify task-related hemodynamic responses on the subject-level, three regressors were included, modeling subsequent hits, subsequent misses and subsequent associative events, convolved with a canonical hemodynamic response function. Six regressors modeling head movement parameters were included. For group level analysis, we used subject level contrasts of subsequent hits vs baseline and subsequent misses vs baseline. Baseline included nullevents and jitters. We conducted a 2x3 full factorial model in SPM8 (ANCOVA) to compare groups (Young, Elderly, MCI) and events (subsequent hits, subsequent misses), using subsequent individual memory performance as covariate (percentage of subsequent hits). In order to identify subsequent memory performance, we contrasted subsequent hits and subsequent misses.

All coordinates refer to MNI space as used in SPM8. Anatomical locations were determined using the Anatomy Toolbox (Eickhoff et al., 2005). Activation results are reported whole brain FWE corrected ($p < .05$, peak-level) unless otherwise specified.

3. Results

3.1 Behavioral Data

Data of one young participant were excluded after scanning due to anomalously large ventricles. Data of one healthy elderly participant were excluded due to a physical inability to press the response buttons. Data of two healthy elderly were excluded due to missing data. Data of one MCI patient were excluded due to a high depression score (GDS). Thus, behavioral and fMRI measures were analyzed for 20 healthy young participants, 31 healthy elderly participants and 23 MCI patients. Descriptive statistics of all participants included in further analysis are summarized in Table 1.

Memory performance is summarized in Table 1. There was no difference in percentage of subsequent hits; young, healthy elderly and MCI patients reached a similar level of memory accuracy in regard to subsequently recognized faces.

3.2 fMRI Data

We compared brain activation across groups and events with a 2x3 ANCOVA to compare groups (Young, Elderly, MCI) and events (subsequent hits, subsequent misses) in the face-name encoding task, regarding individual memory performance as covariate (percentage of subsequent hits).

First, we contrasted subsequent hits vs. misses in the collapsed groups and for each group separately. Contrary to previous studies, we did not find activation when contrasting subsequent hits vs. subsequent misses, despite investigating this contrast across groups and for young, healthy elderly and MCI patients individually. Therefore we used contrasts of successful encoding (subsequent hits vs baseline) for further analysis, since percentage of subsequent hits was similar across groups and this contrast has been used in earlier studies to investigate subsequent memory performance (Gould et al., 2005; Kennedy et al., 2012; Kircher et al., 2007; Vannini et al., 2011).

3.2.1 DMN

To evaluate changes in DMN areas, patterns of deactivation (baseline > subsequent hits) across groups were of interest (see Fig 1). As expected, deactivation occurred primarily in DMN regions, despite our whole brain approach (see Table 2). A conjunction analysis for deactivation showed

overlaps across all three groups in left angular gyrus (-42 -76 40) and left ACC (-6 50 12) (unc. p <.001, see Fig 1). Regarding the influence of age, an analysis of parameter estimates showed age and magnitude of deactivation to be inversely related in posterior DMN regions, in PMC ($r = .23$, $p < .05$) and bilateral IPL (left: $r = .24$ ($p < 0.05$); right: $r = .23$ ($p < 0.05$)). The older the participants were, the less deactivation was found in these DMN regions.

Direct group comparisons (Young (Y) <> Healthy elderly (HE), HE <> MCI, MCI <> Y) revealed group effects in DMN regions. In hippocampus, the one DMN region showing activation during encoding, comparison of parameter estimates across groups for peak activations within a hippocampal ROI showed increased activation for healthy elderly (see Fig 2). Regarding posterior DMN regions, healthy elderly showed stronger activation in bilateral PMC and IPL in comparison to young, the increased activation of DMN regions indicating increased effort (Table 4). Magnitude of PMC deactivation and hippocampal activation were correlated only in healthy elderly (left: $r = .44$ ($p < 0.05$), right: $r = .48$ ($p < 0.05$). MCI did not show additional activation of DMN regions.

3.2.2 TPN

With regard to activations in TPN regions (subsequent hits > baseline) we found similar patterns of activation across all three groups. A conjunction analysis (whole brain) showed a network involving bilateral fusiform gyri; lateral parietal and precentral regions as well as bilateral insulae (see Table 3). While fusiform gyrus is not usually seen as part of TPN, it is associated with TPN regions (Grady et al., 2010). Direct group comparisons (Y <> HE, HE <> MCI, MCI <> Y) revealed group effects in TPN regions (Table 4). For older participants in general, we found increased activation in several regions, when comparing them to young: healthy elderly and MCI showed increased activation in bilateral precentral and postcentral regions, which are part of TPN.

4. Discussion

In our study we investigated the changes occurring in large-scale brain networks with age and cognitive decline during the formation of new episodic memories in young, healthy elderly and MCI patients. All groups had a similar level of subsequent memory performance regarding correctly identified faces (hits), indicating a successful adaptation of encoding task difficulty for older participants. While we did not find differences in brain activation for subsequent hits vs subsequent misses, we did find magnitude and spatial extent of brain activation to vary with age and cognitive status when observing successful encoding (subsequent hits vs. baseline).

Regarding DMN regions, we found an overlap of patterns of deactivation in all three groups. Furthermore, there were decreases in magnitude of deactivation with increasing age. Increased age was related to less deactivation, especially in posterior DMN regions. But DMN activity was also influenced by memory status, since overrecruitment (less deactivation) of posterior DMN regions was especially prominent in healthy elderly, whereas MCI patients did not exhibit overrecruitment of posterior DMN regions. Hippocampal activation was also increased in healthy elderly, but not in MCI. Overrecruitment of DMN regions in healthy elderly may indicate compensational processes not available in MCI.

In TPN regions, a conjunction analysis revealed a similar pattern of activations across the three groups. Direct group comparisons showed overrecruitment of pre- and postcentral TPN regions in older participants, regardless of memory status, suggesting dedifferentiation processes with age.

4.1 DMN

Whereas we found an overlap of patterns of deactivation in DMN regions in all three groups, we also found decreases in magnitude of deactivation with increasing age, especially in posterior DMN regions (Fig 1).

Similar to a study by Lustig and colleagues, both older groups show robust positive activations, but only sparse deactivation in comparison to young (Lustig et al., 2003). Suppressed DMN deactivation occurred especially in PMC and bilateral IPL. Decrease of deactivation in these DMN regions is usually interpreted as reallocation of neural resources for focused attention (Vannini et al., 2011). In our study, we adjusted encoding task difficulty in favor of the

elderly, but nevertheless healthy elderly showed less PMC and IPL deactivation than young and increased age was correlated to less deactivation in PMC and bilateral IPL. Neural activity in PMC is an important marker to discern effects of aging, since this critical node of the DMN network is generally intact in young but may be particularly challenged in the context of aging (Miller et al., 2008). We attribute the additional recruitment of DMN regions to increased effort in healthy elderly, in combination with additional recruitment of TPN regions.

In addition to less deactivation in PMC and IPL, we found more hippocampal activation in healthy elderly. Hippocampus is the only DMN associated region which is active during encoding as well as retrieval. While other DMN regions deactivate during encoding and activate during retrieval, hippocampus is dissociated from DMN deactivation and is also activated during encoding (Huijbers et al., 2011). In previous studies posterior lateral parietal and PMC regions were found to respond to variations in memory load (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003). Stronger deactivation in PMC was coupled to stronger hippocampal activation and both decreased with a decline in memory (Celone et al., 2006; Miller et al., 2008). Consistently, we found less deactivation in posterior DMN regions to be related to increased hippocampal activation in healthy elderly. Magnitude of PMC deactivation and hippocampal activation were correlated only in healthy elderly and hippocampal activation was increased in healthy elderly, but not in MCI.

Thus, DMN activity was also influenced by cognitive status, since overrecruitment (less deactivation) of posterior DMN regions and hippocampus was especially prominent in healthy elderly. MCI patients did not exhibit overrecruitment of posterior DMN regions, whereas in earlier studies, failure to reduce activity in PMC and IPL during encoding was most striking in older adults with AD or at-risk states for AD (Celone et al., 2006; Greicius, Srivastava, Reiss, & Menon, 2004; Lustig et al., 2003; Petrella, Prince, Wand, Hellegers, & Doraiswamy, 2007; Pihlajamäki et al., 2009). One possible explanation for this is that while all three groups showed a similar level of accuracy in the face-name encoding task, MCI show associative memory impairment in the following recognition of newly presented faces and face-name associations (Oedekoven et al. 2012, submitted). This may indicate that overall, MCI did not encode face-name combinations adequately, since they fail to put up the additional resources needed to compensate their age-related decline, whereas in healthy

elderly, the overrecruitment of DMN regions provides additional neural resources.

Adding to this argument is the adapted task difficulty. Due to adaptation of task difficulty, older adults judged fewer events. Looking at the older groups only, there is a difference in number of subsequent hits, underlining the extra compensational resources of healthy elderly in comparison to MCI.

Consistent with previous studies investigating hippocampal activation in MCI and beginning AD, we found lesser activation in hippocampus in MCI during encoding compared to healthy elderly (Johnson et al., 2006; Machulda et al., 2003, Mandzia et al., 2009, O'Brien et al., 2010; Petrella et al., 2006; Schwindt & Black, 2009, Sperling et al., 2003). A possible explanation for this decline in hippocampal activation has been examined by De Rover and colleagues: MCI patients activated significantly more than controls at low cognitive loads and significantly less at higher loads (De Rover et al., 2011). Since our task required a higher memory load and complex associative memory in comparison to other studies, healthy elderly who compensated for age-related loss, showed increased hippocampal activation. Therefore the inverse u-shape proposed in earlier studies, peaks in healthy elderly instead of MCI, since MCI patients show no compensational attempt (Dickerson et al., 2005).

The fact that elderly showed increased activation in hippocampus in comparison to MCI shows this activation to be related to memory performance not age, similar to earlier studies (Sperling et al., 2003). Furthermore, the failure to compensate through additional activation may indicate a disconnection of hippocampus with progress of AD to be present in MCI (Dickerson & Sperling, 2008).

DMN regions overlap with regions showing an encoding/retrieval flip which signifies that the same network of regions is deactivated during encoding and positive activation during retrieval (Daselaar et al., 2009; Huijbers et al., 2011; Vannini et al., 2011). Whereas during encoding we found PMC, IPL and ACC deactivated in young, in a recent study we found in the same subjects activation in these DMN regions during face retrieval (Oedekoven et al., 2012).

4.2 TPN

Regarding activations in TPN regions, the network of activations was similar across the three groups. TPN is a large-scale functional brain network implicated in cognitive control and attention (Fox et al., 2005). This network, including frontal and parietal regions, is engaged in encoding and retrieval of face-name associations, and involved in cognitive control (Cole & Schneider, 2007; Kim et al, 2010; Salami et al., 2012). Similar to earlier studies, we found evidence for an increase of activation with age in TPN regions, attributed to an upregulated recruitment cognitive control with age (Grady et al., 2010; Salami et al., 2012). A similar network was activated in associative face-name recognition including fusiform gyri, bilateral insulae, parietal and frontal regions (Oedekoven et al., submitted). When investigating episodic memory, increased activations with age are typical findings, especially in frontal and parietal regions (Grady, 2008; Kircher et al., 2008; Morcom, Li, & Rugg, 2007; Park & Reuter-Lorenz, 2009; Spreng, Wojtowicz, & Grady, 2010). Overrecruitment of these regions in elderly is often explained by compensational processes or dedifferentiation, which can also co-occur in elderly during retrieval (Grady, 2008; Zarahn, Rakitin, Abela, Flynn, & Stern, 2007) and their increased reliance on cognitive control (Salami et al., 2012; Schwindt & Black, 2009).

In direct group comparisons, we found increased activation in healthy elderly and MCI in precentral and postcentral regions, which are part of TPN. This additional activation of TPN, typically involving pre- and postcentral as well as parietal regions has been found regularly in older adults (Grady et al., 2010; Heun et al., 2007; Kennedy et al., 2012; Oedekoven et al., 2012; Sperling et al., 2010).

The additional activation of pre- and postcentral TPN regions is generally thought to signify increased effort, due to compensation or dedifferentiation processes. We adjusted the encoding task to enable similar performance in healthy elderly and MCI and both groups showed this effect. Since the effect occurred regardless of cognitive status, it is not likely, that it has a compensatory function. Precentral regions of TPN are active in encoding and novelty detection activity and are part of the cognitive control network (Cole & Schneider, 2007; Kim et al., 2010). Since the additional TPN activation in our study occurred in healthy elderly and MCI patients it might be an indicator of dedifferentiation rather than compensational processes, because there is

supposedly no advantage for memory performance with increased activation in these areas. This is in line with the idea of age related changes in neural efficiency, where elderly show overrecruitment for a similar level of memory accuracy (Grady et al., 2008; Morcom et al., 2007).

4.3 Limitations

We adjusted task difficulty to allow the same memory performance in elderly, in order to be able to compare activations across groups (Price & Friston, 1999). To increase the likelihood of recognition success in elderly adults, we increased the amount of time each face-name pair was presented, reduced the total number of stimuli presented, and used three encoding trials to allow subjects enough time similar to earlier studies (Rand-Giovanetti et al., 2006). We were successful insofar as that all three groups showed a similar percentage of subsequent hits. This measure was therefore used to evaluate memory performance.

The adaptation of the encoding task may have influenced the comparison of subsequent hits and misses, since contrary to earlier studies; we did not find a difference in activation. This might have been due to the smaller absolute number of events or due to repeated viewings for older adults. We adjusted memory performance between young and elderly to avoid large differences in task performance. But the increased task load in young might have caused greater deactivation in this group because, dependent on task load, increased deactivation with increased task load have been found (Gould et al., 2006).

4.4 Conclusions

To conclude, in our study we assessed the influence of aging and cognitive status on changes in DMN and TPN in episodic memory encoding. We used a face-name encoding task, contrasting successful encoding and baseline. All groups had a similar level of subsequent memory performance regarding correctly identified faces (hits), indicating a successful adaptation of encoding task difficulty for older participants. There were overlapping deactivations in DMN regions (angular gyrus and ACC), but magnitude of deactivation varied with age especially in posterior DMN regions (PMC and bilateral IPL). Hippocampal activation was also increased in healthy elderly, but not in MCI. We observed DMN activation to change with age, but observed a further

modification with memory status. While healthy elderly showed overrecruitment in posterior DMN regions and hippocampus, MCI patients did not. Possibly the recruitment of DMN regions is a compensational attempt not affordable for MCI patients.

Regarding TPN regions, we observed an overlapping activation in TPN regions for all three groups. In accordance with earlier studies, we noticed an increase of activation in TPN regions with age. This additional activation in pre- and postcentral regions occurred regardless of memory status, indicating a loss of neural efficiency and resulting dedifferentiation processes with age.

Disclosure statement

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Table 1: Descriptive statistics and memory performance

	Young	Elderly	MCI
Participant statistics			
n	20	31	23
Age	24.5 ± 3.7	61.3 ± 7.9	65.8 ± 9.8
Sex ratio F/M	11/9	16/15	11/12
Education*	16.4 ± 2.1	15.1 ± 3.1	14.1 ± 3.3
GDS score*		1.8 ± 1.8	3.1 ± 1.9
Face-name encoding task			
Hits %	75.9 ± 11.0	79.1 ± 11.5	73.7 ± 18.0
Reaction time in sec*	1.677 ± 0.2	1.518 ± 0.3	1.842 ± 0.6
Selected CERAD scores			
MMSE***		29.2 ± 0.8	26.6 ± 1.4
Total CERAD score***		91.8 ± 4.1	78.7 ± 9.8
Total Word list***		24.8 ± 2.6	19.0 ± 4.0
Delayed world list***		9.0 ± 1.1	5.9 ± 2.1

Descriptive statistics are of all subjects included in fMRI data analysis
Means ± Standard Deviations; * $p<0.05$; *** $p<0.001$
GDS = Geriatric Depression Scale, MMSE = Minimental State Examination

Table 2: Deactivations in DMN Regions

	Hemisphere	x	y	z	T
Young					
IPL[a]	L	- 40	- 78	38	7.80
Angular Gyrus[a]	L	- 50	- 72	30	6.85
IPL[a]	L	- 62	- 40	- 44	6.82
IPL[a]	R	44	- 76	34	4.82
Supramarginal Gyrus[a]	R	62	- 36	40	4.82
PMC[a]	L	- 10	- 38	40	6.57
PMC[a]	R	6	- 38	46	5.71
ACC[a]	L	- 6	34	- 4	6.68
ACC[a]	R	4	34	- 4	5.83
Middle Frontal Gyrus[a]	L	- 28	30	50	4.68
ITG[a]	L	- 60	- 56	- 6	5.38
STG[a]	R	62	- 14	2	5.20
Cuneus[a]	L	- 12	- 58	20	4.97
Precentral Gyrus[a]	R	42	- 24	64	4.25
Healthy Elderly					
IPL[a]	L	- 44	- 76	34	5.75
Angular Gyrus[a]	L	- 52	- 66	38	4.33
ACC	R	4	48	22	3.72
ACC	L	- 6	50	12	3.66
Middle Frontal Gyrus	L	- 40	20	54	4.44
Superior Frontal Gyrus	R	14	52	46	4.42
ITG	L	- 60	- 20	- 24	3.90
MCI					
IPL	L	- 44	- 76	36	4.39
Angular Gyrus	L	- 42	- 76	40	4.26
ACC	L	- 6	48	8	4.00
Middle Frontal Gyrus	L	- 38	16	58	3.76

Bold script indicates DMN region; xyz: MNI coordinates; unc p <.001; [a] FWE corrected p <.05 (peak-level); ACC = Anterior Cingulate Cortex, IPL = Inferior Parietal Lobe, ITG = Inferior Temporal Gyrus, PMC = Middle Cingulate, STG = Superior Temporal Gyrus

Table 3: Conjunction of Activations across all three groups

	Hemisphere	x	y	z	T
Fusiform Gyrus	R	40	- 46	- 22	11.70
Fusiform Gyrus	L	- 40	- 68	- 14	10.44
IPL	L	- 28	- 56	48	9.44
Angular Gyrus	R	30	- 58	48	8.59
SMA	R	4	4	56	8.49
Precentral Gyrus	L	- 40	- 12	62	8.46
Precentral Gyrus	R	44	8	30	8.42
Insula	L	- 32	22	4	7.32
Insula	R	32	24	2	6.57
Middle Frontal Gyrus	R	38	0	60	5.35

Bold script indicates TPN regions; xyz: MNI coordinates; FWE corrected p <.05 (peak-level);
IPL = Inferior Parietal Lobe SMA = Supplementary Motor Area

Table 4: Group effects in activations

	Hemisphere	x	y	z	T
Elderly > Young					
Precentral Gyrus	R	34	- 18	52	7.05
Precentral Gyrus	L	- 28	- 16	56	6.79
Postcentral Gyrus	R	52	- 26	42	6.12
Postcentral Gyrus	L	- 34	- 30	50	6.08
SMA	R	8	- 4	50	6.53
PMC	L	- 12	- 32	42	6.00
PMC	R	6	- 36	50	5.45
Supramarginal Gyrus	R	62	- 22	18	5.62
IPL	L	- 58	- 36	48	5.30
IPL	R	44	- 32	20	5.17
Middle Occipital Gyrus	L	- 28	- 72	38	5.70
MCI > Young					
Precentral Gyrus	R	32	- 14	62	6.00
Precentral Gyrus	L	- 32	- 12	62	6.00
Postcentral Gyrus	L	- 32	- 32	56	6.53
SMA	L	- 8	- 12	66	5.80

xyz: MNI coordinates; FWE corrected $p < .05$ (peak level);
IPL = Inferior Parietal Lobe, PMC = Middle Cingulate, SMA = supplementary motor area

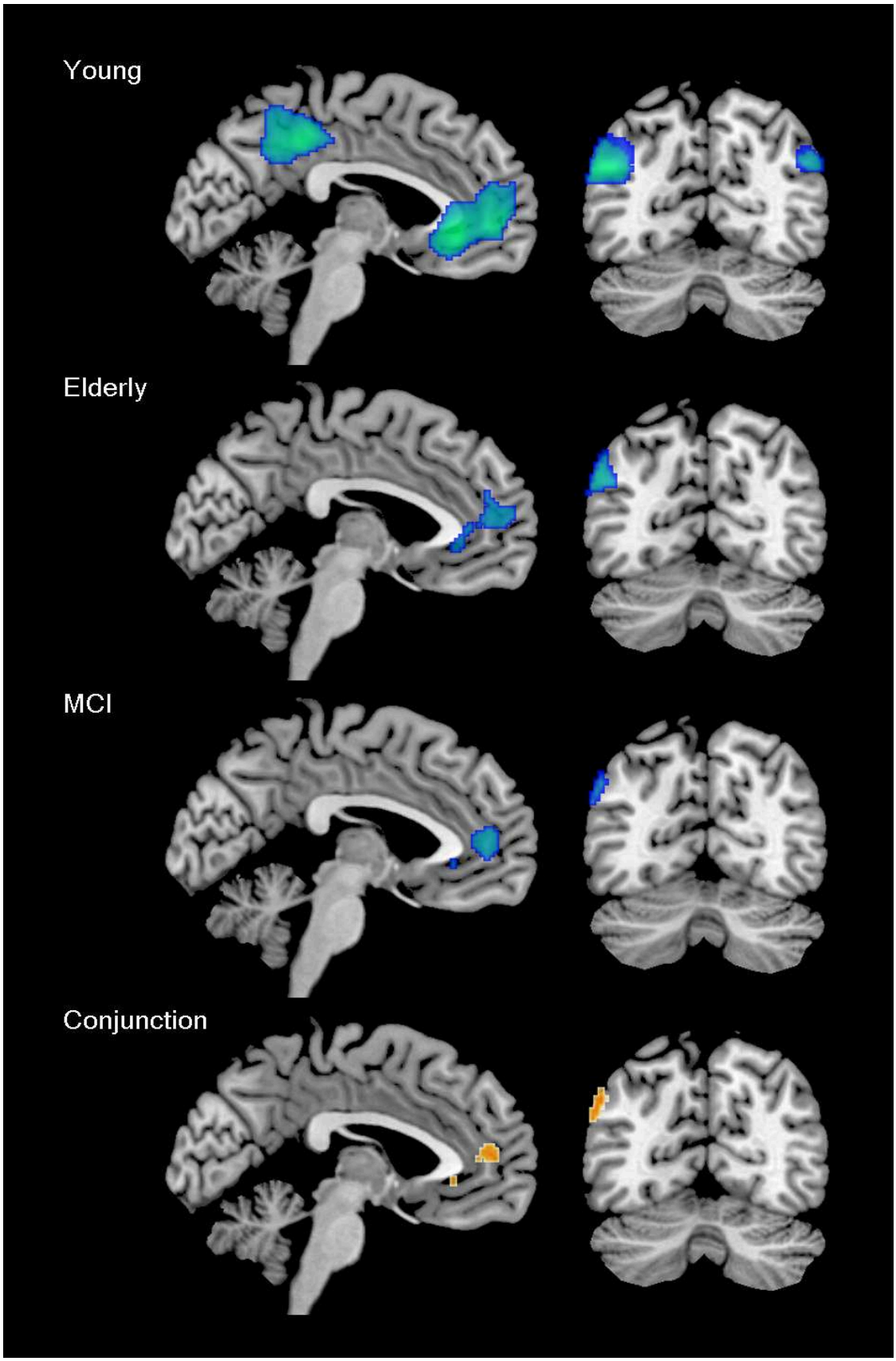

Fig 1: Deactivation of DMN regions in groups. p <.001 uncorrected, for visualization. For MNI coordinates see Table 2.

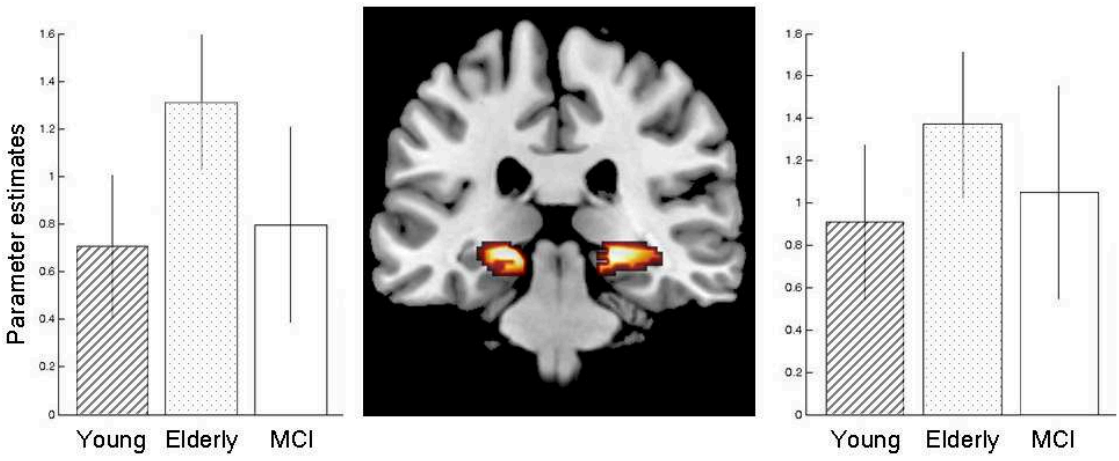

Fig 2: Hippocampal activation in subsequent hits > baseline, in relation to age and memory status.Left Hippocampus -20 -28 -6.Right Hippocampus -22 -30 -4. Hippocampal ROI for visualization.

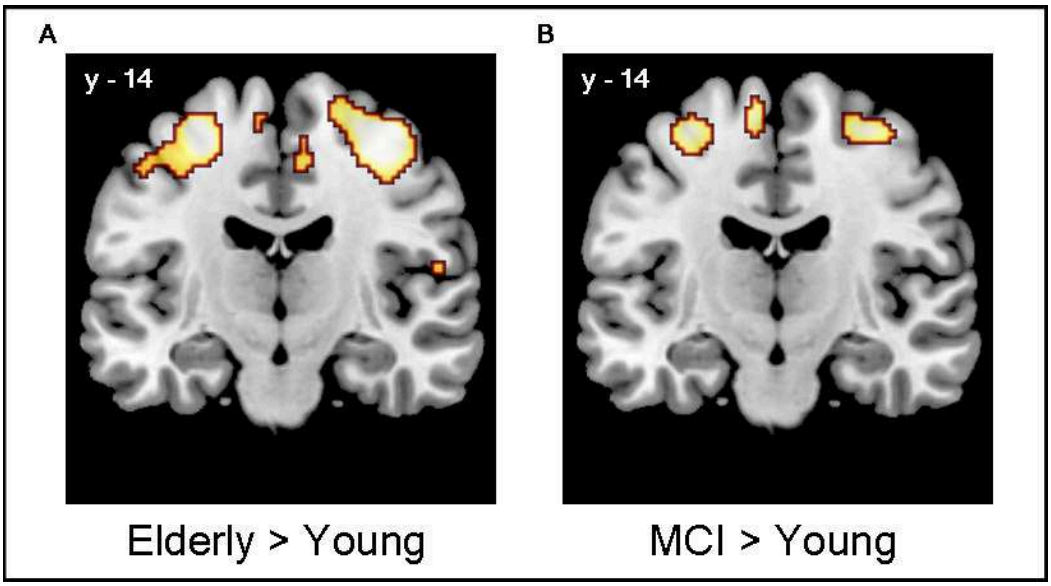

Fig 3: Stronger activation in precentral TPN regions. Group effect in healthy elderly and MCI. FWE corrected p < .05 (peak-level). For MNI coordinates see Table 4.